Hilla University College Journal For Medical Science

Volume 2 | Issue 4 Article 8

2024

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How to Cite This Article

Ramadhan, Hanan Hamid and Mohammed, Rasha Naseer (2024) "Biomarkers and the Identification of Kidney Damage in Patients with Diabetes Mellitus," *Hilla University College Journal For Medical Science*: Vol. 2: Iss. 4, Article 8.
DOI: https://doi.org/10.62445/2958-4515.1037

REVIEW

Hilla Univ Coll J Med Sci

Biomarkers and the Identification of Kidney Damage in Patients with Diabetes Mellitus

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Abstract

The condition of diabetic renal disease is the most prevalent manifestation of chronic kidney disease and renal failure worldwide. It acts as the major diabetes complication and is characterized by the excretion of abnormal urinary albumin, impairment of glomerular filtration rate (GFR), and diabetic glomerular renal lesions. It is also associated with microvascular complications in diabetes mellitus.

The exact pathogenesis is complicated and unexplained. The pathogenesis pathways initiated and sustained in the kidney by increased glucose levels. They are enhanced by numerous different factors that involve several metabolic variables (excess of carbonyl, fatty acids, and oxidative stress) and hemodynamic variables such as transmitted systemic hypertension-induced shear stress, autoregulation damage, and renin-angiotensin-aldosterone system (RAAS) activation with hyper and hypo-perfusion

Early diagnosis and intervention may delay the progression of the disorder. Recently, various biochemical indicators have been linked to diabetic nephropathy, which were essential for predicting the progression and incidence of the diabetic disease. The simultaneous evaluation of several biomarkers concerning microalbuminuria is a method for diagnosing the primary phases of diabetic kidney disease. The major progress in the invention of novel biomarkers might eventually result in the development of "the ideal" biomarker for the future to detect the early phase of diabetic nephropathy. The current study emphasizes identifying early biomarkers correlated to the etiology and pathophysiology of diabetic nephropathy and alteration in renal function. The review aims to update the information on biomarkers for the diagnosis and identification of diabetic kidney disease.

Keywords: Diabetes disorder, Diabetic nephropathies, Biomarkers, Albuminuria

1. Introduction

1.1. Definition

The condition of diabetic renal disease or diabetic Nephropathy (DN) is the most prevalent manifestation of chronic kidney disease and renal failure worldwide. It described by the existence of abnormal excretion of urinary albumin levels, damage in glomerular filtration rate (GFR) and glomerular lesions [1–4]. In diabetes status, DN occurs as commonly microvascular complicated as result of continuous have high glucose levels [5, 6].

1.2. Epidemiology

There are about 387 million people suffering from DM worldwide due to an update of (International Diabetes Federation IDF) in 2014 [7]. The rate of occurrence of DM increased and is expected almost 592 million individuals, or one person in ten, having Diabetes by 2035 [7, 8]. Diabetes mellitus with Type 2 (T2 DM) is more dominant and constitutes around (85–95%) of all diabetes cases [7, 9]. However, the incidence of diabetic renal disease increases during the first 10 to 20 years, reaching about 3% per year after the onset of diabetes. Among all diabetic patients,

Received 1 October 2024; accepted 15 November 2024.
Available online 13 January 2025

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https://doi.org/10.62445/2958-4515.1037

nearly (20–40%) will ultimately develop diabetic kidney disease [10]. Nowadays, Diabetic Kidney Disease (DKD) may develop as the major reason for end-stage renal disease ESRD), and it is related to the rates of cardiovascular morbidity and death [11]. Renal damage in Type2 DM consequences in high health care expenditure and costs. Therefore, in diabetic T2DM, chief role is to delay the development of the disease to be the end-stage renal disease, which happens due to both preventions of diabetic renal syndrome and the administration of the appropriate treatment [11–13]. Moreover, the occurrence of kidney disease in United States has increased from (5.5%) in the (1986–1995) decade to (19.1%) in the 2006–2015 decade, elsewhere the rated principle to cause of ESRD [5].

1.3. Pathophysiology

The structural and functional modifications are general characteristics of DN. Some evidence occurred in glomeruli in DN as an expansion of mesangial, basal cell membrane thickening, and nodular glomerular sclerosis (Kimmelstiel- Wilson nodules). The pathogenesis pathways initiated and sustained in kidney within increased glucose levels, so they enhanced by numerous different factors which involve both several metabolic variables as (excess of carbonyl, fatty acids and oxidative stress) and hemodynamic variables (transmitted systemic hypertension induced shear stress, autoregulation damaged, and stimulation of the system of renin-angiotensin-aldosterone(RAAS) with hyper and hypo perfusion) [4, 14, 15].

