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Review Article

An Overview of Major Clinical Predictive Factors and Prognostic Biomarkers of Diabetic Kidney Disease in Children and Adolescents

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Abstract:

The onset and progression of diabetic nephropathy represent a significant issue in diabetic management as it is the primary microvascular consequence of both type 1 and type 2 diabetes mellitus and a significant contributor to end stage renal disease-related mortality. Major risk factors for nephropathy in children and adolescents include hyperglycemia, HbA1c, diabetes duration, gender, blood pressure, dyslipidemia, uric acid, family history and genetic factors, smoking, puberty, and obesity. Metabolism and hemodynamic variables interact on a complex basis during disease development. A series of intricate molecular events take place in response to hyperglycemia, which disturbs the body's metabolic environment and causes glomerular enlargement, tubular inflammation, mesangial expansion, oxidative stress, and renal fibrosis. Fortunately, the main approaches for preventing the beginning and reducing the progression of diabetic kidney damage are rigorous glucose control and antihypertensive medications. As children and adolescents with T1D are at risk for developing early diabetic nephropathy, patients with T1D must have the best metabolic control, an early diagnosis, and timely treatment of dyslipidemia and hypertension. Prospects for better diabetic nephropathy outcomes are improving as novel approaches are developed. Novel biomarkers are increasingly proven to be more reliable instruments than the traditional microalbuminuria, which can forecast the development of disease. In addition to glomerular and tubular indicators, inflammation and oxidative stress markers have proven to be reliable diagnostic aids. In order to emphasize the methods being employed lately to enhance therapeutic approaches in diabetic nephropathy, certain emerging critical biomarkers are illustrated in this review.

Keywords: Diabetes, diabetic kidney disease, diabetic nephropathy, risk factors, biomarkers, microalbuminuria.

Introduction

As one of the most prevalent chronic diseases, diabetes affects an increasing number of children and adolescents each year. Type 1 diabetes (T1D) is estimated to affect 1211900 children and adolescents (aged <20) worldwide, with 651700 of those being younger than 15 years old, according to the International Diabetes Federation (IDF) Atlas 10th Edition. T1D is a condition that affects more than 132000 children and adolescents annually [1]. The prevalence of T1D among children and adolescents varies greatly on a regional and national level, and the risk is significantly higher for racial and ethnic minorities [1, 2]. The majority of cases—about half—are found in Europe and North America (Fig.1.a, b, c, d) [2]. The three nations with the largest populations of people with T1D under 20 are the United States, India, and Brazil. Type 2 diabetes (T2D) in this age group has the potential to become a global health problem with major health consequences because of the rising rates of overweight and obesity in children and adolescents in many nations. The knowledge of the epidemiological patterns and trends in the incidence rates of T1D at the worldwide level is currently plagued by significant data gaps. There are not enough data on youngsters for many African nations. Additionally, the disease burden is being increased by a lack of understanding of aspects including the natural history of the illness, etiology, potential consequences, and the ability of healthcare systems to provide adequate medical care to people who have T1D in a variety of situations.

Childhood obesity has increased over the past 20 years, and as a result, T2D in children and adolescents has risen as well. In fact, it currently matches and occasionally even exceeds T1D

in minority kids, especially after the age of 15[3]. It has long been recognized that diabetes is significantly linked to an increase in mortality, primarily due to its long-term consequences. When compared to the general population of children without diabetes, the life expectancy of the diabetes group was shown to be significantly lower (around 15 years), according to Rhodes et al [4]. In children who develop T1D before turning 10 years old, the life expectancy is much lower (loss of 17.7 years for females versus 14.0 for males) compared to those diagnosed between the ages of 25 and 30 (loss of 10.0 years for women and 9.4 years for men) [5]. Recently, it has been discovered that the subset of diabetics who also acquire renal disease, whether they have type 1 or type 2, is where the majority of this extra mortality occurs [6, 7]. Even more concerning is the finding that a sizable sample of young people with T2D had a 4-fold higher risk of renal failure than those with T1D [8]. Additionally, those with young-onset T2D had a 39-fold higher risk of end-stage renal disease (ESRD), a 23-fold higher risk of severe renal injury, and a 16-fold higher risk of kidney disorders compared to the control group [8].

These findings underline the significance of diabetic kidney disease (DKD), at the very least as a marker of a population at high mortality risk and probably as a risk factor directly causing excess mortality. Kidney biopsies performed as soon as 1.5 to 5 years following the onset of diabetes show structural alterations typical of DKD in both adults and children, even though more severe instances of DKD take decades to develop and are therefore infrequently seen in children [9-11]. This shows that the DKD course starts shortly after the development of diabetes and that this early period may represent a crucial window for diagnosis and intervention in the disease course, necessitating close monitoring and management of risk factors in kids and teenagers. The American Diabetes Association (ADA) currently advises screening children with T2D upon diagnosis and every year after that for microalbuminuria (MA), which should be done after they are 10 years old and have had T1D for five years. Due to the diversity in albumin excretion rates, a clinical diagnosis can only be made if two out of three readings are abnormal.

