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Review Article

Diabetic Kidney Disease: Epidemiology, Risks, Manifestations, Diagnosis, and Management

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Abstract

Introduction: Diabetes is the most common cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in the world. Both type 1 and type 2 diabetic patients are commonly to have Chronic kidney disease (CKD), which defined as three months history of a glomerular filtration rate (GFR) reduction and/or an increased albumin excretion in the urine. The prevalence of diabetes in the United States has raised from 6 to 10 per cent over the last 20 years. While the percentage of diabetic patients CKD has maintained.

Aim of the Work: An overview of diabetic kidney disease (DKA), also known as diabetic nephropathy, will be presented in this paper.

Methodology: This paper is a nonsystematic review of medical literature regarding diabetic kidney disease. The literature search was conducted by using PubMed database and google scholar search engine.

Conclusion: Diabetic kidney disease and CKD are more common in women, African American, and Latino. Obesity is considered an essential risk factor for type 2 diabetes and coexists with type 1 diabetes. Persistently raised levels of albuminuria and/or persistent (eGFR) reduction are considered the most frequent clinical finding. Majority of patients' presentation are asymptomatic for that, regular and routine checkup is the method of detection. If non-diabetic kidney disease is suspected, a kidney biopsy should have conducted. Management of DKD include general measures such as controlling blood pressure, glycemic control, and lifestyle modification. Angiotensin inhibition is the drug of choice in cases with severe albuminuria.

Keywords: *Diabetic Kidney Disease; Diabetic Nephropathy; Diabetes Mellitus Chronic Complications*

Introduction

Diabetes is the most common cause of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) in the world. Most diabetic patients are diagnosed with clinical history and laboratory assessment without taking a biopsy of the kidney. Although this invasive procedure is the gold standard for the diagnosis of diabetic nephropathy, physicians avoid it as it does not affect the treatment plan.

Both type 1 and type 2 diabetic patients are commonly to have Chronic kidney disease (CKD), which defined as three months history of a glomerular filtration rate (GFR) reduction and/or an increased albumin excretion in the urine. GFR and albuminuria are the major indicators for classifying and staging CKD. Accordingly, diabetic patients need to have GFR and albuminuria screening at least one time per year.

An overview of diabetic kidney disease (DKA), also known as diabetic nephropathy, will be presented in this paper.

Methodology

This paper is a nonsystematic review of medical literature regarding diabetic kidney disease. The literature search was conducted by using PubMed database and google scholar search engine. The result were initially screened by title then by abstract. Only directly relevant papers were fully examined. The term used in search include diabetic kidney disease, diabetic nephropathy, and diabetes mellitus chronic complications.

Terminology and misconception

"Diabetic nephropathy" is a medical term, which was referred to as the presence of both albuminuria and retinopathy in type 1 diabetes patients [1]. Diabetic nephropathy was divided into two categories considering albuminuria as an early sign of classical diabetic glomerulopathy, which means thickening of the glomerular basement membrane and damaging of the endothelium. These two categories were "overt nephropathy" by "macroalbuminuria" and "incipient nephropathy" by "microalbuminuria", which reflect the severity of the disease. Nevertheless, recent studies have shown a wide range of diabetic kidney disease including tubulointerstitial disease and non-classical impairments.

"Diabetic kidney disease" refers to clinical findings of albuminuria, glomerular filtration rate (eGFR) reduction, or both in diabetes. Although, "diabetic nephropathy'" is the most common cause of diabetic kidney disease, there are wide variations related to patients' conditions. For example, five years of history of albuminuria or more with type 1 diabetic patient lead to diabetic kidney disease. However, in type 2 diabetes there are various causes related to the prevalence of diabetic kidney disease.

Historically, patients with normal or elevated glomerular filtration (GFR; hyperfiltration) rates thought to have diabetes type 1 [2]. Estimated GFR (eGFR) reduction below 60 mL/min/1.73 m^2 was thought to proceed by the development of moderate and severe albuminuria.

Recently, studies have revealed that decreased eGFR may lead to chronic kidney disease (CKD) with or without albuminuria [3]. Although albuminuria has a limited role in diagnosis, it is helpful as a prognosis factor [4].

