Original Article

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Association of D-dimer Level with Renal Parameters and Cardiovascular Events in Type 2 Diabetes Mellitus: A Retrospective Cohort Study

Biochemistry Section

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ABSTRACT

Introduction: D-dimer is a biomarker that can detect early stages of renal and cardiovascular dysfunction in Type 2 Diabetes Mellitus (T2DM). It serves as a key indicator and is readily available in laboratory settings, along with other risk factors.

Aim: To investigate the association between D-dimer levels and renal parameters, as well as cardiovascular events, among T2DM subjects.

Materials and Methods: This retrospective cohort study was conducted at Visnagar's Nootan Medical College and Research Centre, Visnagar, Gujarat, India, involving subjects who visited the centre for health checks between September 2021 and December 2022. Screening was performed on all adult individuals with T2DM. Clinical records of 550 consecutive T2DM patients, aged between 18 and 80 years, receiving care at the centre were analysed. After applying exclusion criteria, 155 patients with T2DM diagnosis were enrolled. Parameters such as cystatin C, D-dimer, serum creatinine, urea, estimated Glomerular Filtration Rate (eGFR), and albuminuria were evaluated in all subjects. Bivariate logistic regression analysis was conducted to determine whether renal indicators are associated with high D-dimer levels, generating an odds ratio. Multivariate logistic regression analysis was then performed, correcting for sex and age, to determine which kidney indicators are linked to high D-dimer levels.

Results: A total of 155 participants were included in this study, and were divided into high and low D-dimer groups. The mean ages of the low and high D-dimer groups were 40±13 years and 55±10 years, respectively. Compared to the low D-dimer group, the high D-dimer group had a higher frequency of males (p-value <0.001). Patients with high D-dimer levels exhibited significantly increased levels of HbA1c, creatinine, urea, cystatin C, and UAE compared to patients with low D-dimer levels (p-value=0.001, p-value=0.001, p-value <0.001, p-value <0.001, and p-value=0.001, respectively).

Conclusion: D-dimer may be beneficial in identifying patients with early-stage diabetic kidney disease, thereby promoting the early adoption of renal and cardioprotective therapy. Additionally, elevated D-dimer levels are associated with an increased risk of cardiovascular disease.

Keywords: Albuminuria, Blood glucose, Cardiovascular diseases, Renal complications

INTRODUCTION

Almost 30% of diabetic patients are thought to have renal dysfunction [1,2]. Compared to people without diabetes, those who have diabetes have a twofold greater risk of cardiovascular illnesses [3]. Patients with T2DM who maintain stable blood sugar levels are significantly less likely to experience microvascular complications but not macrovascular disease. Therefore, it's imperative to create strategies for preventing cardiovascular problems in diabetics. Biomarkers like D-dimer can be used to predict the chance of cardiovascular diseases in high-risk diabetic patients [4,5]. D-dimer is a cross-linked fibrin degradation product that circulates in the blood and is produced during thrombus development. Higher D-dimer levels reflect a propensity for increased thrombosis and increased systemic fibrin formation. D-dimer is a specific breakdown byproduct of cross-linked fibrin clots and serves as a traditional biomarker of hypercoagulability, aiding in the identification of thromboembolic events. D-dimer levels are linked to the emergence of atherothrombosis and cardiovascular problems in diabetic patients, suggesting that D-dimer may be helpful in assessing the risk of cardiovascular disease in these individuals. High D-dimer concentrations have reportedly been associated with the occurrence and prognosis of cardiovascular illnesses [6,7]. D-dimer levels also rise as renal disease progresses in diabetic patients, suggesting that hypercoagulability may be a factor in the association between diabetic kidney disease and an elevated risk of cardiovascular events [8-10].