There are currently few and insufficient resources available for the early detection of DKD in children and adolescents. However, given the serious effects of childhood diabetes on morbidity and mortality later in life, we must make the most of the tools and resources already in place while also redoubling our efforts to create new diagnostic techniques and treatments. This review examines the risk factors for developing DKD and the newly investigated predictive biomarkers, which will undoubtedly increase our understanding of how to create novel treatments that can slow or even stop the progression of the disease.

Figure1: Analysis of global type 1 diabetes incidence rates based on age category: (a)- 0-4 years; (b)- 5-9 years;(c)- 10-14 years;(d)-15-19 years [2].

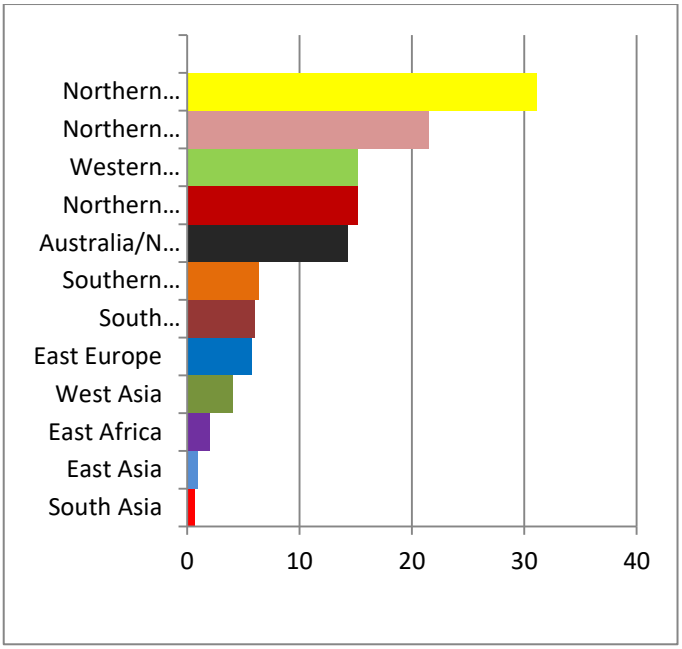

Figure 1 (a): 0 – 4 years

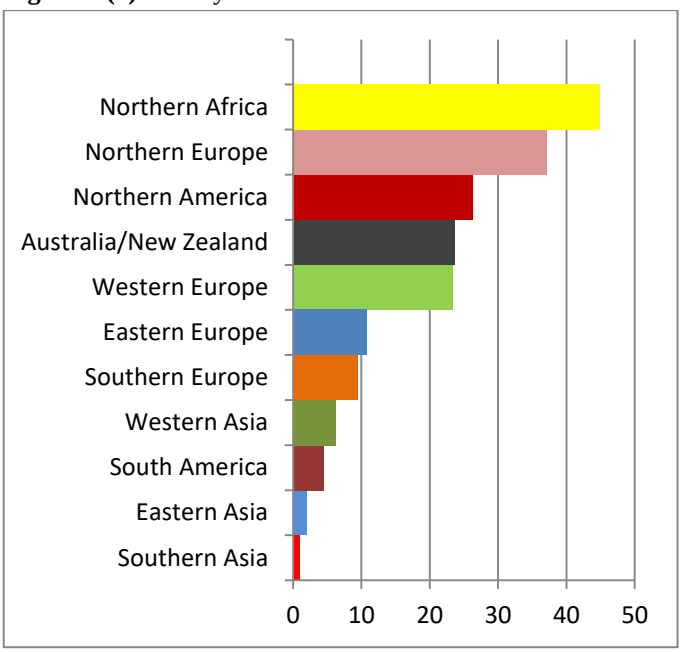

Figure 1 (b): 5 – 9 Years

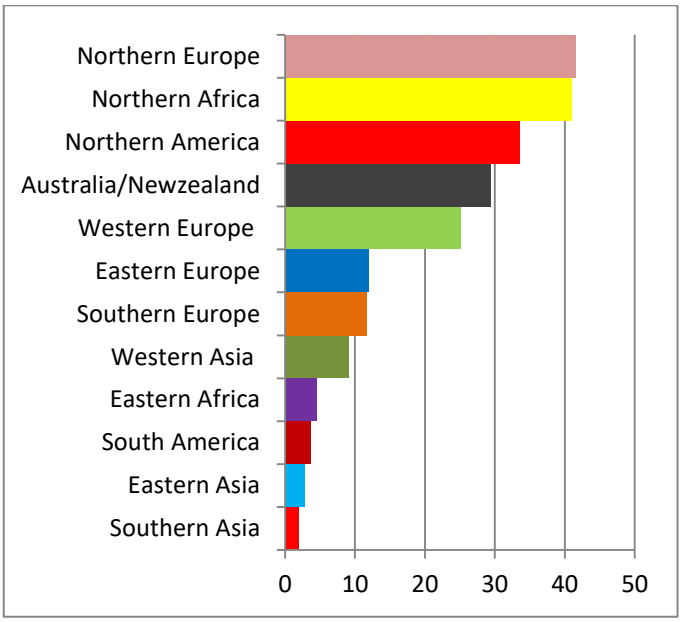

Figure 1(c): 10 – 14 Years

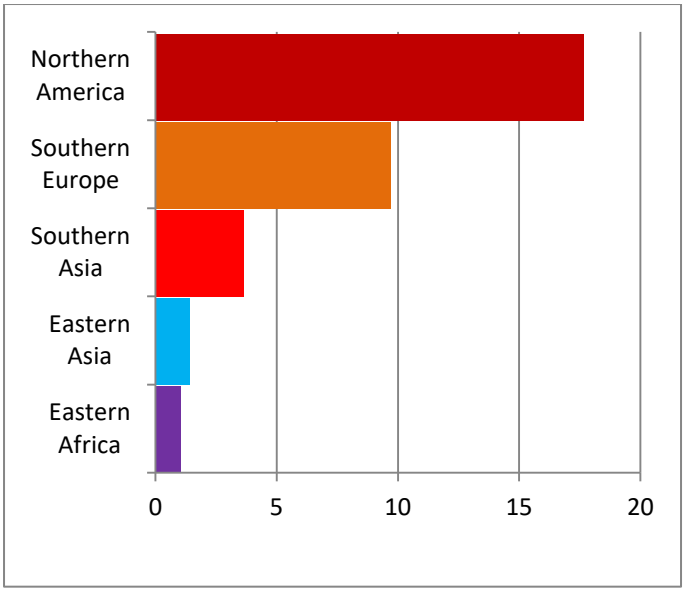

Figure 1(d): 15 – 19 Years

Onset of DKD

Microalbuminuria (MA), also known as occult or incipient nephropathy, is a degenerative condition that first manifests as a little amount of albumin loss into the urine. The terms "macroalbuminuria" or "overt nephropathy" were adopted as albuminuria (albumin loss in the urine) became evident by dipstick urine examination (300 mg/day). After this clinical presentation, there was a steady deterioration in kidney function, renal impairment, and finally ESRD over several decades [12]. The United Kingdom Prospective Diabetes study demonstrated that progression to MA occurred at the rate of 2.0% annually and from MA to macroalbuminuria at the rate of 2.8% annually from the diagnosis of diabetes [13].The majority of T2D patients and most T1D patients, however, do not follow this conventional pattern in contemporary clinical practice. Many diabetic patients with renal impairment may not have a significant loss of urine albumin[14-15]. Additionally, MA does not lead to a faster rate of glomerular filtration rate (GFR) decline [16].This finding led to the hypothesis that MA