1.3.1. Hemodynamic factors

The metabolic-mediated disturbance of capillary vasoregulation involves complex mechanisms, which include the increase of Transforming Growth Factor-β1 (TGF-β1) and Nitric Oxide (NO). These factors are imperative in the vasodilation process in both efferent and afferent glomerular arterioles. They contrasted with the stimulation of the renin-angiotensin-aldosterone system (RAAS)in tissue and local production of excess angiotensin II [1, 16]. Efferent glomerular arteriole verse afferent, it high sensitivity to the vaso-constriction effects of angiotensin II. This participates in the arteriole tone inequity, resulting in higher glomerular capillary pressure and hyper-filtration as well as cellular mechanisms activation leading to glomerular destruction. Additionally, increased the concentration of (Endothelin-1 and Urotensin II), which leads to arteriole vaso-constriction [1, 16, 17].

1.3.2. Metabolic factors

Glucose can bind to proteins of the kidneys reversibly and ultimately irreversibly [18]. It also forms advanced glycosylation products (AGEs) in the blood circulation. During the years of hyperglycemia, AGEs can form cross-links and contribute to damage of the renal system by stimulating the fibrotic and growth factors through specific receptors for AGEs [Fig. 1] [18, 19].

In addition, due to the obvious altered hemodynamic of the glomeruli, mechanical strain and shear stress arising in tandem that activate the release of multiple cytokines, growth factors, and pro-inflammatory agents that induce numerous pathways of oxidative stress [19, 20] like (MAPK, PKC, NF-κB, and Reactive Oxygen Species ROS) [1]. ROS can trigger all significant pathogenic mechanisms, as increasing the entrance of glucose to the polyol pathway, enhancing the creation of AGEs, and stimulating PKC. As well, the endothelial glycocalyx is directly damaged by ROS, which results in albuminuria without harming the GBM itself simultaneously [21].

1.3.3. Growth factors and inflammation

Extracellular matrix formation and fibrosis induced by stimulation of (TGF-β) and subsequent cytokine, vascular endothelial growth factor (VEGF), and CTGF [1, 18]. Diabetes mellitus is also correlated with the recruitment of activated white blood cells (WBC), primarily T cells and macrophages, into the glomerulus and tubule-interstitium, even in the initial phase of diabetic nephropathy (DN) [1, 4, 15]. In DM, the inflammatory cells influx into the kidney due to their response to the tissue damage, unfortunately, that induced DKD. Inflammatory cells and their metabolites (cytokines, activated complement, chemokines, and ROS) act as mediators of DKD that modify the renal microenvironment [4, 15].

1.4. Risk factors

Diabetic nephropathy does not occur in all patients with DM, but it may be developed by many risk factors, these factors are classified into two groups: modifiable and unmodifiable. The major modifiable factors are hyperglycemia, dyslipidemia, hypertension, obesity, and smoking. Whereas the unmodifiable factors are involved in family history, gestational diabetes, ethnicity, age, and genetic predisposition [1, 8, 22].

1.4.1. Hyper glycaemia

It is a significant risk factor of diabetic nephropathy is a weak metabolic mechanism. The studies approved the regulation of early glucose level mainly conducted on normal albuminuria diabetic patients or in the initial phase of DKD. In addition, previous studies confirmed the intensive regulation of the level

