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Estimation of some biochemical markers in diabetic patients with renal impairment

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Diabetes mellitus (DM) is a chronic disorder involving multiorgan dysfunction on the long term, uncontrolled DM could have many complications on top renal impairment, peripheral neuropathy and retinopathies. The study involved 120 DM cases of which 60 with renal impairment and 60 without renal impairment who attended Diabetic clinic at private clinics during June to August 2024 in addition to 60 control healthy subjects. All patients and control subjects were assessed for basic renal function and glomerular filtration rate (GFR) as well as serum Potassium and HbA1c in addition to Early region 2 binding factor (E2F1), Amylin and Glucagon-like peptide 1 (GLP-1) via ELISA assay. Our data revealed that mean age and BMI of DM cases were 58.18 years and 28.03 respectively. Blood urea, HbA1c and GFR were significantly higher in BM with renal impairment compared to control $P<0.05$. All the protein markers (E2F1, Amylin and GLP-1) were significantly elevated in DM cases compared to control $P<0.05$.
In conclusion, DM patients with renal impairment expressed elevated protein retention due to the malfunction of filtration function of the kidneys indicating significant role of these proteins in DM prognosis
Key words: DM, Renal impairment, Amylin, E2F1, GLP-1.

Introduction

Diabetes Mellitus is a chronic metabolic disorder characterized by hyperglycemia, which occurs due to impaired insulin production or secretion, or the inability of cells to respond to insulin. Most diagnosed cases fall into the categories of Type 1 diabetes and Type 2 diabetes (1). The prevalence of diabetes is increasing worldwide among adults aged 20 to 79 years, with an expected rise from 10.5% in 2021 to 12.2% by 2045. (12). Many pathogenic processes are involved in the development of diabetes, including the autoimmune destruction of beta cells in the pancreas, leading to insulin deficiency, and abnormalities that result in insulin resistance (23). The risk of developing diabetes is associated with a range of genetic and metabolic factors, as well as other factors including race, family history, and previous gestational diabetes. Additionally, aging, weight gain, and obesity increase the risk of the disease, and an unhealthy diet, lack of exercise, and smoking also contribute to the increased risk of diabetes. There are also social and demographic risk factors associated with diabetes (4). As is well known, type 2 diabetes is a widely prevalent chronic disease associated with complications such as diabetic retinopathy, nephropathy, neuropathy, and myopathy (13).

Diabetic nephropathy (DN) is a kidney disorder caused by diabetes, it is a common complication that generally appears together in both type 1 and type 2 diabetes (3). This can be the most common complication in patients with end-stage albuminuria (chronic kidney disease (CKD)). (4). Management of chronic kidney disease describes this disease as costly and a significant challenge for communities and healthcare systems (50). Nasli-Esfahani et al. kidney disease is also an indicator of kidney function impairment, and kidney damage caused by diabetes can be severe. Once affected, the kidneys become unable to perform their tasks regularly, including filtering blood, resulting in kidney failure (13).
The transcription factor E2F 1 (E2F1) is a member of the E2F transcription factor family. E2F1 binds to DNA with dimerization partner proteins (DP) through the E2 recognition site. The dissociation of

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E2F1 from the retinoblastoma protein (Rb) restores its transcriptional activity, driving the cell cycle from the G1 phase to the S phase. It has been shown that E2F1 is involved in cell proliferation, differentiation, and programmed cell death in colon cancer. It has recently been found that E2F1 is also involved in metastasis and chemoresistance in colon cancer (3) . GLP-1 is an intestinal hormone produced by L cells in the intestine and pancreatic cells. It works through hormonal and neural pathways to regulate islet function, satiety, and intestinal motility, and supports the development of GLP-1 receptors (GLP-1R) for the treatment of diabetes and obesity. The classical concepts regarding the action of GLP-1 as a meal-stimulated hormone from the distal intestine challenge the data supporting the production of GLP-1 in the endocrine pancreas, and the importance of brain-derived GLP-1 in regulating neural activity (8). While the E2F1 and Gip-1 pathways are involved in regulating β-cell function and mass, it is still unknown whether they are physiologically connected.

