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A study of relationship between renal biomarkers and D-dimer levels in patients with type 2 diabetes mellitus attending the Diabetes and Endocrinology Centre in Sebha city

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Keywords
Chronic kidney disease
Creatinine
D-dimer
eGFR
Type 2 diabetes mellitus.

ABSTRACT

Background: Persistent hyperglycemia can lead to abnormal blood coagulation because of glycated hemoglobin and other clotting proteins. Changes in clotting factors and biochemical indicator levels may suggest an increased risk of blood clot formation, which can impact kidney function and result in vascular diseases. **Objective:** The main purpose of the study was to demonstrate the relationship between renal biomarkers and D-dimer levels in patients with type 2 diabetes mellitus attending the Diabetes and Endocrinology Centre in Sebha city. **Materials and methods:** Samples were collected from the diabetic patients attending the centre (50 patients, and 50 as a control), also kidney patients attending Sebha Medical centre were included (40 patient). Laboratory determination including Urea, creatinine, eGFR, FBS, HbA1C and D-dimer. **Results:** The results show that the mean of waist, hip, BMI, FBS, and HbA1C was significantly higher in the T2DM group as compared with other groups. mean of Urea, Creatinine and D-dimer was significantly higher in CKD group as compared other groups, while eGFR was decreased. No statistical difference was found between T2DM and control groups in urea, creatinine, and D-dimer. A positive correlation was found between (HbA1C, creatinine, and BMI) and D-dimer, while a negative correlation was demonstrated with eGFR. **Conclusion:** a positive significant association were found between D-dimer and both creatinine and HbA1C, but it was negatively correlated with eGFR.

دراسة العلاقة بين المؤشرات الحيوية الكلوية ومستويات الدي-دايمر لدى مرضى السكري من النوع الثاني الذين يترددون على مركز السكري والغدد الصماء في مدينة سبها.

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الكلمات المفتاحية:
الدي-دايمر
الكرياتينين
داء السكري من النوع الثاني
مرض الكلى المزمن
معدل الترشيح الكبيبي المقدر

الملخص

المقدمة: يمكن أن يؤدي ارتفاع سكر الدم المستمر إلى تخثر غير طبيعي في الدم بسبب الهيموجلوبين السكري وبروتينات التخثر الأخرى. قد تشير التغييرات في عوامل التخثر ومستويات المؤشرات الكيميائية الحيوية إلى زيادة خطر تكوين جلطات الدم، مما قد يؤثر على وظائف الكلى ويؤدي إلى أمراض الأوعية الدموية. الهدف: تهدف هذه الدراسة الى دراسة العلاقة بين المؤشرات الحيوية الكلوية ومستويات الدي-دايمر في مرضى السكري من النوع 2 المترددين على مركز السكري والغدد الصماء في مدينة سبها. المواد والطرق: أجريت هذه الدراسة في مركز السكري والغدد الصماء في مدينة سبها. جُمعت عينات من 50 مريض سكري المترددون على المركز و50 من الاصحاء كمجموعة ضابطة، بالإضافة الى 40 من مرضى الكلى المترددين على مركز سبها الطبي. الاختبارات المعملية شملت قياس تركيز كل من اليوريا، الكرياتينين، الجلوكوز، نسبة الهيموجلوبين السكري، والدي- دايمر، وحساب معدل الترشيح الكبيبي. النتائج: أظهرت النتائج أن متوسط تركيز الجلوكوز في الدم والهيموجلوبين السكري أعلى بشكل ملحوظ في مجموعة مرضى السكري من النوع الثاني مقارنة بالمجموعات الأخرى.، في حين ان متوسط تركيز اليوريا والكرياتينين والدي-دايمر أعلى بشكل ملحوظ في مجموعة مرضى الفشل الكلوي المزمن مع انخفاض في معدل

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الترشيح الكبيبي المقدر مقارنة بالمجموعات الأخرى. كما بينت النتائج وجود علاقة ارتباط إيجابي بين الدي-دايمر وكل من HbA1C، الكرياتينين ومؤشر كتلة الجسم، بينما ارتبط سلبياً مع معدل الترشيح الكبيبي المقدر.
الاستنتاج: خلصت هذه الدراسة إلى وجود ارتباط إيجابي بين الدي-دايمر وكلا من الكرياتينين وHbA1C، و ارتباط سلبي مع معدل الترشيح الكبيبي في المرضى المصابين بمرض السكري من النوع الثاني.

