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A story of microalbuminuria and diabetic nephropathy

Bijan Roshan[1,*], Robert C. Stanton[2]

[1] Division of Renal Diseases and Hypertension, University of Colorado Denver, 12700 East 19th Ave. Room 7015Aurora, CO 80045, USA
[2] Joslin Diabetes Center and Harvard Medical School, One Joslin Place, Renal Division. Boston, MA 02215, USA

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ABSTRACT

Context: It is estimated that more than 346 million people worldwide have diabetes mellitus . By the year 2030, it is predicted that diabetes will become the seventh leading cause of death in the world. Development of chronic kidney disease (CKD) in patients with diabetes adds significantly to the morbidity and mortality and significantly increases health care costs, even before the development of end stage renal disease (ESRD).

Evidence acquisitions: Directory of Open Access Journals (DOAJ), Google Scholar, Pubmed (NLM), LISTA (EBSCO) and Web of Science have been searched.

Results: Diabetic nephropathy (DN) is increasing rapidly worldwide. It is the leading cause of new cases of ESRD in the USA. Interestingly, although DN is the most common cause of ESRD in diabetic patients, diabetes mellitus is also an independent and strong risk factor for ESRD ascribed to causes other than DN (e.g. hypertensive nephropathy).

Conclusions: It is important to be aware of the pitfalls of using the urine albumin level in predicting development and progression of diabetic nephropathy in order to treat and advise the patients accurately. Research into finding new markers is rapidly evolving but current progress makes it likely we will be using the urine albumin level for some years into the future.

Review Article

Implication for health policy/practice/research/medical education:
It is important to be aware of the pitfalls of using the urine albumin level in predicting development and progression of diabetic nephropathy in order to treat and advise the patients accurately. Research into finding new markers is rapidly evolving but current progress makes it likely we will be using the urine albumin level for some years into the future.

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1. Context

It is estimated that more than 346 million people worldwide have diabetes mellitus (1). By the year 2030, it is predicted that diabetes will become the seventh leading cause of death in the world (1). Development of chronic kidney disease (CKD) in patients with diabetes adds significantly to the morbidity and mortality and significantly increases health care costs, even before the development of end stage renal disease (ESRD) (2).

2. Evidence acquisition

Directory of Open Access Journals (DOAJ)

*Corresponding author: Dr. Bijan Roshan, MD, FASN1 Division of Renal Diseases and Hypertension, University of Colorado Denver, 12700 East 19th Ave. Room 7015Aurora, CO 80045, USA. email: bijan.roshan@ucdenver.edu

Google Scholar, Pubmed (NLM), LISTA (EBSCO) and Web of Science were searched with key words relevant to microalbuminuria, diabetic nephropathy, and chronic kidney disease.

3. Results

Diabetic nephropathy (DN) is increasing rapidly worldwide. It is the leading cause of new cases of ESRD in the USA. Interestingly, although DN is the most common cause of ESRD in diabetic patients, diabetes mellitus is also an independent and strong risk factor for ESRD ascribed to causes other than DN (e.g. hypertensive nephropathy) (3).

Diabetic nephropathy may be accurately diagnosed by renal biopsy. But a biopsy is usually not done unless there is suspicion that a kidney disease would be discovered that would be treated in different manner than diabetes and hypertension. Recently a new classification of DN was develop by the Renal Pathology Society with the intent of providing researchers and clinicians with a consistent way to assign biopsy results for future studies (4, Table 1 and figure 1). It is based on glomerular lesions, with a separate evaluation for interstitial and vascular lesions as well (4). In this classification, progression evolves from GBM thickening to mesangial expansion to so-called Kimmelstiel–Wilson (KSW) lesions, and finally to global glomerulosclerosis in different glomerular DN classes. This is a pathologic classification only at this juncture. The authors hope that this classification system will be helpful to unify the terminology of DN among various clinicians, researchers, and pathologists for future studies but they also acknowledge that this classification is not intended to be predictive of clinical outcomes (4). Hence the diagnosis of diabetic nephropathy has remains primarily based on the development of increased albuminuria usually associated with preexisting retinopathy and decreasing GFR. But as discussed below, recent studies have significantly altered our traditional diagnostic expectations.

