Diabetic Kidney Disease Without Albuminuria: A New Entity in Diabetic Nephropathy

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Non-albuminuric diabetic kidney disease (NA-DKD) is characterized by progressive loss of kidney function with an annual loss of estimated glomerular filtration rate (eGFR) more than 3 mL/ min/ 1.73m^2 per year. NA-DKD is also associated with the late manifestation of diabetic kidney disease, characterized by reduced eGFR (< 60 mL/min/ 1.73m^2), in the absence of albuminuria (urine albumin-to-creatinine ratio [UACR] less than 30 mg/g. The typical glomerular changes seen in diabetic nephropathy are less frequently observed in normoalbuminuric patients, while they predominantly show mesangial expansion and tubulointerstitial and vascular changes. The prevalence of NA-DKD has been increasing during the past decade, with a wide range of prevalence in different studies. It seems that patients with NA-DKD are more likely to be female and have better metabolic profile including a lower Hb A1c, lower triglyceride, lower cholesterol, lower BMI and systolic blood pressure, and lower rate of retinopathy. Compared to patients with albuminuria, those with NA-DKD show a lower risk for progression to end-stage kidney disease (ESKD), or rapid decline in eGFR. They also have increased risks of death and hospitalization for heart failure compared with non-DKD diabetic patients, but a lower risk in comparison with albuminuric DKD, regardless of GFR. There is no effective treatment for this phenotype of the disease, but limited data support the use of SGLT2 inhibitors to slow chronic kidney disease progression along with appropriate metabolic risk factor control. More clinical research and pathologic studies are needed for a better understanding of the phenotype, prevention, and treatment methods of the disease.

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INTRODUCTION

Diabetes mellitus (DM) is a chronic disorder that necessitates regular medical care as well as continuous patient training and support in order to prevent its acute and chronic complications. The management of diabetes requires attending to a wide range of concerns in addition to glucose control.[1] Diabetic nephropathy (DN) is the most frequent form of chronic kidney dysfunction among Americans, and the number of affected patients is steadily increasing.[2] According to a meta-analysis, 30.6% of type 2 diabetes patients in Iran developed DN.[3] Diabetic nephropathy is typically identified by the presence of Kimmelstiel-Wilson lesions in the glomerulus in renal biopsy, as per conventional opinion. According to these traditional beliefs, the typical clinical course of DN is characterized by the appearance of microalbuminuria (urine albumin-

to-creatinine ratio [UACR] 30 to 300 mg/g) and its progression to macroalbuminuria (UACR > 300 mg/g), followed by renal dysfunction (defined as estimated glomerular filtration rate [eGFR] < 60 mL/min/ 1.73m^2), and finally end-stage kidney disease (ESKD).[4] In other words, the hallmark of diabetic nephropathy has long been thought to be persistent albuminuria, which is also thought to be the early sign of glomerular disorders.[2] New research suggests that a sizable proportion of individuals with type 1 or type 2 diabetes mellitus also have kidney impairment (eGFR < 60 mL/min/ 1.73/m^2) without albuminuria, raising doubts on this long-held assumption about a condition known as non-albuminuric diabetic kidney disease (NA-DKD).[5] This type of diabetic kidney impairment demonstrates that albuminuria and kidney function do not always match up in diabetic patients, highlighting the need for a greater awareness of kidney failure other than those associated with an increase in albuminuria.[6]

In this study, we focus on the epidemiology, pathology, renal prognosis, and mortality of non-albuminuric diabetic kidney disease versus albuminuric type, as well as potential mechanisms and disease perspectives.

SEARCH STRATEGY AND ARTICLE SELECTION

In this narrative study, to retrieve the relevant studies, a search was conducted on articles published between June 2001 and June 2023. The terms "diabetic nephropathy" AND "diabetes mellitus" AND "albuminuria" AND "non-albuminuric diabetic nephropathy" were used to search the databases of Web of Science, Google Scholar, and PubMed/Medline. The studies that focused on the pathology of kidney diseases, or those that provided data on the definition, etiology, diagnosis, risk factors, pathogenesis, and treatment of diabetic kidney disease were included in this study. According to the inclusion criteria, 47 studies were selected. Two authors independently assessed the titles and abstracts of the selected studies, including review and research articles. Our evaluation focused on whether these studies were related to the scope and issues raised. Eligible articles had to meet the following requirements: a) being a scholarly peer-reviewed paper b) observing the guidelines of Standards of Medical Care in Diabetes. Definitions and diagnostic criteria for diseases were based on the Standards of Medical Care in Diabetes published in 2012 and 2020.

