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Narrative Review

NON-PROTEINURIC DIABETIC KIDNEY DISEASE: CLINICAL MANIFESTATIONS, RENAL PROGNOSIS, AND MORTALITY - A NARRATIVE REVIEW.

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ABSTRACT

Background:

Diabetic nephropathy (DN) is usually diagnosed by proteinuria before renal function diminishes. Many people with type 1 and type 2 diabetes develop non-proteinuric diabetic kidney disease, which worsens kidney function without proteinuria. Non-proteinuric DKD is becoming more common, but data is scarce.

Objective:

The objective of this narrative review is to provide a comprehensive examination of non-proteinuric diabetic kidney disease. This review aims to outline the clinical and pathological characteristics of non-proteinuric DKD, investigate its implications for renal prognosis, and assess mortality rates among individuals affected by this specific condition. By synthesizing existing knowledge and research, this review seeks to enhance our understanding of non-proteinuric DKD.

Summary of Narrative Review:

Non-proteinuric DKD is a lesser-known form of diabetic nephropathy. It discusses the clinical and pathological aspects of this illness and its unique diagnosis and therapeutic issues. Non-proteinuric DKD renal prognosis and mortality rates are also examined in the review. This narrative review illuminates non-proteinuric DKD in diabetic nephropathy by providing a broad overview.

Future Research:

To improve early detection and treatment of non-proteinuric DKD, future research should focus on more accurate diagnostic markers and risk factors. Targeted therapeutics need to understand the processes and pathways that cause renal failure without proteinuria. Long-term outcomes and progression of non-proteinuric DKD must be examined in longitudinal studies to determine its natural history and best therapy.

Clinical Practice and Policy Development:

Clinical consequences of non-proteinuric DKD should be considered, especially in diabetics with unexplained renal function decreases. Clinical standards and treatment algorithms for this condition are needed to improve patient care. Policymakers should fund non-proteinuric DKD research and attempt to improve healthcare system detection and management. Public health policy should educate doctors and diabetics to promote early intervention and better outcomes.

Keywords: Non-proteinuric diabetic kidney disease, Diabetic nephropathy, Renal function, Clinical features, Pathological features, Mortality rates

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INTRODUCTION

Diabetic nephropathy represents not only the most widespread manifestation of chronic kidney disease (CKD) but also the foremost etiology of end-stage kidney disease, or ESKD, on a global scale [1]. In the past, proteinuria, often referred to as macroalbuminuria, was thought to be the sole risk element for ESKD and the definitive clinical sign of diabetic nephropathy [2]. The prevailing consensus suggests that individuals afflicted with diabetic kidney disease commonly manifest proteinuria as an antecedent to the subsequent worsening of kidney function. Nevertheless,

emerging evidence has cast doubt upon this widely accepted notion, as it has brought to light a considerable subset of individuals afflicted with either type 1 or type 2 diabetes who experience a deterioration in renal function without the presence of proteinuria. The present ailment is commonly denoted as non-proteinuric diabetic nephropathy [3,4]. The present manifestation of diabetic nephropathy highlights a detachment between kidney function and levels of albuminuria in individuals with diabetes, thereby emphasizing the imperative for a more comprehensive comprehension of renal function decline that extends beyond its correlation with heightened albuminuria. However, there is a paucity of research about non-proteinuric diabetic kidney disease (DKD).

This comprehensive review aims to explore the epidemiological, pathological, renal prognostic, and mortality aspects of non-proteinuric DKD, while also comparing and contrasting them with those of proteinuric DKD. Furthermore, this study delves into potential mechanisms and provides insights into non-proteinuric DKD.