The clinical syndrome of DN was initially characterized more than 60 years ago by investigators at the Joslin Diabetes Center (5). Soon after, it was recognized that hyperglycemia may lead to an increase in the level of urine albumin (6). Later, the term microalbuminuria (7) was

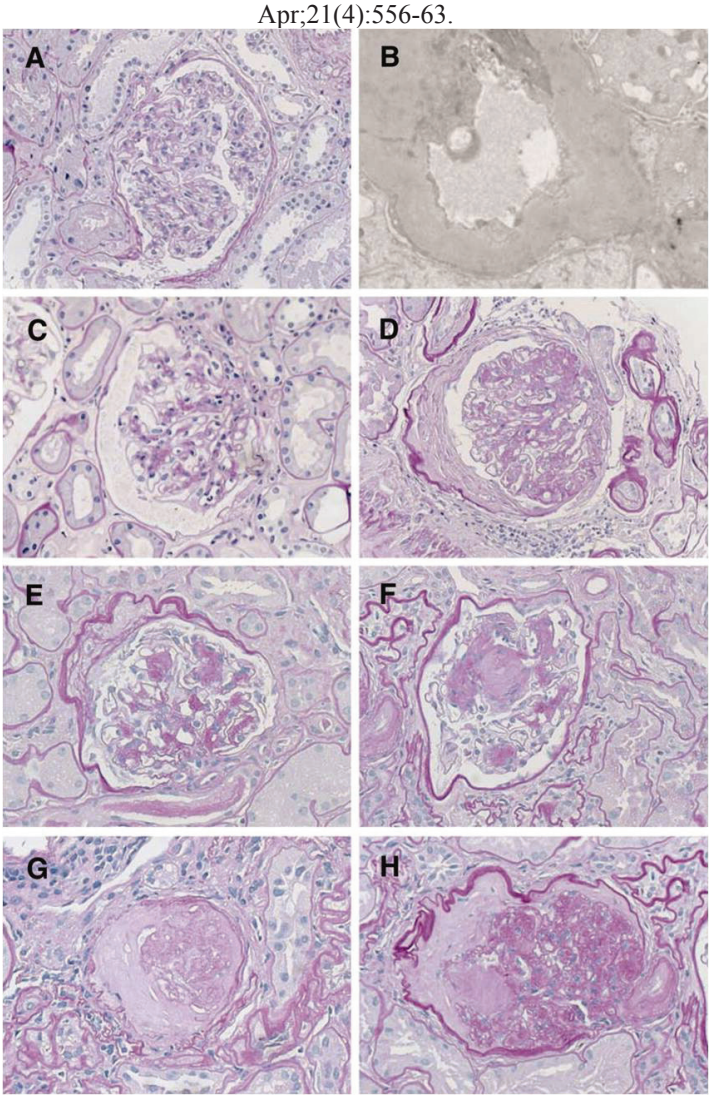
Table 1. Glomerular Classification of Diabetic Nephropathy (adopted with permission from J Am Soc Nephrol. 2010 Apr;21(4):556-63).

Class	Description	Inclusion Criteria
I	Mild or nonspecific LM changes and EM-proven GBM thickening	Biopsy does not meet any of the criteria mentioned below for class II, III, or IV
		GBM > 395 nm in females and >430 nm in males> 9 years old
IIa	Mild mesangial expansion	No criteria for class III or IV
		Mild mesangial expansion in >25% of the observed mesangium
IIb	Severe mesangial expansion	No criteria for class III or IV
		Severe mesangial expansion in >25% of the observed mesangium
III	Nodular sclerosis (Kimmelstiel–Wilson lesion)	No criteria for class IV
		At least one convincing Kimmelstiel–Wilson lesion
IV	Advanced diabetic glomerulosclerosis	Global glomerular sclerosis in >50% of glomeruli
		Lesions from classes I through III

LM: light microscopy. GBM: glomerular basement membrane. GBM thickness based on direct measurement of GBM width by EM

coined to describe a small increase in the level of albumin of normal urine protein without an associated significant rise in the total urine protein level (the term has caused some confusion as micro refers to quantity and not protein size). Initial definitions were based on an hourly excretion rate of urinary albumin and subsequently the 24 hour excretion of 30-300 mg of albumin was adopted as the microalbuminuric range that correlated to the hourly definitions. 25 years ago studies showed that a spot urine sample used to measure the albumin to creatinine ratio (ACR) accurately reflects the total 24 hour level of urine albumin excretion and the ACR is now recommended by the American Kidney Foundation as the screening tool for patients with diabetes. The spot ACR in a first-morning void has been shown to be superior to a 24-hour urine collection in predicting

Figure 1. Pathologic stages of DM nephropathy (adopted with permission from J Am Soc Nephrol. 2010. Apr;21(4):556-63.