A BRIEF ON ALBUMINURIC DIABETIC KIDNEY DISEASE

Patients with long-term diabetes proceed to glomerular hyperfiltration, accompanied by the appearance of albumin in urine (30 to 300 mg/d), known as microalbuminuria, followed by macroalbuminuria (UAE > 300 mg/d), which was once thought to be the starting point of a sequential process toward end-stage kidney disease (ESKD). As a result, it was assumed that after developing macroalbuminuria, a decline in kidney function with an estimated glomerular filtration rate (eGFR) less than 60 mL/min/ 1.73m^2 would occur.[6] Najafian *et al.* have stated that thickening of glomerular basement membranes (GBM), mild mesangial expansion, and arteriolar hyalinosis make up the earliest lesions in diabetic nephropathy. The mesangial matrix eventually increases as a result of mesangiolysis and intense mesangial repair. The so-called Kimmelstiel-Wilson nodules consist of mesangial expansion that may be nodular. Hyaline deposition in both afferent and efferent arterioles, and significant thickening of GBM seen by electron microscopy are characteristics of organized nephropathy.[7] Especially, glomerular nodular sclerosis is the main symptom of diabetic kidney disease, which is often seen in patients who have albuminuria, prolonged diabetes, and reduced kidney function.[8]

NON-ALBUMINURIC DIABETIC KIDNEY DISEASE

A growing body of evidence suggests that a large proportion of patients with type 1 or 2 diabetes without clear albuminuria have decreased kidney function,[9] and a significant percentage of these patients are diagnosed in the advanced stages of kidney failure (stages 3 to 5).[10] This type of disease, which is known as diabetic kidney disease without albuminuria or non-albuminuric diabetic kidney disease (NA-DKD), is characterized by a progressive loss of kidney function (with an annual loss of eGFR more than 3 mL/min/ 1.73m^2),[11] or a decrease in eGFR to less than 60 mL/min/ 1.73m^2, and an albumin-to-creatinine ratio (ACR) of less than 30 mg/g. Although it is not yet clear

whether this phenotype of diabetic kidney disease is due to the increasing age of diabetic patients or the increased use of kidney support treatments and better blood pressure control by using drugs that inhibit the renin-angiotensin system (RAS), the number of patients with NA-DKD has been increasing in recent years.[12]

PREVALENCE OF NA-DKD

Current reports show that the prevalence of NA-DKD is common in patients with type 2 diabetes.[9] A 15-year follow-up in the England Prospective Diabetes Study (UKPDS) between 1977 and 1991 showed that 14% of patients with type 2 diabetes had NA-DKD, while 38% of diabetic patients developed albuminuria.[13] In addition, the third national health and nutrition survey study in 2003 reported the prevalence of NA-DKD in patients with type 2 diabetes to be 14.29% (171 cases out of 1197 patients).[5] In a multicenter Italian study conducted in 2011, 37.5% of the patients with type 1 diabetes had varying degrees of chronic kidney disease (CKD) with 18.8% having eGFR < 60 mL/min/ 1.73m^2, and 56.6% of patients with eGFR < 60 mL/min/ 1.73m^2 were normoalbuminuric.[12]

In another study, Thomas *et al.* found that 23% of 3893 patients with diabetes had CKD, and half of them were normoalbuminuric. Although individuals with diabetes mellitus exhibited higher rates of both albuminuric and non-albuminuric CKD than the general population, comparing the prevalence of NA-DKD in the normal population and patients with diabetes mellitus revealed that NA-DKD was seen 30% more in the normal population than in patients with diabetes.[9]

In a large Swedish cohort of 94 446 patients with type 2 diabetes, 17% had CKD, and 62 % of these patients were normoalbuminuric; it was assumed that the use of RAS inhibitors eliminated microalbuminuria over the past decade, thereby increasing the prevalence of NA-DKD; however, this study showed 25% of these patients did not use RAS inhibitors, and the use of RAS inhibitors was not a risk factor for NA-DKD.[14]

