Early Recognition and Treatment of Diabetic Kidney Disease

Ahmed SS[1], Rizwan MASM[2], Khan MAM[3], Laila TR[4], Hafez MA[5]

Abstract

Diabetic kidney disease (DKD) is a progressive condition and is an important cause of end stage renal disease (ESRD) as well as a risk factor for cardiovascular morbidity and mortality. This paper reviews various evidence based clinical guidelines, scientific papers and research studies on early detection and treatment of DKD. Microalbuminuria describes the urinary excretion of small amounts of albumin which identifies the early stage of DKD. In addition to an earliest marker of kidney damage, microalbuminuria is an established high risk factor for cardiovascular morbidity and mortality. Patients with microalbuminuria who progress to macroalbuminuria are likely to progress to ESRD. However effective treatment in the early stage of DKD reduces the risk and slows the progression of kidney damage. There is general agreement that people with diabetes should be screened regularly to detect early markers of kidney damage. People with diabetes and microalbuminuria should be treated with a multifactorial intervention approach to retard the progression of DKD. Studies have clearly demonstrated that the use of angiotensin converting enzyme inhibitors or angiotensin 2 receptor blockers with improved glycemic control, hypertension control, lipid lowering, aspirin use, smoking cessation, exercise programs and dietary intervention reduced the development of overt nephropathy and ESRD.

Key words: *Diabetic kidney disease, Diabetic nephropathy, Microalbuminuria, Macroalbuminuria, End stage renal disease.*

1. Corresponding Author:
Prof. Dr. Sheikh Salahuddin Ahmed
MBBS, FCPS (Internal Medicine)
Professor & Head of the Department of Medicine
Bangladesh Institute of Health Sciences (BIHS)
125/1, Darus Salam, Mirpur-1, Dhaka 1216, Bangladesh
E mail: drsksalahahmed@yahoo.com

2. Dr. Md. Abu Saleh Mohammad Rizwan, MBBS
Bangladesh Institute of Health Sciences (BIHS)
125/1, Darus Salam, Mirpur-1, Dhaka 1216, Bangladesh

3. Dr. Md. Abdul Mahid Khan, MBBS, D Card, MRCP
Assistant Professor, Department of Cardiology
Bangladesh Institute of Health Sciences (BIHS)
125/1, Darus Salam, Mirpur-1, Dhaka 1216, Bangladesh

4. Dr. Tarafdar Runa Laila, MBBS, FCPS, MS (Obs & Gyne)
Assistant Professor, Department of Obstetrics & Gynecology
Bangabandhu Sheikh Mujib Medical University
Shahbag, Dhaka, Bangladesh

5. Prof. Md. Abdul Hafez, MSc (Statistics), MSc (Med Demog)
Professor & Head, Department of Biostatistics
Bangladesh University of Health Sciences (BIHS)
125/1, Darus Salam, Mirpur-1, Dhaka 1216, Bangladesh

Introduction

Diabetes mellitus (DM) has been found to be the leading cause of ESRD in the developed countries like United States (US), Europe and Australia[1-5]. DKD occurs in 20–40% of patients with diabetes[6]. In Bangladesh, there is no national data on the prevalence of kidney disease in people with diabetes. Microalbuminuria is the earliest marker of DKD and a risk factor for the development of cardiovascular morbidity and mortality[7-10]. The prevalence of microalbuminuria in patients with diabetes is 10-30%[11]. DKD is a progressive condition; patients with microalbuminuria who progress to macroalbuminuria represents a more severe and established form of renal disease, are likely to progress to ESRD, and are more predictive of cardiovascular mortality and morbidity than microalbuminuria[2,12]. Patients who progress to ESRD require renal replacement therapy (RRT) to sustain life. RRT includes maintenance dialysis and kidney transplantation. But most of the people in our country are not able to afford the treatment cost as dialysis or kidney transplantation is very expensive and facilities of such treatment are not widely available. However, there is strong evidence that a number of interventions if initiated at early stage of DKD reduce the risk and slow the progression of kidney damage[6]. Therefore the two main purposes of early detection and treatment of DKD are (i) to prevent progression to ESRD and (ii) to prevent cardiovascular morbidity and mortality.

