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ABSTRACT

Diabetic kidney disease (DKD) represents a major component of the health burden associated with type 1 and type 2 diabetes. Recent advances have produced an explosion of 'novel' assay-based risk markers for DKD, though clinical use remains restricted. Although many patients with progressive DKD follow a classical albuminuria-based pathway, non-albuminuric DKD progression is now well recognized. In general, the following clinical and biochemical characteristics have been associated with progressive DKD in both type 1 and type 2 diabetes: increased hemoglobin A1c, systolic blood pressure, albuminuria grade, early glomerular filtration rate decline, duration of diabetes, age (including pubertal onset) and serum uric acid; the presence of concomitant microvascular complications; and positive family history. The same is true in type 2 diabetes for male sex category, in patients following an albuminuric pathway to DKD, and also true for the presence of increased pulse wave velocity. The following baseline clinical characteristics have been proposed as risk factors for DKD progression, but with further research required to assess the nature of any relationship: dyslipidemia (including low-density lipoprotein, total and high-density lipoprotein cholesterol); elevated body mass index; smoking status; hyperfiltration; decreases in vitamin D, hemoglobin and uric acid excretion (all known consequences of advanced DKD); and patient test result visit-to-visit variability (hemoglobin A1c, blood pressure and high-density lipoprotein cholesterol). The development of multifactorial 'renal risk equations' for type 2 diabetes has the potential to simplify the task of DKD prognostication; however, there are currently none for type 1 diabetes-specific populations. Significant progress has been made in the prediction of DKD progression using readily available clinical data, though further work is required to elicit the role of several variables, and to consolidate data to facilitate clinical implementation.

INTRODUCTION

The prediction of kidney disease progression in patients with type 1 and type 2 diabetes mellitus represents an important clinical and public policy challenge. In many regions, diabetes is now the leading cause of end-stage renal disease (ESRD)[1,2]. Conversely, between a one-quarter and half of patients diagnosed with diabetes might develop chronic kidney disease (CKD)[3–5]. Diabetic kidney disease (DKD) contributes significantly to the excess mortality[6–8] and healthcare cost[9] associated with diabetes. Indeed, much of the cardiovascular death in diabetes appears to be related to the development of CKD[10–12].

In developing individualized glycemic targets, clinicians are in need of information to help balance the risks of prolonged hyperglycemia and its associated complications, such as DKD, with the risk of hypoglycemia[13]. A strong association has been shown between intensive glycemic control in type 1 diabetes mellitus and a slower rate of decline in kidney function, as measured by eGFR decline[14]. Similarly, patients with type 2 diabetes mellitus and intensive glycemic control in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation trial had a lower incidence of ESRD[15]. From a public policy perspective, prediction of those most at risk of renal impairment might better inform the allocation of health resources. For example, referral to specialist nephrology clinics could result in significantly lower rates of undertreatment[16] and decrease the risk of ESRD/mortality[17], but at increased cost to either the patient or health system. Despite the apparent need, the ability to predict the progression of DKD using classically described risk markers remains relatively poor[18].

Although rates of classical 'nephropathy' development might be similar, a smaller proportion of those with type 2 diabetes mellitus will progress to ESRD than with type 1 diabetes mellitus[19,20]. This difference in course might be at least in part accounted for by differing baseline characteristics[21], including age and relative lead-time to other causes of death, such as cardiovascular disease. The overall higher burden of type 2 diabetes mellitus means that despite this apparently lower rate, a much greater proportion of those with ESRD have type 2 diabetes mellitus than type 1 diabetes mellitus[20].

The remainder of the present article will focus on known risk factors for the progression of DKD in both type 1 diabetes mellitus and type 2 diabetes mellitus, with a special focus on clinical variables available to the practicing clinician. The emphasis will be on changes in GFR rather than albuminuria status. Where available, studies with direct measurement of GFR have been used. It should be noted that the demonstration of predictive utility does not necessarily imply a direct mechanistic role in the pathogenesis of DKD.

MATERIALS AND METHODS

An Ovid-Medline search was carried out in 2015 dating back to 1990 combining the following subject headings:

- Diabetes Mellitus
- Diabetic Nephropathies
- Humans
- Disease Progression OR Risk Factors.

This retrieved a total of 286 results. Articles were selected based on their clinical relevance for the prognostication of DKD in both type 1 diabetes mellitus and type 2 diabetes mellitus. Other literature was sourced through PubMed or an exploration of references in previously sourced articles.