In another study, the prevalence of NA-DKD among patients with type2 diabetes with eGFR < 60 mL/min/ 1.73m^2 was 51.8%, and after considering the use of the renin–angiotensin system (RAS) inhibitor, the prevalence decreased to 42.7%.[15]

In the study of An. *et al.*, which consisted of 562 patients with diabetes, 26.9% of the participants had eGFR < 60 mL/min/ 1.73m^2, out of which 29.1% were normoalbuminuric and after excluding the patients using renin-angiotensin system (RAS) inhibitors, the prevalence of normoalbuminuric renal insufficiency increased to 35.3%.[16] In interpreting the high prevalence of NA-DKD, the effects of recent treatments of diabetes should also be taken into account. For example, during the last two decades, the number of diabetic patients with hypertension and/or nephropathy, treated with renin-angiotensin system blocking agents, has dramatically increased.[17,18] As a result, it is likely that NA-DKD patients were mostly those patients who responded well to renin-angiotensin system blockers, and these drugs lead to a reduction in albuminuria through glomerular protection.[6] Therefore, it seems that the prevalence of NA-DKD is increasing during recent decade with a wide range of prevalence, reported in different studies.

RISK FACTORS OF NA-DKD

Studies show that multiple factors are associated with the development of NA-DKD. This new phenotype of diabetic kidney disease (DKD) is more prevalent in those aged 60 to 79. This association with older age raises the question of whether the decline in glomerular filtration rate is due to age-related vascular changes or if there are other causes involved.[19]

Renal aging occurs with increasing age, which may decrease the eGFR to less than 60 mL/min/ 1.73m^2, even if the effect of diabetes on kidney function is minimal and negligible in these individuals. Additionally, underlying conditions such as hypertension, dyslipidemia, obesity, and hyperuricemia are frequently present in older diabetic patients, and may all contribute to atherosclerosis-related kidney dysfunction.[20-23]

There is a constant sex difference in various studies, and almost all studies evaluating risk factors for NA-DKD show that female sex is an independent risk factor.[24,25] Penno *et al.* has showed that NA-DKD is more frequent in females, and nonsmokers, and have a shorter duration of diabetes.[26]

It seems that patients with NA-DKD have a better metabolic profile with lower Hb A1c,[27,28] lower triglyceride, lower cholesterol,[27] lower BMI, lower systolic blood pressure,[14,24] a lower rate

of retinopathy, and antihypertensive treatment, including angiotensin-converting enzyme inhibitors (ACE-Is)/angiotensin II receptor blockers (ARBs), than those with albuminuric renal impairment.[29] The use of RAAS inhibitors as a risk factor for NA-DKD has shown conflicting results. Although some studies have shown that use of RAAS inhibitors is a risk factor,[24] others have reported that treatment with RAS inhibitors was seen less in NA-DKD than albuminuric diabetic kidney disease.[27,28] Taken together, a more favorable cardiovascular risk factor profile was seen in normoalbuminuric DN.

GENETIC FACTORS

It is worth noting that all patients with diabetic kidney injuries do not progress to ESKD. Earlier studies have shown that nearly 30 to 40% of DM patients advance to ESKD,[13,24] implying that genetic polymorphisms may play a role in the onset and progression of DN and ESKD. Therefore, it is assumed that genetic susceptibility to DN plays an important role in these patients, even when they are exposed to the same environmental factors. Family clustering supports the significance of inherited factors in diabetic nephropathy and ESKD.[26] As a result, a series of genetic studies have been performed to distinguish the possible candidate genes which may aid in the investigation of the pathogenesis of DN in large cohorts of diabetic patients.[29] Numerous DN nominee gene loci have been identified through advances in genetic methods such as linkage and candidate gene studies and genome-wide association studies (GWAS),[30] but it is difficult to comprehend the true impact of genetic variations, due to the variation in study methods, study population, type of diabetes, and phenotypes.[25] It is worth nothing that data regarding genetic foci comparing non-albuminuric and albuminuric DKD is lacking.