might really represent reversible endothelium injury rather than being a definite indication of particular and irreversible DKD. Improved hyperglycemia and blood pressure management increases the likelihood of MA regression to normal albuminuria, but this occurs in both adults and children and is unrelated to rennin-angiotensin system (RAS)inhibition. According to a study by Molitch et al. [16], a significant proportion of T1D patients experience GFR loss either after MA (16%) or even in the absence of any albumin (24%). This is despite the fact that the conventional presentation of MA followed by GFR (glomerular filtration rate) impairment is seen in the majority of instances in T1D. This observation implied that severe renal damage could happen even in the absence of macroalbuminuria or even MA.

Two additional factors need to be taken into account when interpreting albuminuria in children and adolescents. First, transitory and orthostatic proteinuria are the most common benign causes (75–95%) of proteinuria in children and adolescents [17-20]. Up to 50-74% of cases of observed proteinuria in children and adolescents are found to be transient, and they may be related to activity, fever, cold stress, dehydration, or seizures [17-19]. Orthostatic proteinuria has been documented in 6-20% [21] of healthy children and adolescents and has no negative consequences up to 50 years after the initial diagnosis. The likelihood of incorrectly classifying albuminuria status by using a single threshold of 30 mg/g of creatinine in children of varied ages, sizes, genders is the second hurdle to proper interpretation of albuminuria in children. Age-related increases in albumin [22-23] and creatinine [22, 24] excretion are observed in children and adolescents. In addition, albumin excretion is higher in African Americans than in Caucasians [25], while creatinine excretion is generally higher in boys [22, 26]. When evaluating spot urine samples, a single threshold of 30 mg/g is likely to overestimate albumin excretion in younger, smaller, and female children whose daily creatinine is more likely to be substantially lower than 1 gm.