RESULTS

Study approaches

The approach of many studies into DKD risk prognostication has been to collect a range of baseline patient data, and then to assess for a relationship with a chosen outcome measure. Alternative approaches have involved analysis of longitudinal test results, or sometimes proposed aggregate 'renal risk scores.' Novel biomarkers might improve predictive ability above routine clinical information alone[22]; nevertheless, barriers to clinical implementation remain significant[23]. An exhaustive discussion of experimental biomarkers is outside the scope of the present review.

Three broad study outcome measures have been assessed[24]: hard renal end-points (e.g., death, ESRD, CKD); albuminuria status; and the rate of GFR/eGFR decline. While studies attempting to use hard renal end-points require large sample sizes to reach statistical significance, questions remain surrounding the other two aforementioned outcome measures.

Changes in albuminuria as a surrogate marker have become more controversial, as it has become clearer that not all patients with diabetes who develop renal function decline experience significant albuminuria[25–28]. This limits the generalizability of findings from studies using established albuminuria as an inclusion criterion. Knowledge of non-albuminuric renal disease has prompted a trend in nomenclature away from 'diabetic nephropathy' (implying albuminuria) toward the more inclusive term, DKD[24]. This shift should not undermine the association between cardiovascular death and higher-grade albumin excretion[29].

The majority of studies cited in the present review assessing glomerular function used eGFR rather then measured GFR (mGFR). mGFR is determined by renal clearance of exogenous tracers (e.g., inulin), which undergo glomerular filtration, but no further tubular processing (neither secretion nor absorption)[30]. Creatinine levels and derived estimates of GFR are less precise, but more commonly carried out than mGFR[31]. Both CKD-EPI and MDRD formulas for eGFR have been criticized for being even less accurate in diabetic patients than in the general population[32–35]. These formulas might underestimate the rate of mGFR decline in patients with diabetes[35,36]. Nevertheless, early decline in eGFR (defined as >3.5 mL/min/1.73 m^2/year) has been positively correlated with ESRD in type 1 diabetes mellitus[37].

Finally, it should be noted that none of the aforementioned outcome measures confirm the true histopathological pattern of renal injury. 'Non-diabetic renal disease (NDRD)' (renal disease confirmed by biopsy as more consistent with a classically 'non-diabetic' pathology occurring in a patient with diabetes) might be common in some populations with type 2 diabetes mellitus[38–40], and could be associated with lower rates of albuminuria[41]; however, the reported proportions have varied wildly between investigators and study populations[42]. Careful exclusion of patients with known NDRD is important to avoid confounding. We have previously shown that typical renal structural changes of diabetic nephropathy were observed in patients with type 2 diabetes and elevated albuminuria. By contrast, in normoalbuminuric renal insufficiency, these changes were seen less frequently, likely reflecting greater contributions from aging, hypertension and arteriosclerosis[41].

CLINICAL PREDICTIVE FACTORS IN DIABETIC KIDNEY DISEASE PROGRESSION

Studies in patients with type 2 diabetes mellitus

Several large cohort studies examining the risk of progression to 'hard renal end-points' have been published in patients with baseline eGFR around 75 mL/min/1.73 m^2.

Elley et al.[43] describe a retrospective analysis of members of the large multicenter New Zealand Diabetes Cohort Study, assessing for 5-year risk of ESRD. Baseline median eGFR was 75 mL/min/1.73 m^2. Using baseline patient data, they produced a multivariable 'renal risk score' predictive equation. Direct statistical analysis of the individual candidate risk factors was not presented. Nevertheless, weighted models

incorporating albuminuria, serum creatinine, ethnicity, previous cardiovascular disease, glycemic control and systolic blood pressure (SBP) were shown to have statistically significant associations with development of ESRD.

Jardine *et al.*[44] released their own renal risk score based on results from the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation study, following 11,140 participants with type 2 diabetes mellitus for 5 years. Mean eGFR was 74.6 mL/min/1.73 m^2. The most important mediating factors identified were eGFR, urinary albumin:creatinine ratio, SBP, hemoglobin A1c (HbA1c), the presence of diabetic retinopathy, male sex and educational attainment.

Studies examining eGFR decline in patients with type 2 diabetes mellitus have used smaller sample sizes.

In one prospective observational cohort study, Zoppini *et al.*[45] followed 1,682 participants with eGFR ≥60 mL/min/1.73 m^2. They identified baseline hypertension, HbA1c, diabetes duration, obesity, insulin treatment and micro/macroalbuminuria as significant risk factors. In a smaller study population, Altemtam[46] reviewed medical records of 270 Saudi Arabian patients with type 2 diabetes mellitus and established CKD, arriving at similar conclusions; baseline SBP, HbA1c and proteinuria, but also serum uric acid and vascular comorbidities were strongly and independently associated (by multivariate analysis) with eGFR decline. Again, in a cohort of 729 Japanese patients with type 2 diabetes mellitus and normoalbuminuria, Yokoyama *et al.*[47] reported baseline HbA1c, eGFR, SBP and low plasma total protein as predictive of subsequent eGFR decline.