The key question that guided this comprehensive review is to address the evolving understanding of diabetic kidney disease (DKD) by exploring the epidemiological, pathological, renal prognostic, and mortality aspects of non-proteinuric DKD. This review seeks to investigate the clinical and pathological characteristics of non-proteinuric DKD in individuals with both type 1 and type 2 diabetes, shedding light on the detachment between kidney function and levels of albuminuria. By comparing and contrasting non-proteinuric DKD with its proteinuric counterpart, the aim is to provide a more nuanced comprehension of renal function decline in diabetic patients. Additionally, the review delves into potential mechanisms underlying non-proteinuric DKD, offering valuable insights into this complex manifestation of diabetic nephropathy.

METHODOLOGY

The methodology for this narrative review involved an extensive literature search using electronic databases, including PubMed, Scopus, and Google Scholar. Relevant articles published between 2000 and 2023 were identified using a combination of keywords such as "diabetic nephropathy," "non-proteinuric DKD," "renal prognosis," "mortality," and "pathology." The inclusion criteria were studies that focused on non-proteinuric diabetic kidney disease and provided insights into its clinical, pathological, renal prognostic, and mortality aspects. Studies were excluded if they did not meet these criteria or if they were published before 2000. The selected articles were critically reviewed, and relevant information was extracted to compile a comprehensive overview of non-proteinuric DKD.

PROTEINURIC DIABETIC KIDNEY DISEASE

An overview of the natural history of diabetic proteinuric kidney disease

The understanding of the progression of proteinuric DKD has mainly been derived from research conducted on individuals with diabetes before the widespread adoption of modern multidisciplinary treatments. These treatments include strict blood pressure management, intensive blood sugar control, and kidney-protective [5]. Typically, individuals with long-standing diabetes initially experience glomerular hyperfiltration, which is an increase in their glomerular filtration rate. Subsequently, they may develop proteinuria, characterized by a high urine protein to creatinine ratio (PCR) exceeding 500 mg per gram creatinine, or macro-albuminuria, indicated by urine albumin to creatinine ratio (UACR) exceeding 300 mg per gram creatinine or mg per day. Later on, they might progress to microalbuminuria, which was once believed to mark the beginning of an irreversible process eventually leading to ESKD. Consequently, it was widely accepted that the development of proteinuria (macroalbuminuria) occurred before the decline in renal function, as represented by an eGFR (estimated glomerular filtration rate) of lower than 60 mL/min/1.73 m2 (see Fig. 1).

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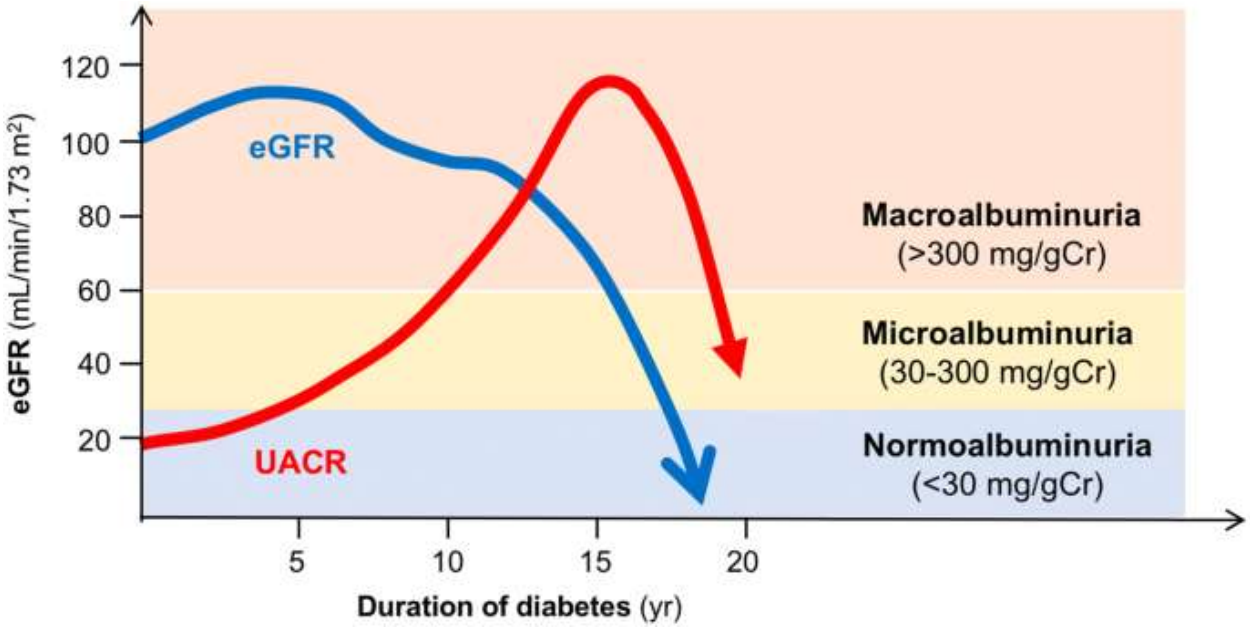