1. Materials and Methods

The study involved 180 subjects, 60 diabetic patients with renal impairment, 60 diabetic patients without renal impairment who attended Dietetic Clinic at Azadi Teaching Hospital as well as 60 control group. Blood specimens were drawn from all participants after obtaining written consent from all participants and serum was separated after brief centrifugation. Whole blood and sera were submitted to routine assessment of some biochemical tests (blood urea, S, creatinine, S. Potassium, HbA1c and Glomerular filtration rate) in addition to some immune markers related to diabetes (E2F1, Amylin and GLP-1) via an ELISA test.
Patient's data were gathered and the results of the biochemical as well as the immune markers were processed and organized and comparisons were made with Qi square test and One Way ANOVA test via Graph Pad Prisim software version 10.1

2. Results and discussion

The current data revealed that the mean age of DM patients with renal impairment was 58 years, while it was 47 years in diabetic patents and 36years in control group as depicted in Table 1.1. These data were in line with Yan Z et al who showed that most of renal impairment associated with diabetes were in age group above 55 years. While, it disagrees with another report that conducted on diabetic cases and revealed that most of the DM patients were below 55 years (14). Generally, renal impairment could be associated with advancing in age due to many factors on top un controlling blood sugar could assume in the process of damaging various tissues including renal cells which lead to renal function impairment. In addition to, the prolong diabetes condition could affect the patient commitment to regular diet or regular medication which eventually lead to un controlling sugar level and resulting in chronic damage of various organism (15).

Table1.1: The mean age of participants

	DM with RT	DM	Control
Age	Mean ±SD	Mean ±SD	Mean ±SD
	58.18±19.61	47.63±18.94	36.42±12.37
Total	60	60	60
	180		

Regarding gender, table 1.2 reveal that most of the affected patient with renal impairment with diabetes male 65%, while in diabetic patient malware 55 percentage and in control group female represented nearly 52 percentage these data are in line with other research which shows that most affected patients with diabetes were males (16, 17). On the other hand, other research conducted by

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Nasri H et al revealed that gender distribution is not related to diabetes miniatures (16,18). The discrepancies between our data and other researchers could be explained by many factors of which the design of the experiment and the number of patients involved in each study in addition to the bias selection of males or females and some study setting however gender distribution could be equally affecting both males and females (18).

On the other hand, our data revealed that most of diabetes patients involved in the current study were residing urban areas 73.33%, while the remaining 26.67% we are living in rural settings as displayed in table 1.3. Our data is an agreement with other report which conducted on diabetic patients and found that most of the affected patients were living in in urban area (19,20). However, these data in conflict with Gopisetty D et al reported that the patient group involved in their study were mostly living in remote areas (20). The differences between the data found here and other reports could be attributed to the design of the experiment for each research as some of these researches were conducted in remote setting could have more cases residing in local areas while those reports conducted in urban places could have more cases residing in city center (20).

Table1.2: Gender and residency distribution of patient and control group

Participant profile		DM with RI		DM		Control	
		No	%	No	%	No	%
Gender	Male	39	65.00	33	55.00	29	48.33
	Female	21	35.00	27	45.00	31	51.67
Total		60	100.00	60	100.00	60	100.00
Residency	Rural	16	26.67	14	23.33	10	16.67
	Urban	44	73.33	46	76.67	50	83.33
Total		60	100.00	60	100.00	60	100.00

In terms of body mass index, diabetic patients with renal impairment had body mass index of 28.03 while diabetic patients without renal impairment with 31.15 and the control group were having BMI of 23.25 as shown in table 1.3. the result of this study is inconsistent with Wan JF et al who found that diabetic patient could have higher BMI than control group (21). whereas it conflicts with another research that noted BMI of DM patient could be within normal range (21). The variation of this data and other researchers could be due to the bias selection of the cases of DM patients involved in each study or due to the careless habits of feeding especially with those patients with diabetes as they tend to become more carefree for the feeding habits and focus on satisfying their craving. In addition, older people with diabetes may have less commitment to diet restriction which could play a major role in increasing BMI in those cases (21,20)

