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Review Article

Controversies in the Early Diagnosis of Diabetic Kidney Disease

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ABSTRACT

Diabetes mellitus is a leading cause of end-stage renal disease (ESRD) a condition which needs dialysis or kidney transplantation to sustain life. Early diagnosis of diabetic kidney disease (DKD) is important because there is strong evidence that a number of interventions if initiated at an early stage of DKD prevent or slow the progression to ESRD. The criteria for early diagnosis of DKD vary between different guidelines. The controversies in the early diagnosis of DKD will be the focus of this review article. Various international guidelines that were published through Jan 2001 to Jan 2016 were reviewed for the recommendations on early diagnosis of DKD. The issues in considering early diagnosis of DKD include (i) defining abnormal albuminuria, number of tests and duration (ii) presence or absence of impaired renal function (iii) the necessity of presence of diabetic retinopathy (iv) whether the diagnosis of DKD should be different for type 1 and type 2 diabetes and (v) whether the duration of diabetes should be taken into account. These issues need to be addressed in defining DKD. In most guidelines microalbuminuria or impaired renal function has been considered for early diagnosis of DKD.

KEYWORDS: Controversies, Diabetic Kidney Disease, Diabetic Nephropathy, Diagnosis.

INTRODUCTION

Diabetes mellitus (DM) is a global public health problem and is the leading cause of end-stage renal disease (ESRD)[1]. The prevalence of ESRD due to DM is increasing[1]. To sustain life, the treatment of ESRD needs renal replacement therapy (RRT) which includes dialysis or kidney transplantation. Dialysis & kidney transplantation are not free of complications. The prognosis of diabetic patients on dialysis is poor, with survival comparable to many forms of cancer. Moreover availability of donor and facilities of kidney transplantation are limited in the developing countries. Kidney transplantation requires long-term immunosuppressive drugs which are not free of risks. There is strong evidence that a number of interventions if initiated at an early stage of diabetic kidney disease (DKD) reduces the risk and slows the progression to ESRD. Therefore early diagnosis of DKD is important. Traditionally early stages of DKD have been defined by the presence of microalbuminuria in a person with diabetes. In 2007 the National Kidney Foundation (NKF), a US health organization, defined microalbuminuria as: (i) excretion of 30-300 mg of albumin in a 24 hour urine collection sample, or (ii) urinary albumin excretion rate (AER) of 20-200µg/min in a timed collection of urine, or (iii) urinary albumin creatinine ratio (ACR) of 30-300 mg/gm without regard to age & sex in a random or spot sample of urine[2]. Albuminuria values >300mg/24 hour is defined as macroalbuminuria. However the criteria for early diagnosis of DKD vary somewhat between different guidelines. The controversies in the diagnosis of DKD in its early stage are the focus of this review article. Various international guidelines that were published through Jan 2001 to Jan 2016 were reviewed for the recommendations on criteria for early diagnosis of DKD.

DIABETIC KIDNEY DISEASE

The term DKD has been used to describe chronic kidney disease (CKD) resulting from diabetes[2]. The term diabetic glomerulopathy is reserved for biopsy-proven kidney disease caused by diabetes[2]. In most individuals as biopsy may not alter management, the diagnosis of DKD is made clinically by the presence of persistent albuminuria in a patient having diabetes in the absence of another identifiable cause of albuminuria or kidney disease. People with diabetes may develop kidney disease for other reasons not related to diabetes. A kidney biopsy may be required in some patients with

diabetes and CKD to determine the underlying cause of the kidney disease in situations like rapidly declining kidney function, increasing proteinuria (particularly if nephrotic), active urinary sediment, resistant hypertension, or evidence of other systemic disease raising concerns about nondiabetic glomerular disease[2-4]. Because the development of CKD resulting solely from diabetes has been considered defining DKD, the definition of CKD needs to be discussed.

DEFINITION OF CHRONIC KIDNEY DISEASE

In 2002 the NKF, defined CKD as either kidney damage or glomerular filtration rate (GFR) <60ml/min/1.73m^2 persisting for 3 months or more irrespective of the etiology[5]. Persistent albuminuria >300mg in 24 hour urine was considered as one of the important marker of kidney damage. Equations recommended for calculating estimated GFR (eGFR) in adults, were the Modification of Diet in Renal Disease (MDRD) Study and Cockcroft-Gault equations. The guidelines provided by NKF for managing kidney disease are referred to as the KDOQI (i.e. Kidney Disease Outcomes Quality Initiative) guidelines. The publication by the NKF in 2002 provided important landmark guidelines in definition, classification and stratification of CKD, which had been adopted by countries and institutions worldwide since then.

