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Research Article

Early Diagnosis of Diabetic Nephropathy in Patients with Diabetic Mellitus Type 2: A Systematic Review

Alyaa Kadhum Huliel[1*], Huda Furhan Ahmed[2], Hiba Abdul-Hussein[3]

[1]Department of Medical Laboratory Techniques, University of Baghdad, Baghdad, Iraq; [2]Department of Anesthesiology, University of Baghdad, Baghdad, Iraq; [3]Department of Medical Techniques, University of Baghdad, Baghdad, Iraq

ABSTRACT

Diabetic Nephropathy (DN), is a major micro vascular complications of the diabetes mellitus type 1 or 2 and the major reason of end-stage kidney disease. Primary diagnosis for diabetic kidney disease will help early intervention to reducing the progression rate to end-stage kidney disease. Protein in urine and measure estimated Glomerular Filtration Rate (GFR) are the two measures for diagnostic and diabetic kidney disease prognosis. Many significant biomarkers for kidney damage and disease that aid in diagnosis of nephropathy. Biomarkers may help for diagnosis, treatment, reduces prevalence and slows the progression of nephropathy, this review concentrated on biomarkers that could make it possible for primary diagnosis, treatment and reduce the progression of diabetic nephropathy.

Methods: A systematic review of studies published in 2024 was conducted in PubMed NCBI, Science Direct, Google Scholar, Springer Link and African Journal Online (AJOL). It included the studies that are published from June 2018 and March 2024, which depend on a population with type 2 diabetes mellitus patients. Evaluates the effect of diabetes on renal function using serum creatinine, blood urea, Albumin Creatinine Ratio (ACR), ketone bodies, insulin, Fasting Blood Sugar (FBS), Hemoglobin A1C (HbA1c) levels and also evaluate levels of nephrin protein, Wnt/beta-catenin, Monocyte Chemoattractant Protein-1(MCP-1) and Transforming Growth Factor-β (TGF-β).

Results: 21 studies with available full text. These could be characterized as glomerular biomarkers; inflammatory biomarkers and tubular biomarkers. The biomarkers panel development showed more significant results in early detection diabetic kidney disease than those with a single biomarker.

Conclusion: The study findings revealed that prevalence of diabetic nephropathy remains a high in diabetes patients. This study revealed that the diabetic patients with advanced age, longer duration of diabetes, family history of kidney disease, overweight and a poor glycemic control, were determinant factors of DN.

Keywords: Biomarkers; Diabetes mellitus type 2; Diabetic nephropathy

INTRODUCTION

Diabetic Nephropathy (DN) is also called as Diabetic Kidney Disease (DKD), is a major micro vascular complications of diabetes mellitus which affects about forty percent of patients with type 1 or 2 diabetes mellitus. This complication is the main reason of kidney disease [1]. End Stage Kidney Disease (ESKD), can be define as the final stage of chronic kidney disease, which is an irreversible and progressive that can reach to its final stage in ten to twenty years. ESKD patients lack their ability to control of the renal normal function which lead to accumulation of urea and other nitrogenous compounds in the blood [2].

Type 2 Diabetes Mellitus (T2DM), is the most metabolic disorders that caused by the two factors: Beta cell in the pancreas insufficient produce of insulin or the tissues that are sensitive to insulin were failed to respond to insulin. Insulin is a hormone that produced by beta cells in the pancreas, this hormone take glucose from the blood stream transported it to the body cells, where can be transformed into the energy form. Diabetes remains the main form and the cause for the renal disease [3,4].

Diabetic kidney disease is clinically diagnosed on the basis of Glomerular Filtration Rate (GFR), increased albumin in urine or both. Nearly twenty to forty of type 1 and type 2 DM patients, will developed of diabetic nephropathy. If not properly treatment, will reach to stage, known as ESKD. Diabetes Mellitus (DM), is defined as metabolic disorder that designed by complete

Correspondence to: Alyaa Kadhum Huliel, Department of Medical Laboratory Techniques, University of Baghdad, Baghdad, Iraq, E-mail: EDC4003@mtu.edu.iq

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or insufficient generation of insulin. Type 1 Diabetes Mellitus (T1DM), is the common DM in childhood and adolescence compared to Type 2 DM (T2DM), which is more common in adulthood [5-7].