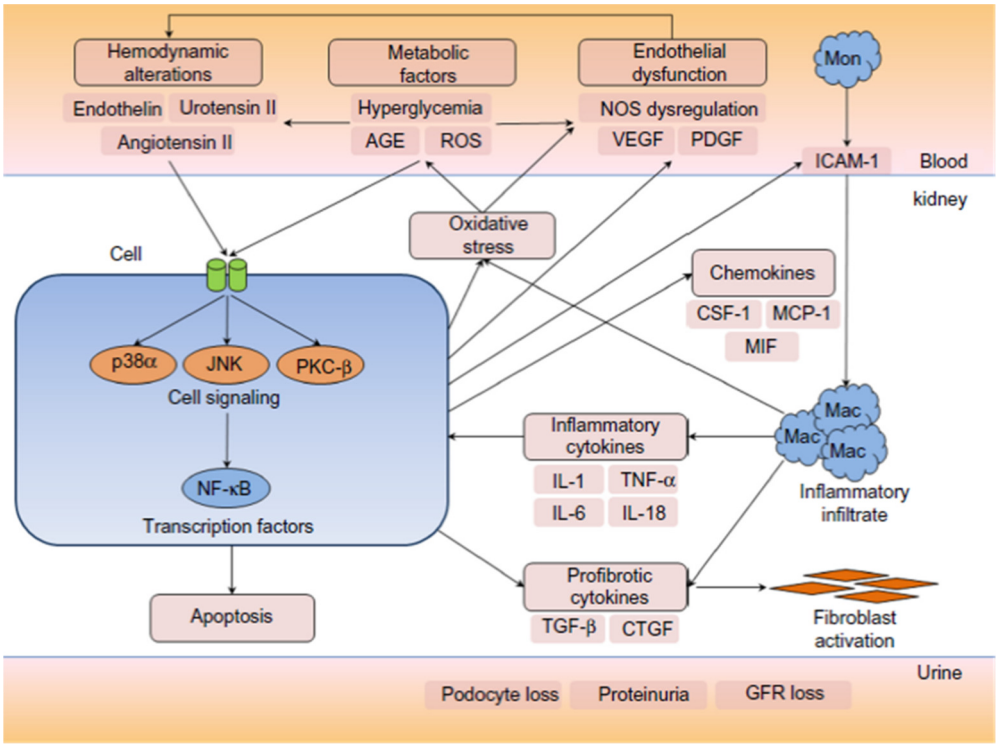

Fig. 1. ***Pathological*** *pathways in diabetic Nephropathy [1].* ***Abbreviations:*** *GFR: Glomerular Filtration Rate, AGE: Advanced Glycation End-products, GBM: Glomerular Basement Membrane, Mon: Monocyte, Mac: Macrophages, NOS: Nitric Oxide Synthase, ROS: Reactive Oxygen Species.*

of blood glucose in kidney disease created unpredictable outcomes [2, 23]. The finding of Krolewski et al observed the predominance of end-stage kidney failure was about 36% in the worst hyperglycemic control patients while 9% in the well-glycemic controlled group [21]. Hyperglycemia inhibits the activation of the polyol and hexosamine pathways, as well as the synthesis of Advanced Glycation End Products and protein kinase C, resulting in improper glucose metabolism. Abnormal glucose metabolism increases renal structural and functional changes, as well as kidney damage [22].

1.4.2. Hypertension

Hypertension is another important factor that causes diabetic nephropathy; it occurs due to the retention mechanism of concentrated sodium and associated blood vessel resistance. Additionally, hypertension develops in conjunction with clinical albuminuria [7, 24].

1.4.3. Dyslipidemia

In the evolution of renal damage, there are abnormalities in both the lipid profile and the metabolism of lipoprotein, which illustrate a vital role in lipid changes. The changes in lipid levels mediated by the liver are proportional to proteinuria, resulting in qualitative and quantitative changes in the body system. Additionally, obesity and metabolic disease are tightly correlated to DN, resulting in chronic kidney disease worldwide [9, 25].

1.4.4. Smoking

Smoking contributes to the progression of DN, it has a critical role to enhance the renal dysfunction, increased the frequency of end-stage renal disease, and lowering the survival rate at the initiation of dialysis. Smoking has an impact on the course of renal disease and its effects on arterial pressure. Indeed, arterial pressure increases during and after each cigarette smoked. Additionally, nicotine in cigarette smoking may increase plasma endothelin level and influence excessive oxygen-free radicals formation that potentiate the worsening effect [26].

1.4.5. Predisposition of genes

The prevalence and severity of diabetic kidney disease are significantly determined by genetic predisposition. The risk of this condition is increased in children and siblings with diabetic nephropathy parents, regardless of the type of diabetes. The probability of 14% for a child without proteinuria parents develop to become clinical proteinuria while it about 23% for a child with one parent with proteinuria and

46% in a case for the child with both parents having proteinuria [21, 27].

1.4.6. Age

Adverse effects of diabetes are enhanced in elderly diabetic patients. It involves the end-stageof renal disease (ESRD) and death. Control of diabetes status and regulation of glycemic level have beneficial effects in decreasing the occurrence of ESRD in elderly individuals with DM.

As people get older, their body functions become less efficient. It has been discovered that increasing age correlates with a faster drop in GFR. Despite this, older individuals had a lower overall risk of renal failure [28].

1.4.7. Obesity

Chronic renal disease in obese people with DM is more common and rapidly than in their normal-weight peers. Bodyweight reduction and adequate nutrition in these patients can reduce proteinuria and improve renal function. However, it is not clearly confirmed that obesity plays a role as a risk factor for DN. Previous findings indicated a higher BMI was independently related to an increased risk of developing DKD, and that both generalized and abdominal obesity are risk factors in the pathogenesis of DKD, independent of their involvement in hypertension and DM [4, 29].

