TITLE PAGE

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Clinical Update: The important role of dual kidney function testing (ACR and eGFR) in primary care: identification of risk and management in type 2 diabetes.

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Abstract

Diabetic kidney disease (DKD) is common complication of type 1 and type 2 diabetes and may lead to progressive kidney dysfunction culminating in end-stage kidney disease. Kidney function is evaluated less frequently than other care procedures in patients with diabetes, even though the opportunity to identify DKD early and slow or even halt renal damage early in the disease progression represents a potentially important clinical opportunity for early intervention. The following review provides an overview of the under-recognised importance of kidney function in T2D and current best-practice to support the identification of DKD as part of primary care T2D management.

Title

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Introduction

Diabetes is a chronic condition associated with increased morbidity and mortality [1], primarily due to cardiovascular disease (CVD) [2-6]. Diabetes is also a key risk factor for chronic kidney disease (CKD), such as diabetic nephropathy, also known as diabetic kidney disease (DKD), and affects people with both type 1 diabetes and type 2 diabetes (T2D) [7, 8]. Although short-term hyperglycaemia does not result in serious clinical complications, extended hyperglycaemia, a hallmark of diabetes, is a major causative factor in initiating kidney damage [9]. Dysregulated metabolism is a key factor in DKD initiation and progressive microvascular damage due to hyperglycaemia ultimately leads to kidney dysfunction and end-stage kidney disease (ESKD) [8]. In patients with a new diagnosis of diabetes, the risk of cardiovascular death, heart failure, and all-cause mortality increases in the presence of CKD [10, 11]. It is important to note that the risk of CVD outcomes is greater than the risk of progression to ESKD for most people with CKD [12].

Up to 42% of people with T2D will develop DKD [13, 14], and kidney disease attributed to diabetes is a major but under-recognized contributor to the global disease burden [15]. The number of adults with diabetes globally increased from 108 million in 1980 to 422 million in 2014 and the number of deaths attributed to DKD rose by 94% between 1990 and 2012 [15, 16]. Most of the excess risk of all-cause and CVD mortality for people with diabetes is related to DKD,[10] which is also the single most common cause of ESKD globally [17].

There are numerous reasons to improve on the identification and prevention of DKD, primarily because once progression to ESKD has occurred, only limited treatment options such as dialysis and

kidney transplant remain, both of which have a high impact on the individuals' quality of life and costs [18, 19].

DKD is also an indicator of mortality, as DKD predominantly accounts for the increased 10-year mortality observed in T2D [10], and also accounts for a 16-year reduction in life expectancy compared with people without DKD [20]. The 5-year survival of patients with ESKD secondary to diabetes receiving dialysis is 61–64%, and 54% in patients with ESKD and diabetes-related complications, which is worse than the survival rate for major cancers, such as colon and breast cancer [21].

Patients with T2D are also more prone to frailty due to impaired muscle function, neuropathy and vascular dysfunction. People with CKD are also more likely to have anaemia, sarcopenia, and bone mineral disorders, all of which could predispose to frailty [22]. Frailty has been reported in over 60% of dialysis-dependent CKD patients, and is associated with adverse clinical outcomes in all stages of CKD and increases the risk of mortality and hospitalization in CKD patients [23].

Additionally, DKD constitutes a significant and growing financial health care burden, which with an ageing population and rapid increase in T2D is likely to continue to rise [16, 24-27]. Although even with current best practice standards of care, including lifestyle modification, blood pressure management, and use of renin-angiotensin-aldosterone system blockaders, the level of progression to ESKD remains high for patients with DKD [28, 29]. However, early detection of kidney disease allows for interventions to slow the rate of progression and to manage complications such as anaemia, CVD, hypertension and mineral and bone disorders, and also allows for more lead-time to prepare for renal replacement therapy [30].

The diabetic kidney disease monitoring paradox in type 2 diabetes

Primary care, with the support of a multidisciplinary care team, is well versed in the management of comorbidities associated with T2D [31, 32]. International guidelines from the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) have recognised both CVD and DKD as key considerations for the management of diabetes patients [33], and international guidance is now permeating through to national guidelines. In the UK, THE ABCD guidance on management of hyperglycaemia in renal impairment recommends that SGLT2 inhibitors should be considered over other glucose-lowering therapies for patients with stage 2 CKD [34]. Similarly, the Diabetes Canada Clinical Practice Guidelines Expert Committee recommends SGLT2 inhibitors with proven renal benefit for adults with inadequately controlled T2D, clinical CVD, and an eGFR >30 mL/min/1.73 m^2 [35].

