Early Prediction of Nephropathy in Iraqi Patient with Diabetes Type II by Evaluating Some Relevant Biochemical Factors

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Abstract

Type 2 diabetes mellitus (T2DM) is a complex disease, which affects many organs besides the pancreas such as the kidney, liver, brain and eye. Due to hyperglycemia at long periods and uncontrolled on diabetes with presence of other risk factors, diabetes complications could occurr. Diabetes complications include microvascular and macrovascular complications that target the kidneys. The aim of this study is to predict early fibrosis of the renal glomeruli and tubules by evaluating the levels of angiotensin-converting enzyme -2(ACE-2), connective tissue growth factor (CTGF) and some relevant biochemical factors in patients with type 2 diabetes. The study included 120 male and female ranging in age 30-65 years old, they were subdivided into three groups according to ACR criteria include normoalbuminuria, microalbuminuria, macroalbuminuria (30 patients for each group) and 30 healthy people served as the control group, who visited Baghdad Teaching Hospital / Medical City and Al-Yarmouk Teaching Hospital, at the period between December 2021 and May 2022. Lipid profile, FBS, urea levels were estimated using calorimetric techniques. ACE-2, CTGF levels were determined using the ELISA technique. The results showed significant differences between groups of patients and control group for (CTGF), (ACE-2) levels were found to be significant increase in patients' groups than healthy control. Also, the results showed that both fasting blood sugar (FBS) and hemoglobin A1c (HbA1C) were significantly increased in patients' groups compared to healthy group. Furthermore, estimated glomerular filtration rate (eGFR) revealed high significant differences among all the studied groups, as well as albumin to creatinine ratio (ACR) which showed high significant differences among the three patients' groups which represents the basic criteria for classification of patient groups. On the basis of the obtained results in this study, it can be concluded that each of ACE-2 and CTGF markers can be applied as early reliable prognosticated factors for detection disease progression.

Keywords: Angiotensin converting enzyme-2, albumin to creatinine ratio, connective tissue growth factor, Diabetes Mellitus. Diabetic Nephropathy.

Introduction

The definition of diabetes mellitus refers to a multi-etiological metabolic state characterized by chronic hyperglycemia, and disorders of lipid and protein metabolism resulting from insulin secretion,

insulin action, or both[1]. Symptoms of diabetes include long-term multiple tissue damage, dysfunction and kidney failure. Diabetes mellitus (DM) may present with characteristic symptoms such as thirst, urination, blurry vision, and weight loss[2]. Hyperglycemia may progress to life-threatening diabetic ketoacidosis while persistent hyperglycemia is associated with macrovascular complications, increasing the risks of myocardial infarction, stroke, and microvascular complications that contribute to diabetic nephropathy, retinopathy and neuropathy 3. While the different forms of diabetes have many treatment options[3].

Diabetic kidney disease is an illness of the glomerulus that interferes with the glomerular filtration barrier (GFB)[4]. It works in tandem to enable water and solutes to be selectively purified, while limiting the movement of large macromolecules such as albumin[5]. The glomerular filtration membrane consists of 3 membranes, the glomerular basement membrane (GBM), the podocyte, and the fenestrated endothelium. Cellular holes that can take up to 40% of the cell surface are what distinguish glomerular endothelial cells from other cell types. This modification makes the glomerular endothelium highly permeable to water, resulting in effective filtration function [6]. The glycocalyx, a layer of proteoglycans and glycoproteins covered the glomerular endothelial cells with particular molecular and charge properties that controls endothelial permeability and glomerular filtration[7].

The glomerular basement membrane GBM, which is made up of a layer of extracellular matrix (ECM) proteins positioned between the glomerular endothelium and the podocyte, divides the urine area from the vasculature[8]. Renal hypertrophy and increased glomerular blood flow are the primary pathogenic changes in DN, which are then followed by mesangial cell enlargement and the onset of glomerular fibrosis. Glomerular fibrosis is caused by an excessive buildup of extracellular matrix (ECM), such as collagen I and fibronectin (FN)[9].