1.5. Diagnosis

1.5.1. Diabetic nephropathy stages

Kidney damage initiates by excretion of low quantities of albumin protein in urine around (30–300) mg/day, which is identified as microalbuminuria or occult. The terms macro-albuminuria or overt nephropathy were known when gradually greater quantities of albumin lost in urine and albuminuria become observable by standard dipstick urinalysis nearby (>300 mg/day) [1, 4, 8]. Macroalbuminuria in type1 DM develops after several years, but in type2 diabetes may be present in any diagnosis time [1]. Proteinuria is the main aspect of type2 DKD and risk agent for end-stage kidney disease [30].

Diabetic nephropathy (DN) has been divided into five phases of development, dependent on basement membrane involvement, mesangial propagation, nodular sclerosis, or progressive glomerular sclerosis [21, 31] (Table 1).

Stage I: Hypertrophy and hyperfiltration

In this phase, GFR appears either normal or elevated. The phase lasts from the commencement of the disorder for about five years [18, 21]

It is well established that elevated by (10–15%) in the renal plasma flow and the size of the kidney amplified by 20%, whereas the level of albuminuria and blood pressure remain within the normal range [21, 32].

Stage II: Quiet stage:

It initiates after two years the commencement of disease; it categorized by kidney impairment with increase the thickness of the basement membrane wall with mesangial propagation [18, 21, 33, 34]. The clinical symptoms of the disease are still not clearly observed and GFR returns within a normal range. Many diabetic patients stay in this phase until their end of life [21, 32].

Stage III: Microalbuminuria

The main characteristic of this stage is Microalbuminuria, which occurs in 30–50% of patient after the onset of diabetes. Approximately 80% tend to develop nephropathy (1–10 years). The rate of glomerular filtration either increases or returns to a normal level, while blood pressure begins to elevate in about 60% of patients [2, 32, 33].

Stage IV: Irreversible phase (Chronic Kidney Failure, CKF),

Its characteristic concludes by the proteinuria which albumin level more than 300 mg/dU with a decreased GFR as a smaller amount than (60 mL/min/1.73 m2), and it also increased the blood pressure [21, 32].

Stage V: Terminal Kidney Failure (TKF)

In this Phase, GFR is less than (15 mL/min/1.73 m2). Virtually half (50%) of the TKF individuals need renal replacement therapy, as (hemodialysis, peritoneal dialysis, and kidney transplanting) [21, 32].

In the early stage of DKD, the size of the kidney and the Doppler indicators. It is perhaps to the primary morphological signals of kidney injury, however, the level of proteinuria and amount of GFR are the greatest indicators of the extent of kidney impairment [21, 33].

1.5.2. Screening

The presence of DKD was detected by evaluating the level of urinary albumin and the GFR [40]. The timing of DN diagnosis is crucial to disrupt the normal progression of the disease and slow down the advancement of sickness to ESRD. Furthermore, albuminuria level is measured by the ratio of urinary albumin to creatinine (u ACR, mg/g) in the first vacuum spotting of the urine sample [40, 41]. The collection of urine in 24-hour is usually taken in specific tube, that diagnosis within gold standard test. Based on KDOQI and the (American Diabetes Association

Table 1. Classifications of diabetic kidney disease.

DN Stages	Albumin level excretion (mg/g Cr) or proteins level excretion (g/g Cr)	Glomerular filtration rate (mL/min/1.73 m2)	References
Stage-I Hypertrophic hyper filtration	Normal albuminuria <30	≥30	[21, 32, 35, 36]
Stage-II Quiet stage	Microalbuminuria 30–299	≥30	[21, 22, 32, 37]
Stage-III Microalbuminuria	Macro albuminuria ≥300 or proteinuria ≥ 0.5	≥30	[2, 32, 33, 38]
Stage-IV (Chronic Renal Failure CKF)	Albuminuria / Proteinuria in any conditions	<30	[21, 32, 39]
Stage-V Terminal Kidney Failure (TKF)	Continued dialysis therapy in Any conditions	<30	[21, 32, 39]

ADA), the relation of Albumin to creatinine ACR is presently choosing as first diagnostic test, particularly due to the void test is accomplished on the early morning [19, 42–44]. Previous studies have shown this time is highly sensitive and specificity nearly 85% when compared to other collection times [43]. For accuracy, an abnormal finding is imitation for a few months [1]. Screening begins at the diagnosis of DM type 2 and typically after 5 years of disease onset [1, 45].