Table1.3: BMI distribution of patient and control group

BMI	DM with RI	DM	Control	*P* value
	Mean ±SD	Mean ±SD	Mean ±SD	
	28.03±12.05	31.15±8.46	23.25±7.92	<0.05
Total	60	60	60	
	180			

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In terms of her hip/waist ratio our data illustrated that hip/waist ratio between the tested groups were not significantly different with P value greater than 0.05 as demonstrated in table 1.4, with mean hip waist ratio 4 diabetic patient with renal impairment 0.94, diabetic only 0.9 and in control group 0.84. Our data is in line with Alicic RZ.et.al research which conducted on diabetic patient and found that hip waist ratio is not significantly different between diabetic and controlled group (22). while it disagrees with Rafsanjani K et al which concluded that of the hip waist ratio is greater in diabetic patient done in control group (47). The variation between our data and other researchers could be explained by the fact that each patient has different BMI and you to the nature of the patients involved in the study and the carefree feeding habits most of the patient are following which will lead to increase in the waste ratio in comparison to the hip size in addition most of the patients involved in the study follow no diet restricted regime eventually lead to increase in the body mass of the participants (48).

Table1.4: Hip/waist ratio distribution of patient and control group

Hip/waist ratio	Mean	±SD	*P* value
Control	0.84	0.05	>0.05
DM	0.90	0.07	
DM with RI	0.94	0.09	

Regarding the biochemical test associated with patient group, our data demonstrated that the results of blood urea was significantly elevated in diabetic patient within with renal impairment in comparison to diabetic patients only and control with P value less than 0.05 and mean 59, 43 and 27 mg/dl respectively. Our data is close to another research conducted by Laville SM et.al(24) who reported that patient with renal impairment have elevated blood urea levels compared to control also it is close to Laville SM et.al reported similar data to what we found above (24). The reason behind the elevated blood urea could be explained by the fact that patient with impaired renal function could have more by products accumulating in the blood circulation which is eventually reflect elevated levels of urea and other byproducts, in addition due to the poor infiltration in the renal tubules results from renal tubular damage or renal cell damage this condition could decrease the secretion of the waste materials through the kidney and eventually lead to increase blood urea and creatine and affected cases (25).

Unlike S creatinine and S. K^+ which revealed no significant defenses between the tested groups P>0.05.

As for HbA1c the results were significantly differencing between the tested group with P<0.05 and mean 9.4, 7.8 and 4.9% accordingly as illustrated in table 1.5. Our results are in confined to Alzahrani BA et al. and Singh V et al who noted that HbA1c levels is significantly increased in cases with uncontrolled diabetes and it is even higher and patient with renal diseases (26,27). The elevation of HbA1c in diabetic patients could be explained by the fact that patient with diabetes could have elevated blood sugar and on the long term if the glucose level is not controlled and lowered to normal values the glycosylated hemoglobin in the red blood cells will eventually elevated and reflect uncontrolled blood sugar for a period of three months which is why it has been seen elevated and patient with diabetes both in an impairment and diabetes only without renal impairment (28).

With regard to GFR, the test was significantly lower in DM patients with renal impairment 51.60 ml/min/1.37m^2 compared to DM patients without renal impairment 78.72 ml/min/1.37m^2 and to control group 98.04 ml/min/1.37m^2 as depicted in table 1.5. Result of this report is in line with other reports that recorded decline in the GFR especially in patients with impaired renal function with significant difference between renal impaired patient and healthy control (29,49). The decline in GFR

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in renal impaired patients and generally in diabetic cases on the long term could be due to the slow damage effect of glucose on the function of the filtration of the glomeruli in addition to the poor perfusion of fluid in the renal tubular cells which eventually slow down the filtration rate from the kidney and hence lowering the GFR right in comparison to healthy unaffected individuals (30,31).

