Chapter 45

Evaluation of Diabetic Nephropathy: Clinical Recommendations

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Diabetic nephropathy is clinically defined by the presence of persistent proteinuria of > 500 mg/day in a diabetic patient who has concomitant diabetic retinopathy and hypertension and in the absence of clinical or laboratory evidence of other kidney or renal tract disease. The presence of diabetic retinopathy is an important pre-requisite because in its absence, albuminuria in a Type 2 diabetic patient may be due to diabetic or non-diabetic glomerulosclerosis and the chances for both are equal[1].

Diabetic nephropathy is the leading cause of chronic renal failure worldwide.

Racial differences in the prevalence of diabetic renal disease between the people of Asian ethnic origin and White Caucasians have been reported in the United Kingdom. According to Shaw, et al migrant Asian Indians had 40 times greater risk of developing end stage diabetic nephropathy (ESRD) when compared with the Caucasians[2].

Thus with India leading the rest of the world in claiming highest diabetic population and diabetes mellitus leading the rest of the diseases in being one of the commonest causes of end-stage renal disease and chronic renal failure, it becomes imperative for us in this country to evolve definite guidelines for evaluation of diabetic nephropathy and suggest practicable clinical recommendations to combat it.

To understand the precise methods of evaluation of diabetic nephropathy at different stages, it is important to briefly dwell on the clinical course and presentation of diabetic nephropathy.

CLINICAL COURSE AND MARKERS FOR EVALUATION

Although natural history of diabetic nephropathy has been better described in Type 1 DM, the classification of nephropathy (Table 1) by Mogensen into several distinct phases in general, can be applied to both forms

Table 1: Stages of renal involvement in type 1 DM

Stage		Main features	Blood pressure	Duration
1.	Hyperfiltration and hyperperfusion	More often seen in Type 1 DM. Large kidneys, Glomerular hyperfiltration GFR supra-normal UAE <15 µg/min	Normal	Found at diagnosis
2.	"Silent stage" Normoalbuminuria	GBM thickening Glomerular hypertrophy Mesangial thickening interstitial expansion UAE <15-20 µg/min GFR ↑↑	Normal or Slightly elevated	Found at about 2 years of diabetes
3.	Microalbuminuria Incipient diabetic Nephropathy or 'At Risk Patients'	UAE 20-200 µg/mt GFR still ↑ but begins to decline. Can be reversed by anti-hypertensive treatment and tight glycaemic control	Often elevated	Develops after about 8-12 years of diabetics
4.	Overt diabetic nephropathy	Clinical proteinuria albustix positive GFR ↓ N or ↓↓ UAE ↑↑↑	Frank hypertension	After 15-20 yrs of diabetes
5.	Stage of ESRF	Glomerular sclerosis and very low GFR		

UAE : urinary albumin excretion, GFR: glomerular filtration rate

of diabetes. Microalbuminuria is defined by urinary albumin excretion rate of 20-200 µg/minute in the absence of urinary tract infection, exercise, malignant hypertension and left ventricular failure. It is predictive of overt proteinuria particularly in Type 1 DM. Prospective studies have shown that blood pressure slowly rises during the transition of the patient from normoalbuminuria to microalbuminuria. It predicts development of overt nephropathy and ultimately renal failure, especially in Type 1 DM. However, in Type 2 DM, microalbuminuria may be associated with many other conditions. It is a good marker for development of cardiovascular disease and left ventricular diastolic dysfunction. Microangiopathy such as diabetic retinopathy, endothelial dysfunction, dyslipidemia, elevated apolipoprotein B, low HDL, insulin resistance and smoking may also be associated with micro-albuminuria.

STAGE I: STAGE OF HYPERPERFUSION AND HYPERFILTRATION

This stage is seen at diagnosis of Type I DM. Renal vasodilatation and hyper-filtration occur at this stage[3]. Glomerular filtration rate (GFR) is increased in 90-95% of Type 1 DM and in 41% of Type 2 DM[4]. Increased renal plasma flow (RPF) and low plasma oncotic pressure are main causes of increased GFR. Interestingly, GFR is greater for any given RPF. This indicates increased glomerular capillary hydrostatic pressure in diabetics.

STAGE II: SILENT STAGE

Clinically silent morphological changes in diabetes begin to occur at about 2 years in the form of GBM thickening. This is followed by increase in mesangial volume and interstitial expansion in those patients in whom the renal disease progresses. Similar changes also occur in Type 2 DM although at variable timing[5]. There is a basic difference between Type 2 DM and Type I DM in their histological changes. Early in the course of nephropathy, typical Kimmelstein-Wilson lesions of diabetic glomerular sclerosis are seen less frequently in Type 2 DM, because of ageing, ischemia or both. Instead they have more of nonspecific vascular and interstitial changes. However, in advanced cases of diabetic nephropathy, KW lesions occur in high percentage of patients.