Figure 1: Diabetic kidney disease with proteinuria, its natural history. Proteinuria precedes renal failure in diabetic kidney disease. UACR and eGFR are urine albumin to creatinine ratio and eGFR, respectively.

Remarkably, the phrase "diabetic nephropathy" was first used to characterize some kidney abnormalities seen under a microscope, including glomerular basement membrane thickening, mesangial expansion, and nodular glomerular sclerosis [6]. It was previously utilized to medically characterize renal disease in people with long-standing diabetes who also had proteinuria, since those who had biopsy-confirmed diabetic nephropathy also presented with proteinuria. But in 1995, Dr. Krolewski coined the phrase "diabetic kidney disease" to refer to kidney damage in diabetic patients who had a clinical diagnosis [7]. The phrase "diabetic kidney disease" was subsequently adopted by the National Kidney Foundation in 2007 [8] in its guidelines and recommendations for the diagnosis and treatment of people with diabetes and chronic kidney disease (CKD). The guidelines proposed the replacement of "diabetic nephropathy" with "diabetic kidney disease" in order to facilitate better communication between patients, caregivers, and policymakers. They defined "diabetic kidney disease" as an assumed detection of kidney disease induced by diabetes. Since then, the term "diabetic kidney disease" has been used to refer to a wider range of illnesses than just the particular proteinuria or glomerular abnormalities linked to "diabetic nephropathy." Interestingly, the guidelines suggested saving the name "diabetic glomerulopathy" for kidney illness that was biopsy-verified. Furthermore, biopsy-confirmed diabetes-related kidney disease is still referred to as "diabetic nephropathy" [9].

Pathophysiology of diabetic kidney disease with proteinuria

Similar to the evolution of proteinuric DKD, the majority of research on the kidney issues commonly associated with diabetes has been conducted on individuals with the condition from the pre-ubiquity of modern treatment options [6]. Extensive problems such as glomerular basement membrane thickening and expansion of the mesangial area, as well as nodular changes called Kimmelstiel-Wilson nodules and hyalinosis (involving exudative/insudative lesions and fibrin caps) were observed in early studies on poorly controlled diabetes. Nodular glomerular sclerosis, in particular, has been identified as the characteristic of proteinuric DKD in individuals with chronic diabetes and deteriorating kidney function.

Unless there is a suspicion of a new kidney condition unrelated to diabetes or of another kidney illness unrelated to diabetes, kidney biopsies are rarely conducted on diabetic patients these days. In particular, biopsies are rarely performed on patients whose urine contains neither protein nor albumin. Nonetheless, a few earlier research investigations utilizing kidney biopsies showed that even individuals lacking protein in their urine may have a variety of microscopic renal problems. This implies that people with DKD vary not only in how the disease affects their kidney

tissues but also in how it manifests itself in terms of clinical symptoms [10].