Introduction

In diabetes mellitus, chronic hyperglycemia and inappropriate glucose metabolism are the results of a malfunction in insulin production or activity [1,2]. Imperfections in the secretion or function of insulin hormone may cause certain metabolic abnormalities that indicate the development of hyperglycemia [3,4].

There are two clinically important types of DM (Type 1-IDDM & T2-NIDDM), Type 2 DM is a common metabolic disorder that accounts for 90% of all adult cases of diabetes worldwide and is characterized by high blood sugar levels due to insulin resistance. It is caused by a combination of two main features: inadequate insulin secretion by the pancreatic β-cells and the tissues' inability to respond appropriately to insulin [5]. The body produces insulin when there is insulin resistance; however, insulin sensitivity is decreased, and the insulin does not function as well as it should [6].

A significant risk factor for the onset of end-stage renal disease (ESRD) and chronic kidney disease (CKD) is type 2 diabetes mellitus [7, 8]. One of the main causes of end-stage renal disease (ESRD) is diabetic nephropathy, a microvascular consequence of diabetes that is defined by increasing kidney destruction [7,9]. A number of biomarkers, including creatinine, urea, glomerular filtration rate (GFR), UAE, and cystatin C, can be used to assess renal function in diabetic individuals. Urea is the main nitrogenous metabolite produced by the breakdown of proteins, whereas creatinine is produced by the metabolism of creatine and phosphocreatine in muscle cells. The estimation of GFR is more frequently utilized in clinical practice, nonetheless, because a number of factors other than renal illness might affect their levels [10,11]. The amount of blood the kidneys can filter in a minute is known as the glomerular filtration rate (GFR), and it serves as a gauge of general renal health. Equations like the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or the Modification of Diet in Renal Disease (MDRD) equation are used to compute eGFR based on blood creatinine levels, age, sex, and race [12].

One of the numerous problems linked to diabetes mellitus that arises from hyperglycemia is hypercoagulability [13]. The endothelium layer, which helps to regulate blood flow by inhibiting platelet aggregation and its anticoagulant qualities as well as by inducing the fibrinolytic system, may be impacted by type 2 diabetes mellitus [14]. By irreversibly glycating collagen and other sub-endothelial structure proteins of the vessel, hyperglycemia directly causes endothelial damage. This results in the formation of advanced glycation end products (AGEs), which build up in the endothelium over time under the influence of elevated blood sugar levels and are directly linked to atherosclerosis [15].

Although the exact processes underlying the association between D-dimer levels and renal failure in type 2 diabetes are unknown, they may include oxidative stress, inflammation, endothelial dysfunction, and coagulation activation [16-18]. These mechanisms may contribute to renal injury and microvascular damage and are linked to the pathophysiology of diabetic nephropathy.

This study aims to demonstrate the relationship between renal biomarkers and D-dimer levels in patients with type 2 diabetes mellitus attending the Diabetes and Endocrinology Centre in Sebha city.

While we didn't found specific studies directly examining the relationship between renal function and D-dimer levels in T2DM patients without complications, the findings suggest that even in the absence of overt complications, renal function may influence D-dimer levels in T2DM patients.

In 2016 study made at Alneelain University, Faculty of medical laboratory Sciences and Omdurman Military Hospital, Renal disease unit, Khartoum, Sudan. Found that A higher level of D-dimer was observed among patient with chronic kidney disease. Both males and female's patients were showed positive D-dimer levels above the normal range [19]. Siddappa and Ramprasad demonstrated that the most precise indicator of a hypercoagulable state, D dimer levels, were considerably higher in individuals with later-stage CKD than in those with earlier-stage CKD [20]. One more study conducted in 2023 at the Enugu State University of Science and Technology Teaching Hospital Parklane, Enugu State, Nigeria. Aimed to determine the impact of gender on glycemic and coagulation control in type 2 diabetes mellitus showed that gender has a great impact on coagulation activation and glycemic control in type 2 diabetes mellitus with females being more susceptible to poor glycemic control and coagulation activation compared to males [21].