At this stage patients still have UAE between 15 and 20 mgm/min. There may be transient microalbuminuria with exercise, which normalizes at rest. Glomerular filtration rate is high and blood pressure is usually normal or slightly elevated. Type 2 DM patients with microalbuminuria show increased glomerular volume suggesting microalbuminuria is a marker for diabetic renal disease irrespective of GFR.

STAGE III: MICROALBUMINURIA STAGE

This stage is said to have arrived when UAE is between 20-200 mg/min or 30-300 mg/24 hr. Patients with microalbuminuria have negative urine dipstick for protein and less than 300 mg in 24 hours. This stage is also called stage of incipient diabetic nephropathy, typically found after 8-12 years. Glomerular filtration rate is still high and blood pressure starts to increase, more so during exercise.

In Type 1 DM microalbuminuria is a risk factor for progression to nephropathy. In Type 2 DM it is less predictive because of comorbid conditions which are also associated with microalbuminuria and death may occur before development of nephropathy. Micro-albuminuria is also associated with increased risk of cardiovascular death in both forms of diabetes. Recent studies have shown that better glycemic control and use of angiotensin converting enzyme (ACE) inhibitor can retard the progression in Type 1 DM[6].

STAGE IV: OVERT DIABETIC NEPHROPATHY

This stage is defined by onset of clinical proteinuria, i.e. persistent dipstick positive albuminuria (UAE > 300 mg/ day or urinary protein excretion of more than 500 mg/ day) and it occurs 15-20 years after onset of Type 1 DM and after 10-12 years of Type 2 DM. It is characterized by classical morphological lesions but diagnosis is made on clinical grounds. In Pima Indians incidence of proteinuria has been found to be 23% after 15 years of diabetes and 50% after 20 years[7]. Recent studies show that the incidence of nephropathy in Type 2 DM is as high as it is in Type1 DM[8].

STAGE V: END-STAGE RENAL FAILURE

This stage is characterized by generalized glomerular sclerosis and very low GFR. The development of uremia is associated with number of other complications such as fluid retention and edema.

Apart from uremia, many patients have hyper-kalemia due to type IV renal tubular acidosis, diabetic cystopathy or autonomic neuropathy. Gastroparesis and intestinal hurry may present as feature. Associated infections such as urinary tract infection, carbuncles, cellulitis, pulmonary tuberculosis, spontaneous bacterial

peritonitis are fairly common in our patient population. Some elderly diabetic renal failure patients may have an additional problem of benign hyperplasia of prostate, with obstructive uropathy complicating diabetic nephropathy.

Disturbances of lipid metabolism of diabetes and uremia, combined with systemic hypertension contribute to the development of severe atherosclerotic disease.

RISK FACTORS FOR NEPHROPATHY IN TYPE 2 DM

1. Duration of diabetes
2. Poor glycemic control
3. Hypertension
4. Genetic Predisposition
5. Renal hypertrophy
6. Race
7. Smoking

DETECTION

Increased urinary protein excretion is the earliest clinical finding of diabetic nephropathy[9,10].

MICROALBUMINURIA

Establishing the presence of microalbuminuria requires demonstration of a persistent elevation in albumin excretion. Fever, exercise, heart failure, and poor glycemic control are among the factors that can cause transient microalbuminuria.

A 24 hour urine collection is the gold standard for detection of microalbuminuria[11]. However, it has been suggested that screening can be more simply achieved by a timed urine collection or an early morning specimen to minimize changes in urine volume that occur during the day.

One problem with measuring the albumin concentration alone or estimating it with a sensitive dipstick is that false negative and false positive results can occur since the albumin concentration (but not the rate of albumin excretion) is also influenced by the urine volume. The confounding effect of the urine volume can be minimized by repeated measurements on early morning specimens.

In Type 2 Diabetes Mellitus, however, microalbuminuria is a marker of generalized endothelial dysfunction and

- May be non-specific

- Correlated with systolic hypertension
- Associated cardiovascular disease
- Associated peripheral vascular disease
- Coronary artery disease occurs earlier than ESRD
- Associated with premature atherosclerosis
- Abnormal lipid profile
- Pronounced increased mortality
- Correction of microalbuminuria in isolation may not affect events appreciably[12].

Screening for Albuminuria

The methods adopted may be

24 hour collection along with measurement of creatinine clearance (mg/24 hours).

Timed collection (µg/min).

Spot collection to look for albumin to creatinine ratio (µg/mg creatinine). Sample should not be taken in the immediate post-exercise period.

RECOMMENDATIONS FOR SCREENING

In Type 1 DM, screening should begin with puberty and after 5 years duration of diabetes.

In Type 2 DM, however, screening is recommended at the time of diagnosis and if negative, every year.

Routine urinalysis should be performed annually.

An algorithmic approach[13] is outlined in Flow Chart 1.

The effect of volume can be avoided entirely by calculation of albumin-to-creatinine ratio in an untimed urine specimen.