Surprisingly, despite the evidence around the negative impact of DKD, there seems to be an imbalance in the identification of DKD in patients with T2D in primary care, as the UK's National Diabetes Audit (2017–18) reported that the test for DKD (urinary albumin) had the lowest implementation rate of eight annual care processes that the National Institute for Health and Care Excellence (NICE) recommend for T2D, with just 66% of patients receiving the test. In comparison, patients received 85% or more of each of the other seven care processes [36].

Measurement and monitoring of kidney function: the estimated glomerular filtration rate and the albumin creatinine ratio

In spite of current standard of care, which includes angiotensin II receptor blockers (ARBs) and angiotensin-converting-enzyme inhibitors (ACEi), eGFR declines over time [37, 38]. In addition to a general decline in eGFR, the speed with which eGFR declines is also associated with poorer outcomes [39]. An analysis of data from the ADVANCE trial was used to assess the relationship between the eGFR slope (i.e., the rate of eGFR decline) and cardio-renal end points. The results

showed that an annual substantial decrease in eGFR over 20 months was strongly associated with detrimental cardio-renal outcomes, such as renal replacement therapy, renal transplant, renal death, fatal and non-fatal MI, fatal and non-fatal stroke and all cause-mortality [40].

However, not all individuals with diabetes develop all possible complications of the condition, which has led to systematic screening for relevant complications such as DKD becoming a major part of diabetes management [41]. It is important to take into consideration that measurement of renal function is complex, and no individual method of measurement provides an accurate overall assessment of renal function, which has led to the monitoring of general trends being used in clinical practice to guide treatment decisions and predict prognosis [42]. Two separate measures of kidney function, albuminuria and glomerular filtration rate (GFR), (Figure 1) are both independently associated with increased risks of all-cause mortality in presence or absence of diabetes, and the combination of increased albuminuria and decreased GFR with diabetes have even worse clinical outcomes [10, 43].

GFR is a measure of kidney excretory function, and represents the flow rate of filtered fluid across the glomerulus into Bowman's space [44]. In people with type 2 diabetes, measurement of serum creatinine alone without GFR may underestimate renal impairment [45]. Normal GFR in young adults is approximately 125 ml/min/1.73 m^2, and declines at a rate of approximately 6.3 ml/min/1.73 m^2 per decade [46, 47]. The decline in GFR with age may be of clinical importance, as low GFR in older adults risks being misdiagnosed as CKD, although it is part of the normal aging process [47]. Additionally, an accelerated GFR decline has been observed in T2D patients [48]. The organization Kidney Disease Improving Global Outcomes (KDIGO) defines CKD as GFR <60 ml/min/1.73 m^2, or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause (Table 1) [43, 46]. An impaired GFR is the final common pathway of kidney disease, and once the GFR is impaired, progression to ESKD and CVD may occur even with appropriate medical

management [49]. Both the Modification of Diet in Renal Disease (MDRD) Study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) are recommended for estimating GFR, however, the CKD-EPI equation which applies different coefficients to the same 4 variables used in the MDRD Study equation (age, sex, race, and serum creatinine level) [50-52] has been reported to be more accurate, and is a better predictor of death, cardiovascular mortality, but not end stage kidney disease [53].

In clinical practice, GFR is evaluated by the estimated GFR (eGFR), and albuminuria is usually measured using the albumin to creatinine ratio (ACR) [10]. Serum creatinine, an endogenous glomerular filtration reference marker that is frequently used in clinical practice [54], is predominantly formed from creatine and phosphocreatine in skeletal muscle [55]. Creatinine is freely filtered by the glomerulus and is not metabolized or reabsorbed but is secreted by the proximal tubule [42], and has demonstrated good diagnostic performance in detecting even minor impairment of renal function [56]. However, serum creatinine is influenced by age, body build, chronic illness, gender, skin colour and ethnicity, diet, drugs that block proximal tubule creatinine secretion (e.g., trimethoprim) and nutritional status [57]. Additionally, creatinine-based estimates of GFR are not very reliable for the diagnosis of glomerular hyperfiltration [58, 59].

Cystatin C, another endogenous reference molecule, is produced in all nucleated cells with a constant rate of release into the bloodstream, and is freely filtered at the glomerulus with no renal tubular secretion [60]. Several studies have demonstrated that an eGFR based on serum cystatin C as a reference molecule may be an alternative to using serum creatinine as a reference to calculate eGFR [61, 62]. eGFR measurements based on serum creatinine may underestimate true GFR, which may lead to an overdiagnosis of CKD compared with an eGFR calculated using serum cystatin C as

reference [61, 62]. The addition of cystatin C as an additional reference point in addition to serum creatinine for renal function evaluations may be beneficial, as the use of cystatin C alone or in combination with creatinine strengthens the association between eGFR and the risks of death and ESKD across diverse populations [61]. Based on these studies, using an eGFR based on the average values of eGFR (creatinine) and eGFR (cystatin C) may therefore give the most accurate eGFR [43]. It is, however, important to take into account that thyroid dysfunction has a major impact on cystatin C levels, and therefore has to be considered when cystatin C is used as a marker of kidney function [63]. However, limited capabilities to quantify cystatin C in clinical laboratories has thus far limited the implementation of eGFR (cystatin C) in routine clinical practice [64].