Risk factors for the development of MA and macroalbuminuria

1. Hyperglycemia (measured by hemoglobin A1c)

A high risk of micro- and macrovascular consequences exists in children with T1D [26-27]. There are two types of glycemic variability: short-term (intra- and inter-day blood glucose variability) and long-term (HbA1c variability)[28-29]. During the first two decades following the diagnosis of T1D with a childhood beginning, there was a strong correlation between HbA1c variability and the rate of MA development [30]. This demonstrates the link between long-term glycemic fluctuation and the risk of microvascular problems in T1D patients. Independent of the mean A1c, HbA1c variability in the Diabetic Control and Complications Trial group (DCCT) was substantially related to the length of time it took for MA, nephropathy, and retinopathy to develop [31]. Higher HbA1c variability was strongly associated with higher MA progression to macroalbuminuria. Additionally, in T1D patients, HbA1c fluctuation was linked to time to MA, renal disease progression, and acute cardiovascular events [32].The authors of a UK registry-based investigation with juvenile patients found a statistically significant correlation between SD-A1c and the emergence of MA [33]. The study also found a connection between mean-A1c and the likelihood of MA. However, it is still unclear how daily glycemic fluctuation and HbA1c variability are related.

To reduce the likelihood of developing MA, it is crucial that T1D patients' children and teenagers maintain adequate and consistent glycemic control over the first decade following their diagnosis. It is important to develop and test interventions that specifically affect the level of HbA1c variability. Additional studies are required to assess the association between HbA1c variability and both intra- and inter-day glycemic variability as well as how HbA1c variability might be used to risk-stratify juvenile T1D patients. Finally, eGFR-derived metrics should be used as outcome variables in future studies that aim to assess HbA1c

fluctuation as a risk factor for incidence of early-stage nephropathy.

2. Gender

It has been established that age is a factor in the influence of sex on nephropathy. For men and women of different age groups, the DKD presentation and results are different. The discrepancies are mirrored by variations in lifestyle factors, such as smoking habits and adherence to low-sodium, low-phosphate, and low-potassium diets, that are known to or are hypothesized to influence albuminuria and the course of chronic kidney disease (CKD)[34]. More particular, despite having fewer referrals and identical baseline GFR, hypertension, diabetes management, and complications from diabetes between sexes, baseline albuminuria was lower in adult females [35]. Additionally, only in adult females did albuminuria continue to decline throughout the course of the follow-up, highlighting significant variations in how men and women present with DKD clinically. Unlike in adult females, several studies reported that the adolescent females had increased risk of MA [36-39]. The fact that female adolescents have higher HbA1c scores may assist in explicating why female subjects excrete albumin at a higher rate than male subjects do [35].

Boys are more likely to develop overt diabetic renal disease over their lifetimes than girls, despite girls having a higher frequency of MA during adolescence [40]. According to reports, while the prevalence of MA in girls is more stable, it is stated that the prevalence increases in boys during the 10 to 25 years of diabetes [41]. For a number of years after puberty, these disparities in prevalence can continue. It is not yet known why the male preponderance supervenes or at what age it does. For clinical trials in women who are at high risk of DKD progression, it is necessary to create DKD progression risk algorithms that are specifically tailored to females. The definition of albuminuria as a marker of a high risk of rapid development in diabetics should be revisited in further investigations.

3. Diabetes duration

A correlation between MA and prolonged diabetes duration has been discovered, with MA frequency being notably high, exceeding 15%, with duration ≥ 10 years [42]. Children and adolescents with prolonged duration of diabetes, particularly if more than 60 months, were more likely to have raised albumin to creatinine ratios (ACR) among T1D participants. With a mean age of 16.2 years and a mean duration of diabetes of 1.9 years, the study estimated that 22.2% of youth with T2D may already have an elevated ACR, raises the possibility of a relatively faster progression to diabetes-related vascular complications in this population. This is since elevated ACR has been shown to predict progression to diabetic nephropathy and cardiovascular disease [43-44]. The younger age of T2D onset may contribute to an increase in morbidity and death in the future. Due to the potential future burden of associated vascular problems, efforts to prevent or delay T2D diabetes in children could have a significant positive influence on the public health. According to Holl et al [37] and a number of other studies [45-48], 10% of patients with diabetes had persistent MA after 14 years, despite having strict metabolic control, and 5% of patients did so after 11 years. The findings from Sweden on 155 children who were followed for 10 years show how crucial early metabolic control is for diabetes patients in the prepubertal stage [49]. Early puberty rather than late puberty was reported to be associated with the occurrence of MA in a prospective Swiss study, and screening was advocated [50]. These results highlight the need for adequate metabolic control from the outset of diabetes in order to avoid MA consequences, even though retinopathy or nephropathy typically manifests after puberty.