Rossing *et al.*[48] carried out a retrospective analysis of 366 Caucasian patients with type 2 diabetes mellitus. Only patients with persistent macroalbuminuria were enrolled. Nevertheless, they assessed for decline in measured GFR over 3 years. Multivariate regression analysis showed baseline risk factors for mGFR deterioration included albuminuria, SBP, HbA1c, GFR, age and degree of diabetic retinopathy. On follow up, the rate of change in albuminuria, SBP, HbA1c and lower hemoglobin, heavy smoking, and progression of diabetic retinopathy were also associated with lower mGFR. That study included two alternative outcome measures: all cause mortality (associated with higher baseline albuminuria, HbA1c, SBP and age) and 'doubling of serum creatinine or ESRD' (associated with higher baseline albuminuria, HbA1c and SBP, together with lower GFR and hemoglobin).

Studies in patients with type 1 diabetes mellitus
Studies in patients with type 1 diabetes mellitus are both fewer and smaller in participant size, but follow similar study design.

Skupien *et al.*[37] examined the occurrence of ESRD in 161 type 1 diabetes mellitus patients with 'normal' renal function (eGFR ≥60 mL/min) and macroalbuminuria at baseline. Although they were able to determine that baseline HbA1c and urinary albumin:creatinine ratio, and early eGFR slope predicted the risk of ESRD, statistical significance was not achieved for SBP, body mass index (BMI) or smoking.

In a smaller 5-year prospective study involving 72 type 1 diabetes mellitus patients of 'low socioeconomic level' in Saudi Arabia, Bentata *et al.*[49] found elevated diastolic BP and lower hemoglobin to be associated with progression to ESRD on multivariate analysis. That study was in the setting of advanced baseline diabetic complications and limited medical access.

In the study by Molitch *et al.*[50] 1,439 patients with type 1 diabetes mellitus in the multicenter Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications study had normal baseline eGFR, and were assessed for progression to eGFR <60 mL/min/1.73 m^2. That study stressed the importance of macroalbuminuria as a strong indicator, but also noted that screening for this alone would have missed many patients who went on to develop eGFR <60 mL/min/1.73 m^2.

Hovind *et al.*[51] were able to measure changes in mGFR in patients with type 1 diabetes mellitus. All participants had baseline albuminuria and diabetic retinopathy on enrolment[52]. With 301 participants, baseline blood pressure, albuminuria, HbA1c and serum cholesterol were shown to be independent predictors of a further decrease in mGFR.

Examples of studies in type 1 diabetes mellitus have struggled more with sample size, and often included patients with lower baseline kidney function than in type 2 diabetes mellitus.

DISCUSSION
Recent large-scale studies have explored risk factors for progression toward ESRD in type 2 diabetes mellitus. Similar studies in populations with type 1 diabetes mellitus have generally been somewhat limited by sample size, follow-up time or have followed patients from relatively advanced baseline kidney disease. Studies examining surrogate outcome measures have sometimes restricted themselves to populations with pre-existing albuminuria.

A range of other potential risk-markers have either incomplete or conflicting results based on the aforementioned studies, and are discussed below in detail. Irrespective of association with DKD, many of the proposed clinical variables (e.g., dyslipidemia and smoking) have a strong association with overall cardiovascular risk, making the control of such variables extremely important for patients with diabetes.

Evaluation of baseline clinical characteristics as renal risk markers
HbA1c, BP, albumin excretion rate, eGFR, microvascular complications and duration of diabetes
Evidence from a range of studies in both type 1 diabetes mellitus and type 2 diabetes mellitus patients (as above) highlight the utility of the following clinical findings in the prediction of DKD progression: elevated baseline HbA1c, elevated BP (systolic or mean arterial, but not diastolic), elevated albumin excretion rate (AER), decreased pre-existing renal function

(eGFR/mGFR), the presence and severity of concomitant microvascular complications (most especially retinopathy, but also peripheral/autonomic neuropathy, as has been corroborated by biopsy findings showing a link between retinopathy and renal structural changes[53]), and duration of diabetes. Individual discussion of these risk markers and progressive DKD have been extensively reviewed previously[24,54]. Below, we review the evidence for other candidate clinical risk markers for progressive DKD.

