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EPIDEMIOLOGY OF DIABETIC KIDNEY DISEASE, RISKS, DIAGNOSIS, AND MANAGEMENT.

Magbol Yahia Yahia Arishi[1*], Mishaan Mohamed Ahmed Aljhani[2], Mohammed Abdu Ammash Khobrany[3], Hazib Hassan Darraj[4], Naif Mohammed Ahmed Al Johani[5], Waleed Yahia Arishi[6], Mohammed Ali A Mojamammi[7], Ahmed Mohammed Ahmed Shtefi[8], Mohammed Mossa Rajeh Darraj[9], Naif Mohammed Jaber Kalufah[10], Mohammed Ali Majari[11], Fatimah Mohammed Naseeb[12], Othman Ahmed Shajiri[13], Ahmed Mohammed Qaba Ahmed[14]

[1*,4,5,6,7,8,9,10,11]Abu Arish Hospital – Jazan - Saudi Arabia
[2]Irada Mental Health Hospital - Jazan - Saudi Arabia
[3]Department of Death Services - Saudi Arabia
[12,13,14] Central Sector Administration - Ministry of Health - Jazan - Saudi Arabia

***Corresponding author:** Magbol Yahia Yahia Arishi
*Abu Arish Hospital – Jazan

Abstract

Introduction: Diabetes is widely recognized as the primary etiology behind the development of chronic kidney disease (CKD) and end-stage kidney disease (ESKD) worldwide. Both type 1 and type 2 diabetic individuals commonly manifest CKD, which is characterized by a history of reduced glomerular filtration rate (GFR) and increased albumin excretion in the urine lasting for a minimum of three months. The prevalence of diabetes in the United States has experienced a notable increase from 6 to 10 percent within the past two decades, while the proportion of diabetic patients with concomitant CKD has remained constant. Diabetic nephropathy and chronic kidney disease (CKD) exhibit a higher prevalence among female individuals, African Americans, and individuals of Latino descent. The presence of obesity is acknowledged as a pivotal risk factor for type 2 diabetes and frequently coexists with type 1 diabetes. The most prevalent clinical manifestation is the persistent elevation of albuminuria levels and sustained reduced estimated glomerular filtration rate (eGFR). Most patients with this condition remain asymptomatic, thus necessitating regular and routine checkups for detection. In cases where non-diabetic kidney disease is suspected, a kidney biopsy should be performed. Management of diabetic kidney disease encompasses general approaches involving blood pressure regulation, glycemic control, and lifestyle modifications. In instances of severe albuminuria, angiotensin inhibition represents the preferred pharmacological intervention. This paper will comprehensively examine diabetic kidney disease (DKA), or diabetic nephropathy.

Keywords: Diabetic kidney disease; diabetic nephropathy; diabetes mellitus chronic complications.

Introduction

Diabetes is the predominant etiology of chronic kidney disease (CKD) as well as end-stage kidney disease (ESKD) on a global scale. The diagnosis of diabetic patients primarily relies on clinical history and laboratory evaluation, obviating the need for a kidney biopsy. While this invasive

procedure is conventionally regarded as the diagnostic gold standard for diabetic nephropathy, physicians refrain from utilizing it as it offers no impact on the treatment regimen.

Both type 1 and type 2 diabetic patients commonly exhibit symptoms of chronic kidney disease (CKD), which is characterized by a three-month history of diminished glomerular filtration rate (GFR) and elevated albumin excretion in the urine. GFR and albuminuria serve as the primary indicators for the classification and staging of CKD. Consequently, diabetic patients must undergo GFR and albuminuria screening at least once annually. This paper will provide an overview of diabetic kidney disease (DKA), also called diabetic nephropathy.

Terminology and misconception

The medical condition known as "diabetic nephropathy" is characterized by the simultaneous occurrence of albuminuria and retinopathy in individuals with type 1 diabetes [1]. Diabetic nephropathy has been classified into two distinct categories based on the presence of albuminuria as an early indication of classical diabetic glomerulopathy. This condition is characterized by the thickening of the glomerular basement membrane and damage to the endothelium. The two identified categories are referred to as "overt nephropathy" when accompanied by "macroalbuminuria" and "incipient nephropathy" when accompanied by "microalbuminuria." These classifications serve as indicators of the severity of the disease. However, recent research has revealed a broader spectrum of diabetic kidney disease, encompassing tubulointerstitial disease and non-classical impairments.