Materials and Methods

One hundred and twenty men and women, aged 30-65 participated in the study, 90 patients with

Connective tissue growth factor (CTGF) is engaged in numerous diseases, including the growth of tumors and tissue fibrosis, as well as numerous biological processes, including cell proliferation, angiogenesis, and wound healing. It is considered one of the most important proteins that belong to the CCN family of proteins, and one of the most important components of cysteine, as it contains (22 cysteines in the N-terminal region and 16 cysteines in the C-terminal region) [10]. The mechanism causing excessive extracellular matrix accumulation transforming growth factor-β (TGF-β) has been suggested as the main trigger for both the increased collagen production and decreased matrix degradation pathways in fibrosis, being recognized as a central mediator in the development of fibrosis[11]. Renal fibrosis is a common pathological manifestation of chronic kidney disease (CKD) significantly accelerated due to the activation of the renin angiotensin system[12]. Renin is excreted in the kidneys in the event of a decrease in renal ischemia. Renin enzyme is produced by the kidney acts in converting angiotensinogen protein synthesis in liver to angiotensin 1 by removing 10 amino acids from peptide[13]. Lung and kidney produce angiotensin converting enzyme to convert angiotensin Ι to angiotensin ΙΙ by removing 2 amino acids from peptide[14,15]. Angiotensin ΙΙ Na, potassium K execration. Stimulation adrenal gland cortex secretion of aldosterone hormone acts in H2O retention. Angiotensin ΙΙ stimulation arteriolar vasoconstriction increase in blood pressure and antidiuretic hormone (ADH) secretion by pituitary gland collecting duct H2O reabsorption. Water and salt retention effect circulating volume increase. Perfusion of the juxtaglomerular apparatus increase due to inhibition renin enzyme product by kidney[16].

The aim of this study is to predict early fibrosis of the renal glomeruli and tubules by evaluating the levels of angiotensin-converting enzyme -2(ACE-2), connective tissue growth factor (CTGF) and some relevant biochemical factors in patients with type 2 diabetes.

diabetes who visited Baghdad Teaching Hospital / Medical City and Al-Yarmouk Teaching Hospital

between December-2021 and May-2022 and 30 healthy persons acted as control group.

Groups of Analysis Included:

1) Control group: included 30 healthy looking subjects without any diseases.

2) Patients groups: included 90 patients who were divided into three groups according to ACR criterion:

- Normoalbuminuria group: Included 30 patients the range of ACR <30 mg/g
- Microalbuminuria group: Included 30 patients the range of ACR 30-300 mg/g
- Macroalbuminuria group: Included 30 patients the range of ACR >300 mg/g

Inclusion Criteria:

- Patients ranging in age from 30 to 65 years.
- Type 2 diabetes medical history.
- All selected patients fasted for a period of 10-14 hours for the purpose of conducting a comprehensive lipid profile.

Control Group of Volunteers Was Formed Using the Following Criteria:

- Clinically healthy.
- Negative for clinical indicators of systemic illnesses.
- Negative for diabetes.

Exclusion Criteria

- Patients over the age of 65.
- Behaviors such as smoking, drinking, and chewing tobacco.
- Patients with diabetic neuropathy.
- Patients with diabetic retinopathy.
- Patients with systemic lupus erythematosus (SLE).
- Patients with diabetic heart disease.

Results

Table 1 shows, the results of FBS mg/dL, HbA1c% and lipid profile in all the studied groups (patients and control). FBS, HbA1c revealed a highly

