Review Article

Diabetic kidney disease: pathophysiological changes and urinalysis contribution to diagnosis—a narrative review

José Antonio Tesser Poloni[1,2], Liane Nanci Rotta[3]

[1]Health School, Universidade do Vale do Rio dos Sinos, São Leopoldo, Brazil; [2]Controllab, Rio de Janeiro, Brazil; [3]Post-graduation Program in Health Sciences, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, Brazil

Contributions: (I) Conception and design: Both authors; (II) Administrative support: Both authors; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: Both authors; (VII) Final approval of manuscript: Both authors.

Correspondence to: José Antonio Tesser Poloni. Health School, Universidade do Vale do Rio dos Sinos, Av. Unisinos, 950 Bairro Cristo Rei, São Leopoldo, Brazil. Email: jatpoloni@yahoo.com.br.

Background and Objective: Diabetic kidney disease (DKD) is a term used to identify the effect of diabetes mellitus (DM) in the kidneys, and DKD is the most frequent and severe chronic complication of DM. The major risk factors involved in the DKD pathogenesis are smoking, hypertension, hyperglycemia, high protein diet and renal hyperfiltration. DKD constitute the leading cause of end-stage kidney disease and occurs as a result of renal microvascular lesions causing distinct and progressive morphological changes inducing albuminuria and progressive loss of kidney function. Either albuminuria or glomerular filtration rate decline are DKD unspecific markers, then newer more specific markers for DKD are needed. In this narrative review, we aimed to identify the urinalysis parameters and its possible contribution to DKD diagnosis.

Methods: We evaluated the information available in the English literature (articles published on PubMed indexed journals and book chapters) related to DKD and urinalysis published between 1999 and 2021.

Key Content and Findings: This narrative review contains information on the urinary particles observed or not in patients with DKD and non-diabetic kidney disease (NDKD) and their use on differential diagnosis of these clinical conditions. Of note, in dipstick analysis, we address the parameters glucose and ketone bodies, besides the protein (albumin).

Conclusions: The urine sediment is useful to differential diagnosis of DKD and NDKD, with acanthocytes identifying NDKD, when observed in DM patients. In urine, the presence of podocytes may be a useful marker of disease activity in DKD. The perspectives point to development of laboratory technologies with the possibility of urine sediment cell identification and quantification, which could contribute to DKD diagnosis.

Keywords: Diabetic kidney disease (DKD); urine sediment; urinalysis

Received: 05 April 2021; Accepted: 06 January 2022; Published: 30 January 2022.

doi: 10.21037/jlpm-21-20

View this article at: https://dx.doi.org/10.21037/jlpm-21-20

Introduction

Chronic kidney disease (CKD) occurs in individuals with diabetes mellitus (DM) and is named diabetic kidney disease (DKD). Approximately 40% of patients who are diabetic develop DKD and it is the leading cause of CKD; worldwide DKD is the leading cause of end-stage renal disease (ESRD) (1). In patients with DM, improved understanding of the shared and distinct mechanisms driving DKD and non-diabetic kidney disease (NDKD) is likely to improve outcomes (2,3).

DKD can result from microvascular lesions (in renal glomeruli and tubuli), or can be associated with macrovascular atherosclerotic pathophysiological processes.

Table 1 The search strategy summary

Items	Specification
Date of Search (year)	2021
Databases and other sources searched	PubMed and Nephrology, Urine microscopy book chapters
Search terms used	"Diabetic kidney disease + urine sediment"; "Diabetic kidney disease + urinalysis"; "Diabetic nephropaty and urine sediment"; "Diabetic nephropathy and urinalysis"
Timeframe	Articles/Book chapters published between 1999 and 2021
Inclusion and exclusion criteria	Any type of study/book chapter published in English language related to the subjects of the work
Selection process	Selection process was conducted by one of the authors (JATP) and reviewed by the other author (LNR)

DKD result from the effects of hyperglycemia on the kidney of patients with DM [type 1 and type 2 (T1/T2DM)], inducing to specific pathologic functional and structural changes. DKD incidence is being increased annually worldwide (4), and its prevalence varies between regions of the same country, countries, and continents (5). Smoking, hypertension, hyperglycemia, hyperfiltration and high protein diet are the major risk factors in the DKD pathogenesis, that can present a genetic component (probably polygenic) (6). Indeed, the presence of a first-degree relative with T1/T2DM and DKD, induces to substantially more risk for developing DKD, compared to those without an affected relative (7).

Many diverse causes are associated to the reduced kidney function in DKD, such as the unresolved acute kidney failure and hypertensive nephrosclerosis, resulting in clinical presentation characterized by hypertension, proteinuria, and progressive reduction in the kidney function (7).