Kidney disease is a sign that the kidney normal function has been compromised, the kidneys are not having ability to perform any regular works, involving filtration of the blood which lead to kidney failure, the body will have filled up with the water and the waste materials. The common structural abnormalities that lead to diabetic nephropathy in the diabetes are the Glomerular Basement Membrane (GBM) thickening, enlargement of mesangium, also there are lesions in the arteriolar, interstitial and tubular [8-14].

At the cellular level, elevated hyperglycemia cause highly production of advanced Glycation end Products (AGEs), Reactive Oxygen Species (ROS), protein kinase C activation and Renin-Angiotensin System (RAS) activation, also lead to generation of Transforming Growth Factor-β1 (TGF-β1), which is the major cytokine in the fibrosis and inflammation process [1].

Risk factors for DKD, sub optimal glycemic control, high blood pressure, increase body weight, advanced age, male gender, long standing of diabetes and family history. DKD pathophysiology include 4 pathways are: Metabolic, hemodynamic, fibrotic and inflammatory pathways. These pathways cause the functional, structural and biochemical alterations [7]. Therefore, the aim of this systematic review was to review the impact of diabetes mellitus on the renal function. We hypothesized that the diabetes is the major risk for decline the normal function of the kidney and can lead to renal failure.

MATERIALS AND METHODS

Search strategy

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched Google Scholar, Pub Med, Science Direct, Springer Link and African Journal Online (AJOL). We used the Boolean operator 'AND' and limited the search to a date range between 2018 and 2024. The search terms were 'diabetes mellitus,' 'type 2 diabetes,' 'early detection' and 'microvascular complications'. Other terms used were 'diabetic kidney disease,' 'diabetic nephropathy,' 'biomarkers of diabetic kidney disease,' 'chronic kidney disease' and 'end-stage renal disease,' [15-17].

Study design

The review contains studies using observation that concentrate on the nephropathy risk of T2DM, which include cross-sectional research and subsequent research. In the study selection process for research, the inclusion and exclusion criteria play an important role. The study for the systematic review has been selected based on some criteria. Those studies are selected for the systematic review which are written in English, are available in the proper PDF format and has page and volume number. On the other hand, some articles are also selected have relevant information related to the subject matter of the present study: Opinions, case reports, narrative reviews and letters to the editor.

Study selection

A title reading was the first step used to detect pertinent articles. The abstract of those articles considered relevant was retrieved and further scrutinized. Duplicate articles and those for which the full text was unobtainable or those which did not fulfil the selection criteria were excluded. Articles that lacked information on the survival and prognosis of diabetic nephropathy were also excluded.

The information was found through searches of digital sources such as Google Scholar, Pub Med, Science Direct, Springer Link and African Journal Online (AJOL). The investigator separately reviewed each abstract and title in comparison to predetermined inclusion and exclusion standards. Google Scholar was used for further research. Using terms, a thorough search plan was created. The terms 'type 2 diabetes,' 'early detection' and 'microvascular complications.' Other terms used were 'diabetic kidney disease,' 'diabetic nephropathy,' 'biomarkers of diabetic kidney disease,' 'chronic kidney disease' and 'end-stage renal disease,' have been utilized. To translate the results for other databases, the original search was done in PubMed. To find additional pertinent papers, reference lists of the research included and previously released reviews were also examined.

Data extraction and quality assessment

For the extraction of data, the research papers that had been selected at the full-text step were carried over. Data are gathered and the details pertaining to the topic are interpreted. The research papers were carefully chosen to ensure the calibre of the study. From the papers that are specifically focused on the topic, only pertinent information is taken. Existing journals that contain peer-reviewed articles about medical issues are gathered as secondary data for this research. A systematic evaluation is carried out to assess the results. The criteria for choosing and the number of papers utilized in this research are presented in a flow chart using the PRISMA table. The following information was taken out of the research: (a) Creator and article information; (b) Region or country; (c) Objective of the study; (d) Methodology employed; (e) Participant and population sub-group demographic information; (f) Additional primary results; (g) Conclusion.