Epidemiology

The prevalence of diabetes in the United States has raised from 6 to 10 per cent over the last 20 years. While the percentage of diabetic patients CKD has maintained (approximately 25 to 30 percent) [5].

In diabetic patients, the prevalence of persistent moderately to severely increased albuminuria (i.e. urinary albumin-to-creatinine ratio ≥ 30 mg/g) reduced from 21 per cent to 16 per cent between 2009 and 2014. On the other side, the prevalence of decreased estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2, elevated from 9 to 14 per cent.

Although diabetic kidney disease is a frequent cause of ESKD, the incidence of ESKD in diabetic patients with CKD is remarkably uncommon as the majority of diabetic patients with CKD die before applying renal replacement therapy [6].

The natural history and frequency of development of diabetic renal disease are uncertain if it is changeable according to the type of diabetes. Type 2 diabetic patients' onset mostly after the age of 40 and other associated factors such as age-related hypertension and kidney functions. Type 2 diabetes may be asymptomatic for years, which leads to a late diagnosis after a long duration of hyperglycemic exposure.

Recently, type 2 diabetes among youth have been common particularly in obesity pandemic areas [7]. Studies have shown renal complications and rapid deterioration are more common in youth onset type 2 diabetes than type 1 [8]. A longitudinal, cohort study of youth-onset type 1 and type 2 diabetes have demonstrated a greater frequency of raised albuminuria after eight years of diabetes diagnosis in type 2 diabetic patients compared with type 1 diabetes (20 versus 6 percent) [9].

Risk factors

Diabetic kidney disease is a multi-factors disease associated with changeable and non-changeable environmental risk factors which damage the renal tissue directly or even indirectly.

The prevalence of diabetic kidney disease is increasing with ongoing age due to the long duration of exposure to diabetes [10]. Therefore, the manifestation of progressive kidney disease appears. Diabetic ESKD incidence rates are 142, 274, 368 and 329 cases per 100,000 for diabetic patients < 45, 45 to 64, 65 to 74 and ≥75 years of age, respectively [11]. Diabetic kidney disease and CKD are more common in women [12]. However, men are at a higher risk for progress from late-stage CKD to ESKD [13]. The cause of that is still unclear but mostly related to gender and lifestyle factors. Historically, African American, Latino and populations showed higher rates of eGFR reduction and albuminuria compared with white Americans. However, nowadays frequency rates of ESKD among them are approximated at 409, 307 and 266 cases per 100,000 diabetics which have shown reduction rates [5]. Decreased eGFR (< 60 mL/min/1.72 m^2) and albuminuria are more frequent in population with lower education level. Poorer individuals are at high risk of affection due to an unhealthy environment.

Obesity is considered an essential risk factor for type 2 diabetes and coexists with type 1 diabetes. General obesity has a weak association with diabetic kidney disease progression compared with visceral one, which has a stronger link [14]. Tumour necrosis factor-alpha (TNF-alpha), interleukin 6 and leptin in obese people are highly produced. Consequently, transforming growth factor-beta (TGF-beta) is highly produced.

Recently, a meta-analysis of nine cohorts and more than 200,000 persons have shown a moderate link between diabetic kidney disease and smoking as reduced eGFR < 60 mL/min/1.73 m^2 or increased albuminuria [15]. Besides, smoking stimulates different pathogenic pathways which are associated with diabetic kidney diseases, such as inflammation and endothelial dysfunction.

Studies including both type 1 and type 2 diabetes have illustrated that improve hyperfiltration is associated with lower levels of HbA1c, which can be occurred even in the advanced stages of diabetic kidney disease. Blood pressure, particularly the systolic, is highly associated with an increase in the risk for (< 140 mmHg) [16]. Accordingly, blood pressure control is significant as hyperglycemia.

Several genome-studies have demonstrated genes and genes regions for different diabetic renal disease phenotypes in type 1 and type 2 diabetes [17]. Although a few studies showed that some individuals with diabetic kidney disease have a homogenous disease due to failure of genetic basis identification, this disease is a heterogeneous one [18].

Although patients with diabetic renal disease have a higher risk for AKI, acute kidney injury (AKI) is considered a significant risk factor for CKD. Accordingly, Diabetic kidney disease with glomerulopathy and tubulointerstitial fibrosis may be deteriorated by AKI.