CKD, regardless of etiology, is identified as a decrease in kidney function and/or evidence of kidney damage. Generally, a decrease in kidney function is described by an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 or persistently high urinary albumin-to-creatinine ratio >30 mg/g (8). To diagnose DKD, several tubular and glomerular damage markers have been recently identified and is crucial for the health professionals to understand the important information that these laboratory tests convey, as well as their limitations (8).

Currently, to identify patients, guide therapy, and establish the prognosis of patients, the assessment of urinary albumin excretion (UAE) and eGFR has been suggested in patients with T1DM for ≥5 years, and annually in T2DM patients (beginning at the diagnosis), and in T1DM/T2DM patients with concurrent arterial hypertension (4).

Urinalysis (dipstick evaluation coupled with urine sediment analysis) is one of the most common tests performed in the clinical laboratory to screen patients with suspected or diagnosed kidney diseases. Information like proteinuria and observation of elements in the urine sediment that appears when the kidneys are injured are possible using this test.

The objective of this review work was to evaluate the information available in the literature (articles published on PubMed indexed journals and book chapters) related to DKD pathophysiology changes and the urinalysis contribution to the diagnosis of this clinical condition. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-21-20/rc).

Methods

Literature review and evaluation of the information available (articles published on PubMed indexed journals and book chapters) related to DKD and urinalysis in the last 20 years approximately (*Table 1*).

Natural history of DKD

Five clinical stages of DKD are characterized in T1DM, that are similar in T2DM patients: (I) time of initial diagnosis; (II) the first decade (characterized by hyperfiltration and renal hypertrophy); (III) the second decade in the absence of clinical disease, with glomerulopathy [microalbuminuria (MA)]; (IV) clinically detectable DKD (proteinuria, hypertension, and a progressive decline in renal function); (V) ESRD.

Stage I

Functional changes are experienced at the DM onset: increased kidney size, MA (reverses with the control of glycemia), and an increased GFR (in most patients it decreases with initiation of insulin therapy).

Stage II

An increase in GFR may occur predicting the later development of nephropathy (it remains controversial). The hyperfiltration may be partly caused by activation of the renin-angiotensin-aldosterone system and hyperglycemia. Glomerular basal membrane (GBM) thickening, within 1.5–2.5 years, begins in nearly all patients. The GBM thickening and clinical renal function do not present correlation, and approximately 5 years after the onset of disease begins the mesangial expansion.

Stage III

Stage III is characterized by MA (the amount of albumin excretion is below the level of sensitivity of the urine dipstick). However, there are some new technologies added by some manufacturers in automated systems like a reactive area specific to albumin and a reactive area specific to creatinine. The reactive area to albumin can detect levels of albumin as low as 10 mg/dL (limit detection of dipstick to protein is usually approximately 30 mg/dL). This kind of new information can be useful in the identification of patients with DKD if available in many laboratories (9). In the first or second decade of DM, occurs a slightly elevated UAE (thresholds ranging from 15 to 70 µg/min to classify patients is a harbinger of the later development of clinical DKD). MA, when it is progressive over time and is associated with hypertension, best predicts DKD (3).

Stage IV

Stage IV is recognized by positive albuminuria at dipstick (>300 mg/day) with a slow gradual decline in GFR (with a rate of decline stated to be 1 mL/min/month and can be slowed by antihypertensive therapy) that may result in ESRD.

Stage V

ESRD may develop in consequence to the continuous decline of GFR. Diabetic patients often experience more uremic symptoms at higher GFR (15 mL/min) than nondiabetic patients, because of associated cardiac disease and autonomic neuropathy (10).

DKD

The histopathologic descriptor to DKD is the diabetic glomerulosclerosis. Usually is not necessary a renal biopsy (gold-standard for definitive diagnosis, treatment guidance and prognosis for other types of nephropathies) to establish DKD in T2DM patients since the risk of such intervention is not justified due to the complicated clinical situation. This occurs unless there is a need of an exclusive or differential diagnosis (11).

In most patients with classic presentations, a clinical DKD diagnosis is appropriate, but the maintaining clinical suspicion for NDKD is necessary especially in patients presenting DM with atypical features, such as concurrent systemic disease, short diabetes duration, very high proteinuria with sudden onset, rapid eGFR deterioration, and/or urine sediment presenting erythrocytes and leukocytes and/or cellular casts (12).

Family history, sex, age, and race/ethnicity, constitute susceptibility factors to DKD; acute kidney injury (AKI) and hyperglycemia are DKD initiation factor, while obesity, diet and hypertension are progression factors associated to the DKD. Among these, hypertension and hyperglycemia are the most prominent factors (1,9,13). There are no other options available for DKD treatment beyond the current treatment to the optimal control of glycemia, lipemia, hypertension, and lifestyle fitness.