Age
Previous studies have generally favored older age as a risk factor for DKD progression – independent of diabetes duration. An independent association between higher age and increased risk of DKD progression have been reported by most[43,45,48], but not all[46] of the aforementioned studies in type 2 diabetes mellitus patients; these studies assessed for changes in eGFR/mGFR amongst predominantly adult patients. This is in keeping with a slow progressive eGFR decline seen in the general population after approximately age 40 years[55]. However, several studies of type 1 diabetes mellitus have suggested that diagnosis significantly before puberty is protective for DKD development[56–59] (although this finding has not been universal[60,61]). Emerging evidence suggests that those patients with youth-onset type 2 diabetes mellitus might also be at increased risk of DKD[62]. Poor glycemic control as a result of changes in both hormonal and social factors occurring around puberty might drive this apparent risk window[56,63].

Sex category
The sex category is better examined in studies of patients with type 2 diabetes mellitus than those with type 1 diabetes mellitus. Male sex was reported as a risk factor for DKD progression by two of the aforementioned studies examining hard renal end-points in type 2 diabetes mellitus[43,44]. However, the sex category was found to be insignificant in other studies examining either eGFR or mGFR decline in patients with type 2 diabetes mellitus[45,46,48], and was unreported in most studies retrieved for patients with type 1 diabetes mellitus[37,49–51]. It is now appreciated that different risk factors are associated with patients following albuminuric and non albuminuric pathway to renal impairment with more females following the non-albuminuric pathway[26].

BMI
Elevated BMI has been reported as a significant risk factor for DKD progression in some, but not all studies. This is despite the established obesity-related complication of focal segmental glomerulosclerosis[64–66]. In their prospective observational study, Zoppini et al. found BMI was not associated with a more rapid eGFR decline unless adjusted for age[45]. Insignificant findings were reported by a range of other studies into type 2 diabetes mellitus[46,48], including one large-scale epidemiological review based on the Coronary Risk of Insulin Sensitivity in Indian Subjects study.

Huang et al.[67] even reported high BMI to be associated with *slower* eGFR decline in a 24-month prospective study of 105 patients with type 2 diabetes mellitus and CKD. Available studies in patients with type 1 diabetes mellitus did not report an analysis on BMI as a candidate DKD risk factor[37,49–51].

Smoking status
Elley et al.[43] presented current smoking status, but not past smoking status as a predictor of ESRD in patients with type 2 diabetes mellitus. Similarly, Rossing et al.[48] reported an association between 'heavy' smoking and mGFR decline over the course of follow up, but not at baseline in type 2 diabetes mellitus. Several studies of patients with type 2 diabetes mellitus have presented a positive association between eGFR decline and either current or former smoking status[45,46]. Meanwhile, studies into the rate of eGFR/mGFR decline in type 1 diabetes mellitus have reported a mixture of statistically significant[68,69] and insignificant[37,51] results. Nevertheless, ongoing basic and animal research continues to elicit potential mechanisms for tobacco being associated with structural renal damage in diabetics[70,71]. It is possible that baseline reported smoking status has been a poor predictor of ongoing exposure in certain study populations.

Lipid profile
Aspects of the lipid profile and their relationship with DKD have often either not been presented[37,43,44,50], have been found to be insignificant[45,48] or reported to have a complex relationship. In patients with type 2 diabetes mellitus, Altemtam et al.[46] reported that high serum triglycerides are associated with eGFR decline; however, despite collecting a full lipid profile, the present study did not report on any other aspects of the lipid profile[46]. Meanwhile in patients with type 1 diabetes mellitus, Hovind et al.[51] reported higher total serum cholesterol as significantly predicting greater mGFR decline. Chang et al.[72] have reported an association between higher triglycerides and lower high-density lipoprotein cholesterol (HDL-C), but not with higher low-density lipoprotein cholesterol (LDL-C) and the development of albuminuria end-points. Using a mixed set of albuminuric/creatinine-based outcome measures in type 1 diabetes mellitus, Thomas et al.[73] reported a significance of association with LDL-C only.

Aside from standard methodological limitations (e.g., sample size, incomplete presentation of results), some of the existing confusion with regard to the role of the lipid profile might relate to inherent limitations of available assays. For example, HDL-C, although usually considered as vascular-protective, might be altered and instead cause endothelial dysfunction in patients with CKD[74]. Emerging work points toward a more specific predictive utility of lipid subtype analysis[75,76]. This field of 'lipidomics'[77] has already reported a cross-sectional relationship between the lipid-subtype 'fingerprint' and advanced kidney disease[78].