In 2012 the Kidney Disease: Improving Global Outcomes (KDIGO), a foundation governed by an international board, revised the definition of CKD and made certain changes[6]. CKD is now defined as presence of kidney damage or impairment of kidney function persisting for >3 months with implications for health. The addition of 'with implications for health' has been intended to reflect that some abnormalities of kidney structure or function may not have any clinical significance (e.g., simple cysts). The proposed classification of CKD is based on three variables (CGA): (i) cause of CKD, (ii) GFR category (G1-G5), and (iii) albuminuria category (A1, A2 & A3). Previously CKD had been staged solely by the GFR. However, the risk of worsening of kidney function is found closely linked to the amount of albuminuria, and so it has been incorporated into the new classification. The term microalbuminuria (30-300mg/24 hour) has been eliminated and replaced by albuminuria categorizing by specific values. Albuminuria has been grouped into 3 categories: (i) category A1 represents normal or mild (<30mg/24 hour) albuminuria, (ii) A2 with moderate (30-300mg/24 hour) albuminuria and (iii) A3 having severe (>300mg/24 hour) albuminuria. Now the threshold for albuminuria of >30mg/24 hour has been chosen as one of the important marker of kidney damage to indicate CKD based on a meta-analysis that demonstrated associations of albuminuria >30mg/24 hour with subsequent risk of all-cause and cardiovascular mortality, kidney failure and CKD progression in general population as well as patients with kidney disease[7-11]. The threshold values of G1-G5 are same as the CKD stages 1–5 recommended previously by NKF in 2002. GFR category 3, has been further refined into 3a and 3b, based on substantial data that there are differences in outcomes and risk for those who have GFR values 45—59 versus 30—44 ml/min/1.73m^2. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation has been recommended for reporting eGFR because it was found to be more accurate than other equations[12]. In 2014 NKF in their commentary has approved the new definition of CKD as well as the threshold of albuminuria (of >30mg/24 hour) as a marker for kidney damage[13]. The new definition and classification of CKD is now becoming popular and recently has been accepted by various organizations and has been started adopting in their guidelines[14-16].

CRITERIA FOR EARLY DIAGNOSIS OF DIABETIC KIDNEY DISEASE

Diabetic kidney disease occurs in 20–40% of patients with diabetes and is the leading cause of ESRD[17]. It is diagnosed on the basis of a raised urine albumin or a reduced GFR <60ml/min/1.73m^2 persisting for 3 months or more.

The criteria for early diagnosis of DKD vary between different guidelines as stated below.

(a) According to NKF (2007), in most people with diabetes, CKD should be attributable to DKD in the presence of (i) macroalbuminuria or microalbuminuria plus retinopathy, and (ii) in people with type 1 diabetes (T1DM), in the presence of microalbuminuria plus duration of diabetes longer than 10 years[2]. They also commented that concomitant presence of retinopathy is only partly helpful in discriminating kidney pathology in patients with type 2 diabetes (T2DM)[18-21]. The guideline strongly suggests DKD in the presence of retinopathy with T2DM and macroalbuminuria; and its absence in microalbuminuria suggests non-DKDs. Based on study showing positive relationship between the duration of diabetes and DKD, particularly in T1DM, they expressed that the presence of elevated albuminuria in diabetes of short duration should raise possibilities about non-DKD[22].

(b) Recently NKF has again expressed concern that the presence of macroalbuminuria without retinopathy, especially if present within 10 years of diabetes onset, suggests a need for investigations to rule out non-DKDs[1]; as studies have shown that there is spontaneous remission of microalbuminuria in up to 40% of patients with T1DM[23-25]. About 30–40% remains with microalbuminuria and do not progress to macroalbuminuria over 5–10 years of follow-up.