NON-PROTEINURIC DIABETIC KIDNEY DISEASE

General concept of non-proteinuric diabetic kidney disease

As was previously mentioned, people with long-standing diabetes who have not undergone extensive therapy are most commonly affected by proteinuric diabetic kidney disease, which usually involves a progressive decline in kidney function. Recent data, however, indicates that a sizable portion of patients—whether they have T1 or T2 diabetes—may experience a decrease in renal function even though their urine contains normal levels of albumin, or they may experience a decrease in renal function without any visible indications of protein in the urine [11]. It's not totally apparent if the rise in this specific form of DKD is a result of an increase in senior diabetic individuals or a rise in the usage of comprehensive treatments that involve kidney-protecting drugs.

The term for this condition is non-proteinuric DKD, and it is currently gaining more attention in the medical community. It is identified by having a UACR of no more than 300 mg per gram creatinine and an eGFR below 60 mL/min/1.73 m^2. Recent reports indicate that non-proteinuric DKD affects approx. 20 percent of individuals with T1 diabetes and around 40 percent of those with T2 diabetes, indicating a wide range in how diabetic kidney disease presents clinically [12]. Despite this growing awareness, there is still a significant amount that remains unknown about the kidney prognosis, clinical features, pathological characteristics, and mortality associated with non-proteinuric DKD.

CHARACTERISTICS OF NON-PROTEINURIC DIABETIC KIDNEY DISEASE

According to cross-sectional studies, non-proteinuric DKD and specific clinical variables are related. These include taking renin-angiotensin system-affecting drugs, being a woman, having high blood pressure, smoking, having raised blood sugar, and not having diabetic retinopathy—a symptom of microangiopathy [13]. Nevertheless, there hasn't been a clear trend in the clinical characteristics of individuals with non-proteinuric diabetic kidney disease in these earlier reports.

These discrepancies might result from the fact that most diabetic patients do not have kidney biopsies performed, and diabetic kidney disease is usually diagnosed primarily on clinical findings. Therefore, some people who have been diagnosed with diabetic kidney disease may actually have renal issues that are unrelated to their diabetes. Additionally, a patient's clinical features could change depending on when they receive a diabetes kidney disease diagnosis. Age can affect the length of diabetes and kidney function, so for example, the clinical features of patients diagnosed at age 35 may differ from those of patients diagnosed at age 65.

NON-PROTEINURIC DIABETIC KIDNEY DISEASE PATHOLOGY

The physical characteristics of non-proteinuric DKD have been the focus of only a number of researches, and their findings have varied depending on the type and duration of diabetes. In the early 2000s, a study involving individuals with T1 diabetes found that non-proteinuric DKD often exhibited kidney features similar to those seen in diabetic nephropathy, also known as diabetic glomerulopathy. However, this study did not extensively examine other kidney aspects such as the interstitial and arterial characteristics [14]. Conversely, studies conducted after 2010 on individuals with T2 diabetes indicated that while findings regarding the interstitial and arterial aspects varied across studies, the typical kidney features associated with DN were less common in non-proteinuric diabetic kidney disease [10]. These inconsistent results could be attributed to the partial number of participants in these studies or variations in the timing of kidney biopsies. Individuals with the same background but different eGFR levels may have distinct kidney characteristics. Factors like age and the duration of diabetes might also influence the pathological findings. To address these disparities, we conducted a study using a propensity score to match individuals with non-proteinuric and proteinuric DKD in a statewide sample of patients with biopsy-confirmed DKD [15]. The findings revealed that individuals with non-proteinuric DKD have fewer typical physical characteristics associated with diabetic nephropathy, not only in the glomerulus but also in the kidney's interstitial and arterioles.

RENAL PROGNOSIS AND MORTALITY OF NON-PROTEINURIC DIABETIC KIDNEY DISEASE

Recent research indicates that individuals with non-proteinuric DKD face a reduced risk of renal function decline and mortality. For instance, a study conducted at the Steno Diabetes Center tracked kidney function over a 16-year period in 935 individuals with T1 diabetes and 1,984 individuals with T2 diabetes who had reached stage 3 CKD with an eGFR below 60 mL/min/1.73 m^2. This study

revealed that non-proteinuric DKD experienced a milder decline in kidney function compared to proteinuric DKD [16].