A gradual rise in Urine Albumin Excretion (UAE), which causes glomerular filtration to decline and ultimately results in renal failure, is known as diabetic kidney disease [1,11]. It is the primary contributor to end-stage renal disease, a standalone cardiovascular disease risk factor, and an increase in mortality. Several biomarkers, including creatinine, urea, GFR, UAE, and cystatin C, can be used to assess renal function in diabetic individuals. Although other variables besides renal disease can affect their levels, GFR estimation is more frequently used in clinical practice as it allows for the early discovery of renal parenchymal injury. UAE is a vital biomarker of renal injury used for the diagnosis and prognosis of diabetic kidney disease, even though its levels can be influenced by factors other than renal disease. Cystatin C, a low molecular weight protein produced by all nucleated cells, plays a role in controlling cysteine proteases [12,13]. It has been shown to be very effective in identifying kidney disease in diabetic patients during its early phases [12,13].

The first stage in a prevention program is to identify high-risk patients, and D-dimer can be used as an early biomarker in detecting renal disease among T2DM patients. However, data regarding the association of D-dimer levels and renal diseases are very limited. Hence, the present study was conducted to study the association between D-dimer levels with cardiovascular events and renal parameter alterations among T2DM population.

MATERIALS AND METHODS

This single-centre retrospective cohort study was conducted at Visnagar's Nootan Medical College and Research Centre, Visnagar, Gujarat, India. Data were collected from January 2020 to August 2021 and analysed between September 2021 and December 2022. The project was approved by the Research Ethics Committee of Nootan Medical College and Research Centre in Visnagar (Ref: NMCRC: HREC/23/SESSION 4/12). Prior to enrollment in the study, written informed consent was obtained from each patient.

Inclusion criteria: Patients aged >18 years who used antidiabetic drugs or were diagnosed and classified as having DM in accordance with the American Diabetes Association (ADA) Guidelines [14] were included in the study.

Exclusion criteria: Subjects with Type 1 diabetes, gestational diabetes, hepatic disease, alcoholism, abnormalities of coagulation or haemostasis, malignant diseases, acute infectious diseases, a history of kidney transplantation, pregnancy, untreated endocrine conditions, haemodialysis, or malignant hypertension were excluded from the study.

Sample size: A total of 550 consecutive DM type 2 patients, aged between 18 and 80 years, receiving care at the centre had their clinical records examined. After applying the exclusion criteria, a total of 155 patients with DM type 2, diagnosed both clinically and through laboratory tests, were enrolled in the study.

Data collection: Medical records were used to gather information on age, sex, weight, height, date of DM Type 2 diagnosis, antihypertensive medication, statin use, and acetylsalicylic acid use.

For all study subjects, data for creatinine, urea, cystatin C, UAE, D-dimer, and HbA1C were collected. Enzymatic colorimetric techniques were used to measure serum creatinine and urea. Serum albumin was measured using dry chemistry and colorimetric techniques. HPLC was used to measure HbA1c. Cystatin C and D-dimer were measured using Enzyme Linked Immuno Sorbent Assay (ELISA). Urinary albumin was normalised by urinary creatinine in urine samples obtained after atleast four hours of urinary retention to evaluate UAE. Urine albumin was tested using an immunoturbidimetric approach, and urinary creatinine was assessed using an enzymatic method. UAE was calculated as the ratio of urine albumin to creatinine. Each renal biomarker was used to assess the presence of renal disease, and cut-offs of 1.3 mg/dL, 40 mg/dL, 0.94 mg/L, and 30 mg/g were used for creatinine, urea, cystatin C, and UAE, respectively.

The CKD-EPI equation, expressed as a single equation, is:

$GFR=141*\min(Scr/\kappa,1)^{\alpha}*\max(Scr/\kappa,1)^{-1.209}*0.993^{age}*1.018$ (if female)* 1.159 (if black)

Here, Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males. 'min' indicates the minimum of Scr/κ or 1, and 'max' indicates the maximum of Scr/κ or 1 [15].

D-dimer levels were used to categorise the patients into two groups: those with low D-dimer levels (<318 ng/mL), which included the first and second D-dimer tertiles, and those with high D-dimer levels (>318 ng/mL), which included the third D-dimer tertile [16].