4. Hypertension

Pediatric T1D studies have demonstrated an association between MA and diastolic blood pressure [36-37,39,52-57]. In the DCCT, it was found that intensive diabetes management decreased the risk of developing MA and macroalbuminuria by 39% and 54%, respectively, in the entire cohort [5]—and that the risk of developing MA was reduced by 55% in participants who were 13 to 18 years old at enrolment [58]. It has also been demonstrated that ACEI/ARB blood pressure regulation can slow the development of MA into proteinuria [59]. Systolic and diastolic blood pressure were suggested by Raile et al [34] to be independently linked with MA. In patients who had macroalbminuria or were receiving dialysis, hypertension was less of a risk factor for nephropathy. The stringent anti-hypertensive therapy regimens used on patients with severe renal illness may be the cause of this phenomena. Danne et al [60] demonstrated that arterial hypertension aggravated diabetic nephropathy but whether the rise in blood pressure precedes or succeeds MA is questionable. Another study showed that raised arterial blood pressure both succeeds and aggravates early diabetic nephropathy [43]. Another study found that systolic blood pressure was associated with development of MA [61]. But regardless of whether blood pressure is the cause or effect of nephropathy, paediatric and adolescent patients should receive stringent treatment. Age, diabetes duration, sex, body mass index (BMI), haemoglobin A1c, and insulin dosage were all associated with changed blood pressure profiles, according to a large European cohort study of children with T1D (n=2105 aged 15–18 years)[62]. The study additionally discovered that teens with T1D had significantly higher nocturnal blood pressure (systolic BP +0.50, diastolic BP +0.58, and mean arterial pressure +0.80), which was predominantly responsible for MA. TODAY Study Group evaluated youth and young adults for hypertension and nephropathy and followed them for an average of 3-9 years. Subjects (mean age 14 years) were enrolled within two years of their diagnosis and received complete diabetic care. 11.6% of participants had hypertension at the start of the study, which is defined as blood pressure that is greater than or equal to 130/80 mmHg or a blood pressure that is greater than 95% for age, sex, and height. Modifying one's lifestyle (including diet, exercise, and sodium education) was the initial step in the therapy of hypertension (ACE inhibitor, escalated as needed). 33.8% of the participants had hypertension after 3–9 years of

follow-up. The study concluded that numerous variables, including poor lifestyle modification compliance, behavioural influences, obesity-related factors, ineffective medical treatments, possible hormones, sex, and the aggressive nature of T2D in young people, are likely to blame for the rise in the prevalence of hypertension.

Males were more likely to develop hypertension than females, and each additional year of age increased the risk by 14%. Additionally, there was a link between BMI and hypertension, with a 6% increase in risk for each unit higher BMI [63].

5. Dyslipoproteinemia

Patients with diabetes frequently have dyslipidemia. Serum cholesterol may be a key factor in the onset and progression of diabetic nephropathy, according to numerous clinical and experimental studies [64]. Greater levels of total and low-density lipoprotein (LDL) cholesterol as well as higher glyceride levels were linked to the development of MA in the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) study[65]. In people with diabetic nephropathy, elevated blood cholesterol functions as an independent progression promoter [66]. After a median of 6 or 12 years of follow-up, high blood cholesterol at baseline has become a highly reliable predictor of persistent MA or overt DN in T1D patients [48, 67]. Low levels of both cholestrol and triglycerides were independently linked to regression of MA in MA with a short duration [68]. Lipid control seems to be crucial in the prevention and treatment of DN in adolescents, despite the paucity of large scale prospective randomized trials.

6. Older age and puberty

Some researchers have hypothesized that the prepubertal years do not significantly increase the risk since MA is uncommon in prepubescent children and only seldom manifests during puberty [69]. This assumption has been refuted by MA data, especially in prepubescent children [39,70-71]. It has been established that prepubertal diabetes duration increases the risk of MA [36-37], but that younger age at onset or longer prepubertal diabetes duration may delay the onset of MA [62, 72-73], or later ESRD [74]. This is true despite some discrepancies among studies that looked at the significance of prepubertal diabetes duration in relation to the development of MA.

In matched prepubertal, pubertal, and postpubertal patient groups from MA, the annual progression of AER was considerably higher in the pubertal group than in the prepubertal or postpubertal groups [75]. When children with diabetes had been diagnosed at ages 5, 5–11, and >11, the cumulative probability of MA was comparable (30%–40%). Having diabetes for a prolonged period of time before puberty may increase the chance of MA, but this is not immediately apparent [71]. Therefore, prepubertal length of diabetes does contribute to the development of MA, whereas pubertal variables speed up both the onset and progression of MA, imparting a three- to four-fold increase in risk of MA after correcting for other significant risk factors [71].