"Diabetic nephropathy" refers to the clinical manifestations of albuminuria, a decrease in the glomerular filtration rate (eGFR), or both in individuals with diabetes. However, considerable variations exist in the etiology of diabetic kidney disease based on patients' specific conditions. For instance, the presence of albuminuria for five years or longer in patients with type 1 diabetes is indicative of the development of diabetic kidney disease. Conversely, in individuals with type 2 diabetes, the causes of diabetic kidney disease are multifactorial and influenced by a range of factors. Historically, it has been believed that patients with normal or increased rates of glomerular filtration (known as hyperfiltration) are likely to have type 1 diabetes.[2] The decline in estimated glomerular filtration rate (eGFR) to levels less than 60 mL/min/1.73 m2 was believed to occur due to the emergence of albuminuria of moderate and severe degrees.

In recent times, investigations have exposed that a decline in eGFR can potentially result in the development of chronic kidney disease (CKD), regardless of the presence or absence of albuminuria [3]. While the diagnostic value of albuminuria is restricted, it does offer valuable insights as a prognostic factor [4].

Epidemiology

The occurrence of diabetes in the United States has experienced an increase from 6 to 10 percent over the past two decades. Concurrently, the proportion of individuals with both diabetes and chronic kidney disease (CKD) has remained relatively stable, fluctuating between approximately 25 and 30 percent [5].

Within the subset of diabetic patients, the frequency of persistently elevated levels of albuminuria, specifically a urinary albumin-to-creatinine ratio of 30 mg/g or higher, decreased from 21 percent to 16 percent between the years 2009 and 2014. Conversely, the prevalence of diminished estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m2 rose from 9 to 14 percent.

Although it is a well-known fact that diabetic kidney disease is a prevalent and significant contributor to end-stage kidney disease (ESKD), it is quite intriguing to note that the occurrence of ESKD in individuals with CKD who also have diabetes is surprisingly infrequent, mainly due to the unfortunate reality that a significant portion of diabetic patients with CKD tragically succumb to their condition before they have the opportunity to undergo renal replacement therapy [6].

The uncertain nature and occurrence rate of the progression of diabetic kidney disease remains unclear about the specific type of diabetes. The onset of this disease is typically observed in individuals over the age of 40 who have type 2 diabetes, and it is often accompanied by other influential factors such as age-related hypertension and kidney functionality. Additionally, type 2 diabetes can usually be

asymptomatic for an extended period, resulting in a delayed diagnosis following a prolonged duration of exposure to elevated blood sugar levels.

In recent times, there has been an increase in the prevalence of type 2 diabetes among young individuals, particularly in areas affected by the obesity pandemic [7]. Various research studies have indicated that renal complications and rapid deterioration are more prevalent in individuals with youth-onset type 2 diabetes compared to those with type 1 diabetes [8]. Furthermore, a longitudinal cohort study focusing on youth-onset type 1 and type 2 diabetes has revealed a higher incidence of raised albuminuria among type 2 diabetic patients as compared to those with type 1 diabetes eight years after the initial diagnosis (20 percent versus 6 percent) [9].

Risk factors

Diabetic nephropathy is a complex condition that is linked to modifiable and non-modifiable environmental risk factors, which can result in direct or indirect harm to the renal tissue.