The percentage distribution with high and low D-dimer groups and statistical significance were analysed for both conventional variables (hypertension, Body Mass Index (BMI), HbA1C, duration of diabetes, age) and therapies (only diet therapy, anti-thrombotic drugs, diabetic medications, and use of statin, Angiotensin Receptor Blockers/Angiotensin Converting Enzyme Inhibitors (ARB/ACEI), beta-blocker).

STATISTICAL ANALYSIS

The analysis was conducted using MedCalc and Excel 2019, commercially available statistical software. A statistically significant p-value of <0.05 was used. The normality of the variables was assessed using the Shapiro-Wilk test. For normally distributed data, the mean and standard deviation were examined using a t-test. Categorical variables were expressed as frequencies and compared using a chi-square test (χ^2). Bivariate logistic regression analysis was performed to determine the association between dichotomised renal indicators and high D-dimer levels, generating odds ratios. Multivariate logistic regression analysis was then conducted to determine the association between dichotomised renal biomarkers and high D-dimer tertiles, adjusting for sex and age, and generating odds ratios.

RESULTS

A total of 155 participants were included in this study and were divided into high and low D-dimer groups. In the low D-dimer group, the mean age was 40±13 years, while in the high D-dimer group, it was 55±10 years. The high D-dimer group had a significantly higher frequency of males compared to the low D-dimer group (p<0.001). Patients with high D-dimer levels had significantly increased levels of HbA1c (p-value=0.001), creatinine (p-value=0.001), urea (p-value <0.001), cystatin C (p-value <0.001), and UAE (p-value=0.001) compared to patients with low D-dimer levels. Additionally, patients in the high D-dimer group had lower levels of serum albumin (p-value=0.003) and eGFR (p-value <0.001) than those in the low D-dimer group [Table/Fig-1].

Parameters	Low D-dimer group	High D-dimer group	p-value
Number of individuals (n)	102	53	
D-dimer (ng/mL)	204 (134-233)	489 (381-639)	<0.001
Age (years)	40±13	55±10	0.002
Sex/(male/female) (male %)	60/42 (58.8)	32/21 (60.3)	<0.001
BMI (kg/m^2)	24±3	27±3	0.003
Duration of diagnosis of Type 2 DM (years)	17±7	20±5	0.08
HbA1c (%)	8.5 (7.5-9.8)	10.2 (8.6-10.4)	0.001
Creatinine (mg/dL)	0.82 (0.67-0.93)	1.04 (0.71-1.47)	0.001
eGFR (mL/min/1.73 m^2)	120 (97-130)	76 (43-104)	<0.001
Urea (mg/dL)	27±7	45±15	<0.001
Albumin (g/dL)	4.1±0.4	3.2±0.4	0.003
Cystatin C (mg/L)	0.77 (0.67-0.88)	1.15 (0.90-2.02)	<0.001
UAE (mg/g of creatinine)	17 (13-27)	42 (37-158)	0.001

[Table/Fig-1]: Characteristics of patients with diabetes and renal markers classified according to D-dimer levels.
test, level of significant p-value <0.05

In the present study, the low D-dimer group had a higher proportion of patients receiving antihypertensive or antihyperglycaemic medications. Patients taking aspirin and metformin were more common in the low D-dimer group compared to the high D-dimer group among them (p-values of 0.001 and 0.001, respectively), while the high D-dimer group in the statin group had a higher percentage (p-value of 0.001). The incidence of Cardiovascular Disease (CVD) events was significantly higher in the high D-dimer group compared to the low D-dimer group [Table/Fig-2].