7. Smoking

In teenagers with diabetes, smoking is documented in 7–48% of cases [76-77]. Typically, smoking starts in the teen years, which is also when preventive initiatives may have the best chance of being effective. The rate of nephropathy progression is decreased by 11%, 53%, and 33%, respectively, in non-smokers compared to smokers and patients who have given up smoking [78]. The incidence rates of MA were greater in smokers compared to non-smokers in a large observational study of 943 patients: 7.9 versus 2.2 per 100 persons per year. Additionally, smoking altered the impact of hyperglycemia, enhancing the impact of poor glycemic control [79]. In a recent large study, it was discovered that smoking history, after 25–30 years of diabetes duration, was a reliable predictor of renal disease and that, in comparison to smokers, non-smokers had a significantly lower risk of developing MA or established nephropathy in both patient groups with childhood-onset and adult-onset diabetes [80]. In T1D and T2D patients with normal or nearly normal renal function, smoking lowers GFR without regard to other confounding variables, such as the severity of MA [81]. Smoking was more common in the borderline albuminuria and MA groups, and is linked with AER in diabetic children regardless of age or other factors [82]. In addition, smokers had higher baseline GFRs and a propensity for greater GFR declines than nonsmokers; smoking was a separate risk factor for GFR decline. Comparing smokers to nonsmokers, all of the structural metrics showed a more noticeable worsening [83].

8. Obesity

Several studies confirmed that one of the most important global public health issues of the present century is childhood obesity [84]. Obese children frequently carry their obesity into adulthood, which increases their risk of kidney disease and other undesirable clinical consequences [85-87]. Obesity is closely linked to the onset and progression of CKD. Obesity in children and adolescents with T2D was substantially more common (79%) than it was in those with T1D (13%) [88]. Glomerular hyperfiltration has been proposed to have a significant role in the relationship between obesity and renal damage [89]. Offspring are more likely to have CKD and obesity if their mothers are obese. According to one hypothesis, vasodilation of the renal afferent arterioles and efferent arteriole constriction improve renal plasma flow, glomerular hydrostatic pressure, and single-nephron filtration rate [90]. Another theory contends that the main cause of decreased sodium transport to the macula densa, deactivation of the tubuloglomerular feedback, afferent arteriolar vasodilation, and ensuing glomerular hyperfiltration is an increase in the proximal tubular reabsorption of sodium and water [91-92]. Increased tubular sodium reabsorption in the kidney of obese patients may be caused by increased sodium transporter activation in the nephron [93]. Additionally, increased sympathetic activity and the renin-angiotensin-aldosterone system overexpression in obese people may have a significant impact on glomerular hyperfiltration by increasing sodium retention and hypertension [90].

9. Serum uric acid

Uric acid was not a predictor of persistent MA in an observational study done on T1D patients [94]. As opposed to this, the study showed a strong and independent correlation between the amount of uric acid early in the course of T1D and the subsequent development of chronic macroalbuminuria leading to overt nephropathy. These findings lend credence to the hypothesis that uric acid, by activating the renin-angiotensin system and inhibiting endothelial nitric oxide, may contribute to the pathophysiology of microvascular problems in diabetes [95]. According to a cross-sectional study by Rosolowsky et al [96], patients with T1D and normo- or MA had decreased renal function when their SUA levels were in the high-normal range.

In patients with T2D, SUA is a significant pathogenic factor in the development of nephropathy. Numerous investigations revealed that the presence of high SUA in patients with T2D was a significant contributor to the onset of nephropathy [97-98]. According to a large study [99], age, age at diabetes onset, and overall diabetes duration all positively correlated with SUA concentration and urine albumin excretion (UAE). According to a small clinical investigation, lowering blood uric acid was linked to a slower drop in GFR in CKD patients [100], which gave rise to the possibility that delaying the progression of DKD by targeting SUA would be a viable new approach. Unfortunately, two recent clinical trials aimed at SUA reduction with allopurinol and febuxostat failed to demonstrate any effect on the progression of DKD/CKD [101]. Therefore, more investigations focused at detecting and treating hyperuricemia in diabetic patients at an early stage may stop the progression of renal failure.

10. Family history and genetics

Because only a subset of patients with both T1D and T2D will develop DN regardless of glycemic management, the risk of diabetes complications is most likely partially hereditary [40, 102-104]. The observation of familial clustering of DN and studies of potential genes connected to the development of nephropathy provide evidence for genetic or familial predisposition to the development of DN [103-104]. When compared to diabetics whose siblings did not have nephropathy, the likelihood that diabetic siblings of a diabetic proband with nephropathy will also have nephropathy was three to four times higher [105-106]. Similar conclusions were obtained from an analysis of the DCCT cohort [107]. Although there was no concordance on glycemic control when the glomerular structure of sib pairs with T1D was evaluated, there was a very strong correlation in the severity and pattern of the glomerular lesion [108]. Families have been shown to increase the risk of nephropathy in the offspring by having a history of hypertension and cardiovascular disease in the parents [109-110] as well as T2D [109,111]. Patients with T1D may be more susceptible to developing hypertension and DN due to increased activity of the sodium-lithium or sodium-hydrogen exchanger, according to studies on participants with essential hypertension and those who also have T1D and nephropathy [112-113].