Collection and Analysis of Samples

Seven ml of blood from antecubital vein were withdrawn and divided into two parts. Part (1): 5 ml were placed in gel tubes and coagulated at room temperature for 30 minutes. After 10 minutes of centrifugation, the serum was separated and kept in Eppendorf tubes. The first part was utilized to rapidly identify (FBS, urea, creatinine, Na, K, and lipid profile) in serum using an Auto Spectrophotometer which is a clinical chemistry analyzer that performs diagnostic tests[17]. Also, it was utilized after being maintained at -20°C to assess CTGF, ACE-2 which were evaluated using a My BioSource manufactures an enzyme–linked immunosorbent test (ELISA) kit, USA. Part (2) of the blood was kept in test tube containing anticoagulant for HbA1c measured by I-chroma a device (2 ml)[17]. The glomerular filtration rate (GFR) was calculated by applying the formula of modification of diet renal disease (MDRD) and expressed per 1.73 m^2 per minute. MDRD is the most common equation for estimating GFR, this includes age, gender and race as muscle mass measures. This equation needs no weight since the result is a normalized body surface area of 1.73m^2 which is an acceptable average adult surface area. Urine samples were collected in a clean glass tube for the purpose of determination of urinary albumin/creatinine. Albumin/creatinine ratio (ACR) was measured using the device FUS 3000 urinalysis [18].

Statistical Analysis

SPSS software version 22 was used to statistically analyze the data. The variables' means and standard deviations were reported. To ascertain whether there are statistically significant variations in the means of the four independent studied groups, one-way analysis of variance (ANOVA) was utilized (control, DM with normoalbuminuria, DM with microalbuminuria, and DM with macroalbuminuria[19].

significant difference (p=0.0001**), (p=0.0001**) between patient groups (macro, micro and normoalbuminuria) and healthy subjects

respectively. All lipid profile revealed triglycerides TC mg/dL (p=0.002**), total cholesterol TGs (mg/dL) (p=0.002**), low–density lipoprotein LDL (mg/dL) (p=0.0001**) and very low–density lipoprotein VLDL (mg/dL) (p=0.005**) significant differences increased between patient groups compared to control group except high –density lipoprotein HDL(mg/dL) level which showed decrease significant differences (p=0.0001**) among macro, micro, normoalbuminuria and control groups, (34.94 ± 4.96 d), (36.33 ± 4.57 c), (43.06 ± 6.59 b) and (51.23 ± 4.93 a) respectively, as recorded in Table 1.

Table 1. FBS, HbA1C and lipid profile of the studied groups.

Groups Parameters	Control N=30	Normo-albuminuria N=30	Micro-albuminuria N=30	Macro-albuminuria N=30	P value
FBS (mg/dL)	87.46 ± 5.66 [a] (77-96)	209.03 ± 48.44 [b] (130-298)	211.16 ± 42.02 [b] (161-321)	214.03 ± 69.49 [b] (134-461)	0.0001**
HbA1c	5.18 ± 0.32 [a] (4.5-5.8)	9.68 ± 1.94 [b] (6.9-13.3)	10.08 ± 1.96 [b] (7.30-14.40)	10.49 ± 2.78 [b] (7.10-19.20)	0.0001**
TC (mg/dL)	121.10 ± 19.26 [a] (93-178)	146.5 ± 40.35 [b] (100-255)	138.16 ± 34.14 [b] (93-244)	152.41 ± 33.06 [b] (94-244)	0.002**
TGs (mg/dL)	91.39 ± 13.87 [a] (70-123)	136.66 ± 72.22 [b] (60-397)	119.82 ± 55.44 [b] (61-297)	139.13 ± 46.83 [b] (61-256)	0.002**
HDL-C (mg/dL)	51.23 ± 4.93 [a] (43-59)	43.06 ± 6.59 [b] (31.40-57.30)	36.33 ± 4.57 [c] (30-45.60)	34.94 ± 4.96 [d] (26.80-46.20)	0.0001**
LDL-C (mg/dL)	51.18 ± 21.04 [a] (21.80-112.8)	78.85 ± 34.87 [b] (26.50-162.40)	81.67 ± 30.35 [b] (23.70-148.8)	82.41 ± 34.40 [b] (21.50-162.7)	0.0001**
VLDL-C (mg/dL)	19.50 ± 3.47 [a] (15.2-27.2)	27.74 ± 14.14 [b] (12.2-79.4)	24.55 ± 11.23 [b] (12.20-59.30)	28.55 ± 10.72 [b] (12.20-59.30)	0.005**

**Significant difference between means using ANOVA -test at 0.01 level. , Significant variants are denoted by different small letters .Non-significant variations are denoted by identical small letters. If there are significant differences between the patient groups, they are all denoted by the same letter B and the healthy control group is denoted by a. If there are differences for each individual group, the groups are denoted by b,c and d, respectively, and the control group is denoted by A. If two groups are denoted by the same letter, there are no significant differences between them.