(c) According to American Diabetes Association (ADA) persistent microalbuminuria is an early indicator of DKD in T1DM and a marker for development of DKD in T2DM[15]. ADA has recommended MDRD equation or the CKD-EPI equation for the calculation of eGFR; but they preferred currently the CKD-EPI equation[15]. Recently ADA commented that the presence of diabetic retinopathy in patients with urinary ACR >300mg/gm strongly suggests DKD, and its absence in those with reduced eGFR and urinary ACR <300mg/gm suggests non-DKD[26].

(d) Scottish intercollegiate guidelines network (SIGN) classifies DKD, on the basis of the extent of urine albumin excretion, as either microalbuminuria or nephropathy (having macroalbuminuria)[4]. They consider microalbuminuria as the earliest, clinically detectable manifestation of classic DKD. The SIGN guidelines do not consider DKD in the absence of albuminuria even if there is a sustained low GFR.

(e) According to National Institute for Health and Care Excellency (NICE) guidelines of UK, CKD has been defined as abnormalities of kidney function or structure present for more than 3 months, with implications for health. In people with diabetes microalbuminuria should be considered clinically significant[16]. However they are moving away from using the term 'microalbuminuria' and the equivalent value of albuminuria (>30mg/24hr) has been considered to be clinically significant for defining DKD.

(f) According to International Diabetes Federation (IDF), DKD is usually diagnosed on the basis of a raised urine albumin or a reduced GFR (<60 ml/min/1.73m^2) persisting for 3 months or more[27].

(g) According to Malaysian guidelines the diagnosis of DKD is made clinically by the presence of persistent proteinuria (either microalbuminuria or macroalbuminuria). Microalbuminuria has been considered as the earliest sign of diabetic nephropathy as it predicts increased cardiovascular mortality and morbidity and ESRD[28].

SCREENING

Universal recommendation is that screening for DKD should be performed annually from the onset in T2DM and 5 years after onset in T1DM. It has been reported that up to 25% of newly diagnosed patients with T2DM already have microvascular complications, and there is a 6 to 7 year time lag between the onset and the diagnosis of T2DM[29]. Microalbuminuria rarely occurs with short duration of T1DM[30]. Screening is important for early diagnosis, staging and monitoring progression of DKD. Two investigations are done for screening (i) urine test: spot urine test for ACR, or timed collection of urine to see AER and (ii) serum creatinine with estimation of GFR.

Urinary ACR is the recommended method for screening microalbuminuria in people with diabetes[3,16,31]. Urinary ACR provides accurate estimates of the urinary albumin excretion, and is not affected by hydration. Measurement of ACR in a random urine sample is often found to be easiest method to carry out by patients. ACR is best measured on an early morning specimen of urine[32]. Studies have shown that ACR measured in early morning samples correlates closely with 24 hour proteinuria[33,34]. If a spot urine ACR is positive for microalbuminuria it should be confirmed next day by examination of early morning sample for ACR[35]. An early morning sample is also required for the exclusion of orthostatic (postural) proteinuria. Urine screening for albuminuria should not be done during intercurrent illness or when other factors are present causing 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)[3,30,36]. The best possible metabolic control of diabetes should be achieved before investigating patients for microalbuminuria[36].

Dipsticks test is usually negative for microalbuminuria[37]. If protein is detectable on a standard urinalysis dipstick, macroalbuminuria is probably already present. Positive dipstick tests should be confirmed in the laboratory by measuring the ACR preferably on an early morning urine sample[36]. According to one national guideline urine should be screened first for proteinuria with conventional dipstick on an early morning urine specimen[28]. If proteinuria is detected a 24 hour urine collection for protein (or a urine protein-creatinine ratio) should be performed. If urine dipstick for proteinuria is negative, screening for microalbuminuria should be performed on an early morning urine specimen. If microalbuminuria is not detected, re-screening should be performed annually. This is probably a cost-effective guideline.

As a significant proportion of people with T2DM may have or develop CKD in the absence of albuminuria, serum creatinine and eGFR should be done in all DM patients regardless of albuminuria. GFR is most commonly estimated using the MDRD equation which is based on serum creatinine, age, sex and race. Recently the CKD-EPI equation has been recommended by KDIGO for reporting eGFR in adults, because it was found to be more accurate than other equations[6]. Study also revealed that when GFR is >60ml/min/1.73m^2, MDRD equation does not perform well[38].