In T1DM and T2DM, the incidence of MA is around 30% and depends on the glycemia control (albuminuria does not occur in the absence of hyperglycemia), but in T2DM is usually associated with hypertension, being an important risk factor for cardiovascular mortality (14,15). MA is the earliest detectable clinical manifestation of DKD, and approximately 50% of patients with established MA will progress to macroalbuminuria, in the absence of early intervention. The glycemia control is the main determinant of progression to overt DKD and the improving of HbA1c level can prevent progression to ESRD in patients with proteinuria and T1DM (16,17). An intensive glucose control intervention, especially in early stages, targeting a HbA1C <7% reduced the 9-year risks of developing macroalbuminuria and MA by 56% and 34%, respectively, and induced 24% reduction in development of microvascular complications in T2DM, including DKD,

compared with standard (with 10 years of glycemic control) (18,19). Macroalbuminuria presents tenfold higher risk of ESRD progression than that of patients normoalbuminuric (13,20). This "legacy effect/metabolic memory," suggests that early intensive glycemic control can prevent irreversible damage, such as epigenetic alterations associated with hyperglycemia (4). In T1DM, pancreas transplantation can reverse diabetic glomerulosclerosis following 10 years of normoglycemia (21).

Non-DKD

In patients with DM, CKD can be caused by diabetes-independent factors, besides the modifiers of CKD related to the diabetic milieu and aforementioned causes. In T1DM many conditions can cause kidney injury precedent, concomitant or subsequent, such as: immunoglobulin A (IgA) nephropathy, genetic kidney disorders, secondary focal segmental glomerulosclerosis, cholesterol embolism, infection-related glomerulopathies and minimal change disease, and all types of AKI (22-25).

CKD before the onset of diabetes

CKD before the onset of diabetes indicates that CKD is a NDKD. It is most likely for patients with, for example, early-onset genetic forms of CKD or CKD following an episode of AKI. The susceptibility to T2DM, consequently exacerbating pre-existing CKD, can increase in presence of autoimmune and renal disease (renal vasculitis and lupus nephritis, and in kidney transplant recipients) with a long-term steroid use (22,26).

CKD present at the time of DM diagnosis

T2DM and CKD present at an unknown time of development are often diagnosed together, with the DM typically developing many years before the onset of CKD. Most likely, the presence of NDKD is indicated when the diagnosis of CKD (stages G3–G5) occurs simultaneously at the time of DM diagnosis (22,27).

Undiagnosed CKD at the time of DM diagnosis

Current approaches to the diagnosis of CKD, including eGFR, urinalysis (secondary to normal serum creatinine levels), and imaging studies, can be unspecific. Due to the lack of specific symptoms, concern exists that certain forms of CKD remain unrecognized presenting absence of urine abnormalities. A clinically relevant CKD stage can be masked by a normal serum creatinine and eGFR is inaccurate for initial CKD stages (G1 or G2). No urinary abnormalities are observed in CKD presentation, associated to kidney hypoplasia, previous AKI episodes, ageing nephropathy or polycystic kidney disease. The "silent CKD" can be unmasked by the sudden increase in filtration pressure and GFR induced by the onset of DM. Therefore, such forms of precedent CKD are diagnosed only years after the onset of DM—a series of events that increase the likelihood of misdiagnosing NDKD as DKD (20,22,28,29).

Pathophysiology of DKD

Alterations in the structure of kidney compartments contribute to DKD development. The thickening of glomerular basement membrane is the earliest consistent change (apparent within 1.5–2 years of T1DM diagnosis) and of capillary and tubular basement membrane (30), associated to loss of podocytes with effacement of foot processes, endothelial fenestration, and mesangial matrix expansion.

Indeed, extracellular matrix deposition occurs (primarily in the mesangium), proliferative changes, and tubular atrophy, resulting in glomerulosclerosis (the final common pathway of many kidney diseases) and interstitial fibrosis. Within 5–7 years after T1DM diagnosis, mesangial volume expansion is detectable (31) and with DM progression is observed the segmental mesangiolysis, Kimmelstiel–Wilson nodules and microaneurysms (32). In T1DM, hypertension, low GFR and albuminuria are somewhat less strongly associated with glomerular basement membrane width and are strongly correlated with mesangial expansion. In T2DM the renal structure changes are similar to those in T1DM, but they are less predictably associated with clinical presentations and more heterogeneous (4,31).

The DKD and ESRD pathophysiology shows that the diabetic milieu leads to the generation and circulation of growth factors and advanced glycation end-products, and hemodynamic and hormonal changes that release inflammatory mediators and reactive oxygen species (7). Oxidative stress (OS) is strongly involved in the renal damage onset and progression. An important factor to the development of nephropathy is the polyol pathway, which is increased in persistent hyperglycemia. The hyperglycemia increases the glomerular lipid peroxidation, and hydrogen peroxide production among mesangial cells leading

towards OS and the ultimate depletion of hydrogen sulfide. Upstream of these major pathways, hyperglycemia is the major driving force of the progression to ESRD from DKD (6,33,34).