Diabetic Kidney Disease

The term DKD refers to kidney disease caused by diabetes[13]. DKD is usually diagnosed on the basis of a raised urine albumin or a reduced glomerular filtration rate or GFR (< 60 ml/min/1.73 m2) persisting for 3 months or more[2,13]. Traditionally termed "diabetic nephropathy," is a clinical diagnosis that historically has been based on the findings of albuminuria with no other cause, in a person with diabetes[13]. The term diabetic glomerulopathy is reserved for biopsy-proven kidney disease caused by diabetes[13]. In most individuals the diagnosis of DKD is made clinically, as biopsy may not alter management of such patient. However a kidney biopsy may be required in some patients with diabetes and chronic kidney disease (CKD) to determine the underlying cause; and referral to a physician experienced in the care of kidney disease should be considered when there is uncertainty about the etiology of kidney disease (patients having heavy proteinuria, hematuria, active urine sediment, absence of retinopathy, rapid decline in GFR, resistant hypertension)[6].

The criteria for diagnosis of DKD vary somewhat between different guidelines. Most of the clinical guidelines consider microalbuminuria as the earliest stage of DKD[6-9,14]. American Diabetic Association (ADA) has considered microalbuminuria as the earliest clinical evidence of DKD, and patients with microalbuminuria are referred to as having incipient nephropathy[1]. The term overt nephropathy has been used to those diabetic patients having macroalbuminuria. Scottish intercollegiate guidelines network (SIGN) classify DKD, on the basis of the extent of urine protein excretion, as either microalbuminuria or nephropathy (having

macroalbuminuria)[8]. National Kidney Foundation (NKF), an organization in the US, considers CKD attributable to DKD in the presence of (1) macroalbuminuria or microalbuminuria plus retinopathy, and (2) in people with type 1 diabetes, in the presence of microalbuminuria plus duration of diabetes longer than 10 years[13].

Microalbuminuria and Macroalbuminuria

NKF, defines microalbuminuria as excretion of 30-300 mg of albumin in a 24 hour urine collection sample {equivalent to albumin excretion rate (AER) of 20-200 µg/min in a timed collection of urine; or albumin creatinine ratio (ACR) 30-300 mg/g without regard to age & sex in a random or spot sample of urine}, with values >300 mg/24 hour being defined as macroalbuminuria[13]. Macroalbuminuria is also known as clinical albuminuria or proteinuria (as it correlates with a urinary protein excretion 0.5 g/24 hour) [1,15].

Cut-off values and units of measurement for microalbuminuria differ somewhat among various clinical guidelines. ADA has defined microalbuminuria as excretion of 30-299 mg of albumin in a 24 hour urine collection (equivalent to albumin excretion rate of 20-199 µg/min in a timed collection of urine; or ACR 30-299 µg/mg creatinine in a random or spot sample of urine irrespective of sex), with values ≥300 mg/24 hour being defined as macroalbuminuria[1]. Microalbuminuria has been defined as 2.5-30.0 mg/ mmol (men) and 3.5-30.0 mg/mmol (women) in Europe[8,15,16], 2.0-20.0 mg/mmol (men) and 2.8-28.0 (women) in Canada[17], and 2.5-25.0 mg/mmol (men) and 3.5-35.0 (women) in Australia[3] and macroalbuminuria as > 20/28 mg/mmol, > 30 mg/mmol and > 25/35 mg/mmol respectively[2]. National Institute for Health and Clinical Excellence (NICE), a health organization in the United Kingdom (UK), defines microalbuminuria as ACR 2.5 to 25.0 mg/mmol in men and ACR 3.5 to 35 mg/mmol in women[18]. International Diabetes Federation (IDF) considers microalbuminuria ACR > 2.5 mg/ mmol in men, > 3.5 mg/mmol in women. An ACR > 30 mg/mmol indicates macroalbuminuria[2].