Family history and ethnicity
While formal genetic profiling remains unavailable for the average practicing clinician, family history and ethnicity are readily

available, and could assist in risk stratification for DKD[79,80]. In a retrospective British study of 3,855 patients with type 1 diabetes mellitus/type 2 diabetes mellitus, a more rapid rate of GFR decline was reported in those of either black or South Asian ethnicity than those of Caucasian ethnicity[81]. Elley *et al.*[43] (as aforementioned) presented those of Pacific Islander and Maori descent having higher rates of progression than those of 'European' descent, with those of East Asian and Indo-Asian ethnicity having the lowest rates of decline of all. Indigenous peoples might experience a higher rate of disease progression, including Australian Aboriginal and Torres Strait Islander peoples[82,83]. The relationship between ethnicity and outcomes is complicated greatly by an interplay of economic, social, and educational factors[84].

Hemoglobin

In a relatively small study of 174 patients with type 1 diabetes mellitus and pre-existing albuminuria, baseline hemoglobin concentration was shown by Conway *et al.*[85] to be inversely proportional to the risk of the development of ESRD. Also, in patients with type 1 diabetes mellitus with advanced DKD, Bentata *et al.*[49] found an independent association between lower baseline hemoglobin and ESRD. In patients with type 2 diabetes mellitus, Rossing *et al.*[48] found low *baseline* hemoglobin was significantly associated with the composite end-point risk of 'doubling of serum creatinine or ESRD,' and low *ongoing* (over course of follow up) hemoglobin concentration was significantly associated with the rate of decline in isotopic mGFR. With the exception of the aforementioned studies, many of the notable studies retrieved by the present literature review did not document an analysis of baseline hemoglobin[37,43–46,50,51].

Anemia is a known sequelae of advanced DKD[86,87], resulting from tubulointerstitial damage[88]. Therapeutic use of erythropoietin analogs in diabetic CKD3/4 does not appear to slow the rate of progression to ESRD[89]. This suggests low hemoglobin is a marker of pre-existing tubulointerstitial damage[88,90]. Notwithstanding the need for replication in a broader population, correction for eGFR in the aforementioned studies does help to imply a potential role for baseline hemoglobin in the prognostication of DKD above existing risk factors.

Vitamin D

Baseline vitamin D can become similarly deficient in patients with advanced CKD, and has been proposed as a DKD risk factor. Fernandez-Juarez *et al.*[91] followed 133 patients with type 2 diabetes mellitus, in which all had established type 2 diabetes mellitus and pre-existing albuminuric CKD. Using a composite end-point (serum creatinine >50% increase, ESRD and mortality), these investigators reported low vitamin D as being independently associated with DKD progression. Though encouraging, these results require replication in order to be extrapolated to the broader type 2 diabetes mellitus population.

Uric acid

Elevations of uric acid are also known to occur in late-stage DKD[92,93]. However, unlike hemoglobin and vitamin D, high-normal serum uric acid has been shown to be associated with the development of the risk of CKD3 in patients with type 2 diabetes mellitus[94,95], and eGFR decline in type 1 diabetes mellitus[96], even with relatively preserved baseline eGFR. Though the results of large-scale prospective trials are pending[97], existing data suggest uric acid might play a mediating role in renal damage[98,99]. Recently, decreased urinary uric acid excretion has been cross-sectionally associated with the risk of development of DKD[100].

Arterial pulse wave velocity

In a shift from the blood test dominated approach to risk stratification, Sheen *et al.*[101] have recently advocated for clinical assessment of peripheral arterial stiffness. In their study of 577 patients with type 2 diabetes mellitus, higher brachial-ankle pulse wave velocity was associated with a more rapid 1-year decline in eGFR. Similar results were found by Bouchi *et al.*[102] using carotid-femoral pulse wave velocity in a cohort of Japanese patients with type 2 diabetes mellitus.

Hyperfiltration

Hyperfiltration has been proposed as an early step in the development of 'diabetic nephropathy,' with incompletely understood arteriolar/tubulo-glomerular changes creating elevated mean glomerular hydrostatic pressures, glomerular damage and albuminuria[103,104]. Hyperfiltration is defined as an elevated baseline GFR, but the exact study-specific threshold used to define this phenomenon has varied between 90.7 and 175 mL/min/1.73 m^2[2,105].

A full review of the literature surrounding hyperfiltration is beyond the scope of the present review. Although more evidence exists for studies of patients with type 1 diabetes mellitus than those with type 2 diabetes mellitus, studies to date have relied on either rates of decline in (e)GFR[106–108] or change in albumin excretion rate[107,109]. Not all studies have reported a positive association[110–114].