Characteristic	Low D-dimer group 204 (134-233) N (%)	High D-dimer group 489 (381-639) N (%)	p-value
CVD events	21 (20)	41 (77.4)	<0.001
Treatments			
Only diet therapy	35 (34.4)	8 (14)	0.001
Metformin	76 (75.2)	24 (45.2)	<0.001
Sulphonylurea	26 (25)	17 (32.1)	0.702
Insulin	10 (9.9)	5 (8.9)	0.907

Aspirin	58 (56.8)	24 (45.3)	<0.001
Clopidogrel	11 (10.2)	8 (14.2)	0.302
Warfarin	4 (3.2)	2 (3.7)	0.684
ACE/ARBI	78 (76.6)	16 (30.8)	0.191
β-blockers	12 (11.3)	7 (13.6)	0.160
Use of antihypertensive	55 (53.5)	44 (83.4)	0.001
Use of statin	28 (27.2)	22 (41.8)	<0.001
Use of AAS	13 (12.4)	14 (25.8)	0.195

[Table/Fig-2]: Baseline characteristics of CVD events with treatments according to D-dimer groups.
Chi-squire test, level of significant p-value <0.05
NS: Not significant; BMI: Body mass index; UAE: Urinary albumin excretion; AAS: Acetylsalicylic acid; ACE/ARBI: ACE inhibitors/Angiotensin II receptor blockers, UAE: Urinary albumin excretion

Patients with cystatin C ≥0.94 mg/L showed a stronger association with high D-dimer levels [OR of 9.944 (3.816-26.427), after adjusting for sex and age] compared to patients with UAE ≥30 mg/g, creatinine ≥1.3 mg/dL, eGFR <60 mL/min/1.73 m^2, and urea ≥40 mg/dL [OR of 5.302 (2.168-13.110), 7.974 (2.467-29.459), 9.116 (2.646-30.908), and 3.475 (1.430-8.455), respectively] [Table/Fig-3].

Variable	Low D-dimer levels odds ratio (95% confidence interval) adjusted for sex and age	High D-dimer levels odds ratio (95% confidence interval) adjusted for sex and age	p-value*
Creatinine ≥1.3 mg/dL	5.295 (2.106-13.357)	7.974 (2.467-29.459)	<0.001
eGFR <60 mL/min/1.73 m^2	6.028 (2.335-15.666)	9.116 (2.646-30.908)	<0.001
Urea ≥ 40 mg/dL	3.240 (1.535-7.271)	3.475 (1.430-8.455)	0.007
Cystatin C ≥0.94 mg/L	9.015 (3.853-21.109)	9.944 (3.816-26.427)	<0.001
UAE ≥30 mg/g	5.040 (2.222-11.440)	5.302 (2.168-13.110)	<0.001

[Table/Fig-3]: Association between renal biomarkers and D-dimer levels.
Data was evaluated by bivariate and multivariate logistic regression analysis and are presented as odds ratio (95% confidence interval)
NS: Not significant *p<0.05 for high D-dimer group compared to low D-dimer group

DISCUSSION

In this study, various biomarkers in patients with T2DM and their statistical significance in relation to D-dimer levels were examined. Present study revealed that patients with high D-dimer levels had elevated levels of several renal indicators, including creatinine, urea, cystatin C, eGFR, and UAE. Additionally, there was a significant association between baseline D-dimer concentrations and the risk of cardiovascular disease events in patients with type 2 diabetes. D-dimer is a soluble breakdown byproduct of cross-linked fibrin. Elevated D-dimer levels are typically observed in thrombosis-related diseases such as pulmonary embolism, disseminated intravascular coagulation, and venous thromboembolism. Recent research has also shown an association between baseline D-dimer levels and the occurrence of cardiovascular diseases and poor prognosis in individuals with coronary artery disease [17].