Though the albuminuria is commonly recognized as the chief biomarker for DKD, recently, the consequences of studies have indicated before the diagnosis of albuminuria in diabetic patients, could begin to demonstrate the sign of kidney disease [19, 46]. However, patients with T2DM still having a normal level of albuminuria, who may progress to severe renal damage [47]. These results indicate that despite of albuminuria being a significant finding and disease biomarker, albumin deficiency does not essentially for the disease Status but another indicator as GFR should be used for assessment the disease [19, 47]. GFR is the major indicator for CKD, it has significant roles in the diagnosis and monitoring of diabetes disease; therefore, it should be measured for all diabetic patients [7, 44, 48]. The study equation for GFR estimation confirmed that necessary modified the diet intake in kidney Disease. The phases of CKD classified into five groups according to GFR:

Group 1: (GFR > 90 mL/min/1.73 m2); Group 2: (GFR equal 60–89 mL/min/1.73 m2); Group 3 was separated into (Group 3a and Group 3b) with range (45–59 mL/min/1.73 m2) and (30–44 mL/min/1.73 m2), respectively; Group 4: (GFR equal 15–29 mL/min/1.73 m2); and Group 5 ESRD: (GFR < 15 mL/min/1.73 m2) [19, 43].

1.5.3. Biomarkers

The development of DN is described as a worsening in the staging of (CKD) or decreasing in GFR. It is not necessarily corresponding to advancement of the excretion of urinary albumin. Thus, microalbuminuria may be an insufficient marker to categorize the diabetic patients, especially those at risk of CKD progression [49]. In recent years, these have culminated in active studies on new predictive biomarkers for progressive DN. Of the novel candidate biomarkers, the most promising evidence was provided by (Fibroblast Growth Factor-23 FGF23), serum cystatin C, and (Tumor Necrosis Factor TNF) [49, 50]. Besides, FGF21 and Pigment Epithelium Derived Factor (PEDF). Recently have been demonstrated, two possible novel biomarkers of DN progression [49, 51]. Numerous putative primary biomarkers include {α-1 microglobulin, Nephrin, β-1 microglobulin, etc}. Furthermore, in a proteomic analysis of the disorder collectively were identified other biomarkers called non-albumin proteinuria NAP.

Although these markers which qualify as a sensitive primary detector of renal tubular damage, they currently not standardized or widely accessible [8, 52]. Recent studies by Motawi et al. [13] described that three new exciting biomarkers as {Neutrophil Gelatinase-Associated Lipocalin (NGAL), microRNA-130b (miR-130b), and beta-Trace Protein (beta TP)} presented in type2 diabetes status. They proposed that both (NGAL and BetaTP) significantly increased in type 2 diabetic patients and can represent initial tubular and glomerular biomarkers, respectively [8, 53].

One of the plasma proteins is serum cystatin C, generated in all nucleated cells. It easily filtered and fully metabolized in the renal tubules [19, 48, 54]. The findings of the observational studies by Krolewski et al. have shown that the estimation of serum (cystatin C) level enhanced the incidence of converting nephropathy to the end phase of kidney disease in diabetic patients [55]. Numerous studies have considered the cystatin C protein as an indicator for glomerular filtration rate (GFR). One study used equations of cystatin C–based and inverse creatinine-based to evaluate the GFR in 56 diabetic patients. The precision of cystatin

C was approximately 90% at a concentration (<80 mL/min) for GFR detection, compared to 77% accuracy for creatinine measurements [19, 56].

There is a highly significant correlation between cystatin C protein and GFR in comparison to creatinine-based equations [19]. GFR Assessment by using serum cystatin C is known to be unaffected by body mass measurement, as compared to serum creatinine [57].

The inflammatory biomarkers such as cytokines and chemokines were thought to be possible DN biomarkers [58]. It has been shown that both {FGF23 and TNF receptors (1 and 2)} influence the renal outcome of T2 DM [49, 59]. The expected effects of FGF23 on the risk of development of DN were mostly dependent on the circulating TNF receptor (1), possibly as TNF-a downregulation of Klotho that resistance to FGF23, and compensatory increased expression of FGF23.

These findings suggest the advantage of using circulating TNF receptor 1 over conservative markers, for example, microalbuminuria that might anticipate the regression to end phase of kidney disease, regardless of the existence or disappearing of albuminuria [49, 60].

Urinary Tumor Necrosis Factor alpha (TNF Alpha) is interrelated with N-Aceytyl-β-D glucosaminidase (NAG), tubular lesions biomarker [57]. Furthermore, FGF21 and Pigment Epithelial-Derived Factor (PEDF) are other novel biomarkers in the progression of DN, FGF21is a hormone that possesses many metabolic regulatory characteristics and is is primarily secreted from the liver, whereas PEDF is a secreting glycoprotein have inhibitory effects on inflammation and oxidation processes, and it also has anti-angiogenic effects [49, 57, 61].