Significant methodological challenges exist for the field of hyperfiltration. A pathological decline in GFR might be indistinguishable from a 'beneficial' resolution of hyperfiltration over a short follow up. Additionally, given hyperfiltration is associated with poor glycemic control[115–117], this phenomenon might simply imply worse glycemic control unless this is adjusted for. Ideally, adequate longitudinal data should allow for the development of hard renal end-points, such as CKD or ESRD (Figure 1), with baseline variable adjustment[118]. The true clinical implications of hyperfiltration are currently unknown[119].

Visit-to-visit variability of routine clinical measures

Several of the candidate baseline clinical predictors of DKD progression have been analyzed for the impact of visit-to-visit
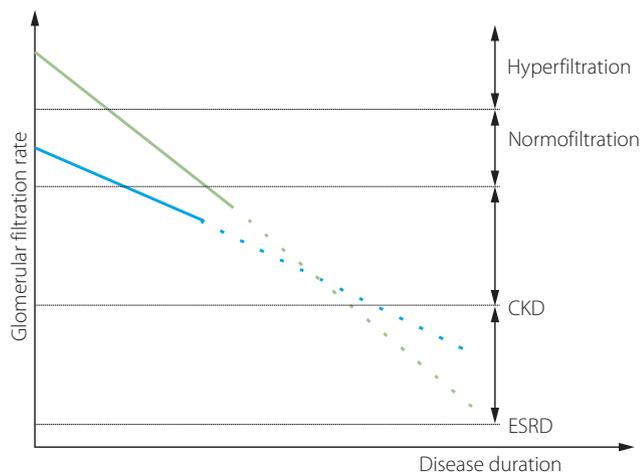
Figure 1 | Graphic representation of proposed glomerular filtration rate decline in patients with either baseline hyperfiltration or 'normofiltration.' Current studies have sometimes suggested a more rapid rate of early glomerular filtration rate decline in those with hyperfiltration as compared with those with normofiltration (solid lines above). It is unknown whether this is associated with a more rapid onset of chronic kidney disease (CKD) or end-stage renal disease (ESRD) (dashed lines).

variability. These include BP, HbA1c and HDL-C. Most studies in this area have used albuminuric end-points.

Blood pressure variability

In a cohort of 354 patients with type 2 diabetes mellitus, Okada et al.[120] compared the changes in albuminuria based on differences in the coefficient of variation of SBP. The average duration of albuminuria surveillance was 3.8 years, after a baseline 1-year period of clinic-BP collection (mean 7.19 readings over this time). Leaving aside the potential limits of an albuminuria-based outcome measure, this study did suggest that clinicians might derive prognostic value by considering not only the baseline BP measure, but historical instability/variability. By contrast, in a much smaller study of patients with advanced DKD (69 patients, mixed type 1 diabetes mellitus/type 2 diabetes mellitus), Yokota[121] found no effect of visit-to-visit variability in BP on eGFR. The median follow-up period was 32 months. There is a growing consensus around the risk of diabetic microvascular complications in general from increased BP variability[122], but its role in DKD progression remains to be confirmed.

HbA1c variability

Rodriguez et al.[123] found that, even adjusting for a broad range of other clinical variables, there was a significantly higher risk of increased albumin excretion in patients with type 2 diabetes mellitus with greater HbA1c variability. That study followed 2,103 patients for mean 6.6 years. Unlike the study by Okada et al. 'variability' was determined over the course of follow up; that is, they did not determine that *historical* variability

determined *future* changes in albuminuria, but instead that ongoing HbA1c variability was correlated with ongoing albumin excretion changes. Similar findings based on concurrent follow up of HbA1c and AER have been reported by Hsu et al.[124] and Wadén et al.[125]. A much larger (15,773 patients, 19 centers) study by Penno et al.[126] found that variability of three to five HbA1c measurements over 2 years of follow up was associated with not only albuminuria, but low eGFR amongst patients with type 2 diabetes mellitus. However, that study did not assess for longitudinal changes in either AER or eGFR. HbA1c variability was not shown to predict future changes for a given individual, but simply to correlate with high AER and low eGFR.

Mechanistically, Thomas[127] has suggested that epigenetic programming and/or post-translational modifications might underlie a relationship between HbA1c variability and diabetic complications. This could then be seen as analogous to the concept of 'metabolic memory' used to explain the renoprotection seen in glycemic intervention trials of early diabetes[128,129].

LDL-C and HDL-C variability

Finally, in the study by Chang et al.[72], higher HDL-C variation was associated with a higher risk of DKD progression in patients with type 2 diabetes mellitus. The outcome measure of that study was AER status. Again, measurements used to derive HDL-C variability appear to have been taken throughout the period of AER follow up. Although that study found no link (despite assessment) between LDL-C variability and DKD progression, LDL-C variability has been linked with adverse cardiovascular outcomes[130]. Further studies into the area of cholesterol variability and DKD are warranted.