The connection between DN and the insertion or deletion (I/D) angiotensin-converting enzyme (ACE) gene polymorphism has been the subject of extensive research. These studies provided conflicting findings about the role of the DD genotype in DN risk. While genotype II guards against the onset of DN, it has been hypothesised that the DD allele causes DN predisposition [114], increased risk for disease progression[115], or reduced renoprotection with ACE inhibitor [116] as well as with antihypertensive therapy that does not block the renin-angiotensin system (RAS) [117].

Another important method for looking for chromosomal regions that include genes that affect susceptibility to DN is the genome-wide scan [103]. The most recent results from Finland corroborate the discovery of linkage in white families with T1D, adding to the evidence for a gene or genes on chromosome 3q that may be associated with DN susceptibility [118].

Emerging biomarkers in DKD

In the past ten years, significant funding and attention have been devoted to the search for prognostic and surrogate endpoint biomarkers for advanced DKD and ESRD (Table 1). However, no novel biomarkers are currently being used often in clinical studies or in the clinic. Although they lack specificity and sensitivity in predicting the course of DKD in diabetics, GFR and albuminuria remain the most often utilized prognostic indicators for predicting ESRD in clinical practice. Even though MA screening has a low specificity to detect early stage DKD, it is still the widely used and considered the "gold standard" marker for prediction and detection of diabetic kidney involvement in pediatric diabetes.

The usefulness of albuminuria as a biomarker for DKD prediction has some acknowledged limits because not all diabetic children with micro- or macroalbuminuria will progress to end-stage renal disease. Since tubular biomarkers are more accurate than glomerular ones because tubular damage occurs before glomerular injury, they may be used for early identification of DKD in both T1D and T2D [134]. To prevent kidney disease from progressing to end-stage kidney disease, conventional and novel biomarkers for early detection of diabetic children and adolescents at risk of renal complications are required, in addition to renoprotective therapies. Because early detection of diabetes in children is crucial, some new potential biomarkers are discussed below.

1. Ferroptosis genes

Numerous studies have hypothesised that the imbalance between ferroptosis driver, suppressor, and marker genes may be related to a variety of underlying pathogenic factors that contribute to kidney disease, with immunity and inflammation serving as the primary correlates that are crucial for identifying a variety of targets for ferroptosis interventions. Ma et al. [135] sought to discover new diagnostic markers to aid in the treatment and diagnosis of DKD as well as examine the potential mechanism of ferroptosis-related genes in DKD and their interaction with immune inflammatory response. Based on the bioinformatics analysis, this study discovered

that many pathogenic variables associated with immunity and inflammation in DKD were linked to ferroptosis. After accuracy evaluation, DKD and CON could be successfully distinguished by seven hub ferroptosis genes (PRDX6, PEBP1, ZFP36, TSC22D3, GABARAPL1, and RGS4). Based on their investigation of immune infiltration, the researchers discovered that immune infiltration quantity and hub ferroptosis genes were primarily adversely regulated, with PRDX6 being particularly negatively regulated with immune cells. This promotes diabetic kidney disease by causing CD8+ T lymphocytes to express more IFN-γ and TNF-α through cytotoxic activities. Additionally, it was discovered that RGS4 exhibited positive correlations with type 2 T helper cells, activated dendritic cells, natural killer T cells, mast cells, and T folicular helper cells [136]. These results suggested that the diversity and complexity of the DKD milieu are significantly influenced by ferroptosis alteration, and that the ferroptosis score system may be utilized to efficiently confirm the association between ferroptosis and immune cell infiltration in DKD patients.

2. Metabolomics

In order to look into the peculiarities of the urine metabolism in 79 people, including T2D patients and DKD patients, Luo et al.[137] used a liquid chromatography-mass spectrometry-based metabolomics approach in conjunction with bioinformatics analysis. 17 metabolites that were involved in the metabolism of amino acids, purines, nucleotides, and bile acids were shown to be shared between T2D and DKD. Tyramine and phenylalanyl proline were the two metabolites that ultimately led to the development of a combination model with the best diagnostic performance. In addition, they discovered 41 metabolites that were exclusively expressed in the DKD + MA group and 19 metabolites that were co-expressed among the DKD groups. The ferroptosis signalling route, the sirtuin signalling pathway, and the downregulation of organic anion transporter 1 were all implicated in three interaction networks of these 60 metabolites that were discovered using pathway analysis. The sirtuin signalling pathway, the ferroptosis signalling pathway, and the downregulation of organic anion transporter 1 were all involved in three interaction networks of these 60 metabolites that were discovered through pathway analysis. These networks may play a significant role in mediating the progression of DKD and provide a novel approach for researching the underlying causes and treating DKD.