Table 2 shows, the results of creatinine (mg/dL) and urea (mg/dL) in patient and healthy groups. Creatinine the results showed that there was a highly significant difference in the patients' groups (p=0.0001) than control group, and there were significant differences between patient (normo, micro ,and macroalbuminuria) group whereas, urea results revealed higher significant differences among patient (micro and macroalbuminuria) and control groups as recorded in but no significant differences between patient normoalbuminuria with control group.

Table 2. levels of urea, creatinine in the studied groups.

Groups \ Parameters	Control N=30	Normo-albuminuria N=30	Micro-albuminuria N=30	Macro-albuminuria N=30	P value
Creatinine (mg/dL)	0.74 ±0.11 [a] (0.50-0.90)	0.93 ± 0.24 [b] (0.5-1.6)	1.40 ± 0.7 [c] (0.52-3)	3.40 ± 2.89 [d] (1-9)	0.0001
Urea (mg/dL)	30.66 ± 5.19 [a] (22-39)	34.43 ± 9.10 [a] (17-55)	60.12 ± 23.69 [b] (30.1-134)	83.33 ± 38.40 [c] (41-162)	0.0001

**Significant difference between means using ANOVA -test at 0.01 level. Significant variants are denoted by different small letters .Non-significant variations are denoted by identical small letters. If there are significant differences between the patient groups, they are all denoted by the same letter B and the healthy control group is denoted by a. If there are differences for each individual group, the groups are denoted by b,c and d, respectively, and the control group is denoted by A. If two groups are denoted by the same letter, there are no significant differences between them.

Table 3 shows, the results of the estimated glomerular filtration rate (eGFR) (ml./min./m²) in patients' and healthy groups, in addition to the ratio between albumin and creatinine (ACR) (mg/g) in patients' groups. The results of eGFR (ml./min./m²) revealed high significant differences (p=0.0001) among patient groups (macro, micro and normoalbuminuria) and control group, (37.8 ± 25.5 [d], 66.33 ± 35.70 [c], 89.33 ± 23.24 [b] and 109.03 ± 11.04 [a]), respectively. However, the results of ACR (mg/g) showed high significant differences among the patient groups that include macro, micro and normoalbuminuria (558.55 ±233.49 [d], 111.16 ±60.44 [c] and 15.96 ± 5.46 [b]), with healthy control group (14.83± 4.41 [a]) respectively.

Table 3. Values of eGFR , ACR, Na, and K in the studied groups.

Groups \ Parameters	Control N=30	Normo-albuminuria N=30	Micro-albuminuria N=30	Macro-albuminuria N=30	P value
eGFR (ml./min./m²)	109.03 ± 11.04 [a] (82-128)	89.33 ± 23.24 [b] (48-126)	66.33 ± 35.70 [c] (0-121)	37.8 ± 25.5 [d] (5-87)	0.0001
ACR (mg/g)	14.83± 4.41 [a] (9-20)	15.96 ± 5.46 [b] (10-22)	111.16 ±60.44 [c] (34-181)	558.55 ±233.49 [d] (4.02-903)	0.0001
Na (mg/dL)	134.23 ± 5.11 [a] (126.7-143.1)	138.04 ± 4.25 [a] (124.8-145.6)	140.32 ± 3.86 [a] (131.1-147.2)	140.27± 2.47 [b] (135.4-145.3)	0.0001
K (mg/dL)	4.70 ±0.96 [a] (2.5-5.9)	4.39 ±0.49 [a] (3.2-5.3)	4.18 ± 0.45 [ab] (3.5-4.9)	4.06 ± 0.56 [b] (2.5-5.10)	0.001

**Significant difference between means using ANOVA -test at 0.01 level .Significant variants are denoted by different small letters.Non-significant variations are denoted by identical small letters. If there are significant differences between the patient groups, they are all denoted by the same letter B and the healthy control group is denoted by a. If there are differences for each individual group, the groups are denoted by b,c and d, respectively, and the control group is denoted by A. If two groups are denoted by the same letter, there are no significant differences between them.