Early studies into the association between DKD progression and visit-to-visit variability of routine clinical variables are promising, but several methodological challenges in the existing literature warrant further research. Specifically, future studies could use a broader range of study endpoints, and aim to establish the role of baseline historical variability.

Novel biomarkers and progressive DKD

The present review has focused on clinically predictive factors for progressive DKD. Inflammatory mediators, tubular markers and microribonucleic acids (microRNAs) represent three broad families of biomarkers with strong potential for future clinical use and are reviewed below. A full discussion of 'novel' biomarkers is beyond the scope of the present article.

Of all the potential inflammatory markers, soluble tumor necrosis factor (TNF) receptors 1 and 2 (sTNFR1 and sTNFR2) might be the most promising, as a range of investigators have reported them to be independently associated with both eGFR decline and occurrence of either CKD3 or ESRD[131]. The predictive utility of these receptors might even be highest amongst the proteinuric subcohort of patients with type 2 diabetes mellitus[132]. In patients with type 1 diabetes mellitus, Gohda et al.[133] followed 628 patients with baseline normal renal function and

no proteinuria. sTNFR1 and sTNFR2 were strongly associated with time to CKD3 (eGFR <60 mL/min/1.73 m^2). Meanwhile, Niewczas *et al.*[132] followed 410 patients with type 2 diabetes mellitus for 12 years. Despite measuring a range of plasma markers known to be involved in systemic inflammation, endothelial dysfunction and the TNF pathway, only sTNFR1 and sTNFR2 were significantly associated with risk of ESRD. In a group of 193 American Pima Indians with type 2 diabetes mellitus (mean follow up 9.5 years), Pavkov *et al.*[134] showed superior prediction of ESRD by incorporating sTNFR1 and sTNFR2 above clinical markers alone. While we are not aware of documented human renal histological damage correlating with either sTNFR1 or sTNFR2 in diabetes, such a relationship has been reported in immunoglobulin A nephropathy[135].

Markers of tubular dysfunction might reflect the ongoing tubular damage in DKD[136]. Two examples are kidney injury molecule 1 and neutrophil gelatinase-associated lipocalin. Kidney injury molecule 1 is associated with murine renal tubular damage[137], and lower levels might be associated with regression of microalbuminuria in human type 1 diabetes mellitus[138,139]. An association between kidney injury molecule 1 and progressive eGFR decline has been shown in both type 1 diabetes mellitus and type 2 diabetes mellitus, though significance of association might disappear with adjustment for clinical markers[140,141]. Neutrophil gelatinase-associated lipocalin is a recognized marker of acute renal injury[142,143], and has been reported to be cross-sectionally elevated in both type 1 diabetes mellitus and type 2 diabetes mellitus with increasing levels of albuminuria[144,145]. In a study by Nielsen *et al.*,[141] despite a univariate association of neutrophil gelatinase-associated lipocalin with eGFR decline, the association again became non-significant with multivariable adjustment. Urinary liver-type fatty acid-binding protein has also recently been reported as being associated with progressive DKD in observational follow-up studies; this association might be truly independent of AER. In a cohort of 1,549 patients with type 1 diabetes mellitus, Panduru *et al.*[146] showed that liver-type fatty acid-binding protein acted independently to AER, baseline eGFR and triglycerides as a predictor of ESRD. In a smaller cohort of 618 patients with type 2 diabetes mellitus, Araki *et al.*[147] reported that the association between liver-type fatty acid-binding protein and the rate of eGFR decline remained significant even after adjustment for baseline SBP and AER.

MicroRNAs, non-coding RNA involved in gene expression (epigenetic programming), have recently come under increasing attention as potential early markers of DKD[148–150]. Proposed microRNAs of interest might be involved in a range of biological pathways; one example is that of the transforming growth factor-beta pathway, known to be involved in CKD progression[151,152]. The field of microRNA holds much promise, though more work is required to elucidate their potential role as useful risk predictors.

Should they become more clinically available, a selection of currently proposed biomarkers might hold significant individual

prognostic value. An alternative possible approach uses multi-marker 'risk panels' in an attempt to deliver superior predictive utility[22].