Data analysis and synthesis

Obtained data are analyzed using a systematic review method where each article was discussed with their core findings. Each article is contributing to generating a critical analysis on the relevant factors. Using the systematic review method each article was thoroughly explored and only factual information was selected including survey results and descriptive knowledge.

Outcome measures

Increasing rate of Diabetes Mellitus (DM) and diabetic kidney disease is becoming a global concern, hence, through this study a clear understanding of diabetic kidney diseases among diabetes patients is expected. Outcome of this study is to determine the nephrin protein, MCP-1, Transforming Growth Factor-beta (TGFβ) and Wnt/beta catenin role in the diabetic kidney disease risk in DM patients.

RESULTS

Description and characteristics of included articles

A flowchart of the review process is shown in Table 1. A total of 100 articles were identified from searching the databases.

Only 21 studies among those are selected because others are not meeting the inclusion criteria, twenty duplicate articles and twenty-five articles for which the full text was unavailable were removed. Then, twenty-five articles were excluded due to a lack of information on DN prognosis and nine were excluded due to not reporting on the patients with type 2 DM. Finally, 21 articles were included in the qualitative analysis.

Different biomarkers were linked to the primary diagnosis of diabetic kidney diseases. 21 studies were included in this review and 79 studies were excluded from this review. Most of the articles were published between 2021 and 2024 (7-21) and four of them were published in 2020 or earlier. The 21 included studies were from different countries.

Table 1: Summarizes the key points for each review article included in this systematic review.

Study objective	Sample size	Year, country	Main findings
Effect of diabetes on renal function parameters in tertiary care hospital	N=100 T2DM	2018, India	Deflection in urea and creatinine from the normal range indicates reduce in renal function in patients with diabetes
Diabetic retinopathy is a prognostic factor for progression of CKD in T2DM patients.	N=2197 T2DM	2019, Korea	DR severity is a prognostic factor for CKD progression in type 2 DM patients in the future
Clinical study of urine albumin creatinine ratio as an earlier predictor of diabetic nephropathy	N=210 T2DM	2020, India	ACR observed high sensitivity in detection of proteinuria
Prevalence and the risk factors of chronic kidney disease among T2DM patients.	N=1096 T2DM	2020, Thailand	A high prevalence of CKD are related to poor glycemic control
Insulin resistance and specific biomarkers in blood and urine of T2DM patients with or without nephropathy in Basrah, Iraq	N=63 T2DM	2020, Iraq	T2DM patients with or without DN had a significant elevated in glucose, renal function tests, insulin and IR
MCP-1 levels were higher in patient with DN among Balinese	N=116 T2DM	2020, Indonesia	MCP-1 can be considered as a biomarker for DN detection
Evaluation of MCP-1 as a predictor of complications in T2DM in Zagazig University Hospital.	N=27 recent T2DM N=27 old T2DM N=27 Control	2021, Egypt	MCP-1 is elevated in T2DM patients and elevated with progression of diabetes complications as DN
Wnt/β-catenin pathway proteins in ESRD	N=60 ESRD N=30 Control	2021, Iraq	Wnt/β-catenin pathway proteins show significant changes in ESRD
Utility of urinary nephrin in patients with and without DN and its correlation with albuminuria.	N=147 T2DM	2021, India	Urinary level of nephrin are increased in patients with DN
Micro albuminuria as early detection in diabetic kidney diseases	N=60 T2DM N=20 Control	2021, Uzbekistan	Microalbuminuria help diagnosed
Association between serum albumin level and microvascular complications of Type 2 DM	N=951 T2DM	2022, China	Decreased in level of serum ALB may be risk for DKD in patients with T2DM
Association of glycosylated hemoglobin with urinary albuminuria for early detection and progression of renal damage in T2DM patients.	N=100 T2DM N=50 Control	2022, India	Poor glycemic control leads to increased complications in patients with T2DM
Evaluation of renal function status in type 2 diabetic patients at Khartoum state, Sudan	N=50 T2DM N=50 Control	2022, Sudan	Elevated in urea, creatinine and sugar when compared with non-diabetic patients
Evaluation of some parameters to detection of type 2 diabetes induced nephropathy in the population sample of Al Dewaniyah	N=50 T2DM N=40 Control	2023, Iraq	Investigations of urea, creatinine, glucose, insulin, HOMA-IR and HbA1C as indicators for renal failure result from DM complications