Glomerular Filtration Rate

The GFR is the best measure of overall kidney function[19]. The normal level of GFR varies according to age, sex, and body size. In healthy young adult of 30 years or younger, the normal GFR is approximately 125 mL/min per 1.73 m^2 and declines by approximately 1 mL/min per 1.73 m^2 per year thereafter[19]. Estimation of the GFR no longer requires a 24-hour urine collection for creatinine clearance but can be accomplished with similar accuracy using mathematic formulas most commonly used are the Modification of Diet in Renal Disease (MDRD) equation and the Cockcroft-Gault equation. Many laboratories now report an estimated GFR, (eGFR), using the MDRD equation which is based on serum creatinine, age, sex and race[3]. The MDRD has the advantage of being more accurate than the Cockcroft-Gault in persons with a GFR less than 90 mL/minute[19-22]. At GFR below 60mL/min, the prevalence of complications of CKD increases[23-25].

Measurement of creatinine clearance using timed (for example, 24-hour) urine collections does not improve the estimate of GFR over that provided by prediction equations. A 24-hour urine sample provides useful information for (a) estimation of GFR in individuals with exceptional dietary intake (vegetarian diet, creatine supplements) or muscle mass (amputation, malnutrition, muscle wasting), (b) assessment of diet and nutritional status and (c) need to start dialysis[19].

Natural History of Diabetic Kidney Disease

The natural history of DKD is characterized by a sequence of events that was initially defined for patients with type 1 diabetes (T1DM), but appears similar in type 2 diabetes (T2DM). The typical early clinical presentation of DKD is microalbuminuria, which generally appears 5–15 years after the patient is diagnosed with DM[14]. This is the earliest clinical evidence of DKD, and patients with microalbuminuria are referred to as having incipient nephropathy[1]. At this stage of CKD dipstick tests for proteinuria are typically negative. Without specific interventions, diabetic patients with microalbuminuria progress gradually to overt nephropathy by developing macroalbuminuria, edema and nephrotic syndrome; there is steady decline of GFR, rise of blood pressure and the pathological changes in the kidneys are likely irreversible[1,3]. Eventually, the characteristic clinical picture of renal failure develops. ESRD develops in 50% of type 1 diabetic individuals with overt nephropathy within 10 years and in >75% by 20 years[1]. Only 20% of type 2 diabetic patients with overt nephropathy will go on to ESRD within the next 20 years[26].

Reduction in GFR in patients with diabetes but no microalbuminuria is well described both in T1DM and T2DM[27,28]; kidney biopsy in such patients often shows histological evidence of DKD[29]. In one study it was found that up to 30% of people with T2DM who had a GFR < 60 ml/min/1.73 m2 remained normoalbuminuric[30,31]. Therefore, in diabetes, CKD may develop in the absence of abnormalities in urinary albumin excretion[1-3,13].

Screening for Diabetic Kidney Disease

Screening for DKD should include measurement of urinary albumin for microalbuminuria. As a significant proportion of people with DM may develop CKD in the absence of albuminuria, measurement of serum creatinine and eGFR is required in addition to measurement for albuminuria[1-3,13].

NKF and ADA recommends to commence initial screening at 5 years after the diagnosis of T1DM or from diagnosis of T2DM; and thereafter annually[1,6,13]. Microalbuminuria rarely occurs with short duration of T1DM[1]. There is currently no proven role of screening for microalbuminuria in patients who do not have diabetes[15]. Patients should not be screened during intercurrent illness or when other factors are present influencing proteinuria (e.g., urinary tract infection, congestive heart failure, acute febrile illness, menstruation or vaginal discharge, exercise within 24 hours, marked hyperglycemia, and high protein diet)[1,3,6,15]. The best possible metabolic control of diabetes should be achieved before investigating patients for microalbuminuria[15].

ACR is the recommended method for screening microalbuminuria in people with diabetes[6,18,32]. It is a useful surrogate marker for proteinuria and is used instead of the time consuming 24 hour urine collection; 24 hour collections are more burdensome and add little to prediction or accuracy[20,33]. Measurement of ACR in a random urine sample is often found to be easiest method to carry out by patients. But