Accumulated risk factors and renal risk scores
As has been suggested above in the section 'Visit-to-Visit Variability of Routine Clinical Measures,' the progression of DKD might be affected not only by the magnitude of physiological derangement, but also the timing and duration. In terms of glycemic control, both the Diabetes Control and Complications Trial and UKPDS trials (in type 1 diabetes mellitus and type 2 diabetes mellitus, respectively) provided evidence for a strong 'legacy effect' from early and 'tight' glycemic control[128,129,153]. This strong relationship between early glycemic control and lower incidence of micro/macrovascular complications might be at least in part mediated by epigenetic changes[154,155]. The evidence of a legacy effect should not undermine newer evidence (e.g., from the Action to Control Cardiovascular Risk in Diabetes study) supporting individualized glycemic targets[156].

Although the variables above are discussed individually, accurate clinical prediction of DKD risk clearly requires a broad consideration of patient data, whether traditional clinical variables or novel biomarkers. Looker *et al.*[22] compared the predictive utility of a fairly restricted set of five clinical variables (age, sex, HbA1c, eGFR and albuminuria) to a combination panel of these original five clinical variables plus 14 biomarkers; perhaps unsurprisingly, the receiver operating characteristic increased from 0.706 (clinical data alone) to 0.868 (additional biomarkers). Formalized 'renal risk scores' (e.g., of Elley *et al.*[43] and Jardine *et al.*[44] above), represent a possible standardized approach to multivariable risk stratification. Although the current tools are potentially useful for the type 2 diabetes mellitus-specific populations from which they were developed, they might not be applicable to type 1 diabetes mellitus cohorts. For routine clinical practice, equations would most likely need to be 'hidden behind clinical software'[43]. However, given the challenges of encouraging cardiovascular risk calculators in primary care settings[157,158], broad uptake of renal risk scores might be challenging.

CONCLUSION
Although much of the new research published in the area of DKD risk stratification involves novel markers requiring new and potentially expensive tests, research into the use of clinically accessible risk markers is ongoing.

While a true consensus has emerged for the role of several clinical risk factors, the role of several others requires further research (Figure 2). Proposals for 'renal risk score equations,' and assessment of historical trends (including visit-to-visit variability) further the opportunity for prognostication based on readily available patient information.

Existing studies have used a range of outcome measures, over a varied duration of follow up, often with very different study populations and baseline kidney function. Some have used
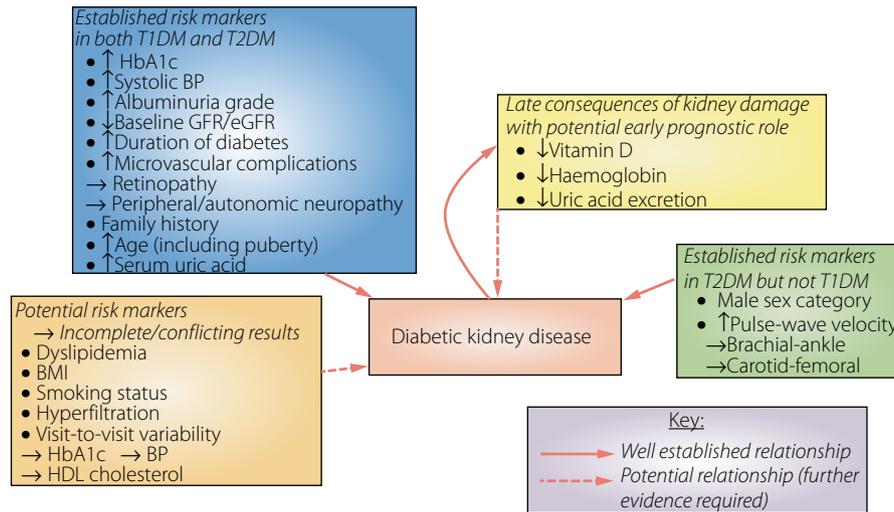
Figure 2 | Summary of established and potential clinically applicable predictive factors in the progression of diabetic kidney disease. BP, blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; GFR, glomerular filtration rate; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

albuminuria grade as a selection criterion, which might limit applicability for patients with diabetes who are progressing down a non-proteinuric DKD pathway. The majority (but not all) of studies have been carried out in developed countries, often in diabetic populations regularly attending tertiary referral centers, or involved in large-scale clinical trials.

Future studies into the prognostication of DKD should aim to optimize outcome measures (by using either hard renal endpoints or decline in accurate measures of GFR) and inclusion criteria. Studies could stratify their analysis by baseline GFR; thereby confirming the relevance of potential risk factors for patients over the full range of existing kidney function. In addition, a focus on presenting the relative magnitudes of association (for example, by hazard ratio or area under the curve[159]) could better inform the field of what factors contribute to the risk of DKD to a clinically meaningful extent.

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DISCLOSURE

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