A, B) **Class I.** Glomerulus showing only mild ischemic changes, with splitting of Bowman's capsule in A. EM of the same glomerulus in B shows the increased width of the GBM consistent with class I.
C, D) **Class II.** Glomeruli with mild and moderate mesangial expansion, respectively that does not exceed the mean area of a capillary lumen in C **(IIa)**, whereas in panel D it does **(IIb)**.
E, F) **Class IIb** vs. **Class III**. In panel F there is a class III KSW lesion. The lesion in panel E is not **a convincing** KSW.
G, H) Glomerulosclerosis vs. **Class IV.** In panel H, DN consist of hyalinosis of the glomerular vascular pole and a remnant of a KSW lesion on the opposite site of the pole. Panel G is an example of glomerulosclerosis of undetermined cause.

renal events in patients with type 2 diabetes and nephropathy (8). Using the ACR, microalbuminuria is defined as being between 30-300 mg/g (9).

In the 1980's based on studies in type 1 diabetic patients with DN, Mogensen and colleagues developed a staging classification for the evolution of DN that became the widely accepted clinicpathologic classification for diabetic nephropathy (10-13) (Table 2). Most studies of the evolution of DN have used Type 1 diabetes patients to avoid the confounding effect of other comorbid factors in type 2 diabetes patients. Indeed, this staging pattern may not be the same in patients with Type 2 diabetes with DN as Type 1 DN patients due to these comorbid factors. For example the pathogenesis of DN is likely also affected by the metabolic syndrome, hyperinsulinemia, and a greater percentage of patients with hypertension as compared to Type 1 DN patients. Yet there are many similar pathologic patterns observed in kidney biopsies from both Type 1 and 2 patients with DN (14). So the staging patterns have been applied to both patients with Type 1 and Type 2 diabetes. The stages are described below.

Stage 1: This may be present at diagnosis of diabetes in patients with Type 2 diabetes as it is not known how long the patient has had diabetes but usually is not seen for at least 3-5 years after the diagnosis of Type 1 diabetes. It is frequently associated with increased kidney size and enlarged glomeruli. It may also be associated with significant increases in the glomerular filtration rate (GFR). This supranormal GFR is called glomerular hyperfiltration. **Stage 2:** GFR may decrease to near normal levels. Blood pressure and urine albumin excretion remain in the normal range and clinically nephropathy remains undetectable at this stage. **Stage 3:** This stage occurs after 6-15 years. Thickening of basement membrane in the glomeruli is observed as well as mesangial matrix expansion. Incipient increases in blood pressure may be seen in Type 1 DN at this time. Type 2 diabetics may have hypertension even before development of nephropathy. GFR may still be supranormal but starting to decline. In **Stage 4**, there is a more pronounced development of structural changes as noted in Table 2. This stage can be seen from 10-25 years after appearance of DM. Increasing hypertension and a more rapid fall in GFR (usually 10 ml/min per year) without treatment are prominent features. **Stage 5:** This is end stage kidney disease. It can occur any time from 10-30 years after diabetes is diagnosed. Of note, proteinuria may decline significantly due to the small number of functioning glomeruli.

This classic model has been challenged by recent studies though as follows:

1. Glomerular hyperfiltration does not have an impact on the development of microalbuminuria in Type 1 diabetes during up to15 years follow up (15).

Table 2. Staging System for Diabetic Nephropathy.

Stage 1.	Glomerular Hyperfiltration.. The earliest observation in development of nephropathy is an increase of up to 50% in the glomerular filtration rate (GFR).
Stage 2.	Thickening of the glomerular capillary basement membrane (BM) is found histologically.
Stage 3.	Development of microalbuminuria (20-200 mcg/min or 30-300mg/24 h, not detectable by routine urine dipsticks).
Stage 4.	Overt diabetic nephropathy and macroalbuminuria (>200mcg/min or >300mg/24 h, that is detectable by routine dipsticks
Stage 5	End-stage renal disease (ESRD) (usually 25-30 years after diagnosis) with glomerular closure and resultant decrease in proteinuria.