The results in Table 3 shows the mean ±SD values of Na (mg/dL) for the studied groups include patient (normo, micro and macroalbuminuria) and control groups respectively. A highly significant differences (p=0.0001) was noticed between patient groups macro with control groups) and non significant differences between normo and micrialbuminuria with control group. Potassium (mg/dL) concentrations were determined in sera of healthy control group and patients' groups as described in Table 3. Significant differences were found between patient macroalbumin and both of normo, and control groups, but there is no significant difference between microalbuminurea with normo, macro and control groups group.

ACE-2 (pg/mL) level was determined in sera of control group and patient groups. The results are described in Table 4 .The results showed mean ± SD of ACE-2(pg/mL) among patient groups including normolalbuminuria, micro and macroalbuminuria [(2239.8 ± 783.8 [b]), (2559.8 ± 755.96 [b]), and (2620.13 ± 1294.84 [b])] respectively in addition to control group(1545.30 ± 779.08 [a]).

The results showed a highly significant difference (p=0.0001) between patient and control groups. And there was no significant difference between patients' (normo,micro,and macroalbuminuria) groups. Table 4 shows mean ± SD of CTGF (pg/mL) among patient groups including normalalbuminuria, micro and macroalbuminuria [(61.54 ± 46.48 [b]), (77.39 ± 44.75 [b]), and (87.54 ± 50.38 [b])] respectively, in addition to control group [18.55 ± 13.83 [a]]. The results showed highly significant difference among the patients' and control groups.

### Table 4. levels of ACE-2 and CTGF in the studied groups

Groups / Parameters	Control N=30	Normo-albuminuria N=30	Micro-albuminuria N=30	Macro-albuminuria N=30	P value
ACE-2(pg/mL)	1545.30 ± 779.08 [a] (500.3-2679.6)	2239.8 ± 783.8 [b] (780.4-3786.1)	2559.8 ± 755.96 [b] (767.16-3707.6)	2620.13 ± 1294.84 [b] (546.61-8416.30)	0.0001
CTGF (pg/mL)	18.55 ± 13.83 [a] (4.11-47.22)	61.54 ± 46.48 [b] (5.8-148.2)	77.39 ± 44.75 [b] (10.77-162.08)	87.54 ± 50.38 [b] (10.84-162.12)	0.0001

**Significant difference between means using ANOVA -test at 0.01 level, Significant variants are denoted by different small letters. Non-significant variations are denoted by identical small letters. If there are significant differences between the patient groups, they are all denoted by the same letter B and the healthy control group is denoted by a. If there are differences for each individual group, the groups are denoted by b,c and d, respectively, and the control group is denoted by A. If two groups are denoted by the same letter, there are no significant differences between them.