2. materials and Methods

Study group

This study was conducted at the Diabetes and Endocrinology Centre in the City of Sebha, Samples were collected from 50 diabetic patients attending the centre, ages ranged between 30-60 years,40 kidney patients attending Sebha Medical Centre during the period between 17/9 - 25/12/ 2023, and 50 blood sample from healthy people as a control.

Indicators of anthropometry such as height, weight, hip circumference (HC), and waist circumference (WC) were measured while subjects were standing and dressed comfortably without shoes. Body mass index (BMI) was determined based on height and weight measurements in meters and kilograms, respectively. WC was measured using a standard flexible inelastic measuring tape to the nearest 0.1 cm in the horizontal plane, midway between the inferior rib margin and the iliac crest, whereas HC was measured at a point over the buttocks yielding the maximum circumference.

Six millilitres of venous blood were collected from all volunteers by vein puncture and transferred to the special tubes for each analysis, and the D-dimer level was measured directly, the samples were placed at room temperature to complete clotting process then centrifuged at 3000 rpm for 5- 10 min. The blood samples were analysed for Fasting Blood Sugar using the glucose oxidase enzymatic method, the Urease method for urea, and the Jaffe method for creatinine. Glycated haemoglobin (HbA1c) and D-dimer were measured using Dry Fluorescence Immunoassay (the test uses the principle of antigen-antibody reaction). The Cockcroft-Gault equation was used to estimate the GFR value from known variables such as serum creatinine (mg/dl), age (years), and body weight (kg) [22].

Formula: (140-age) × weight(kg) × k/ 72× serum creatinine (mg/dl). (K=0.85 for women & 1 for men).

Data analysis was conducted in statistical package for social science (SPSS) version 21.0. Means and standard deviations were calculated for parameters. One-way ANOVA test used to compare means with normal values, and Person correlation used to show the relation between D-dimer and different parameters. P-value < 0.05 considered as significantly difference.

3. Results

Table (1) shows anthropometric and biochemical parameters of control, Diabetic and chronic kidney disease patients, one-way ANOVA test show statistically significant differences in all parameters except Age.

Table (1) Comparison of biochemical and anthropometric parameters between study groups

Parameter	Control n= 50	DM n= 50	CKD n= 40	P-value
	Mean ± SD			

Age (Years)	43.24 ± 8.15	47.06 ± 8.29	45.55 ± 9.74	0.09
Waist (cm)	89.02 ± 10.50	96.34 ± 13.14	87.08 ± 13.72	0.001**
Hip (cm)	102.72 ± 10.85	108.88 ± 14.31	99.30 ± 13.13	0.002**
BMI (Kg/m^2)	23.96 ± 1.95	30.28 ± 2.8	26.62 ± 5.08	0.000**
Urea (mg/dl)	24.92 ± 7.89	26.00 ± 5.74	124.95± 25.52	0.000**
Creatinine (mg/dl)	0.69 ± 0.14	0.80 ± 0.16	7.47 ± 2.40	0.000**
eGFR (ml/min/)	123.85 ± 19.05	118.64 ± 31.12	13.63 ± 3.15	0.000**
FBS (mg/dl)	94.92 ± 11.29	204.92 ± 67.11	95.45 ± 13.08	0.000**
HBA1C (%)	5.63 ± 0.46	9.18 ± 1.88	5.79 ± 0.51	0.000**
D-dimer (µg/ml)	0.23 ± 0.11	0.40 ± 0.18	1.80 ± 1.29	0.000**

**Statistically significant p- value <0.05

Post hoc (Tukey test) revealed that

1. Mean of waist, Hip, BMI, FBS and HBA1C was significantly higher in DM group as compared with control group, while no statistical difference found between them in other parameters.

2. Mean of BMI, Urea, Creatinine, eGFR and D-dimer was significantly higher in CKD group as compared with control group, while no statistical difference found between them in other parameters.