Table1.5: Biochemical markers in patient and control group

Renal function tests	DM with RI		DM		Control		*P* value
	Mean	±SD	Mean	±SD	Mean	±SD	
Urea mg/dl	59.00	28.93	43.51	13.77	27.14	7.06	<0.05
Creatinine mg/dl	2.10	0.93	1.10	0.58	0.73	0.21	>0.05
S. K+ mmol/L	5.90	1.04	4.80	2.07	4.06	1.82	>0.05
HbA1c%	9.40	2.11	7.80	3.61	4.90	1.94	<0.05
GFR ml/min/1.37m^2	51.60	22.90	78.72	29.84	98.04	33.95	<0.05
Total (n)	60		60		60		

In the same way, the immune markers revealed significant increment E2F1 levels in diabetic patients with renal impairment followed by control group and diabetic patient without renal impairment with mean 411.8, 308.24 and 246.3 pg/ml accordingly as showing in table 1.6. This data agrees with Ali Beg MM et al. who found that E2F1 is significant significantly increased in DM patients in comparison to control cases (32). In addition, Li FX et al have reported significant increment of E2F1 protein and diabetic patient compared to healthy control (33). The elevation I E2F1 levels in patients with renal impairment could be explained by the fact that E2F activity controls the transcription of a group of genes that encode proteins important for cell cycle progression (34). E2F transcriptional activity is critical for the regulation of cell cycle progression and is composed of heterodimers formed by the association of one of six E2F family members with one of three DP proteins. This any damage or impairment of the cell function could result in the release of more E2F1 protein in the circulation with is in line with our finding specifically with those patients with DM and renal impairment (35).

On the other hand, amylin level was significantly higher in DM patients with renal impairment followed by control and DM patients without renal impairment with mean 97.14, 78.5 and 19.05pg/ml respectively. Our result is close to Ly H.et.al. who noted elevated level of amylin and diabetic patients compared to control (36) and it disagrees with Mietlicki-Baase EG who noted no significant differences between amylin levels and diabetic patients and control individuals (37). Amylin is derived after an 89-amino acid long precursor protein, referred to as preProIAPP, which is cleaved at the N-terminal yielding ProIAPP and which is subsequently post translationally processed by the prohormone convertase (PC2) (49). These processes occur in pancreatic β cells, and, hence, amylin is secreted together with insulin in a 20 to 1 molar ratio of insulin to amylin. Initially, it was reported that amylin works antagonistically to insulin by inhibiting glycogenesis and promoting glycolysis (38). Since amylin is corelease with insulin, consuming an excess amount of carbohydrates and fat may lead to an elevated amount of amylin being secreted that could eventually initiate amylin aggregation, since it was found that a high carbohydrate or high fat diet promoted amyloid formation in transgenic mice (39).

As for GLP-1 levels, our data revealed that DM with renewal impairment recorded the highest concentration followed by the inpatient alone and then control with mean 138.7, 87.0 and 93.4 pg/ml accordingly. The data shown here is in line with other reports which conducted on renal impairment patients and found that this protein is significantly elevated I in real impaired cases compared to control (40,41). However, these data are in disagreement with another report who recorded no

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significant differences in GLP-1protein in diabetic patient and healthy control (42). The elevation in GLP-1 could be emphasized by the fact that GLP-1 is of particular critical for its glucose-lowering effects (43), as well as its ability to slow gastric emptying and suppress secretion of glucagon (44). (GLP-1) is a peptide hormone most commonly known for its role in stimulating insulin release following meal consumption (45). Additionally, GLP-1 has a well-established role in suppressing appetite and food intake in both animals and humans (46).

Table1.6: Immunity markers levels in patient and control group

Immunity parameters	DM with RI		DM		Control		*P* value
	Mean	±SD	Mean	±SD	Mean	±SD	
E2F-1 (pg/ml)	411.86	321.44	246.38	159.17	308.24	246.70	0.0390
Amylin (pg/ml)	97.14	63.71	19.05	11.56	79.51	48.60	0.0028
GLP-1 (pg/ml)	138.71	76.56	87.09	56.81	93.47	49.62	0.0472
Total (n)	60		60		60		

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