Fig. 1 shows ROC curve of CTGF for patients with microalbuminuria. The results of ROC analysis revealed that CTGF has an excellent ability (AUC =0.90) to be a reliable marker for early diagnosis of the disease under study, as shown in Table 5. The significance level is a very important (P<0.0001). As shown in Fig. 1. In ACE-2 analysis, area under the ROC curve (AUC) is 0.8, thus it considers a very good factor to identify diabetic patients with microalbuminuria related to normal control as shown in Table 5. The significance level is a very important (P<0.0001) as shown in Fig. 2. Criterion of both CTGF and ACE-2 were found to be ≤47.22 and ≤1630.76 pg/ml, respectively, that means value equal or less than criterion value represents healthy condition, while value more than that denotes disease case.
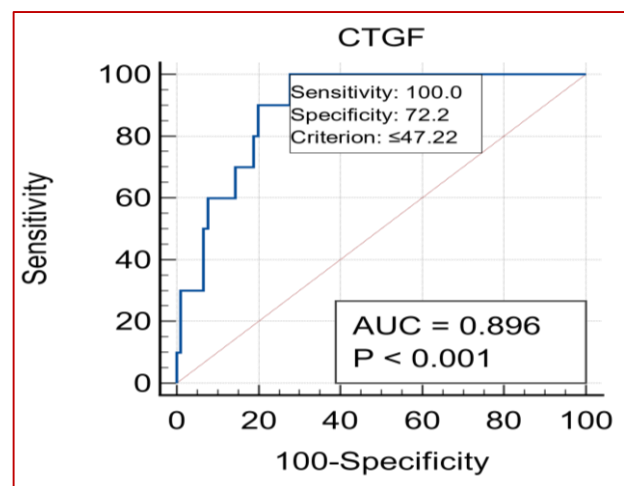
Figure 1. ROC Curves of serum biomarkers including CTGF for diagnosis of DM patients with microalbuminuria.
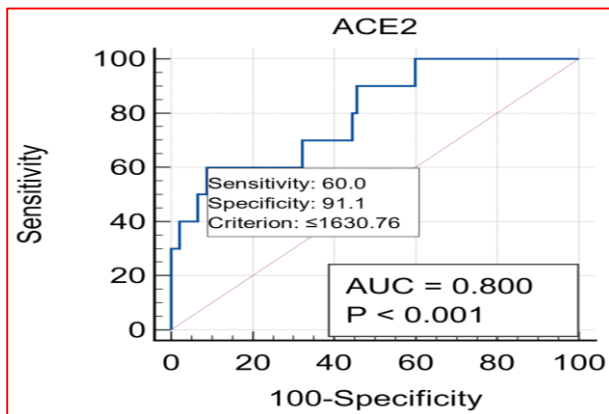
Figure 2. ROC Curves of serum biomarkers including ACE-2 for diagnosis of DM patients with microalbuminuria.

Table 5. Area under the curve value of CTGF and ACE-2 in patients with diabetic microalbuminuria

Test Result Variable (s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval
				Lower Bound Upper Bound
ACE-2	0.8	.000	.000	1.000 1.000
CTGF	.903	.041	.000	.823 .983
a. Under the nonparametric assumption b. Null hypothesis: true area = 0.5				

Discussion

Numerous studies were conducted to know the reasons of damage and fibrosis of glomerulus and tubules and their early prediction by measuring some relevant variables [20].The current study was conducted for diabetic patients with or without nephropathy (micro or macroalbuminuria), characterized by hyperglycemia fasting blood sugar (FBS), albumin to creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) values as depended criteria for classification of patient groups, which are recorded in Tables 1 and 3. In addition to other factors such as urea and creatinine that support the criteria results, as recorded in Table 2, the mentioned parameters denote to the progression of diabetes complication diabetic kidney disease (DKD). The risk conditions for stimulation and progression of diabetic kidney disease (DKD) are associated with hyperglycemia, fibrosis and inflammation[21]. Chronic kidney disease (CKD) is defined as the gradual loss or impairment of kidney function due to damage that occurred in glomerulus and tubules[22].

The diabetic kidney disease (DKD) progresses, plasma lipid profiles shift significantly. Overt proteinuria/hypoalbuminemia raises low–density lipoprotein (LDL-C) dramatically, and kidney dysfunction increases residues and reduces high –

density lipoprotein (HDL-C)[23]. In the current study, dyslipidemia was established within diabetic patients by the increase in cholesterol, triglycerides, and low–density lipoprotein LDL and decrease high –density lipoprotein (HDL). Dyslipidemia is commonly associated with obesity and T2DM. Obesity may activate changes to the body's metabolism that cause adipose tissue to release increased amounts of fatty acids, glycerol, hormones, proinflammatory cytokines, and other factors that are involved in the development of insulin resistance.