Different presentation of DKD in T2DM involve factors underlying that include the impairment of older population, the unreliable timing of T2DM onset (with longer hyperglycemia before diagnosis) compared with T1DM, and a higher burden of atherosclerosis (4).

Albuminuria is not a linearly progressive process; it is a fluctuating and dynamic condition. Then, the low eGFR or a reduction/lack of albuminuria may not necessarily preclude structural DKD. The natural history shows that the classic pattern of DKD not necessarily has an orderly evolution characterized by glomerular hyperfiltration progressing to persistent albuminuria associated with declining GFR and hypertension (35).

In an autopsy study it was observed a considerably higher prevalence of DKD diagnosed histologically (106/168 T1DM/T2DM patients) compared with that indicated by clinical laboratory testing: albuminuria or lower GFR was absent in 20% (20/106) of T1DM/T2DM throughout life. Therefore, all histopathologic classes of DKD presented structural changes highly variable (36).

Both kidney- and non-kidney-related DKD complications develop as GFR declines in DKD later stages, while in the earlier stages bone and mineral metabolism disorders are observed, besides the anemia (erythropoietin deficiency) (4). Critical metabolic changes as hyperglycemia and hyperaminoacidemia (a promoter of glomerular hyperfiltration and hyperperfusion) alter kidney hemodynamics and promote inflammation and fibrosis in early diabetes. In T2DM, obesity and systemic hypertension contributes to glomerular hyperfiltration via mechanisms, such as glomerular enlargement and high transmitted systemic blood pressure (37).

This additional hyperfiltration cannot be accommodated resulting in intraglomerular hypertension and rapid progression to macroproteinuria, leading to glomerulosclerosis, podocyte loss, and accelerated CKD progression (17,22,38-43).

Diagnosis of DKD

Measurement of eGFR and albuminuria, along with clinical features (DM duration, presence of clinical signs) are the basis to the clinical diagnosis of DKD (10). The hypertension and albuminuria are clinical manifestations secondary to some factors that collectively result in glomerular hypertension and hyperfiltration, renal hypertrophy, and altered glomerular composition (44). Usually, the diagnosis is based on a clinical composite of persistently high UAE (45). The earliest marker of DKD is MA, and it has traditionally been considered the primary predictive marker for progression to the advanced stages of CKD (4). However, some limitations exist associated to it, that depends on the health care professional interventions or several patient-related factors. Until now, albuminuria must continue to be used as a marker of kidney damage in DM, but it must be also carefully assessed and monitored for a reasonable period before setting the DKD diagnostic. Indeed, at normoalbuminuric stage, the renal impairment could also occur (46).

MA occurs when the UAE rate reaches 20–200 µg/min or 30–300 mg/24 h, while macroalbuminuria occurs when the UAE rate >300 mg/24 h. MA is considered persistent when confirmed on at least two occasions (3–6 months apart) being able to be transient and reversible. MA heralds macroalbuminuria (proteinuria) and ESRD. Besides the detection of MA, the patient with DM duration of 7–10 years usually presents at least diabetic retinopathy, and the urinalysis is relatively little expressive (4,47).

Screening for albuminuria can be better performed in a random spot urine collection, using urinary albumin-to-creatinine ratio (UACR), that is defined as >30 mg/g (48). Some factors may give false-positive values: exercise within 24 h, infection, congestive heart failure, menstruation, increased body temperature, continuous hyperglycemia, and arterial hypertension. In the absence of prescribed renin-angiotensin-system blockers, the combination normoalbuminuria and low eGFR is noted (48).

Urinary findings on patients with diabetes/DKD

Urine sediment analysis usually is performed coupled with dipstick test. The dipstick evaluation has two valuable information related specifically to DM—glucose and ketone bodies.

Glucose

Glucose at urine dipstick test

When the tubular reabsorption of glucose in the kidneys (the renal threshold: 150–180 mg/dL or 8.3–10 mmol/L) is exceeded, glucosuria is observed. It is frequent in diabetic patients and the renal threshold is on a higher average, as well as in older people or in DM for many years, compared

to healthy person. The degree of glucose excretion depends on the severity of the metabolic disturbance and on the individual renal threshold. Therefore, glucosuria identification presents significance for early DM detection, self-monitoring and control.

Renal glucosuria

If a lowering in the renal threshold occurs, with a reduced renal tubular glucose reabsorption, glucosuria increases, even if glycemia is within the reference interval. In 5–10% of pregnancies, glucosuria is due to the renal threshold lowering, and is no longer observed after the woman has given birth (49).

Glucosuria in the presence of kidney damage

Symptomatic renal glucosuria occurs when kidney function ≤30% of normal renal performance. In acute renal failure the renal DM is also observed (49).

Ketone bodies

Ketone bodies at dipstick test

Relative or absolute insulin deficiency causes reduced glucose utilization in fat and muscle and increased lipolysis with consequent increased breakdown of free fatty acid and excess of acetyl-coenzyme A formation, promoting the synthesis of acetoacetic acid which is partly transformed into β-hydroxybutyric acid and a smaller degree into acetone, that will appear in urine.