The occurrence of diabetic kidney disease is on the rise as individuals continue to age, primarily as a result of prolonged exposure to diabetes. Consequently, the development of advancing kidney disease becomes evident [10]. Incidence rates of diabetic end-stage kidney disease (ESKD) are recorded at 142, 274, 368, and 329 cases per 100,000 for patients with diabetes aged below 45, between 45 and 64, 65 and 74, and 75 years and older, respectively [11]. Diabetic kidney disease and CKD are more common in women. However, men are at a higher risk for progress from late-stage CKD to ESKD [12],[13] The precise reason for this phenomenon remains uncertain, although it is primarily linked to gender and lifestyle variables. In the past, African American, Latino, and certain populations displayed elevated instances of eGFR decline and albuminuria in comparison to their white American counterparts. Nevertheless, presently, the occurrence rates of ESKD in these groups are estimated to be around 409, 307, and 266 cases per 100,000 individuals with diabetes, reflecting a decline in prevalence [5]. Individuals with a lower level of education exhibit a higher prevalence of decreased eGFR (<60mL/min/1.72 m2) and albuminuria. Those of lower socioeconomic status are more susceptible to adverse health outcomes as a result of living in an unfavorable environment.

Obesity is regarded as a critical determinant for the development of type 2 diabetes and is also observed alongside type 1 diabetes. The relationship between general obesity and the progression of diabetic kidney disease is relatively weak in comparison to visceral obesity, which exhibits a stronger correlation. Tumour necrosis factor-alpha (TNF-alpha), interleukin 6, and leptin are significantly elevated in obese individuals. Consequently, there is a heightened production of transforming growth factor-beta (TGF-beta) [14]

A recent meta-analysis performed on nine cohorts involving over 200,000 individuals has revealed a discernible correlation between smoking and diabetic kidney disease, as indicated by a decrease in estimated glomerular filtration rate (eGFR) to a level below 60 mL/min/1.73 m2 or an increase in albuminuria. Furthermore, smoking has been found to activate distinct pathogenic pathways that are closely linked to the development of diabetic kidney diseases, such as inflammation and endothelial dysfunction [15].

Studies that have examined both type 1 and type 2 diabetes have demonstrated that enhanced hyperfiltration is linked to decreased levels of HbA1c. This phenomenon can manifest even in the later stages of diabetic kidney disease. Blood pressure, specifically the systolic pressure, is strongly correlated with an elevated risk for values below 140 mmHg. Consequently, managing blood pressure is of great importance in the context of hyperglycemia [16].

Several studies on the genome have provided evidence of specific genes and gene regions associated with various phenotypes of diabetic renal disease in both type 1 and type 2 diabetes. While a limited number of studies have indicated that certain individuals with diabetic kidney disease exhibit a uniform disease pattern resulting from the inability to identify genetic causes, it is important to note that this condition is predominantly characterized by its heterogeneity [17,18]

Although individuals suffering from diabetic renal disease exhibit an elevated susceptibility to AKI, it is noteworthy that acute kidney injury (AKI) is regarded as a substantial risk factor for CKD.

Consequently, AKI may contribute to the further deterioration of Diabetic kidney disease characterized by glomerulopathy and tubulointerstitial fibrosis.

Manifestation, evaluation, and diagnosis

Persistently elevated levels of albuminuria and persistent reduction in estimated glomerular filtration rate (eGFR) are widely recognized as the most common clinical finding. Most patients exhibit no symptoms, thus necessitating regular and routine checkups for detection.

According to the guidelines provided by the American Diabetes Association (ADA) and the Kidney Disease Improving Global Outcomes (KDIGO), individuals with diabetes should undergo annual serum creatinine-based eGFR and urine tests. However, if these tests yield unusual results, they should be repeated within three to six months [19].

The diagnosis of type 1 diabetes typically occurs earlier than type 2 due to the likelihood of patients being asymptomatic. Consequently, conducting regular testing for complications five years after diagnosis for type 1 and at the time of diagnosis for type 2 is recommended.

Determining the urinary excretion of albumin is commonly done through the albumin-to-creatinine ratio in urine samples. To confirm the presence of albuminuria, two out of three urine samples collected within three to six months must exhibit elevated albumin levels [19,20].

The urine sediment test is regarded as an inadequate diagnostic tool for diabetic individuals suffering from kidney disease. Nevertheless, many patients exhibiting high levels of albuminuria tend to display microscopic hematuria. Furthermore, these patients typically do not show the presence of red blood cells or casts [21].