Our current study showed that there was an increase in the levels of urea, creatinine, microalbuminuria, and a decrease in the glomerular filtration rate (GFR) in the diabetic groups compared to the control group [24]. Hyperinsulinemia indicates a strong positive association between the level of blood sugar with urea and creatinine. Plasma creatinine and urea are known indicators of glomerular filtration, with the more sensitive index of kidney function being serum creatinine[25]. Hyperglycemic injury can affect all forms of renal cells, including podocyte of glomerular, mesangial cells of endothelial, tubular epithelial cells, interstitial fibroblasts and vascular endothelia, which may explain appear both of blood urea, creatinine levels along with chronic hyperglycemia [26].

The findings of this study showed that estimation of albumin to creatinine ratio (ACR) and glomerular filtration rate (GFR) could be useful as markers in this environment for early detection of diabetic nephropathy, prevention of overt nephropathy, and progression to end stage renal disease[27]. When creatinine and urea are normal, but there are early changes in glomerular basement membrane, in addition to presence of accumulated matrix materials in the mesangium, with consequent microalbuminuria, the glomerular changes at this stage can reverse pharmacological interference[28]. So, newly detected or known Type 2 diabetes mellitus (T2DM) patients need monitoring for glycemic control, with simultaneous monitoring for early reversible nephropathy, microalbuminuria. Clinical progression of diabetic nephropathy can be defined in terms of changes in urinary albumin excretion rate and decline in glomerular filtration rate[29].

Sodium and potassium can be used to identify risk factors for decreased kidney function and to understand the mechanisms in the development of chronic kidney disease[30]. Diabetes mellitus type 2 is of particular interest because it is associated with renal sodium retention. The mechanisms of enhanced renal sodium reabsorption have not been clearly established, but evidence has been provided for the involvement of epithelial sodium channel (ENaC)-mediated sodium reabsorption [31,32]. This transport appears to be stimulated by the additive effects of aldosterone and the combined actions of hyperinsulinaemia and hyperglycaemia. In addition to hyperinsulinaemia-mediated renal tubular sodium transports, it has also been suggested that the increased glomerular filtration of glucose may enhance the activity of the proximal tubular Na+-glucose co-transporter and may contribute to sodium retention when decreased renal perfusion stimulation kidney produces renin enzyme [33] .This enzyme can be converting angiotensinogen to angiotensin I..

Renal endothelium produces angiotensin converting enzyme, this enzyme converts angiotensin I to angiotensin II. Angiotensin II acts on tubular Na reabsorption and K excretion[34].

The liver appears as the main source of this protein in the kidney. However, that angiotensinogen can also be synthesized in the proximal tubule and can be secreted to the tubular lumen, playing a potential role in intra tubular angiotensin II (Ang II) synthesis[35,36]. Angiotensin-converting enzyme is also widely expressed throughout the nephron including the glomerular endothelium, mesangial cells, podocytes and the brush border of the proximal tubule, its highest site of expression in the kidney. Increased levels of angiotensin-converting enzyme- 2(ACE) in the kidneys have been associated with elevated levels of renal angiotensin II

(Ang II). Our study agree with other studies that have shown that if inflammation occurs for three days, it leads to the production of monocytes and microphages[37]. These cells are a result of cytokins IL-6, and MCP1 inflammation induced product connective tissue growth factor (CTGF) related with fibrosis[38]. Connective tissue growth factor (CTGF) expression is modest in healthy adult kidneys but is significantly elevated in a number of renal disorders, where it plays an important role in the development of glomerular and tubular interstitial fibrosis involved in cell migration, proliferation and differentiation, connective tissue growth factor (CTGF) acts either directly to promote fibrosis[39].Our current study demonstrated an increase in connective tissue growth factor, which indicates glomerular and tubular damage and fibrosis in diabetic patients. This finding is consistent with Koszegi, S., et al who found elevated serum connective tissue growth factor (CTGF) expression as a strong predictor of renal fibrosis [40].