3. Mean of waist, Hip, BMI, eGFR, FBS and HBA1C was significantly higher in DM group as compared with CKD group, while the mean of Urea, Creatinine and D-dimer was significantly higher in CKD group as compared with DM.

Difference between diabetic patients according BMI

Diabetic group were divided into three groups according to BMI. One-way ANOVA test were applied to differentiate between them and no statistical difference was found between chemical parameters while a statistically difference was found in waist and hip as shown in table (2).

Table (2) Comparison between DM patients depends on BMI

Parameter	18.4-24.9 Kg/m^2 n= 12	25-29.9 Kg/m^2 n= 14	>30 Kg/m^2 n= 24	P-value
	Mean ± SD			
Age (Years)	50.08 ± 9.90	43.71 ± 7.51	47.50 ± 7.48	0.140
Waist (cm)	85.17 ± 7.87	91.29 ± 11.90	104.88± 10.07	0.000**
Hip (cm)	95.75 ± 8.71	104.29 ± 12.65	118.13 ± 10.84	0.000**
Urea (mg/dl)	26.08 ± 5.24	26.79 ± 4.83	25.50 ± 6.57	0.806
Creatinine (mg/dl)	0.75 ± 0.16	0.82 ± 0.17	0.82 ± 0.16	0.417
eGFR (ml/min)	104.18 ± 24.58	115.20 ± 32.08	127.89 ± 31.47	0.085
FBS (mg/dl)	234.06 ± 17.73	171.79 ± 64.60	209.63 ± 61.42	0.056
HBA1C (%)	9.76 ± 2.16	8.80 ± 2.11	9.11 ± 1.59	0.425
D-dimer (µg/ml)	0.44 ± 0.21	0.40 ± 0.18	0.39 ± 0.16	0.758

**Statistically significant p- value <0.05

Difference between diabetic patients according Duration of diabetes

Diabetic group were divided into three groups according to Duration of diabetes. One- way ANOVA test were applied to differentiate between them and no statistical difference found between chemical parameters while a statistically difference was found in age and waist as shown in table (3).

Table (3) Comparison between DM patients depends on Duration of Diabetes

Parameter	<5 years n= 11	5-10 year n= 31	>10 year n= 8	P-value
	Mean ± SD			
Age (Years)	39.82 ± 6.55	47.23 ± 7.07	56.38 ± 4.92	0.000**
Waist (cm)	87.09 ± 11.04	99.71 ± 12.16	96.00 ± 14.66	0.020**
Hip (cm)	100.00 ± 15.33	111.81 ± 12.63	109.75 ± 15.85	0.059
BMI (Kg/m^2)	27.84 ± 4.69	30.89 ± 4.92	31.28 ± 4.93	0.457
Urea (mg/dl)	25.91 ± 4.59	25.42 ± 5.91	28.38 ± 6.54	0.439
Creatinine (mg/dl)	0.80 ± 0.19	0.81 ± 0.16	0.75 ± 0.16	0.586
eGFR (ml/min)	115.93 ± 39.31	121.47 ± 30.01	111.40 ± 24.62	0.688
FBS (mg/dl)	218.55 ± 81.34	201.23 ± 67.26	200.50 ± 55.43	0.760
HBA1C (%)	9.48 ± 2.33	9.11 ± 1.74	9.03 ± 1.97	0.839
D-dimer (µg/ml)	0.49 ± 0.18	0.38 ± 0.18	0.38 ± 0.13	0.216

**Statistically significant p- value <0.05

Difference between Male and Female diabetic patients:

No statistical difference was found using two sample t test between male and female diabetic patients in all parameters except in HC and D-dimer, where were higher in female than male as shown in table (4).