Ketonuria in DM

For checking metabolic decompensation in DM, ketonuria detection (acetoacetic acid and acetone) is particularly important, because the ketoacidosis invariably accompanies the precomatose and comatose states (except for hyperosmolar coma) and is characterized by ketone and glucose excretion in urine. Diabetic coma, a life-threatening event, results from the serum ketone bodies accumulation, associated to pathophysiological changes of the dysregulated metabolism, such as electrolyte shifts and dehydration. Ketonuria is an early symptom of the metabolic disequilibrium and frequently occurs when the diabetic patient is not adequately managed with insulin. Therefore, when coma may develop within a few hours, as in juvenile and insulin-dependent DM, a check for glucosuria and ketonuria should form part of self-monitoring.

Dipstick test has also a reactive area to detect protein. This particular reactive area can be useful in the identification of kidney diseases (49).

Protein

Protein at dipstick test

Proteinuria is a non-specific frequent symptom in renal diseases, and should always be followed by differential diagnostics.

Renal proteinuria

A pathological process leads to an increase in the permeability of the glomerular capillaries with the development of renal proteinuria, that can be persistent and observed in both daytime and nocturnal urine. The range of 200–300 mg/dL of protein is observed in glomerulonephritis, but when it is accompanied with few symptoms, lower values must be reckoned. This proteinuria is usually accompanied by microhematuria. Tubular proteinuria occurs because of disturbance of the tubular uptake of proteins from glomerular filtrate, and/or lesions of the tubular cells, being encountered e.g., in pyelonephritis, cystic kidneys, and gouty kidneys (49).

In the early stage of DKD, only MA is observed. The detection of protein necessitates the use of specific methods such as immunochemical assays utilizing anti-albumin antibodies, high performance liquid chromatography, or appropriate dipsticks. In advanced stages, non-selective proteinuria develops (50).

Urine sediment

In DKD, the urinary sediment is usually defined as unremarkable, occasionally being observed some few erythrocytes. However, studies have shown that microscopic hematuria is not uncommon in DKD, being found in 12.5% to 35% of patients with T1DM clinically diagnosed DKD, and in 15% to 35% of patients with biopsy-proven DKD associated with T2DM. Microscopic hematuria (≥8 erythrocytes/μL) was found in 62% of clinically diagnosed DKD patients, a prevalence which increased to 82% when three consecutive samples from the same patient were analyzed. Interestingly, ≥5% acanthocyturia, a marker of glomerular bleeding, was found in only 4% of diabetic patients, in contrast with 75% of patients with glomerulonephritis (50-57).

Besides microscopic hematuria, it should be remembered that the appearance of an active urine sediment with many erythrocytes, leukocytes and pleomorphic cylindruria in a

diabetic patient should always be considered as a possible sign of superimposed proliferative and active glomerulonephritis such as IgA nephropathy, acute post-infectious glomerulonephritis, or extracapillary glomerulonephritis. Leukocyturia and bacteriuria, are suggestive of urinary tract infection, which is frequent in DM and may be associated to the passage of gas into the urine (i.e., pneumaturia), frequently due to bacteria such as *Enterobacter aerogenes* and *Escherichia coli*. Another complication of urinary tract infection in diabetics is septic papillary necrosis, which can present with flank pain, gross hematuria, and papillary fragments in the urine. *Candida* is also frequently found in the urine of diabetic patients (50-57).

Nakamura *et al.* [2000] evaluated podocytes occurrence in the urine sediment of adult patients with and without nephropathy. In DM patients with normoalbuminuria or chronic renal failure, and in healthy controls urinary podocytes were not observed. Podocytes were detected in the urine of eight (53%) and 12 (80%) DM patients with MA and macroalbuminuria, respectively, with a lower number of urinary podocytes in patients with MA, than with macroalbuminuria. There was no relationship between urinary podocytes and albuminuria however, the number of urinary podocytes correlated with the plasma metalloproteinase-9 concentration. It may suggest that podocytes in urine could be a marker of disease activity in DKD (58).

To clarify the role of acanthocytes in DKD, Heine *et al.* [2004] observed that hematuria was found in 62%, 84% and 20% of patients with the clinical diagnosis of DKD, glomerulonephritis, and in healthy control subjects upon a single urine examination, respectively. Indeed, 4% patients with DKD showed glomerular hematuria, while it was observed in 40% of patients with glomerulonephritis. In contrast to hematuria, acanthocyturia is uncommon in patients with clinical diagnosis of DKD. In DM patients with proteinuria, acanthocyturia can point to nondiabetic glomerulopathies, and renal biopsy should be considered (55).