DISCUSSION

DKD is diagnosed in its early stage by the presence of albuminuria or by the impairment of renal function persisting for 3 months or more[27]. NKF guidelines published in 2007 do not consider albuminuria (micro or macroalbuminuria) for the diagnosis of DKD in T2DM

unless accompanied by retinopathy[2]; NKF recently has re-expressed concerns for diagnosing DKD in patients having macroalbuminuria without retinopathy within 10 years of onset of diabetes[1]. However in a Danish study of 93 people with T2DM, persistent albuminuria and no retinopathy, 69% had diabetic nephropathy, 12% had glomerulonephritis and 18% had normal glomerular structure[39]. Therefore diabetic retinopathy is usually but not invariably present with DKD[40].

The KDIGO guidelines-2012 recommend the threshold for AER rate of ≥30mg/24 hours persisting for more than 3 months to indicate CKD[6]. NKF in their commentary in 2014 accepted the threshold of albuminuria for defining CKD[13]. Then the question remains why presence of persistent albuminuria should not be considered for diagnosing early stages of CKD in a patient with diabetes; whereas the presence of retinopathy has been taken as a prerequisite for making a diagnosis of DKD especially in a patient with T2DM. ADA considers microalbuminuria as indicator of CKD in T1DM, and a marker for development of CKD in T2DM[15].

SIGN does not consider diagnosis of DKD without albuminuria even in the presence of isolated impaired renal function in a person with diabetes[4]. However studies have shown that a significant proportion of people with diabetes having GFR <60ml/min/1.73m^2 develop biopsy proven DKD in the absence of micro or macroalbuminuria[41-43]. A study has shown that upto 30% of people with T2DM who have a GFR <60ml/min/1.73m^2 may remain normoalbuminuric[44]. Therefore, DKD may develop in the absence of abnormalities in urinary albumin excretion.

There is no consensus among the guidelines about how to define abnormal albuminuria in DKD and how many tests over what period of time would be required for diagnosing DKD. IDF considers 2 positive tests out of three done within 4 months[27]. NKF and ADA recommends 2 additional positive tests within 3-6 months[2,40]. Australian guidelines confirm microalbuminuria if at least two of three tests (including the screening test) are positive measured within 3 months[35].

Most of the guidelines consider persistent microalbuminuria as the earliest sign of DKD[4,16,27,28,45] as studies have shown that microalbuminuria predicts increased cardiovascular mortality and ESRD in a person with diabetes as well as in general population[7-11]. Other guidelines do not consider microalbuminuria as the sign of early stage of DKD[1,2,14,15].

The issues in the diagnosis of DKD include (i) the level and the duration of albuminuria or (ii) presence or absence of impaired renal function (iii) the necessity of presence of diabetic retinopathy (iv) whether the diagnosis of DKD should be different for T1DM & T2DM and (v) whether the duration of diabetes should be taken into account.

Diabetes mellitus is the predominant cause of CKD, but there is no universally accepted definition of DKD. The definition and classification of CKD proposed by KDIGO in 2012 based on class, albuminuria and GFR category or CGA, is well accepted by different organizations[6]. Accordingly patients having DKD could be identified, e.g. with eGFR of 21 ml/min/1.73m^2, and albuminuria of 500mg/day can be abbreviated using the terminology "CKD due to diabetes, G4, A3". But this CGA system does not mention anything about retinopathy. Therefore a concrete definition of DKD correlating that of CKD as defined by KDIGO 2012 is warranted which may be based on (i) albuminuria category (ii) eGFR category and (iii) presence or absence of diabetic retinopathy. Because albuminuria>30mg/24 hour is one of the important marker of kidney damage in the new definition of CKD as defined by KDIGO[6], the similar amount may be considered for diagnosing diabetic chronic kidney disease i.e. DKD. Similarly the duration of persistent microalbuminuria may be taken as >3 months to indicate CKD in people with diabetes.

CONCLUSION

Diabetes is the leading cause of CKD which usually progresses to ESRD. A concrete and uniform definition for DKD is warranted so that all healthcare professionals speak in the same language for the best care of patients with DKD. Microalbuminuria in diabetes predicts increased cardiovascular mortality and morbidity as well as ESRD. For early identification of DKD, (i) presence of albuminuria (albumin excretion rate >30mg/24 hour) or (ii) impaired renal function (<60ml/day/1.73m2) with or without (iii) diabetic retinopathy needs consideration.

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