A meta-analysis of 35 studies and over 4000 diabetic patients who underwent urinalysis and kidney biopsy demonstrated that microscopic hematuria alone is insufficient to differentiate between diabetic and nondiabetic kidney disease. The analysis revealed that the ability of microscopic hematuria to determine nondiabetic kidney disease was relatively poor, with a detection rate of only 42 to 72 percent. On the other hand, the presence of dysmorphic red blood cells in the urine was found to be highly specific (94 percent) for identifying nondiabetic renal disease. Therefore, individuals with dysmorphic hematuria are strongly associated with either nondiabetic kidney disease alone or in combination with diabetic kidney disease. [22]

Diabetic nephropathy is typically diagnosed through clinical evaluation, emphasizing the duration of albuminuria and glomerular filtration rate (GFR) reduction, in addition to the duration of diabetes or established diabetic retinopathy. Albuminuria refers to the urinary excretion of albumin at a level equal to or exceeding 30 mg/day or 30 mg/g. GFR reduction is defined as an estimated GFR below 60 mL/min/1.73 m2. These abnormalities should persist for at least three months to establish a potential association with other diseases. It should be noted that the presence of albuminuria is not a necessary factor in diagnosing diabetic nephropathy. The majority of diabetic patients primarily exhibit a reduction in eGFR and albuminuria levels below 30 mg/g, accompanied by histopathologic lesions indicative of diabetic kidney disease.

In comparison to individuals with type 1 diabetes, patients with type 2 diabetes face a higher risk of developing retinopathy and diabetic nephropathy due to the typically asymptomatic nature of the condition, resulting in prolonged exposure to hyperglycemia. Consequently, patients with type 2 diabetes frequently present with kidney disorders at the time of diagnosis. Those affected by kidney disease are more likely to exhibit the characteristics of proliferative diabetic retinopathy, which aligns with the pathological findings associated with diabetic nephropathy. Consequently, individuals with retinopathy often also have diabetic kidney disease, even with a relatively brief exposure to hyperglycemia [23].

Presumptive avoidance of diagnosing diabetic kidney disease should be exercised when any of the subsequent conditions are met: elevated levels of albuminuria (≥300 mg/day or mg/g) within five years from the commencement of type 1 diabetes or elevated levels of albuminuria persisting for numerous years preceding the diagnosis of type 2 diabetes, in addition to the presence of white blood cells, dysmorphic red blood cells, or casts in the urine sediment. Moreover, a diagnosis of concurrent

systemic illness, such as systemic lupus erythematosus, typically accompanied by kidney disease, must also be considered.

The etiology of chronic kidney disease (CKD) is primarily associated with diabetic nephropathy that has developed over a prolonged period of diabetes (in the instance of type 1 diabetes for five years), particularly when retinopathy has been confirmed. The lack of retinopathy and the existence of severe (particularly proliferative) retinopathy are crucial indicators for diagnosing nondiabetic and diabetic kidney conditions, respectively [20,24].

The extended period of elevated blood sugar levels and high blood pressure is regarded as a contributing element to the development of kidney disease in individuals with diabetes. It is crucial to evaluate the occurrence of albuminuria and the estimated glomerular filtration rate (eGFR) to accurately diagnose diabetic kidney disease, as it may manifest as a typical or atypical pattern [25].

In diabetic kidney disease, abrupt increases in albuminuria levels are infrequent, and the sudden decrease in estimated glomerular filtration rate (eGFR) is associated with diabetic renal disease at a rate of 5 mL/min/1.73 m2 per year. However, more expedited disruptions in the eGFR are predominantly linked to alternative causes of kidney disease, particularly in cases accompanied by dysmorphic hematuria.

Because of their limited sensitivity, albuminuria and eGFR reduction are not effective in detecting diabetic renal disease early on. Consequently, certain circulating and urinary agents are currently being developed as tools for diagnosis and prognosis, but they have not yet been implemented in clinical practice.