there is a diurnal variation in urinary albumin loss, so ACR is best measured on an early morning specimen of urine[34]. Studies have shown that ACR measured in early morning samples correlates closely with 24 hour proteinuria[35]. An early morning sample is also required for the exclusion of orthostatic (postural) proteinuria. Where a first void specimen is not possible, a random urine specimen is acceptable[2,15]. Microalbuminuria can be detected by radioimmunoassay but dipsticks test is usually negative for microalbuminuria[36]. If protein is detectable on a standard urinalysis dipstick, macroalbuminuria (>300 mg of urinary albumin per day) is probably already present. Positive dipstick tests should be confirmed in the laboratory by measuring the ACR preferably on an early morning urine sample[15]. In addition to diurnal variation there is also marked day to day variation in urinary albumin excretion. Therefore, it is usual to require multiple positive tests, usually two out of three over a period of months, before microalbuminuria is confirmed. NKF and ADA designates a patient having microalbuminuria when at least two of three urinary collections done in a 3 to 6 month period show elevated levels of albumin[1,13]. Australian guidelines confirm microalbuminuria if at least two of three tests (including the screening test) are positive measured within 3 months. The first abnormal result of spot urine test should be confirmed on an early morning sample[3]. The Australian guidelines recommend a 24 hour urine collection for quantitation of protein excretion if AER or ACR screening is positive for macroalbuminuria[3].

Treatment of Early Diabetic Kidney Disease

Interventions initiated at early stage of DKD may postpone or prevent overt nephropathy. Once overt nephropathy is present, progression cannot be halted, only slowed. Treatments that lower urinary albumin excretion slow progression of DKD and improve clinical outcomes. Therefore albuminuria reduction should be considered a treatment target in DKD.

a. **Use of angiotensin converting enzyme (ACE) inhibitor or an angiotensin-2 receptor blocker (ARB) drugs:** Both ACE inhibitor or an ARB delay progression from micro- to macro-albuminuria in people with DM. A meta-analysis of several trials have shown that ACE inhibitors and ARBs can cause microalbuminuria to regress to no albuminuria in diabetes[37,38]. Systematic review also reveals that there is a reduction in the rate of progression of microalbuminuria to macroalbuminuria in patients with diabetes treated with ACE inhibitors or ARBs[37-39]. This effect appeared to be present in patients with or without hypertension, patients with T1DM or T2DM, and patients with or without normal GFR[40]. Various clinical guidelines have recommended treatment with an ACE inhibitors or ARBs in people with diabetes and microalbuminuria even they are normotensive[8,13,26,32,41,42]. ACE inhibitors and ARBs confer both cardioprotective and renoprotective effects. ACE inhibitors and ARBs preferentially lower intra-glomerular pressure and reduce proteinuria. People with T1DM having microalbuminuria should be treated with an ACE inhibitor irrespective of blood pressure (BP)[8,26]. People with T2DM having microalbuminuria should be treated with an ACE inhibitor or an ARB irrespective of BP[8]. ACE-inhibitors and ARBs have also been shown to delay progression of nephropathy in those who have macroalbuminuria and renal insufficiency (serum creatinine > 1.5 mg/dl) [2]. Therefore ACE inhibitors or ARBs should be used in individuals with micro- or macroalbuminuria, titrated to maximum tolerated dose against albumin excretion, aiming for complete normalization[2].

b. **Diabetes control:** Hyperglycemia is an independent risk factor for diabetic nephropathy[43]. Studies have shown that the glycosylated hemoglobin (HbA1c) level correlates with loss of renal function and that effective glycemic control prevents the onset and delays the progression of kidney disease in both T1DM and T2DM[44-51]. The Diabetes Control and Complications Trial (DCCT) [43] conducted in US, and the United Kingdom Prospective Diabetes Study (UKPDS) [44] have definitively shown that intensive diabetes therapy can significantly reduce the risk of the development of microalbuminuria and overt nephropathy in people with diabetes. Observational studies have reported a faster rate of progression of kidney disease in people with higher HbA1c level[47]. Therefore in diabetes, glycemic control should be optimized to prevent or delay progression of the microvascular complications of diabetes, including DKD.