Table (4) Comparison between Male and Female

Parameter	Male n= 17	Female n= 33	P-value
	Mean ± SD		
Age (Years)	48.47 ± 8.42	46.33 ± 8.26	0.394
Waist (cm)	92.18 ± 15.31	98.48 ± 11.54	0.109
Hip (cm)	102.53 ± 16.37	112.15 ± 12.12	0.023**
BMI (Kg/m^2)	27.74 ± 5.63	31.95 ± 7.74	0.076
Urea (mg/dl)	27.47 ± 5.64	25.24 ± 5.72	0.197
Creatinine (mg/dl)	0.81 ± 0.12	0.80 ± 0.18	0.863
eGFR (ml/min)	124.49 ± 28.71	115.63 ± 32.30	0.346
FBS (mg/dl)	189.65 ± 65.34	212.79 ± 68.84	0.258
HBA1C (%)	8.58 ± 1.48	9.48 ± 2.01	0.112
D-dimer (µg/ml)	0.33 ± 0.17	0.44 ± 0.17	0.031**

**Statistically significant p- value <0.05

The relation between D-dimer and other parameters

Person correlation analysis was done to demonstrate the relationship between D-dimer and other parameters. A positive correlation was found between (HBA1C, Creatinine) and D-dimer, while it was negatively correlated with eGFR as shown in table (5).

Table (5) Person correlation between D-dimer and other parameters

Parameter	D-dimer	
	R	**P**
Age (Years)	-0.178	0.215
Waist (cm)	-0.227	0.112
Hip (cm)	-0.275	0.053
BMI (Kg/m^2)	0.282	0.047**
Urea (mg/dl)	0.161	0.263
Creatinine (mg/dl)	0.352	0.012**
eGFR (ml/min/)	-0.617	0.000**
FBS (mg/dl)	0.227	0.114
HBA1C (%)	0.284	0.045**
DM Duration	-0.076	0.599

**Statistically significant p- value <0.05

4. Discussion

The role of D-dimer as a potential biomarker for early renal dysfunction in T2DM remains an area of active investigation. A study by Liu *et al*., 2020 found that high D-dimer levels were predictive of the progression of kidney dysfunction in T2DM patients, even before the development of significant diabetic nephropathy [23]. Even in the absence of overt diabetic nephropathy, T2DM patients can exhibit changes in renal biomarkers, such as elevated albuminuria, which have been linked to endothelial dysfunction and vascular inflammation [24]. In our study we found a significant difference in BMI, waist circumference, and Hip between groups, which was higher in T2DM as compared to Control and CKD, this study is in agreement with several studies conducted by Shankar et al., 2023; Ali et al., 2017; Ranabhat et al., 2017 [25-27] whom found that mean WC, Hip and BMI were higher in diabetic participants than non-diabetics. Also, Neelofar & Ahmad, 2019 [28]. demonstrated that BMI was a significantly higher in diabetic patients compared to control.

Our study demonstrated that concentrations of urea and creatinine was higher in CKD patients as compared to T2DM and control while eGFR was decreased and no significance difference were found between diabetic and control groups, the results are in agreement with the results reported by Jassim, 2024 [29], who found that levels of creatinine and urea higher in CKD patients in compared with diabetic patients and control, However, the current results disagree with the study by Akinjinmi, 2023 and Musbah et al., 2025 [30, 31] who demonstrated that a significant difference was observed in urea, creatinine, and eGFR between the control and the diabetic groups. Medical practitioners generally agree on the importance of elevated

blood urea and creatinine levels in assessing kidney health, and they are widely a knowledged as trustworthy indicators of decreased kidney function in patients with CKD. These tests are frequently used to evaluate kidney function in people with diabetes and hypertension who are at risk for chronic kidney disease [32].

In the current study no a significant difference was found in D-dimer among T2DM and control, which is in agreement with study by Thukral et al., 2018; Ogbuabor et al., 2023 [33,21]. Whom documented that no significant difference seen in D-dimer among cases and control. In addition, Kanani, 2017; Rustom et al., 2022 [34,35]. Found that the concentration of D-Dimer was within the normal range in diabetic patients without complications, while it was higher in diabetic nephropathy patients. Also, Wieczor et al., 2019 and Marumo et al., 2019 [36,37] their studies showed that; No significant impact was observed of diabetes on D-dimer. This could be because metformin lowers blood glucose levels while also improving fibrinolytic activity and lowering D-dimer levels in people with type 2 diabetes [38]. However, the current results disagree with the study by Pan et al., 2018 [39]. Whom demonstrated that there were increased D-dimer levels in T2DM patients without complications compared with controls.