PATHOLOGIC CHANGES IN NA-DKD

The precise mechanism of renal impairment in non albuminuric DN is not well determined. Several pathogenic mechanisms have been proposed to demonstrate the non-albuminuric nephropathy in type 2 diabetes mellitus (T2DM): a) the existence of a well-preserved tubule that leads to a reabsorption of albumin from the glomerular filtrate, thus resulting in a diminished albumin excretion,[27] b) an increase in intrarenal arteriosclerosis rather than the typical glomerulosclerosis changes, seen in albuminuric participants,[23] c) chronic kidney disease may develop over time as a result of recurrent episodes of acute kidney injury,[28] d) the dominance of macroangiopathic lesions over microangiopathic lesions is one of the most convincing evidence available.[31] Ekinci *et al.* reported that the typical glomerular changes seen in diabetic nephropathy (DN) are less frequently observed in normoalbuminuric patients than in those with micro- or macroalbuminuria with type 2 diabetes and renal insufficiency (eGFR, 60 mL/min/ 1.73m^2). They classified DN into three groups based on the pathological changes under a light microscope using the traditional Fioretto classification.[32] This classification included tubular, interstitial, and vascular lesions: C1, normal or near normal; C2, typical changes of diabetic nephropathy mostly affecting the glomerular tissue; and C3, unusual patterns of injury associated with predominant destruction of tubulo-interstitium or arteriolar hyalinosis with absent or only mild diabetic changes in glomeruli.[32] Ekinci *et al.* also showed that, unlike the patients with micro- or macroalbuminuria that had the typical glomerular changes (C2), those with low eGFR without albuminuria showed predominantly mesangial expansion and tubulointerstitial and vascular changes.[8] This points to the contribution of other risk factors such as age, hypertension, and vascular disease to the development of renal disease in these patients, as well as the potential impact of diabetes.[8] Garofolo *et al.* reported the new finding that the NA-DKD phenotype in type 2 diabetes displayed decreased total renal volume (TRVs) and parenchymal renal volume (PRVs) at comparable lowered eGFR levels with albuminuric DKD patients.[33] In light of this information, imaging may play a role in improving the ability to distinguish between different DKD phenotypes in clinical settings.

RENAL PROGNOSIS AND MORTALITY IN NA-DKD

According to earlier research, patients with NA-DKD have a lower prevalence of diabetic retinopathy than those who have albuminuric DKD. As a result, it is believed that microangiopathy may not be the primary cause of the disease, while a history of macrovascular diseases, such as cardiovascular

disease, may be a potential pathogenic factor for NA-DKD.[34] However, the role of this mechanism in the development of NA-DKD is subject to debate. Several recent studies have simultaneously shown that patients with diabetic kidney disease without albuminuria are at a lower risk of progression to decline in kidney function and death. A study from the Steno Diabetes Center measured eGFR in 935 patients with type 1 diabetes and 1,984 patients with T2DM up to 16 years after developing stage 3 CKD (eGFR < 60 mL/min/ 1.73m^2). This study showed that the rate of reduction of glomerular filtration rate in diabetic kidney disease without albuminuria is lower than in diabetic kidney disease with albuminuria.[35] A study by Vistisen *et al.* confirmed that patients with non-albuminuric diabetic kidney disease have a lower risk of progression to renal failure compared to those with albuminuria,[36] and about 20% of non-albuminuric diabetic kidney disease patients experience progression to advanced chronic failure about 10 years after the onset of the disease.[37] Patients who progressed to chronic renal failure, with or without the need for dialysis, had more severe interstitial fibrosis and tubular atrophy compared to patients who did not progress, a finding suggesting that tubular damage may play an important role in the development of chronic kidney disease.[36]