The role of biopsy

A kidney biopsy is recommended if there is a suspicion of non-diabetic kidney disease. While the primary objective of a kidney biopsy is to establish a diagnosis, it also yields valuable prognostic evidence. Interstitial fibrosis and glomerular disease, including end-stage kidney disease (ESKD), can be identified through this procedure[26]. Among diabetic patients, acute tubular necrosis is a common occurrence, which may be reversible or irreversible depending on the specific case [24].

Healthcare providers typically refrain from conducting kidney biopsies in diabetic patients. Nonetheless, there are numerous cases where patients have kidney diseases unrelated to diabetes that go undiagnosed [24]. An investigation demonstrated that healthcare facilities that had a restrictive policy on kidney biopsy for nondiabetic causes halted the procedure based on clinical symptoms. In contrast, facilities with an unrestricted policy performed kidney biopsies in cases of severe albuminuria, reduced eGFR, or hematuria [27]. The findings revealed that 29 percent of biopsies performed on patients suspected of having an alternative diagnosis resulted in a sole diagnosis of diabetic renal disease without any other underlying condition. However, when biopsies were performed without limitations on patients with suspected diabetic kidney disease, 33 percent of cases revealed the presence of another disease that may have been missed without the appropriate diagnosis.

Management

There exist various critical general considerations concerning patients afflicted with both diabetes and kidney disease, such as the regulation of blood pressure, control of glycemic levels, and modification of lifestyle. It is highly recommended that individuals with diabetic kidney disease (DKD) prioritize the reduction of blood pressure due to its immense efficacy in diminishing rates of morbidity and mortality, particularly in individuals with chronic kidney disease (CKD).

The primary course of antihypertensive treatment for patients coping with DKD entails the utilization of solely one medication, either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB). It is crucial, however, to avoid the combination of both medications. The majority of individuals with DKD requiring combination therapy for hypertension will necessitate a combination of antihypertensive treatments. In certain instances, employing an ACE inhibitor or ARB in conjunction with a dihydropyridine calcium channel blocker is more favorable. Nonetheless, cases exhibiting severe albuminuria are more inclined to use a nondihydropyridine calcium channel blocker or diuretic instead of a dihydropyridine calcium channel blocker [28].

The prevention of diabetic kidney disease (DKD) in patients with type 1 diabetes relies heavily on strict blood glucose control. In this regard, it is preferable to maintain glycated hemoglobin (A1C) levels at 7 percent or lower, as this helps reduce the occurrence of microvascular complications. The target A1C level for type 1 diabetes and DKD is similar to that for type 2 diabetes, although there is less supporting evidence for the former. Depending on the extent of kidney function decline, certain glucose-lowering medications should be avoided or administered at a lower dosage in patients with DKD [29,30].

Lifestyle modification constitutes a crucial approach for individuals with diabetes, regardless of whether they have kidney disease or not. This includes engaging in regular physical activity, shedding excess weight, and refraining from smoking. To mitigate the heightened risk of cardiovascular events, it is recommended that most diabetic patients with diabetic kidney disease (DKD) maintain low lipid levels through the utilization of statin therapy. Atorvastatin or fluvastatin are commonly favored options for diabetic patients with impaired kidney function, as their clearance does not impact the glomerular filtration rate (GFR). Conversely, individuals with stage end-stage kidney disease (sESKD) are not encouraged to utilize statins, as there is no evidence of their efficacy in reducing the incidence of cardiovascular complications.

Conclusions:

Diabetic kidney disease is a condition influenced by various modifiable and non-modifiable environmental risk factors, which result in direct or indirect harm to the renal tissue. The prevalence of this disease increases in individuals of advanced age due to prolonged exposure to diabetes. Diabetic kidney disease and CKD exhibit a higher occurrence among women, African Americans, and Latinos. Obesity is deemed a pivotal risk factor for type 2 diabetes and frequently coexists with type 1 diabetes. The most commonly observed clinical manifestation involves persistently elevated levels of albuminuria and a continuous reduction in estimated glomerular filtration rate (eGFR). A majority of patients with this condition are asymptomatic, necessitating regular and routine checkups for detection. In cases where non-diabetic kidney disease is suspected, a kidney biopsy should be performed.

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