Conclusion

According to reported data in this study, angiotensin-converting enzyme- 2(ACE-2) and connective tissue growth factor (CTGF) found to be excellent factors for early prediction to glomerular and tubular damage and fibrosis in diabetic complications of kidney injury. This result is confirmed by many other results such as significant differences among patient groups and control, especially, the results of ROC, that confirmed both angiotensin-converting enzyme-2(ACE-2) and connective tissue growth factor

(CTGF) found to be as excellent markers for monitoring the progression of diabetic and diabetic nephropathy complications, as early predictors.

Acknowledgment

Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.

- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee in University of Medical City.

Authors' Contribution Statement

This work was carried out in collaboration between all authors. R. K. I. diagnosed the cases and conducted the collection of samples and the test. K. G. wrote and edited the manuscript. A. A. D. did the analysis of the data. All authors read and approved the final manuscript.

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التنبؤ المبكر بالاعتلال الكلوي لمرضى عراقين مصابين بالسكري النوع الثاني بدلالة تقييم بعض العوامل البيوكيميائية ذات الصلة

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الخلاصة

داء السكري من النوع 2 (T2DM) هو مرض معقد يصيب العديد من الأعضاء إلى جانب البنكرياس مثل الكلى والكبد والدماغ والعين. بسبب ارتفاع السكر في الدم لفترات طويلة وعدم السيطرة على مرض السكري مع وجود عوامل خطر أخرى ، يمكن أن تحدث مضاعفات مرض السكري. تشمل مضاعفات مرض السكري مضاعفات الأوعية الدموية الدقيقة والأوعية الدموية الكبيرة التي تستهدف الكلى. تهدف الدراسة الحالية إلى التحقق من مستوى الانجوتينسن المحول للانزيم (ACE-2) ، عامل نمو النسيج الضام (CTGF) جنبًا إلى جنب مع بعض العوامل البيوكيميائية ذات الصلة في النساء المصابات بداء السكري واعتلال الكلية السكري مقارنة بالضوابط الصحية. اشتملت الدراسة على 90 مريض تتراوح أعمارهم بين 30-65 سنة. يعانون من مرض السكري من النوع 2 مقسمون إلى ثلاث مجاميع على أساس معايير ACR تشمل البيلة الألبومينية الطبيعية ، البيلة الألبومينية الدقيقة ، البيلة الألبومينية الكبيرة 30 مريضًا لكل مجموعة و 30 شخصًا يتمتعون بصحة جيدة كانوا بمثابة المجموعة الضابطة ، منمن زاروا مستشفى بغداد التعليمي / المدينة الطبية و مستشفى اليرموك التعليمي ، في الفترة ما بين ديسمبر 2021 ومايو 2022. تم تحديد مستويات ACE-2و CTGF باستخدام تقنية ELISA.أظهرت النتائج وجود فروق ذات دلالة إحصائية بين مجموعات المرضى والمجموعة الضابطة لعامل CTGF ، ووجد أن مستويات ACE-2 تزيد بشكل كبير في مجموعات المرضى عن مجموعة التحكم الصحية. كما أظهرت النتائج أن كلا من سكر الدم الصائم FBS و هيموكلوبينA1C (HbA1C) قد زاد بشكل ملحوظ في مجموعات المرضى مقارنة بالمجموعة الصحية. علاوة على ذلك ، كشفت قيم معدل الترشيح الكبيبي المقدر(eGFR)عن فروق ذات دلالة إحصائية بين جميع المجموعات المدروسة ، وكذلك اظهرت نتائج ACR وجود فروقات ذات دلالة إحصائية بين مجموعات المرضى الثلاثة ، والتي تمثل المعايير الأساسية لتصنيف مجموعات المرضى. على أساس النتائج التي تم الحصول عليها في هذه الدراسة ، يمكن استنتاج ان عاملي ACE-2 و CTGF يمكن تطبيقهما كواسمات تنبؤية مبكرة موثوقة للكشف عن المرض.

الكلمات المفتاحية: الانجوتينسن المحول للانزيم , نسبة الالبومين الى الكراتينين ,عامل نمو النسيج الضام, اعتلال الكلية السكري ,مرض السكري.