Indeed, Dong *et al.* [2016] studied the predictive value of dysmorphic erythrocytes in T2DM patients with non-diabetic renal disease and influences on hematuria. There was a difference between the DKD group and the non-diabetic renal disease group (cutoff point 10 RBCs/ high power field). When the urinary erythrocyte morphology defined the hematuria, a marked difference was observed and glomerular hematuria showed high positive predictive value and specificity in non-diabetic renal disease. Nephrotic syndrome was significantly associated with hematuria and an independent risk factor for it, and the presence of dysmorphic erythrocytes were superior to hematuria for indicating NDKD in T2DM (59).

Morcos *et al.* [2002] observed that renal tubular epithelial cells (RTECs) were found in the urine of 20 of 100 T2DM patients but in none of the healthy control subjects. The presence of RTECs in the urine sediment showed a strong correlation to the degree of albuminuria (60). Broad waxy and finely granular casts can also be observed. However, these findings are not observed in early stages of DKD (10).

According to the very few literatures available, and, despite the report of RTECs and broad waxy and finely granular casts, albuminuria is the key information during routine urinalysis on patients with DKD (especially talking on early-stage diagnosis of DKD). The lack of urine sediment findings can be understood when we look on the natural history of DKD. From stage 1 to stage 3 (a period that can be observed during the 1st and 2nd decades after DM diagnosis) the unique finding observed is MA. On stage 2 usually kidney biopsies performed presents normal findings (with normal biopsies is virtually impossible to identify particles in the urine sediment originated in the kidneys—what supports the lack of findings in the urine sediment in early stages of DKD). Also, the glomerular basement membrane thickening begins within 1.5–2.5 years, while the mesangial expansion occurs approximately 5 years after the onset of disease. These parts of the glomerulus do not correspond to any particle detectable in the urine sediment. Only on stage 4 the amount of protein starts to become higher (>300 mg/day) and consequently detectable by urine dipstick (10).

However, the urine sediment can be useful to differentiate DKD from NDKD using the identification of acanthocytes as a marker of NDKD.

Future perspectives of urinalysis on patients with diabetes

The most recent publication on this subject was produced by Abedini *et al.* [2021] where the urinary single-cell profiling of the kidneys demonstrated that almost all kidney cell types can be identified in urine: cells from the proximal tubule, from the loop of Henle, and from the collecting duct, in addition to bladder cells, lymphocytes, macrophages and the podocytes. The urinary cell–type composition was subject specific and reasonably stable (according to different urine collection methods and over time). Gene expression analyses in urinary cells clustered with kidney and bladder cells (such

as kidney and urinary podocytes) permitted to observe the similarity of the urinary cells, and principal cells of the kidney and urine, generating a reference dataset for cells in human urine. Single-cell transcriptomics can detect and quantify almost all types of cells in the kidney and urinary tract (61).

This study coupled with the identification of podocytes, albumin, and the use of dysmorphic erythrocytes for differential diagnosis of DKD from NDKD can be a future perspective to the urine sediment findings to help in the identification of DKD.

Conclusions

At this moment, the urine sediment findings (at least the particles usually observed during routine urinalysis) does not shows evidence of any particular structure or any urinary profile to be used on the identification of DKD. However, the literature is presenting clarification on the findings and showing the potential use of some urine sediment structures (podocytes—only identifiable securely in the urine sediment using immunological tests—could be a useful marker of disease activity in DKD).

As an already available information to any laboratory, the urine sediment can be helpful in the differential diagnosis of DKD from NDKD, with acanthocytes (when observed in patients with DM) identifying NDKD.

The advance in the development of laboratory technologies points to the perspective of urine cell identification, which will contribute to the DKD diagnosis, in association with the other parameters and with the clinical manifestation of disease.

Acknowledgments

We thank Maria Claudia Saraiva Marnatti for proofreading the English language.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Rafael Noal Moresco) for the series "Laboratory Medicine in Diabetic Kidney Disease" published in *Journal of Laboratory and Precision Medicine*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-21-20/rc

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://jlpm.amegroups.com/article/view/10.21037/jlpm-21-20/coif). The series "Laboratory Medicine in Diabetic Kidney Disease" was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Alicic RZ, Rooney MT, Tuttle KR. Diabetic Kidney Disease: Challenges, Progress, and Possibilities. Clin J Am Soc Nephrol 2017;12:2032-45.
2. Pippias M, Kramer A, Noordzij M, et al. The European Renal Association - European Dialysis and Transplant Association Registry Annual Report 2014: a summary. Clin Kidney J 2017;10:154-69.
3. Saran R, Robinson B, Abbott KC, et al. US Renal Data System 2016 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis 2017;69:A7-8.
4. Papadopoulou-Marketou N, Kanaka-Gantenbein C, Marketos N, et al. Biomarkers of diabetic nephropathy: A 2017 update. Crit Rev Clin Lab Sci 2017;54:326-42.
5. Gheith O, Farouk N, Nampoory N, et al. Diabetic kidney disease: world wide difference of prevalence and risk factors. J Nephropharmacol 2015;5:49-56.
6. Hussain Lodhi A, Ahmad FU, Furwa K, et al. Role of Oxidative Stress and Reduced Endogenous Hydrogen Sulfide in Diabetic Nephropathy. Drug Des Devel Ther 2021;15:1031-43.