Manifestation, evaluation, and diagnosis

Persistently raised levels of albuminuria and/or persistent (eGFR) reduction are considered the most frequent clinical finding. Majority of patients' presentation are asymptomatic for that, regular and routine checkup is the method of detection.

According to the American Diabetes Association (ADA) and the Kidney Disease Improving Global Outcomes (KDIGO) guidelines the diabetic patients should submit for serum creatinine-based eGFR and urine tests annually [19]. However, tests should be repeated from three to six months if have revealed atypical results.

Diagnosis of type 1 diabetes is usually earlier than type 2 as most probably of the patients are asymptomatic. As a result, regular testing for the complication is advised after five years for type 1 while at the time of diagnosis for type 2.

The albumin-to-creatinine ratio by urine sample is the most common method to determine the urinary excretion of albumin. Two of three urine samples collected over a three- to six-month period must demonstrate increased levels of albumin before the albuminuria is confirmed [19,20].

The urine sediment test for diabetic patients with kidney disease is considered a weak test. However, most patients with severe albuminuria showed microscopic hematuria. Also, those patients usually reveal neither red blood cells nor casts [21].

Microscopic hematuria alone is not sufficient to differentiate between diabetic and nondiabetic kidney disease, and that was illustrated by a meta-analysis of 35 studies and more than 4000 diabetic patients who went through urinalysis and kidney biopsy. As a result, the liability of microscopic hematuria for determining nondiabetic kidney disease was almost poor (42 and 72 percent, respectively) [22]. While detecting dysmorphic red blood cells in the urine is extremely specific (94 percent) for nondiabetic renal disease. Accordingly, individuals with dysmorphic hematuria are highly associated with nondiabetic kidney disease alone or accompanied with diabetic kidney disease.

Diabetic kidney disease is usually diagnosed clinically and can be done based on a long duration of albuminuria and/or GFR reduction and a long duration of diabetes or established diabetic retinopathy. Albuminuria means a urinary excretion of albumin ≥ 30 mg/day or ≥ 30 mg/g. GFR reduction means an eGFR < 60 mL/min/1.73 m^2. Ongoing of these abnormalities for three months and more should be established as maybe relate to other diseases. Albuminuria is not essential to the diagnosis of diabetic renal disease. Major of diabetic patients only showed eGFR reduction and < 30 mg/g of albuminuria along with histopathologic lesions related to diabetic kidney disease.

Patients with type 2 diabetes are at higher risk of retinopathy and diabetic kidney disease than type one because it is usually asymptomatic so the patients have long exposure to hyperglycemia [23]. Accordingly, patients with type 2 diabetes mostly have kidney disorders at the time of diagnosis. Patients with kidney disease are likely to demonstrate the features of proliferative diabetic retinopathy which consistent with pathologic findings of diabetic kidney disease. As a result, patients with retinopathy mostly have diabetic kidney disease even with short exposure to hyperglycemia.

Presumptive diagnosis of diabetic kidney disease should be avoided if any of the following relate: High levels of albuminuria (≥ 300 mg/day or mg/g) within five years of onset of type 1 diabetes, or high levels of albuminuria for many years before the diagnosis of type 2 diabetes and presence of white blood cells, dysmorphic red blood cells or casts in the urine sediment. Also, diagnosis with another systemic disease that is usually accompanied by kidney disease (e.g. systemic lupus erythematosus).

The cause of chronic kidney disease (CKD) is mostly related to a diabetic kidney disease based on a long history of diabetes (in the case of type 1 diabetes for five years), especially if retinopathy is established.[20] The absence of retinopathy and the presence of severe (especially proliferative) retinopathy are essential predictors for nondiabetic and diabetic kidney diagnosis, respectively [24].

The long duration of glycemic and blood pressure is considered as a predisposing factor for diabetic kidney disease [25]. The pattern of albuminuria and eGFR is essential to consider in the diagnosis of diabetic kidney disease as a typical or atypical pattern.