Another research from Australia demonstrated that individuals with albuminuria had an annual eGFR decline rate of 1.75 mL/min/1.73 m^2, while those with normoalbuminuria had a rate of 0.6 mL per min [17]. Those without albuminuria had a lower risk of mortality than those with albuminuria. Furthermore, a Japanese study found that the five year CKD progression-free survival rate for individuals with non-proteinuric diabetic kidney disease was higher (86.6%) than for those with proteinuric DKD (30.3%) [15]. All the subgroups analyzed had a lower incidence of kidney issues, and the non-proteinuric group also had a lower overall mortality rate.

DISCUSSION

Diabetic nephropathy has long been characterized by the presence of proteinuria, and it has been considered the leading cause of end-stage kidney disease (ESKD). However, emerging evidence has challenged this traditional view by highlighting the existence of non-proteinuric diabetic kidney disease (DKD), where individuals experience a decline in renal function without significant proteinuria. This narrative review sheds light on the various aspects of non-proteinuric DKD.

Firstly, the review emphasizes the clinical characteristics of non-proteinuric DKD, which can affect both type 1 and type 2 diabetes patients. It explores the epidemiological factors associated with this condition, such as gender, blood pressure, blood sugar levels, and the absence of diabetic retinopathy. Importantly, it underscores the diversity in clinical presentations among individuals with non-proteinuric DKD, making it a complex and multifaceted condition.

The pathological features of non-proteinuric DKD are also discussed, with a focus on kidney biopsies. While early studies associated non-proteinuric DKD with kidney changes resembling diabetic nephropathy, more recent research suggests variations in interstitial and arterial characteristics. The review acknowledges the challenges in conducting kidney biopsies and highlights the need for further investigation to understand the pathology better.

Furthermore, the review delves into the renal prognosis and mortality associated with non-proteinuric DKD. Recent studies have indicated that individuals with non-proteinuric DKD experience a milder decline in kidney function and have a lower risk of mortality compared to their proteinuric counterparts. These findings challenge the traditional belief that proteinuria is the primary marker of poor renal outcomes in diabetic patients.

This narrative review provides a comprehensive overview of non-proteinuric diabetic kidney disease, highlighting its clinical, pathological, renal prognostic, and mortality aspects. It emphasizes the need for further research to better understand this complex condition and its implications for patient care. The review contributes to the evolving understanding of diabetic kidney disease and calls for a more nuanced approach to diagnosis and management, considering the diverse presentations of this condition.

CONCLUSION

Historically, the diagnosis of DKD has been made on the basis of the patient's urine containing protein first, then a deterioration in renal function. A kidney biopsy performed on these patients may reveal particular kidney abnormalities. Nonetheless, as we've covered here, a number of pathological and clinical investigations have shown that diabetic kidney disease can differ significantly in both its microscopic and clinical appearances. This implies that diabetic kidney disease may manifest in many forms. A kind of kidney disease known as non-proteinuric DKD occurs when a patient's eGFR falls below 60 mL/min/1.73 m^2 and their urine protein content is less than 300 mg per gram creatinine. This specific kind of DKD emphasizes the gap between albumin levels in the urine and renal function in individuals with diabetes, underscoring the necessity for more research into renal function decrease beyond its correlation with elevated albumin levels in the urine.

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LIST OF ABBREVIATIONS:

DKD- Diabetic Kidney Disease
DN- Diabetic nephropathy
ESKD- End-stage kidney disease
CKD- Chronic kidney disease
UACR- Urine albumin to creatinine ratio

PCR- Protein to creatinine ratio
eGFR- estimated glomerular filtration rate
T1DM- Type 1 diabetes mellitus
T2DM- Type 2 diabetes mellitus

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CONFLICT OF INTEREST

The authors have no competing interests to declare.

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