7. Umanath K, Lewis JB. Update on Diabetic Nephropathy: Core Curriculum 2018. Am J Kidney Dis 2018;71:884-95.
8. Currin SD, Gondwe MS, Mayindi NB, et al. Diagnostic accuracy of semiquantitative point of care urine albumin to creatinine ratio and urine dipstick analysis in a primary care resource limited setting in South Africa. BMC Nephrol 2021;22:103.
9. Narva AS, Bilous RW. Laboratory Assessment of Diabetic Kidney Disease. Diabetes Spectr 2015;28:162-6.
10. Reilly R, Perazella MA. Nephrology in 30 days. 2.ed. New York: Lange; 2013.
11. Qi C, Mao X, Zhang Z, et al. Classification and Differential Diagnosis of Diabetic Nephropathy. J Diabetes Res 2017;2017:8637138.
12. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008;359:1577-89.
13. Berhane AM, Weil EJ, Knowler WC, et al. Albuminuria and estimated glomerular filtration rate as predictors of diabetic end-stage renal disease and death. Clin J Am Soc Nephrol 2011;6:2444-51.
14. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int 2003;63:225-32.
15. Ahmad T, Ulhaq I, Mawani M, et al. Microalbuminuria in Type-2 Diabetes Mellitus; the tip of iceberg of diabetic complications. Pak J Med Sci 2017;33:519-23.
16. Zoungas S, Arima H, Gerstein HC, et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomised controlled trials. Lancet Diabetes Endocrinol 2017;5:431-7.
17. Wiseman MJ, Saunders AJ, Keen H, et al. Effect of blood glucose control on increased glomerular filtration rate and kidney size in insulin-dependent diabetes. N Engl J Med 1985;312:617-21.
18. Nathan DM; DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. Diabetes Care 2014;37:9-16.
19. Chatzikyrkou C, Menne J, Izzo J, et al. Predictors for the development of microalbuminuria and interaction with renal function. J Hypertens 2017;35:2501-9.
20. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int 2013:Suppl 3:1-150.
21. Fioretto P, Barzon I, Mauer M. Is diabetic nephropathy reversible? Diabetes Res Clin Pract 2014;104:323-8.
22. Anders HJ, Huber TB, Isermann B, et al. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. Nat Rev Nephrol 2018;14:361-77.
23. Hill NR, Fatoba ST, Oke JL, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One 2016;11:e0158765.
24. Sharma SG, Bomback AS, Radhakrishnan J, et al. The modern spectrum of renal biopsy findings in patients with diabetes. Clin J Am Soc Nephrol 2013;8:1718-24.
25. Haider DG, Peric S, Friedl A, et al. Kidney biopsy in patients with diabetes mellitus. Clin Nephrol 2011;76:180-5.
26. Sharif A, Hecking M, de Vries AP, et al. Proceedings from an international consensus meeting on posttransplantation diabetes mellitus: recommendations and future directions. Am J Transplant 2014;14:1992-2000.
27. Steinke JM, Mauer M; International Diabetic Nephropathy Study Group. Lessons learned from studies of the natural history of diabetic nephropathy in young type 1 diabetic patients. Pediatr Endocrinol Rev 2008;5 Suppl 4:958-63.
28. Tsai CW, Grams ME, Inker LA, et al. Cystatin C- and creatinine-based estimated glomerular filtration rate, vascular disease, and mortality in persons with diabetes in the U.S. Diabetes Care 2014;37:1002-8.
29. Romagnani P, Remuzzi G, Glassock R, et al. Chronic kidney disease. Nat Rev Dis Primers 2017;3:17088.
30. Tyagi I, Agrawal U, Amitabh V, et al. Thickness of glomerular and tubular basement membranes in preclinical and clinical stages of diabetic nephropathy. Indian J Nephrol 2008;18:64-9.
31. Fioretto P, Mauer M. Histopathology of diabetic nephropathy. Semin Nephrol 2007;27:195-207.
32. Stout LC, Kumar S, Whorton EB. Focal mesangiolysis and the pathogenesis of the Kimmelstiel-Wilson nodule. Hum Pathol 1993;24:77-89.
33. Wada J, Makino H. Inflammation and the pathogenesis of diabetic nephropathy. Clin Sci (Lond) 2013;124:139-52.
34. Safar MM, Abdelsalam RM. H2S donors attenuate diabetic nephropathy in rats: Modulation of oxidant status and polyol pathway. Pharmacol Rep 2015;67:17-23.
35. Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease. With emphasis on the stage of incipient diabetic nephropathy. Diabetes 1983;32 Suppl 2:64-78.
36. Klessens CQ, Woutman TD, Veraar KA, et al. An autopsy study suggests that diabetic nephropathy is underdiagnosed. Kidney Int 2016;90:149-56.