The research by Koye *et al.* found that, the absence of albuminuria is common and has a lower risk for progression to ESKD, CKD, or rapid decline in eGFR in individuals with diabetes and reduced eGFR compared with those with albuminuria. [38] On the other hand, Jin *et al.* found that patients with NA-DKD had increased risks of death, hospitalization for heart failure, and chronic kidney disease progression but not cardiovascular disease (CVD) risk compared with those without DKD, without considering baseline GFR. But comparing individuals with albuminuric kidney disease to those who did not have it showed that individuals with albuminuric CKD had higher risks of death, CVD, hospitalization for heart failure (HF), and CKD progression, even if their GFR was the same.[20] In the RIACE study, which was conducted by Penno *et al.*, it was shown that the NA-DKD phenotype is a strong predictor of all-cause mortality, especially in patients with eGFR less than 45 mL/min/ 1.73m^2. They showed that the mortality risk in this group was similar to that in patients with macroalbuminuria and preserved eGFR (eGFR > 60 mL/min/ 1.73m^2). These results indicate that kidney failure, even without albuminuria, has a significant impact on mortality.[22]

Numerous biomarkers have been employed in recent years to assess the prognosis and development of different diseases. Independent of the level of albuminuria, studies have shown that inflammatory markers such as TNF, Fas pathways, and markers of tubular damage such as kidney injury molecule-1 (KIM-1) and Neurophil Gelatinase Associated Lipocalin (NGAL) play a role in the development of CKD.[39,40] In this regard, we can point to a study showing that the level of biomarkers such as NGAL increases in the serum and urine of diabetic patients with or without albuminuria.[41] On the other hand, Elizabeth *et al.* showed that normal to high uric acid is one of the factors associated with the progression of chronic kidney disease in patients with NA-DKD.[42] Therefore, it seems that other biomarkers besides the level of albuminuria can cause progression and predict the prognosis of NA-DKD in patients with diabetes.[42] Chronic kidney disease (CKD) 273, a novel proteomic biomarker, reliably predicts the likelihood of incident micro- and macroalbuminuria as well as CKD in non-albuminuric diabetics.[43]

TREATMENT OF NA-DKD

Currently, there is no effective treatment for this phenotype of the disease. In general, reducing the excretion of albumin in the urine with proper blood glucose and lipid control as well as blood pressure control with renin angiotensin (RAS) inhibitors can prevent the progression of kidney disease, but the effectiveness of these measures in patients without albuminuria for blunting the progression of kidney dysfunction is still unclear. Additionally, there is a debate about the role of renin-angiotensin system inhibitors in these individuals for kidney protection.[44]

The DEMAND study discovered that patients with type 2 diabetes who were given angiotensin-converting enzyme (ACE) inhibitors (tandalopril or delopril) had the same drop in glomerular filtration rate as a control group. This was true whether the patients had albuminuria or not.[45] This finding could be explained by the fact that albuminuria

has been somewhat effectively reduced as a result of the use of these medications. However, despite the decrease in albuminuria, these medications may slow down but not stop the rate of loss of renal function. As a result, people with no substantial albuminuria have a decreasing eGFR over time and may advance to end-stage renal disease.[45]

Moreover, there is evidence that sodium-glucose receptor inhibitors (SGL2) may be effective in preventing the progression of kidney disease in patients with diabetes and kidney failure by preventing the decrease of the eGFR.[46] Finally, Cherney *et al.*, in a post hoc analysis from the VERTIS CV (eValuation of ERTugliflozin effIcacy and Safety CardioVascular outcomes) trial, showed that individuals with NA-DKD had the slowest rate of eGFR decline among the subgroups treated with ertugliflozin.[47]

CONCLUSION

Recently, a clinically and pathologically heterogeneous type of diabetic kidney disease called" non-albuminuric diabetic kidney disease (NA-DKD)" has been introduced. It is characterized by a progressive loss of kidney function in the absence of albuminuria. This phenotype of diabetic kidney disease shows that there is not always an association between the reduction of kidney function and the amount of albuminuria in diabetic patients. Therefore, patients with diabetes who have kidney dysfunction (GFR less than 60 mL/min /1.73m^2) and normal urinary albumin excretion (UACR less than 30 mg/g) are considered to have non-albuminuric diabetic kidney disease (NA-DKD) after ruling out other secondary kidney diseases, including hypertensive nephropathy, obstructive nephropathy, or glomerular diseases. The prevalence of NA-DKD has increased during the past decade. This group has a better cardiovascular outcome than the albuminuric group, which has high cardiovascular mortality and morbidity. Data regarding the best treatment for this subgroup is limited, and more clinical research and pathologic studies are needed for a better understanding of the phenotype, prevention, and treatment methods of the disease.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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