Furthermore; this study showed that D-dimer concentration was elevated in CKD patient without another disease, which is in agreement with study conducted by Gubensek *et al.* 2016 [40]. where they found the high prevalence of positive D-dimer values even in hemodialysis patients without additional disease limits the use of D-dimer for exclusion of thromboembolic diseases in hemodialysis patients. Also, Huang et al., 2017; Mohammed and Khalil, 2016 [41,19] found in their studies that D-dimer were significantly higher in patients with CKD than control, these findings in agreement with our study. Traditional risk factors for thromboembolic events, such as obesity, diabetes, and hypertension, are frequently increased in patients with CKD; these factors also have an impact on the coagulation system. We controlled for the aforementioned contributing factors in an effort to understand hemostatic changes in CKD. The findings demonstrated that procoagulant variables were still markedly increased in CKD patients, suggesting that kidney impairment influenced coagulation function activation in addition to conventional risk factors.

In recent years, gender has emerged as a significant issue in healthcare, especially in relation to chronic and metabolic disorders like diabetes mellitus [42]. There is evidence that this risk factor can alter the onset, development, and outcome of numerous diseases [43]. Poor glycemic control and coagulation activation have been identified as the primary factors contributing to the emergence of problems in type 2 diabetes mellitus [44]. So that, in this study compared males and females in the T2DM group and found that a statistical difference in D-dimer concentration, which was higher in females than males this is disagreement with study documented by Nimir, 2020 [45], who didn't found a significant difference between male and female in D-dimer concentration. Also, a significant difference was found in hip between male and female in the current study, this in agreement with study concluded by Snijder, et al., 2003 [46]. while no statistical differences was demonstrated in age, BMI, FBS, HbA1C and DM duration, this study was in agreement with study conducted by Ogbuabor et al., 2023 [21], whom didn't found any significant difference in age, BMI, FBS, and DM duration between male and female and with Misra et al., 2009; Shah et al., 2005 [47,48] who recorded no association between gender and glycemic control, but disagree with study of Ogbuabor, et al., 2023 [21], whom found significant difference in HbA1C between male and female.

A significant difference in age depending on DM duration was illustrated in this study, while, no difference was found in D-dimer which is disagree with study of Nimir et al., 2020 [45], who didn't found a significant difference in age depends on DM duration but in agreement with him in case of D-dimer concentration. On other side, in agreement with our study, Haque et al., 2011 [49] no significant difference in HbA1c & renal functional parameters was noted between groups based on DM duration.

In this study T2DM group divided depending on BMI and no statistical differences in FBS, urea, creatinine, and eGFR demonstrated, this was in agreement with study conducted by Akinjinmi et al., 2023 [30] whom indicated that no statistically significant difference in urea, creatinine, and eGFR between diabetic obese and diabetic non-obese individuals. In addition; no significant difference was demonstrated in HbA1C according to BMI, this is disagreeing with study of Akinjinmi et al., 2023 [30], who documented that there were statistically significant differences between the mean values of HbA1c of diabetic non-obese subjects compared with diabetic obese subjects.

In our study a positive significant correlation was found between D-dimer and BMI, this is disagreeing with study documented by Widjaja & Syahputra, 2020 [50], whom didn't found correlation between D-dimer and BMI. Also, a positive significant correlation was found between D-dimer and HbA1C, these findings are in agreement with the same study [50], Whom found that HbA1C showed statistical correlation with the D-dimer. In addition, the current study showed a positive significant correlation between D-dimer and creatinine. Also, a negative significant correlation was showed with eGFR, the findings suggest that even in the absence of overt complications, renal function may influence D-dimer levels in T2DM patient.

Conclusion

- A positive significant correlation found between D-dimer and both creatinine and HbA1C, while it was negatively correlated with eGFR.
- The findings in the present study show that: patients with T2DM without complication have a normal range of urea, creatinine, eGFR and D-dimer.
- D-dimer concentration was high in all kidney patients who don't suffer from any other diseases.

Recommendations

- Monitoring renal indicators in T2DM patients regularly is very important to avoid kidney damage that results in high D-dimer concentration.

5. References

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