37. Grabias BM, Konstantopoulos K. The physical basis of renal fibrosis: effects of altered hydrodynamic forces on kidney homeostasis. Am J Physiol Renal Physiol 2014;306:F473-85.
38. Anders HJ, Davis JM, Thurau K. Nephron Protection in Diabetic Kidney Disease. N Engl J Med 2016;375:2096-8.
39. Tonneijck L, Muskiet MH, Smits MM, et al. Glomerular Hyperfiltration in Diabetes: Mechanisms, Clinical Significance, and Treatment. J Am Soc Nephrol 2017;28:1023-39.
40. Vallon V. The mechanisms and therapeutic potential of SGLT2 inhibitors in diabetes mellitus. Annu Rev Med 2015;66:255-70.
41. Denic A, Mathew J, Lerman LO, et al. Single-Nephron Glomerular Filtration Rate in Healthy Adults. N Engl J Med 2017;376:2349-57.
42. Helal I, Fick-Brosnahan GM, Reed-Gitomer B, et al. Glomerular hyperfiltration: definitions, mechanisms and clinical implications. Nat Rev Nephrol 2012;8:293-300.
43. Preisig P. What makes cells grow larger and how do they do it? Renal hypertrophy revisited. Exp Nephrol 1999;7:273-83.
44. Tuttle KR, Bakris GL, Bilous RW, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care 2014;37:2864-83.
45. Gluck C, Ko YA, Susztak K. Precision Medicine Approaches to Diabetic Kidney Disease: Tissue as an Issue. Curr Diab Rep 2017;17:30.
46. Tong L, Adler SG. Diabetic Kidney Disease. Clin J Am Soc Nephrol 2018;13:335-8.
47. Williams ME. Diabetic nephropathy: the proteinuria hypothesis. Am J Nephrol 2005;25:77-94.
48. American Diabetes Association (ADA). Standard of medical care in diabetes – 2017. Diabetes Care 2017;40:S4-128.
49. Roche Diagnostics Ltda. Compendium of Urinalysis. Urine Test Strips and Microscopy, Switzerland, Roche; 2011.
50. Fogazzi GB. The Urinary Sediment. 3rd edition. Milano: Elsevier, 2010.
51. Hommel E, Carstensen H, Skøtt P, et al. Prevalence and causes of microscopic haematuria in type 1 (insulin-dependent) diabetic patients with persistent proteinuria. Diabetologia 1987;30:627-30.
52. Waz WR, Quattrin T, Feld LG. Hematuria in children and adolescents with insulin-dependent diabetes mellitus. J Diabetes Complications 1995;9:194-7.
53. Parving HH, Gall MA, Skøtt P, et al. Prevalence and causes of albuminuria in non-insulin-dependent diabetic patients. Kidney Int 1992;41:758-62.
54. Wong TY, Choi PC, Szeto CC, et al. Renal outcome in type 2 diabetic patients with or without coexisting nondiabetic nephropathies. Diabetes Care 2002;25:900-5.
55. Heine GH, Sester U, Girndt M, et al. Acanthocytes in the urine: useful tool to differentiate diabetic nephropathy from glomerulonephritis? Diabetes Care 2004;27:190-4.
56. O'Neill WM Jr, Wallin JD, Walker PD. Hematuria and red cell casts in typical diabetic nephropathy. Am J Med 1983;74:389-95.
57. Kitazawa M, Tomosugi N, Ishii T, et al. Rapidly progressive glomerulonephritis concomitant with diabetic nephropathy. Intern Med 1997;36:906-11.
58. Nakamura T, Ushiyama C, Suzuki S, et al. Urinary excretion of podocytes in patients with diabetic nephropathy. Nephrol Dial Transplant 2000;15:1379-83.
59. Dong ZY, Wang YD, Qiu Q, et al. Dysmorphic erythrocytes are superior to hematuria for indicating non-diabetic renal disease in type 2 diabetics. J Diabetes Investig 2016;7:115-20.
60. Morcos M, Sayed AA, Bierhaus A, et al. Activation of tubular epithelial cells in diabetic nephropathy. Diabetes 2002;51:3532-44.
61. Abedini A, Zhu YO, Chatterjee S, et al. Urinary Single-Cell Profiling Captures the Cellular Diversity of the Kidney. J Am Soc Nephrol 2021;32:614-27.

doi: 10.21037/jlpm-21-20
Cite this article as: Poloni JAT, Rotta LN. Diabetic kidney disease: pathophysiological changes and urinalysis contribution to diagnosis—a narrative review. J Lab Precis Med 2022;7:3.