It implicate in the creation of vascular endothelial growth factor (VEGF) and extracellular matrix. One of the previous studies by Wang JJ et al confirmed that decreased of the PEDF level in kidneys of diabetic mice, it suggests that might be possess a protective effects on microvascular lesions in DM [62]. Elsewhere, the researchers observed the level of PEDF significantly more in DN patients compared to control, that attributed to the probability of PEDF as an effective biomarker [58]. Furthermore, both baseline levels of circulating PEDF and FGF21 are predictors for reduction of the kidney function [49]. The rising of values in both of PEDF and FGF21 may reveal to the compensatory mechanism, and represent the extent of the local inflammation and deterioration of kidneys, which influence the progress of diabetic nephropathy [49, 63].

Moreover, both PEDF and FGF21 levels are often not probable biomarkers for the assessment of patients with DM, who are at incidence of nephropathy evolution, specifically in the initial stages of DN. However, FGF21 may act as a novel new medical approach for treating the diabetic nephropathy patients [49, 64].

Other biomarkers as (Retinol-binding protein4 RBP4, Alpha1-Microglobulin, and low molecular weight proteins) could be spontaneously filtered via the renal glomerular membrane and reabsorbed in the renal tubular cells. These indicated for tubular injury due to rise of biomarker levels excretion in urine.

The studying of many researchers have been shown that both of (alpha1-microglobulin and RBP4) significantly increased in diabetic individuals with normal albuminuria than control, and they correlated with HbA1c level, hence the assessment of these indicators for initial diagnosis of DN [58, 65]. The previous reporting of Petrica et al and Hong et al. described that high urinary alpha1- microglobulin values in normoalbuminuric patients, may be clarified by renal tubular damage that leads the incidence of microalbuminuria, which is high sensitivity and an early renal biomarker [65]. However, in certain patients with albuminuria, alpha1-microalbuminuria biomarkers may be absent. This is the reason the alpha1-microglobulin assessments are related to the estimation of various biomarkers like albumin in urine [57].

The number of biomarkers applied only to evaluate the acute renal damage such as (N-acetyl-β-D-glucosidase NAG, heart-type fatty acid-binding protein H-FABP, Neutrophil gelatinase-associated lipocalin NGAL, and kidney injury molecule-1 KIM-1) [58, 66]. Nowadays, the studying revealed that diabetic individuals with normoalbuminuria have significantly higher (NAG, NGAL, H-FABP, and KIM-1) levels than control individuals and elevated gradually as well with the stages of DN. Additionally, these all significantly associated with levels of urinary albumin, that may be considered early indicators for diagnosis of DN [58, 67].

In diabetic patients, the Urinary NGAL, a selective biomarker has critical effects in the assessment of kidney tubular impairment. its value usually elevated in the initial phases of renal disease [57, 68]. However, level of urinary NGAL raised in diabetic individuals with normal albuminuria, and its rate gradually elevated in microalbuminuria and macroalbuminuria patients.

KIM-1 values increased simultaneously, reflecting the early and progressive injuries [57, 60, 69]. On the other hand, recent studies reported that fatty acid-binding proteins act as potential biomarkers for DN, which are a group of specific protein convoluted

in lipid homeostasis. As well, in diabetic patients have been detected that (urinary liver fatty acid-binding protein L-FABP) level elevated even before the microalbuminuria started. Since DN is described by accumulation of triggered macrophages in renal tubules, it may be attributed to serum an adipocyte-fatty acid-binding protein (A-FABP) independently linked to the stages of nephropathy in type2 DM. According to the information published in (2014), the Diabetes Congress of the International Diabetes Federation in West Pacific Area indicated that level of A-FABP might also specify for an early declining in GFR in type 2 DM [49, 70]. In early glomerular damage, Nephrinuria is considering as a biomarker, which appears in normoalbuminuric patients, followed by microalbuminuria as a result of dysfunction of nephrin in podocytes in diabetic nephropathy [57, 71, 72]. The impairment of Podocyte in diabetic patients involves not just to nephrons but include many other components of podocyte, for instance, (Vascular Endothelial Growth Factor VEGF). Hence, in diabetic individuals with normoalbuminuric, nephrinuria is associated with removal of VEGF [72–74]. Nephrinuria in albuminuria diabetic patients is positively related to albuminuria and negatively associated with GFR, and seems to be as other diabetic nephropathy biomarker [57, 73, 75]. Furthermore, The most diagnostic biomarkers that used in DN are:

1.5.3.1. Serum cystatin C. Is steadily produced and released into the plasma by each nucleated cell in the organism. Its tiny size and has a positive charge that freely filtered at glomeruli then totally reabsorbed by renal tubules. As a result, Serum cystatin C act as biomarkers in early diagnosed of DKD [76]. Numerous studies considered the cystatin C protein as an indicator for glomerular filtration rate (GFR) [19, 56].