c. **Hypertension control:** Elevated BP is strongly associated with the development of albuminuria in people with diabetes. Hypertension control decreases albuminuria, delays nephropathy, and improves survival in both T1DM and T2DM[52]. The UKPDS provided strong evidence that control of BP can reduce the development of nephropathy[53]. Studies have shown that in hypertensive patients with DM, ACE inhibitors/ARBs can reduce the level of albuminuria and the rate of progression of renal disease to a greater degree than other antihypertensive agents that lower blood pressure by an equal amount[53]. ACE inhibitors/ARBs have been shown to reduce major cardiovascular outcomes (i.e., myocardial infarction, stroke, death) in patients with diabetes[54,55], thus further supporting the use of these agents in patients with albuminuria, a cardiovascular risk factor. ACE inhibitors/ ARBs should be used for hypertension in diabetes with microalbuminuria titrated to maximum tolerated dose to control BP. Other drugs, such as diuretics, calcium channel blockers, and β-blockers, should be used as additional therapy if after 4–6 weeks sufficient blood pressure reduction has not occurred, or as alternate therapy in the rare individual unable to tolerate ACE inhibitors or ARBs[6].

When ACE-inhibitor/ARB therapy is started, some patients with CKD may have an initial decrease in GFR (usually less than 10 mL per minute per 1.73 m2), a mild increase in the serum creatinine concentration (less than 20 percent of the baseline value), and a mild increase in the potassium level (usually less than 0.5 mmol per L)[56]. Therefore, in people with CKD, serum creatinine and potassium levels should be measured and the GFR should be estimated before starting ACE inhibitor/ARB therapy. These measurements should be repeated between 1 and 2 weeks after starting ACE inhibitor/ARB therapy and after each dose increase[18]. ACE inhibitor/ARB therapy should not normally be started if the pretreatment serum potassium concentration is significantly above the normal reference range (typically more than 5.0 mmol/L) [18].

d. **Limitation of protein intake:** The effect of dietary protein restriction on kidney disease is the subject of debate. Some studies in patients with varying stages of DKD have shown that dietary protein restriction helps slow the progression

of albuminuria, GFR decline, and occurrence of ESRD[57-61]. However, the MDRD study and other several small trials were unable to demonstrate a robust benefit in delaying progression to advanced stages of CKD with dietary restriction of protein intake[57,62-65]. Nonetheless, restriction of dietary protein intake has been recommended for CKD patients. ADA recommends reduction of protein intake to 0.8–1.0 g/kg body weight/day in individuals with diabetes and the earlier stages of CKD and to 0.8 g/kg body weight/day in the later stages of CKD that may improve renal function[6]. Scottish guidelines do not recommend protein restrictions in patients with early stages of chronic kidney disease (stages 1-3)[8]. NKF targets dietary protein intake 0.8 g/kg body weight per day for people with diabetes and CKD stages 1-4[13]. Diets for people with diabetes have traditionally been 15% to 20% protein[66]. People with diabetes and CKD should avoid high-protein diets (≥20% of total daily calories)[13]. IDF guidelines advise limiting protein intake to 1 g/kg daily if proteinuric[2]. Protein restriction is not advisable in those with cachexia or low serum albumin.

e. **Other interventions:**

(i) Smoking is a strong risk factor for cardiovascular mortality in patients at risk for CKD[67]. Several lines of evidence have shown that smoking increases the risk and progression of diabetic nephropathy[67-69]. The results of one small study showed that smoking cessation reduced the progression of kidney disease by 30 percent in patients with T1DM[70]. People with DM should be informed that smoking increases the risk of CKD and cardiovascular disease, an individuals smoking cessation is an important recommendation irrespective of CKD.

(ii) Microalbuminuria is a well-established marker of increased cardiovascular risk[2,7]. ADA recommends aspirin therapy (75–162 mg/day) as a primary prevention strategy in those with diabetes at increased CVD risk which also includes most men >50 years of age or women >60 years of age who have albuminuria[6].

(iii) Dyslipidemia may contribute to the development and progression of DKD by causing intrarenal arteriosclerosis or direct toxicity to renal cells[71,72]. A recent meta-analysis of 13 small studies showed that lipid reduction preserves GFR and reduces proteinuria[73]. Given the strong association between dyslipidemia and cardiovascular disease, management of blood lipid in DM is recommended irrespective of the presence of indicators of CKD. NKF recommends using LDL-C lowering medicines, such as statins or statin/ezetimibe combination, to reduce risk of major atherosclerotic events in patients with diabetes and CKD[41]. Target LDL-C in people with diabetes and CKD stages 1-4 should be < 100 mg/dL; and <70 mg/dL is a therapeutic option for diabetic patients with CVD[13]. NICE guidelines offer statins to people with CKD for the secondary prevention of CVD irrespective of baseline lipid values[18].