In diabetic kidney disease, the sudden elevation of albuminuria levels is rare and sudden eGFR reduction is related to diabetic renal disease at 5 mL/min/1.73 m^2 per year. However, more rapid disturbances in the eGFR mostly related to other causes of kidney disease, especially when associated with dysmorphic hematuria.

The limitation sensitivity of albuminuria and eGFR reduction makes them have a poor role in the early diagnosis of diabetic renal disease. Accordingly, some circulating and urinary mediators are being developed as diagnosis and prognosis tools, but these are not used clinically yet.

The role of biopsy

If non-diabetic kidney disease is suspected, a kidney biopsy should have conducted. Although the main purpose of a kidney biopsy is the diagnosis, it also has prognosis evidence. The interstitial fibrosis and glomerular disease class findings including end-stage kidney disease (ESKD) [26]. Diabetic patients with acute tubular necrosis are frequent but may be reversible or irreversible [24].

Health care practitioners are usually avoiding kidney biopsy performance in diabetic patients. However, many patients have non-diabetic kidney disease and do not diagnose [24]. For example, one study has shown that health centers with "limited" kidney biopsy performance policy for nondiabetic cause suspension according to the clinical manifestations and centers that had an "unlimited" policy of a kidney biopsy performance in case of severe albuminuria, eGFR reduction, or hematuria [27]. The results revealed that biopsies for particular patients who have been suspected of an alternate diagnosis, 29 per cent had diabetic renal disease alone without another disease. However, when biopsies performance was unlimited and conducted for patients with s diabetic kidney disease suspicion, 33 per cent showed the other disease which may have been passed over without the right diagnosis.

Management

There are some particularly important general considerations related to diabetic patients with kidney disease such as controlling blood pressure, glycemic control, and lifestyle modification. Blood pressure lowering is highly recommended for diabetic patients with DKD because it is very effective in the reduction of morbidity and mortality rates, especially in chronic kidney disease (CKD) patients.

The primary antihypertensive therapy in patients with DKD includes only one drug either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). However, the combination of them must be avoided. Combination antihypertensive therapy will be required for most individuals with DKD who need combination therapy of antihypertension. In some cases, an ACE inhibitor or ARB plus a dihydropyridine calcium channel blocker is more favoured [28]. However, cases with severe albuminuria are more accepted to use a nondihydropyridine calcium channel blocker or diuretic, rather than a dihydropyridine calcium channel blocker.

Insistent blood glucose control has an important role to prevent the development of DKD in type 1 diabetic patients [29]. Accordingly, the target of glycemic control in type 1 diabetes and DKD is preferably glycated haemoglobin (A1C) of 7 per cent or less, which reduce the microvascular complications. The target of A1C is similar to the target of type 2 diabetic patients although fewer studies are supportive than for type 1 diabetes. According to the degree of kidney function reduction, particular glucose-lowering medications should be avoided or used at a lower dose in patients with DKD [30].

Life style modification is an essential strategy in diabetic patients with or without kidney disease. For example, exercise regularly, lose weight and stop smoking. Most diabetic patients with DKD should maintain the lipids at lower levels by using statin therapy because they

have a great risk of cardiovascular. Atorvastatin or fluvastatin are often preferred in diabetic patients with reduced kidney functions as their elimination do not affect the GFR. However, sESKD patients are not advised to use statins as they do not demonstrate any benefits of reducing the risk of cardiovascular complications.

Drug management

Angiotensin inhibition is the drug of choice in cases with severe albuminuria. Most diabetic patients with severely increased albuminuria, which means albumin excretion ≥ 300 mg/day, are treated with an ACE inhibitor or ARB. However, Combination therapy should be avoided as it deteriorates renal functions.

Also, these drugs have not shown benefits over calcium channel blockers or diuretics compared to those without albuminuria. Inhibition of the renin-angiotensin system (RAS) has been the main drug to manage the DKD but now has shown a limited role. In type 2 diabetes, the different outcomes of both ACE inhibitors and ARBs have not established. Accordingly, any one of them can be prescribed for the DKD patient [31].