1.5.3.2. Neutrophil Gelatinase-Associated Lipocalin. The renal glomeruli filters NGAL from plasma then reabsorbed by endocytosis by the megalin system in the proximal renal tubule. Therefore, NGAL may be an essential biomarker for the early diagnosis of diabetic kidney disease [77].

1.5.3.3. Plasma KIM-1. Its transmembrane glycoprotein in the proximal renal tubules.

Serum levels of KIM-1 tend to increase in patients with tubular damage. The previous studies concluded that KIM-1 is strong predicator in end stage renal disease [78].

1.5.3.4. Fibroblast growth factors (FGF21, FGF23) and pigment epithelium-derived factor (PEDF). FGF & PEDF related to inflammatory processes and fibrosis. Thus contributes to pathogenic alterations in early DKS [79]. The expected effects of FGF23 on the risk of development of the DN were depending on the circulating TNF receptor (1).

1.5.3.5. (Retinol-binding protein4 RBP4, Alpha1-Microglobulin, and LMW proteins). Other biomarkers as alpha1-microglobulin and RBP4 could spontaneously filtered via the renal glomerular membrane and reabsorbed in the renal tubular cells [79].

In the therapy and risk management of DKD patients, it is important to indicate the biomarkers that can predict the response of patients to proposed treatments and assess the risk of complication [73].

1.6. Management and treatment of Diabetic Nephropathy (DN)

Common prevention methods can be used to avoid the DN if diagnosed and treated early; these methods include regulating of blood pressure and glucose level (Table 2). As well managed of dyslipidemia by improvement of lifestyle. Eating pattern, physical activity, and reduce of body weight considered suitable basic interference for diabetic patients. It also trend to smoke cessation, evolution of microalbuminuria to macroalbuminuria and increases renal prognosis that important for reducing the risk of cardiovascular disease [2, 80].

1.6.1. Pharmacological treatment

a- Glycemic control

Several Anti hyperglycemic agents control blood glucose level (Table 2).

Table 2. Common anti hyperglycemic agents [19, 81].

Class	Drug
Biguanide	Metformin
Sulfonylureas	Glyburideglimepiride,glipizide
Dipeptidyl peptidase-4 inhibitor	Sitagliptin, linagliptin, saxagliptin, vildagliptin
Thiazolidinedione	Rosiglitazone, pioglitazone
Glucagon-like peptide-1 analogues	Liraglutide, Exenatide
Insulin.	Human insulin, lispro, glargine, aspart, detemir, mixed preparations

b- Antihypertensive

The essential goal of therapy to the diabetic renal disease patients manages of hypertension and the decline of urinary albumin level [24, 82]. Antihypertensive agents are specifically used to treat DN, they are classified to Diuretics, angiotensin converting enzyme inhibitors (ACEI), Aldosterone antagonists, Mineralocorticoid Receptor blockers, Renin Inhibitors, Angiotensin Receptor Blockers [24], and Calcium channel blockers (CCB) [1]

c- Hyperlipidemia

In DN, the use of hypolipidemic drugs highly introducing, diabetes disorder as the same of coronary artery disease where they widely prescribed to take medication like (3-hydroxy-3-methyl-glutaryl- CoA reductase inhibitors). Unfortunately, limited studies directly investigated the effecting of hypolipidemic drugs on the protection of kidney functions. The results of the intervention studies of Diabetes Atherosclerosis, which evaluate 314 participants after consuming fenofibrate drug or placebo; the patients established on fenofibrate alone lower albuminuria than other [19, 83]. On the other hand, Abe et al. examined the influence of Rosuvastatin drugs on oxidative stress and renal function in diabetic nephropathy patients, the results concluded although there were no significantly difference in changing of GFR, the albuminuria level was significantly reduced in the group with statin drugs regardless of the cholesterol level and blood pressure [19, 84].