2. A carefully done recent analysis of albuminuria in Type 1 diabetes patients showed that microalbuminuria often regresses to normoalbuminuria in Type 1 diabetes that is independent of the use of renin-angiotensin blockade (16). This study has changed our view of the inevitability of progression of DN in Type 1 patients and is in contrast to earlier studies of microalbuminuria that showed a 60-85 percent risk of a progression to overt proteinuria within 6 to 14 years (11-13). Development of microalbuminuria increases the risk of progression to overt diabetic nephropathy, but this risk is far less than certain.

3. In diabetic patients with new-onset microalbuminuria the development of advanced chronic kidney disease may not require progression to proteinuria (17).

4. Normoalbuminuric CKD and lack of the presence of retinopathy (it used to be thought that retinopathy always preceded nephropathy in diabetic patients) not attributable to causes other than diabetes is well-recognized in diabetic patients. In a cross sectional study of adults aged 40 years or older with type 2 DM, retinopathy and albuminuria (microalbuminuria or macroalbuminuria) were both absent in 30% of the study subjects. (18). Moreover the use of angiotensin converting enzyme inhibitors (ACEI) did not alter this percentage as 33% of those taking ACEI had no retinopathy or albuminuria (18).

5. A recent evaluation of participants in the DCCT/EDIC Study, a ten-year cumulative incidence of progression to macroalbuminuria was 28%, impaired GFR was 15%, ESRD was 4%, and regression to normoalbuminuria was 40%. (19). This, again is in agreement to the findings that many patients with microalbuminuria regress to normoalbuminuria and do not progress to ESRD.

These recent findings have raised growing concerns about the value of "microalbuminuria" - at least by the accepted definition -as a very predictable marker of progression to ESRD and even to overt diabetic nephropathy in a diabetic patient as the predictive value is even less than 50% over long term. On the other hand, microalbuminuria increases the relative risk of development of diabetic and non-diabetic nephropathy that is significant at epidemiologic scales. Also levels of urinary albumin excretion, even within the "normal" range, are associated with increasing risk for cardiovascular end points among individuals even without DM (20, 21). In a prospective study of women without hypertension and diabetes and with normoalbuminuria from the first and second Nurses' Health Studies, the average ACR was <3mg/g (22). In this study, participants who had an ACR in the highest quartile (with average ACR of only 6.5 and 5.4 mg/g in first and second studies) were more likely to develop hypertension (22). Whereas the threshold of urinary ACR of 30 mg/g is too low to predict renal outcomes in diabetic patients, it is likely that an ACR of 30 mg/g is likely too high to predict endothelial dysfunction and risk for cardiovascular outcomes. Indeed the definition of "normoalbuminuria" of ACR of <30 mg/g is quite arbitrary and does not necessarily represent any statistical definition of "normal". Hence the level of risk for ACR depends on whether one is considering cardiovascular risk or kidney disease risk. Once better predictors/markers/screening tools for diabetic nephropathy are found, it is likely the normal ACR will perhaps be described as <10 mcg/g as an abnormal test and used primarily as a marker for endothelial dysfunction.

Recent studies have provided some possible new markers for DN. Joslin Diabetes Center investigators have looked at a large candidate list of circulating markers in type 1 (23, 24) and

Type 2 diabetic patients (25). Serum concentrations of the soluble receptors 1 and 2 for Tissue Necrosis Factor (sTNFR1 and sTNFR2) had a stronger correlation with decline in GFR than urinary ACR (23, 24). sTNFR1 was associated with development of ESRD in type 2 patients during 12 year follow up (24). Urinary levels of connective tissue growth factor (CTGF) has also been found to be helpful in predicting GFR decline in patients with type1 DM (26). Moreover high uric acid, even in the high normal range has also been associated with prediction of decline in renal function in DN (27). Another approach being evaluated is to use a composite index marker similar to The Framingham Risk Calculator that is used in cardiovascular medicine. This index might be made of known clinical markers (e.g. average A1C, blood pressure, duration of diabetes, presence of retinopathy, etc) and laboratory predictors of progression of DN (including level of albuminuria as well as presence of other biomarkers). Various research groups are working on this research.

4. Conclusions

It is important to be aware of the pitfalls of using the urine albumin level in predicting development and progression of diabetic nephropathy in order to treat and advise the patients accurately. Research into finding new markers is rapidly evolving but current progress makes it likely we will be using the urine albumin level for some years into the future.

Conflict of interest

The author declared no competing interests.

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