However, dual eGFR and ACR testing is the gold standard for identifying DKD, as eGFR screening allows for the identification of existing kidney damage, and ACR screening allows for the identification of kidney damage occurring prior to substantial nephron mass loss [12, 41, 65].

Macroalbuminuria is defined as a urinary albumin excretion of ≥300 mg albumin per 24 hours, and microalbuminuria as 30–299 mg albumin excretion per 24 hours. Both are biomarkers of renal damage [43, 66, 67]. Albuminuria constitutes a clinical continuum of risk and prognosis [68] and reducing albuminuria both in the micro- and macroalbuminuria range is associated with kidney protection [69]. Importantly, microalbuminuria is a potent risk factor for the development of progressive kidney disease, and foretells the future development of overt proteinuria, doubling of serum creatinine, ESKD, and increased mortality [68]. In a study of more than 462,000 adults in Taiwan, 7% of study participants had trace proteinuria, and this carried a mortality risk comparable with smoking [70, 71]. In patients with T2D and hypertension, the GFR of patients with microalbuminuria declines more than the GFR of patients with no microalbuminuria [72], and overall, the severity of CKD increases with declining GFR and increasing albuminuria ([43].

Measuring albumin: the albumin to creatinine ratio vs urinalysis dipstick

The importance of albuminuria, as highlighted above, is under-appreciated in primary care settings [71]. Although urine albumin excretion is a prognostic biomarker for CKD, diabetes and CVD, the laboratory measurement of urine albumin excretion is not standardized in clinical practice, and a variety of methodologies including turbidimetry, immunoassays and chromatography methods are currently used to measure the urine albumin concentration [73].

Historically, urine albumin excretion has been measured as excretion over a 24-hour period using a 24-hour urine collection, but this is impractical for most clinics. The United Kingdom's NICE guidelines recommend monitoring of renal function by checking serum creatinine and eGFR together with a spot urine albumin to creatinine ratio (ACR) to identify accelerated progression of CKD, which is indicated by a sustained decrease in eGFR of 25% or more from baseline *and* a change in CKD category within 12 months; *or* a sustained decrease in eGFR of 15 ml/min/1.73 m^2 within 12 months. It is important to note that small fluctuations in eGFR are common and do not necessarily indicate disease progression. To assess the rate of progression, serum eGFR measurements should be repeated three times over at least 3 months [74].

However, the ACR may also be influenced by the duration of the timed urine collection. Early morning urine is equivalent to an approximate 8-hour timed urine collection. Early morning urine sampling may be used to rule out spurious results caused by orthostatic proteinuria, and to follow up all findings with subsequent early morning collections [73, 75]. UK NICE guidelines state that ACR may be measured at any time, but for the initial detection of proteinuria, if the ACR is between 3 mg/mmol (26.55mg/g) and 70 mg/mmol (619.47mg/g), this should be confirmed by a subsequent early morning sample. If the initial ACR is 70 mg/mmol(619.47mg/g) or more, a repeat sample need not be tested [76].

Measuring urinary albumin excretion can provide an early indication of future risk of kidney function decline

According to KDIGO definitions, an eGFR of below 60 ml/min/1.73 m^2 is considered to indicate mildly to moderately decreased kidney function (Table 1) [77]. However, not only the absolute eGFR, but also the rate of eGFR deterioration (i.e., the slope of eGFR decline), may be clinically relevant. Rapid progression of CKD is defined as loss of >5 ml/min/1.73 m^2 eGFR per year or a change of CKD category (i.e., from CKD 3 to CKD 4) or loss of >25% eGFR from baseline [43]. The overall rate of eGFR decline may also be an indicator of the general CKD prognosis, as cases where a 1-year eGFR decline rate exceeding 7.5% have been associated with a poor prognosis and an increased risk of progression to ESKD [78].

While patients may be able to function with relative normality at an eGFR below 60 ml/min/1.73 m^2, this stage of DKD equates to an irreversible nephron mass loss of approximately 75–80% [77], which highlights the clinical importance of early detection and potential therapeutic and lifestyle interventions in order to slow or halt the rate of kidney function decline [12]. Therefore, monitoring and identification of albuminuria provides an earlier indication of damage to the kidney, at a point where compensation through hyperfiltration may be masking the decline in nephron mass and thus preventing its detection by eGFR measurements [77]. As such, there is an intervention opportunity for primary care providers to slow or prevent the development of symptomatic DKD. In type 1 diabetes, HbA1c, arterial pressure, blood lipids as well as the used of RAAS blockade can lead to a regression of microalbuminuria [79]. Similarly, in the Steno-2 trial, one third of microalbuminuric participants with type 2 diabetes regressed to normoalbuminuria, and their GFR declines were slower than for the others [80].