Use of albumin-to-creatinine ratio has been recommended as the preferred screening strategy for all diabetic patients. It does not require early morning or timed collections, it gives a quantitative result that correlates with the 24-hour urine values over a large range of proteinuria, it is cheap to perform, and repeat values can be easily obtained to ascertain that microalbuminuria, if present, is persistent.

Limitations

There are, however, three important caveats that must be considered to maximize the reliability of this test.

- Vigorous exercise can cause a transient increase in albumin excretion. As a result, patients should refrain from vigorous exercise in the 24 hours prior to the test.

Definitions of Abnormal Albumin Excretion

Category	24 hour collection (mg/24 h)	Timed collection (µg/min)	Spot collection (µg/mg creatinine)
Normal	< 30	<20	<30
Microalbuminuria	30-300	20-200	30-300
Overt albuminuria	>300	>200	>300

- The slope of the relationship between the spot urine and the 24 hour collection varies throughout the day. The correlation is best if samples are taken in the mid-morning; mid-afternoon specimens are also relatively accurate.
- The accuracy of albumin-to-creatinine ratio will be diminished if creatinine excretion is substantially different from the expected value; this is particularly important in patients with borderline values.

RECOMMENDATIONS FOR FOLLOW-UP CARE

Glycemic Control

Microalbuminuria appears to represent a stage of diabetic nephropathy at which treatment is often successful in preventing progress of renal disease. Tight control of plasma glucose concentration (particularly if the HbAlc value is less than 8.5%) can stabilize or reduce the degree of protein excretion particularly in Type 1 diabetics.

Blood Pressure Control

Albumin excretion can also be lowered and progression to overt proteinuria reduced by aggressive blood pressure control, preferably with an ACE inhibitor or Angiotensin Receptor Blocker (ARB).

ROLE OF ACE INHIBITORS AND AR BLOCKERS

ACE inhibitors and ARBs lower protein excretion and may preserve renal function in diabetics with microalbuminuria.

A separate issue is whether ACE inhibitors or ARBs are effective as preventive therapy in normotensive, normoalbuminuric patients with Type 2 Diabetes.

Dietary Protein Intake

Recommended dietary allowance of protein intake by American Diabetes Association (ADA)[14] is 0.6-0.8 gm/ kg body weight/day in patients with diabetic

Flow Chart 1: Algorithmic approach for urinary screening in diabetic population
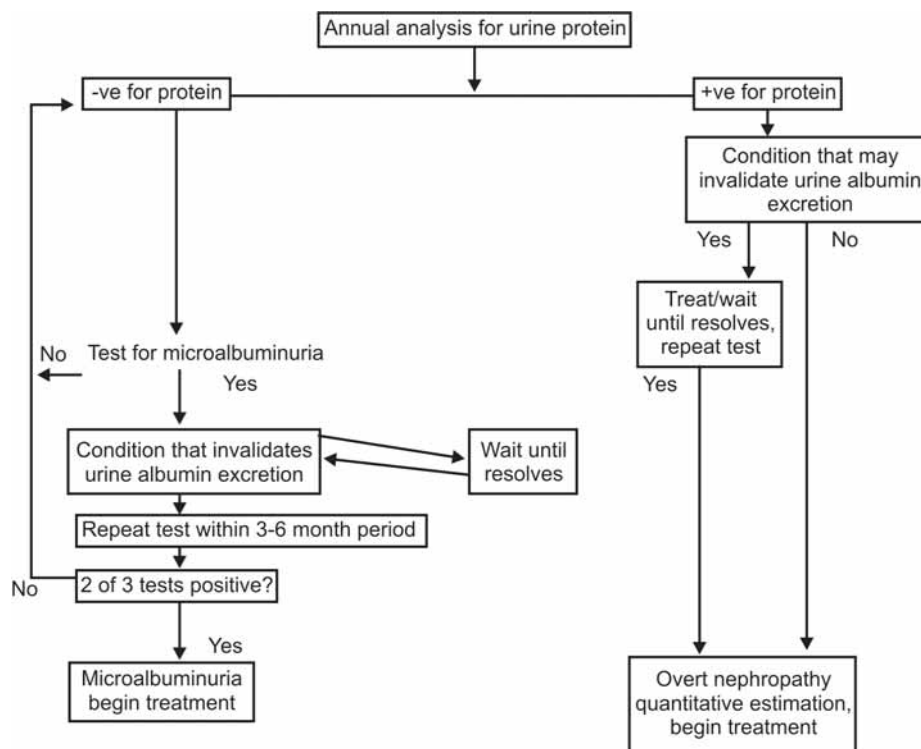
nephropathy. It is generally believed that an average Indian diet does not exceed this limit. In a cross-sectional study by Vijay et al,[15] it was shown that the prevalence of microalbuminuria and macroproteinuria did not differ among vegetarians and non-vegetarians.

Specific Therapies

These include modification and / or treatment of associated risk factors such as hyperlipidemia, smoking and hypertension.

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