(iv) Exercise and weight loss may reduce proteinuria[36].

Key Recommendations

Microalbuminuria is the earliest, clinically detectable manifestation of classic DKD. Persistent microalbuminuria in diabetes has been associated with progression to overt nephropathy and ultimately to ESRD; and is an increased risk of atherosclerosis with cardiovascular morbidity and mortality. Proteinuria reduction should be a treatment target regardless of baseline urinary protein excretion[2]. Therefore there is general agreement that people with diabetes should be screened regularly to detect early markers of kidney damage and receive treatment[2]. The key recommendations can be summarized as follows:

a. Kidney function should be assessed at diagnosis and annually thereafter by (a) urine test for albuminuria and (b) measurement of serum creatinine and calculation of eGFR[2]. ADA recommends yearly screening for microalbuminuria in (a) type 1 diabetic patients who have had diabetes >5 years and (b) all type 2 diabetic patients starting at diagnosis[1].

b. The ACR is the preferred method of detecting albuminuria in diabetes[6,8,18,32]. ACR should be measured using a morning urine sample because studies have shown that it correlates best with 24 hour protein excretion[18,32].

c. ACE inhibitors and ARBs are effective at reducing proteinuria, slowing the decline in GFR and retarding the progression of kidney disease. Therefore all the guidelines recommend treatment initiation with ACE inhibitors or ARBs unless contraindicated in diabetes having persistent microalbuminuria (incipient nephropathy) or macroalbuminuria (overt diabetic nephropathy) independently of the presence of hypertension[1-3,6,13,18,36,41]. People with T1DM and microalbuminuria should be treated with an ACE inhibitor irrespective of BP[8]. People with T2DM and microalbuminuria should be treated with an ACE inhibitor or an ARB irrespective of BP[8].

d. To reduce the risk and/or slow the progression of nephropathy, effective glycemic control should be maintained in diabetes[1,2,6,8]. ADA & Canadian guidelines recommends that plasma values for preprandial glucose be kept in the 5.0–7.2 mmol/L (90–130 mg/dL) range and HbA1c should be < 7% to prevent progression of CKD in patients with DM[32,55].

NKF and Australian guidelines recommend a target HbA1c of 7.0% to prevent or delay progression of the microvascular complications of diabetes, including DKD[3,41].

e. To reduce the risk and/or slow the progression of nephropathy, BP control should be optimized[1,2,6]. An ACE inhibitor or ARB is recommended as antihypertensive for all diabetic patients with microalbuminuria having hypertension[1,3,8]. According to various clinical guidelines, the primary goal of therapy for nonpregnant diabetic patients ≥18 years of age is to decrease BP to and maintain it at <130 mmHg systolic and <80 mmHg diastolic[1-3,6,8,17,18]. For those with microalbuminuria the target is 130/80 mm Hg. It has been suggested that those with total proteinuria >1 g/day the target should be 125/75 mm Hg[74].

f. When ACE inhibitors or ARBs are used, serum creatinine and potassium levels need to be monitored[1,2,6].

DKD is now the leading cause of CKD requiring renal replacement therapy in many parts of the world, and its prevalence is increasing disproportionately in the developing world. The onset and course of DKD can be ameliorated to a very significant degree by several interventions, but these interventions have their greatest impact if initiated at a point very early in the course of the development of this

complication. The benefits of a multifactorial intervention approach in the management of people with diabetes and microalbuminuria have been clearly demonstrated[75,76]. Interventions initiated at the stage of microalbuminuria may postpone or prevent overt nephropathy. Therefore people with diabetes and microalbuminuria should be treated with a multifactorial intervention approach that includes improved glycemic control, BP control, lipid lowering, aspirin use, smoking cessation, exercise programs and dietary intervention to reduce the development of overt nephropathy, ESRD and death.

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