Cheng L et al., found a negative correlation between baseline D-dimer levels and metformin treatment, as well as a positive correlation trend with sulfonylureas treatment, although the difference was not statistically significant [18]. This finding supports the idea that insulin-sensitising drugs, such as metformin, may have more benefits in terms of fibrinolysis and thrombosis balance compared to insulin-providing drugs. In present study, a significant association with metformin treatment, but no statistically significant association was found with sulfonylureas was found. Research suggests that arteries with atherosclerosis contain more cysteine proteases than healthy arteries, which may contribute to the degradation of atherosclerotic plaque. Cystatin C, a protein that inhibits cysteine proteases, can be used as a biomarker to identify early-stage chronic kidney disease. Therefore, cystatin C levels are elevated in patients with renal disease, which may inhibit proteases that promote the breakdown of atherosclerotic plaque. Cystatin C, as a renal biomarker, exhibits a stronger correlation with hypercoagulability status, which contributes to the development of atherosclerosis and cardiovascular disease. However, further testing is required to confirm this theory [19,20]. Diabetic patients with microvascular complications have been found to have higher D-dimer levels compared to diabetic patients without microvascular issues [19]. According to the findings of Soares AL et al., hypercoagulability may play a role in the development of atherosclerosis and microvascular problems in diabetic patients with carotid plaque and elevated D-dimer levels [21].

Alzahrani SH and Ajjan RA discovered, using confocal microscopy methods, that HbA1C levels correlated with clot formation in diabetic patients, which may account for present study findings demonstrating a favourable link between D-dimer levels and HbA1C levels and duration of diabetes [5]. Present study findings confirmed that poor glycaemic control in these populations may increase thrombotic risk. Regardless of the treatment method used, a study by Sobel BE et al., found that changes in D-dimer levels were similar between insulin-providing treatment strategies and insulin-sensitising treatment strategies [22]. According to Haase C et al., as was the case in this study, older individuals and females have higher plasma levels of D-dimer [23], which differs from present study. Limited research has examined the link between D-dimer and cardiovascular disease events in people with type 2 diabetes [24]. However, current study showed a significant association between the risk of cardiovascular disease events in patients with T2DM and baseline D-dimer concentration. Even after adjusting for variables such as hypertension, smoking, BMI, HbA1C, duration of diabetes, age, antithrombotic medications, diabetic medications, and use of statins, ARB/ACEI, and beta-blockers, this association remained significant.

Despite known risk factors and treatments, elevated D-dimer concentration was linked to cardiovascular disease events, suggesting that D-dimer measurement should be considered equally informative as other conventional risk factors, atleast in the diabetes group. The relationship between D-dimer and cardiovascular disease events is not fully understood. It is reasonable to assume that an early elevation in D-dimer may influence the onset or severity of cardiovascular diseases. Patients with high D-dimer levels were more likely to use antihypertensive medications, which is expected since renal disease was more common in these patients. Antihypertensive medications are frequently recommended to diabetics with kidney disease to protect renal function. Additionally, these patients had lower serum albumin levels, which is consistent with higher UAE.

Consistent with this study, odds ratio analysis revealed that cystatin C had a stronger association with higher D-dimer levels than urea, creatinine, eGFR, and UAE, after adjusting for sex and age, two factors that may potentially affect D-dimer levels. Compared to other renal biomarkers, cystatin C levels showed a stronger connection with D-dimer levels. These findings suggest that cystatin C has a stronger relationship with hypercoagulability status than other renal biomarkers and may be able to identify hemostatic alterations that are not fully captured by measures of urea, creatinine, eGFR, and UAE.

Limitation(s)

In the present study, data were collected retrospectively, which limited the ability to conduct follow-up.

CONCLUSION(S)

All renal indicators showed a significant association with D-dimer concentrations, with cystatin C demonstrating the strongest link. These results suggest that cystatin C may be highly useful in evaluating renal function decline and the presence of hypercoagulability in patients with T2DM. Elevated baseline D-dimer levels were associated with

future cardiovascular disease events in a community of individuals with T2DM, regardless of conventional risk factors or treatment methods. Measuring D-dimer levels may enhance the current risk classification criteria for patients with T2DM. However, further research is needed to test this hypothesis. Adding D-dimer as one of the most significant biomarkers in T2DM may help prevent future high-risk situations.

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