Treatment with sodium-glucose co-transporter 2 (SGLT2) inhibitors is highly recommended in type 2 diabetic patients with DKD, along with ARS or ARBs inhibitors. Starting SGLT2 inhibitors should be restricted in patients with an eGFR < 25 to 30 mL/min/1.73 m^2. Although SGLT2 inhibitors may be safe in a patient with reduced eGFR below 25 mL/min/1.73 m^2 [32]. These drugs should be used with attention especially in patients with a history of lower extremity amputation or at risk of amputation. If canagliflozin is used, the approach dose is 100 mg once daily. Initially doses of other SGLT2 inhibitors (e.g. 10 mg once daily of empagliflozin or 10 mg once daily of dapagliflozin) are the approach of DKD treatment in diabetic type 2 patients.

SGLT2 inhibitors have an important role in preventing advanced stages of kidney impairments, including ESKD [33]. Moreover, two other therapies have been shown outcomes improvement in diabetic patients with type 2 with DKD: Glucagon-like peptide 1 (GLP-1) receptor agonists and Nonsteroidal selective mineralocorticoid receptor antagonists (MRAs).

Although the role of GLP-1 receptor agonists has not been established It is highly recommended in type 2 diabetic patients with DKD and commenced on glucose-lowering therapy along with SGLT2 inhibitor and do not achieve the ideal glycemic control [34]. Also, these drugs have shown a strong effect to improve cardiovascular and kidney outcomes with glucose-lowering therapy.

Nonsteroidal selective mineralocorticoid receptor antagonists (MRAs), such as Finerenone, has an important role in delay the deterioration of kidney function and cardiovascular events in type 2 diabetic patients with DKD. However, it does not affect blood pressure and slightly raised levels of serum potassium.

SGLT2 inhibitors mechanism defined as blocking reabsorption of glucose in the proximal tubule, which reduces the renal glucose threshold and substantial glycosuria is established. Also, SGLT2 inhibitors have other effects on the kidney by blocking the co-transporter and reducing sodium reabsorption, which is usually revealed high levels in type 2 diabetic patients because of an excess load of tubular glucose. Consequently, intravascular volume and blood pressure are reduced but the transportation of sodium to the macula densa is increased, which balances tubuloglomerular feedback and lowers the intraglomerular pressure by narrowing the dilated afferent arteriole. This leads to reduce the glomerular hyperfiltration rate and therapy slow the advancement of kidney disease.

Two large trials have illustrated the benefits of SGLT2 inhibitors on patients with DKD, who are already receiving ACE inhibitors (or ARBs) to reduce the deterioration of kidney disease [33], along with the prevalence of cardiovascular complications [33].

The first trial was the Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE). It showed that canagliflozin effect on reducing advanced kidney disease is similar among those with borderline eGFR < 30 mL/min/1.73 m^2

away from cardiovascular system deteriorations. The second trial was the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) trial. According to this trial, the dapagliflozin has shown similar useful effects in both patients with DKD and patients with other types of kidney disease, which is supporting the principle that considering the advantages away from glycemic control. Accordingly, no differences were detected between the groups of treatment with no major side effects.

The mineralocorticoid receptor activation is linked with cardiovascular and kidney disease, by inducing inflammatory and fibrotic cascades. Steroidal MRAs, like spironolactone, decreases albuminuria in DKD patients, but mostly lead to hyperkalemia in patients with eGFR reduction, especially when ACE inhibitors or ARBs are taken. Also, the nonsteroidal MRA finerenone reduces albuminuria and has little effect on the serum potassium [35].

Conclusion

Diabetic kidney disease is a multi-factors disease associated with changeable and non-changeable environmental risk factors which damage the renal tissue directly or even indirectly. The prevalence of diabetic kidney disease is increasing with ongoing age due to the long duration of exposure to diabetes. Diabetic kidney disease and CKD are more common in women, African American, and Latino. Obesity is considered an essential risk factor for type 2 diabetes and coexists with type 1 diabetes. Persistently raised levels of albuminuria and/or persistent (eGFR) reduction are considered the most frequent clinical finding. Majority of patients' presentation are asymptomatic for that, regular and routine checkup is the method of detection. If non-diabetic kidney disease is suspected, a kidney biopsy should have conducted. Management of DKD include general measures such as controlling blood pressure, glycemic control, and lifestyle modification. Angiotensin inhibition is the drug of choice in cases with severe albuminuria.

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