Serum and urinary TGF-β1 in diabetic nephropathy patients	N=50 DN N=50 Without DN N=30 Control	2023, Iraq	TGF β1 level increased in diabetic patients without nephropathy and with nephropathy
Correlation of kidney injury molecule-1 and nephrin levels in Iraqi patients with DN	N=50 T2DM N=50 T2DM DN	2023, Iraq,	Nephrin are specific and sensitive indicators of early-stage diabetic nephropathy
Risk factors for diabetic nephropathy in diabetic patients	N=121 T2DM	2023, Iraq	Age, hyperglycemia, obesity and diabetes duration involved in the DN development
Fasting ketone bodies and incident type 2 diabetes in general population	N=126 T2DM	2023, Stockholm,	Levels of Fasting plasma ketone associate with incident of T2DM.
Study on the estimation of urine albumin for the early diagnosis of DN among patients with DM	N=65 T2DM	2023, India	Albumin in urine consider as an early indicator tool for DN in the DM patients
Association of TGF-β1 with cystatin-C in patients with DN	N=50 DN N=50 without DN N=30 Control	2024, China	TGF-β1 was significantly linked with the serum creatinine and cystatin-C levels
Risk factors for CKD in middle eastern patients with T2DM: A cross-sectional study	N=1603 T2DM	2024, Jordan	Male, older patients, and high blood pressure, longstanding T2DM, significantly higher risk of CKD advanced.

Note: MCP-1: Monocyte Chemoattractant Protein-1; T2DM: Type2 Diabetes Mellitus; TGF-β: Transforming Growth Factor Beta; DN: Diabetic Nephropathy; HbA1c: Glycated Hemoglobin; DKD: Diabetic Kidney Disease; DR: Diabetic Retinopathy, GFR: Glomerular Filtration Rate, ESRD: End Stage Renal Disease, ACR: Albumin Creatinine Ratio, IR: Insulin resistance; CKD: Chronic Kidney Disease; HOMAIR: Homeostatic Model Assessment for Insulin Resistance.

DISCUSSION

This systematic review found that the laboratory markers for early detection of DN are not enough to indicate the diabetic patients at high risk for kidney complications development, discovery of new biomarkers can help to predict the patients that are at elevated risk and may help to delayed or prevent the complication, as well as its advanced to the ESKD [1].

The current study observed the impact of diabetes on the kidney work by measurement the kidney function tests such as urea and creatinine. Renal impairment occur due to T2DM was predicting by measuring the levels of urea and creatinine in patients with diabetes and controls groups, mean of urea concentrations were significantly ($P< 0.05$) increased in patients when compared to controls (47.24 ± 12 mg/dl *vs.* 28.74 ± 2.13 mg/dl), also found that level of creatinine was also significantly (0.79 ± 0.04 *vs.* 1.19 mg/dl ± 0.39 mg/dl) ($P<0.05$) elevated in patients. Creatinine is a waste material that is filtered from the blood and excreted in the urine [18-20]. In other study when compared some parameters of renal function between patients and control group, the results observed that the blood urea, serum creatinine and blood glucose levels of the patients group when compared with the control group were significantly higher (0.000), which indicate abnormality in renal function status. In other study observed that blood urea, creatinine, glucose, insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and HbA1C % as good indicators for diagnosis renal failure that resulting from DM complications and was study done by the parameters of renal function showed significant changes in diabetic patients.