1.6.2. Diet and lifestyle interventions

Diabetic patients with DN and CKD must be managed with intensive dietary interventions, which include bodyweight reduction, improved physical activity, smoking cessation, healthy diet, and sodium limitation [4, 85]. a proper amount of fat is an appropriate diet prescribed to patients especially with reduced kidney function who have been restricted in calories of proteins and carbohydrates [8, 86]. The recommendation of earlier studies to reduce the total fat can be unhealthy practice. Hence, nutritionists advise limiting with saturated fatty acid intake and enhanced taking of omega-rich fatty acids and vegetable oils. Many clinical studies have been demonstrated that diet with low protein level have renal protective effects on DN, despite the protein restriction alone will not contribute to highly beneficial results for patients [8, 85, 87].

However, in diabetic patient with type2, smoking Cessation may be diminish 30% from the risk of evolution and development of disease [26].

1.6.3. The role of Vitamin D

An essential role of vitamin D in DN by preventing the transition of tubular epithelial cells from being epithelial to mesenchymal. In experimental results, the active form of vitamin D has also diminished oxidative stress due to restore the levels of Nrf2, which is essential for the protection of cells against oxidative damage. This was related to decreased activation of NF-κB and reduced albuminuria [1, 88].

1.6.4. New therapeutic strategies in DN

1.6.4.1. Endothelin (ET-1) receptors antagonist. Endothelin 1 (ET-1) is a potent vasoconstrictor factor with vasoactive, inflammatory, and profibrogenic activities. It induces kidney fibrosis in numerous ways, including accumulate of extracellular matrix components and proliferation of endothelial cell that contributes to cardiovascular disorders and DN. avocentan, (ET-1) receptors antagonist reduced albuminuria but this drug under trails due to it has side effects and enhanced the fluid overload [89].

1.6.4.2. Mineralocorticoid receptor antagonist. It has beneficial effects as Renoprotective properties beside ACEI and Angiotensin Receptor Blockers

1.6.4.3. Pentoxifylline (PTF). It is a methylxanthine-derived phosphodiesterase inhibitor, has an antiproteinuric effect in individuals with DN, which is assumed to be attributable to a decrease in proinflammatory cytokines [90].

1.6.4.4. Vitamin D receptor activators. Vitamin D receptor activation VDRA promotes anti-inflammatory, immunological, and nephroprotective effects. VDRA medication (paricalcitol or calcitriol) may provide some protection in DKD. Due to the previous finding that active vitamin D has a critical role in the reduction of proteinuria in diabetic nephropathy [91]

2. Discussion

Diabetic nephropathy has become the major reason of chronic renal disease, originating with alterations in albumin levels, including normal albuminuria, microalbuminuria, and macroalbuminuria, and eventually influencing to end-phase of renal disease (ESRD) [92]. For Prolonged period, the gold standard for assessing and monitoring renal functions has been happened by screening of proteinuria. Renal function can decline before the onset of proteinuria in around one-third of diabetic patients. However, the identification of proteinuria alone is insufficient to detect the existence and development of diabetic renal disease.

Thus, we would need to search for biomarkers that appear early, such as microalbuminuria [58]. This study emphasizes the screening of early biomarkers and physiological modifications in renal function in DN, which correlate with the pathology and pathogenesis of kidney disease. Recent studies by Motawi et al described that three new exciting biomarkers, namely {Neutrophil Gelatinase-Associated Lipocalin (NGAL), microRNA-130b (miR-130b), and beta-Trace Protein (beta TP)} presented in type2 diabetes status [13]. The studies of many researchers have shown that both (alpha1-microglobulin and RBP4) significantly increased in diabetic individuals with normal albuminuria than control [56, 63]. The previous reports of Petrica et al and Hong et al. described that high urinary alpha1- microglobulin values in normoalbuminuric patients, may be explained by renal tubular damage.

Furthermore, recent research has shown that diabetes may negatively affect biomarker performance in predicting the development of kidney disease, identifying appropriate biomarkers for diagnosis, therapeutic response, follow-up, and prognosis. However, the use of these biomarkers is limited by numerous variables such as the availability of test platforms, cost, inconsistency in testing methodologies and findings, and the lack of approval from national and international regulatory organizations [34].

Many studies that analyze and forecast disease progression do not include information regarding the participants' response to the tested drugs, nor do they identify patients with an increased risk of secondary or adverse outcomes from the therapeutic intervention study.

3. Conclusion

Currently, there is no other biomarker that can replace microalbuminuria in practice. Limited studies could not sustain the new biomarkers, and their required validation. At present, the concomitant evaluation of several biomarkers concerning microalbuminuria could constitute a method of diagnosis of initial phases of diabetic nephropathy. The major progress in the invention of novel biomarkers could lead to the introduction of "ideal" biomarkers for the future to detect the early diabetic nephropathy.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

Ethical approvals

This review was approved via the Ethics Committee in the Pharmacy College – University of Basra.

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