Impact of ethnicity on diabetic kidney disease

The risk of developing and progression of DKD may vary among different races and ethnic groups, with a higher incidence rate ratio for ESKD in people of African Caribbean origin than in white Europeans, but the underlying causes are poorly understood [81-83]. A higher rate of disease progression has also been observed in South Asians compared with white Europeans [83].

In an observational analysis of combined data from the Third National Health and Nutrition Examination Survey and the US Renal Data System, which includes patients without diabetes, even though the prevalence of CKD was similar among African American and white patients, the estimated progression rates among those with CKD were fivefold higher among African American patients. Some of the differences in prevalence of microalbuminuria between ethnic groups may be attributable to differences in age and duration of diabetes by ethnicity for the different studies included in this systematic review, and the results of these studies suggest a potential non-albuminuric pathway of progression to ESKD [83]. People with type 2 diabetic and reduced eGFR from the Chinese extraction are at high risk of developing cardiovascular end points and all-cause mortality, independent of albuminuria and metabolic control [84]. Additional management and intervention studies may provide a clearer picture of differences in CKD prevalence and progression between different ethnic groups.

In a post hoc analysis of the ACCORD trial looking at longitudinal change in eGFR, time to development of microalbuminuria, macroalbuminuria, incident CKD, and kidney failure or serum creatinine >3.3 mg/dl (291.8 micromole/L) [85], it was noted that even though the mean values of systolic blood pressure, glycated haemoglobin (HbA1c) microalbuminuria, macroalbuminuria and serum creatinine levels were higher in black participants at baseline, black and white participants achieved similar rapid improvement of both clinical variables, which were maintained during study

follow-up [86]. This suggests that optimization of the delivery of diabetes care prior to the development of CKD may lead to similar short-term kidney outcomes, irrespective of race.

The results of the CREDENCE clinical trial, which investigated the effects of the SGLT2 inhibitor canagliflozin or placebo on a composite renal endpoint similarly demonstrated relatively high homogeneity (interaction *P* value = 0.91) between different race and ethnic demographics regarding the composite risk of doubling of serum creatinine, ESKD and renal or CV death. However, the study end point was not reached in 'Black or African American' and 'other' sub-populations of the CREDENCE study [87]. Similarly, the DECLARE-TIMI 58 cardiovascular outcomes trial, which investigated renal outcomes with the SGLT2 inhibitor dapagliflozin in T2D patients both with and without established atherosclerotic cardiovascular disease and mostly with preserved renal function, reported no differences in composite renal-specific outcomes for white and non-white patients [88]. Further studies are required in order to determine if any differences do indeed exist between white and non-white patient populations.

Conclusion

There is a clear opportunity for greater risk-reduction strategies in patients with T2D and early stages of kidney dysfunction for healthcare professionals in primary care. Through earlier diagnosis and management, primary care physicians have the possibility to slow or even halt the progress of diabetic nephropathy. Given the evidence supporting DKD as an indicator of mortality, DKD is an important complication of diabetes that merits improved identification and management as part of a broader approach to managing complications of diabetes and related cardiovascular disease outcomes.

Figures and Tables

Table 1. CKD classification by GFR function [43]. CKD, chronic kidney disease; GFR, glomerular filtration rate.

CKD stage	**Kidney function**	**GFR (ml/min/1.73m^2)**
G1	Normal or high	≥90
G2	Mildly decreased	60–89
G3a	Mildly to moderately decreased	45–59
G3b	Moderately to severely decreased	30–44
G4	Severely decreased	15–29
G5	Kidney failure	<15

Figure Legend:

Figure 1. Diagnosing Chronic Kidney Disease in Primary Care

Conflicts of interest

KK- reports personal fees from Amgen, personal fees from Astrazeneca, personal fees from Bayer, personal fees from NAPP, personal fees from Lilly, personal fees from Merck Sharp & Dohme, personal fees from Novartis, personal fees from Novo Nordisk, personal fees from Roche, personal

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SS- reports personal fees from Amgen, personal fees from Astra Zeneca, personal fees from NAPP, personal fees from Lilly, personal fees from Merck Sharp & Dohme, personal fees from Novartis, personal fees from Novo Nordisk, personal fees from Roche, personal fees from Sanofi-Aventis, personal fees from Boehringer Ingelheim, grants from AstraZeneca, grants from Sanofi-Aventis, grants from Servier, grants from Janssen, outside the submitted work.

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