In the current study, observed that the diabetic retinopathy patients had elevated risk for DN when compared with patients with no retinopathy, also observed that DR associated with long duration of DM, uncontrolled of blood glucose level, lower GFR level and a large amount of albuminuria [21-24]. Finding of this study was not differ from study done by which shows that DR is associated with increased risk of renal failure about patients with DN and Nondiabetic Kidney Disease (NDKD).

This review showed that urinary ACR have high sensitivity in detection of micro albuminuria, so it should be involved in routine work for early detection of nephropathy in all T2DM patients [25-29]. The result of this study can be compared to other study conducted by which observed that patients with T2DM who have a risk for developing renal failure should be monitored by sensitive biomarkers for nephropathy such as micro albuminuria, Urine Albumin-Creatinine Ratio (UACR), to facilitate early detection of diabetes that cause nephropathy.

The study demonstrated that people over 75 years and people with HbA1c more than 8% had higher for Chronic Kidney Disease (CKD) about 61.3% and 38.6% respectively. There are six factors for development of kidney disease are advanced age, retinopathy, albumin in urine, HbA1c ≥ 7%, anaemia and uric acid more than 7.5 mg/dl [30-33]. Other study show that the development and progression of DN are related to many factors like age, sex, region, race, long standing of diabetes, diabetes type, Body Mass Index (BMI), level of HbA1c and blood pressure. Results of one study in this review observed that the long standing of the disease, sex, advanced age, glycemic control and obesity are included in the DN development in the DM patients. As older people are more

likely to develop DN and End-Stage Renal Disease (ESRD) as a result of T2DM. Findings is agreement with previous study by and study in Iraq done by which showed that glucose intolerance prevalence pre-diabetes and T2DM increased in patients that aged 45 and older. Also other study found there is several factors were associated with highest risk of CKD, including aged>45 years, male gender, hypertension and T2DM duration ≥ 15 years. Previous studies had also reported a similar findings [7].

The results of this study demonstrated that Insulin Resistance (IR) is linked to obesity and play major role in diabetes pathogen city and complications that are an indicator for early stage of DN in patients withT2DM, obesity is a accompanied with increase of insulin and glucose can predict the elevated of the insulin resistance in the diabetic patients with renal disease. Also, the renal diseases is associated with elevated of IR and body mass index in patients withT2DM. In addition, the results when comparable with control group observed that patients with T2DM with or without DN had significantly ($p<0.01$) elevated concentrations of biomarkers (glucose, insulin and HOMA-IR) [34-38]. This finding are not differences than the other study done by which demonstrated that that insulin use was greater in T2D patients with more advanced CKD.

MCP-1 is generated by cells of smooth muscle, tubular, mesangium, podocytes, eosinophils and mast cells. It is made in the kidneys by response to inflammation. Results were observed the MCP-1 level was elevated in T2DM patients and used as indicator for early stage of complications in T2DM. Serum levels of MCP-1 were increased in DN patients ($p<0.001$). Receiver Operating Characteristic (ROC) curve analysis demonstrated that MCP-1 cut-off point with a sensitivity of 83.7% and 84.8% specificity, an Area Under Curve (AUC) was 0.886, this level can consider a good diagnosis accuracy [39-41]. This finding is supported by other study done. Which shows that MCP-1 is associated with later stage of disease. Another study shows that the elevated concentration of MCP-1 in the diabetic patients when comparable with the low level in the control group, these results demonstrated that serum MCP-1 was higher in old diagnosed patients who had diabetic nephropathy, retinopathy and neuropathy [42-45]. Other study also when compared the patients to healthy groups observed MCP-1 concentration to be higher in T2DM patients.

Proteins of Wnt/β- catenin pathway observed changes in ESKD patients, which demonstrated significantly elevated concentrations of antagonists and weakened the activity of this pathway, which is linked to lower GFR level. This finding is consistent with previous study. This study observed that development of normal kidney needed precise and complex cell-cell communications, Wnt pathway signalling is a common mediators.

Our findings of this study found that nephrin level increased in patients with type 2 diabetic nephropathy. The study show that micro albuminuria group had high of urinary nephrin levels than those with normo albuminuria and macro albuminuria groups [46]. Other study showed there is a significantly elevated in the serum and urinary nephrin in patients with nephropathy when comparable with the control. Nephrin in serum is positively correlated with nephrin in urine, creatinine, UACR and negatively correlated with the GFR. Similarly, previous study observed that nephrin are more specific and sensitive marker for early detection of DN.

This study demonstrate the major role of urine albumin as an early diagnostic for DN in diabetic patients and also shows that lower serum albumin levels may be an independent risk indicator of DKD in T2DM patients. According to results of the study, albumin amount in the urine of T2DM patients is 103.9 mg/l ± 13.3 mg/l *vs.* 8.6 mg/l ± 1.2 mg/l in the control ($p<0.001$) [47]. The study's findings also agree with other study. This study shows that decrease level of albumin are the main predictive markers of inflammation in CKD patients. Also other study confirm the importance of urine albumin measurement in early detection of diabetic nephropathy. One study show that the prevalence of microalbuminuria indicate that the kidney dysfunction is present.

This study shows that decreased level of serum albumin may be risk indicator of DKD in patients with T2DM and also is associated with DKD progression. The prevalence of DR, DKD and macro albuminuria increased with decreasing levels of serum albumin [48]. The same finding by observed the lower of albumin level associated with reduced kidney function and poor renal prognosis in T2DM and DN patients.

One study observed that poor glycemic control (HbA1c more than 7%) is a common risk for diabetic nephropathy development. Glycosylated hemoglobin positively correlated with urinary micro albuminuria in patients with T2DM. The same finding by other study show that poor glycemic control in HbA1c, pre-prandial and post prandial hyperglycemia were associated with micro albuminuria. Other results observed that both Fasting Blood Sugar test (FBS) fasting and HbA1c are elevated in patients' when comparable to healthy. So, GFR disclosed a high significantly difference in all the studied groups, as well as ACR observed a high difference in the three groups of patients.

Data of this review observed that the TGF-β1 level elevated in patients with diabetes with no nephropathy and nephropathy (40.19 ng/ml ± 3.56 ng/ml), (51.21 ng/ml ± 5.20 ng/ml) respectively when comparable with controls (24.80 ng/ml ± 3.51 ng/ml) with significantly differences ($P<0.01$) and also evaluated that TGF-β1 was a sensitive biomarker in the early phase of DN. TGF β1 levels observed a positive correlation in this study populations with FBS ($r=0.273$, $P=0.006$). Previous data showed that urinary TGF-β1 levels were elevated in diabetic nephropathy patients when compared to healthy controls. Another study reported that TGF-β1 used as an indicator in DN about T2DM patients. All the data of these studies demonstrate that serum TGF-β1 is an indicator for early DN in T2DM patients.

Results of this study demonstrate that plasma ketone levels associate with incident type 2 diabetes in the general population. This finding have no differences were detected by other studies. Which observed that the total ketone bodies were mildly elevated in T2DM patients.

CONCLUSION

DN is an ordinary complication in diabetic patients. The study observed that kidney disease prevalence remains elevated in patients with diabetes according to the papers involved in this review. Micro albuminuria is a primary indicator for diabetic nephropathy, also the kidney injury may be occur without micro albuminuria.

The studies of this review observed that a long standing of DM, age over 60 years, diabetic retinopathy, female gender, history of kidney disease, poor glycemic control, blood pressure and BMI

over 30 kg/m2, were highly linked to increase the risk of kidney disease in patients with diabetes. ACR shows high sensitivity in the detection and screening for early an early DN.

All biomarkers included in this systematic review observed promising results for indicating the diabetic nephropathy because they correlated with albuminuria, GFR or both. These can be categorized as glomerular, inflammatory and tubular biomarkers.

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