By examining extracellular vesicles (EV) metabolites, Pan et al. wanted to investigate possible biomarkers for the prediction and early diagnosis of DKD. The examination of plasma EVs in this investigation indicated distinctive changes in the metabolomic patterns of T2D patients with and without DKD. The biosynthesis of unsaturated fatty acids, the sphingolipid signalling pathway, and metabolic pathways were the three pathways that were most strongly impacted. As appropriate biomarkers for the early diagnosis of DKD, the metabolites 4-acetamidobutyric acid, S1P, LPC (0-18:1/0:0), and uracil were found. Additionally, a composite model combining these four metabolites demonstrated excellent potential for the early detection of this illness.

3. Short chain fatty acids (SCFAs)

Intestinal dysbiosis and the occurrence of DKD have recently been strongly linked, according to numerous studies. It has been thought that the SCFAs produced by the gut microbiota, which can control fibrosis, oxidative stress, inflammation, and energy metabolism, are useful in both the prevention and therapy of DKD [138]. The underlying molecular metabolism of the gut-microbiota-kidney axis's involvement in the onset of DKD is yet unknown, though. Patients with DKD showed intestinal microbiota dysbiosis, which was linked to the restricted uptake of high-fiber meals and fruits, which led to insufficient SCFA production [139]. The SCFAs are the byproducts of polysaccharide fermentation in the distal gut microbiome and they include acetate, propionate, and butyrate [140]. The development of DKD, which is characterised by proteinuria, loss of renal structural integrity, and renal fibrosis, was sped up in STZ-induced diabetic mice with altered gut microbiota composition, which decreased the concentration of SCFAs and decreased the secretion of PYY and GLP-1 (Glucagon-like peptide-1) [141]. By preventing the growth of the high-glucose-induced mesangial cell lines, producing ROS, and suppressing the expression of pro-inflammatory cytokines like monocyte-chemotactic protein-1(MCP-1) and IL-1 beta, the administration of SCFAs or GPR 41(G-protein coupled receptor 41) Agonists can both slow the development of DKD [142]. These factors together demonstrate that intestinal dysbiosis in DM patients is strongly associated with the development of DKD and that the low level of SCFAs in the intestinal tract caused by this condition is significant.

4. Five hub genes (NFKB1, DYRK2, ATAD2,YAP1, and CHD3)

Ye et al. [143] used integrated bioinformatics analysis to confirm the existence of the five hub genes (NFKB1, DYRK2, ATAD2, YAP1, and CHD3) in the GSE142025-dataset and found that the expression of these genes was highest in advanced stage DKD samples. In contrast, early stage DKD samples showed the poorest expression of ATAD2, NFKB1, and YAP1, whereas healthy live donor samples showed the least expression of CHD3 and DYRK2. CHD3 and DYRK2 were offered as the putative early diagnostic biomarkers of DKD by these hub gene expression patterns, whereas ATAD2, NFKB1, and YAP1 were proposed as the putative biomarkers for tracking the course of DKD. The validation of these elevated hub genes in three additional transcriptome datasets (GSE30122, GSE96804, and GSE104954), however, increased their potential as significant diagnostic or putative biomarkers of DKD. Increased NFKB1mRNA expression was linked to the emergence of a proinflammatory state in children and teenagers with T1D, which may ultimately lead to a decline in renal function and, ultimately, DKD. YAP1 is the main transcriptional coactivator of the Hippo pathway and has been associated with chronic inflammation in a number of organs and tissues [144].

The roles and processes of DYRK2, ATAD2, and CHD3 in

the development of DKD are still poorly understood among these five hub genes. An efficient phosphorylation of P53 at ser46 by the serine/threonine kinase DYRK2 controls cell death in response to DNA damage [145]. While CHD3 participates in chromatin remodeling by deacetylating histones, which are necessary for a number of processes including transcription, ATAD2 has genome-regulatory functions such cell proliferation, differentiation, and death [146]. In order to successfully highlight these recently identified hub genes as viable biomarkers or therapeutic targets for the monitoring and treatment of disease, significant research in several areas is urgently required.

5. VEGF-B and IL-17A

Cao et al. [147] showed that kidney lipid metabolism abnormalities and inflammation dramatically changed in DKD settings by mining public transcriptome data for DKD patient samples. Vascular endothelial growth factor B (VEGF-B) and interleukin 17A (IL-17A) signal pathways were further shown to play a crucial role in the course of DKD, suggesting that VEGF-B and IL-17A may be attractive targets for DKD treatment. With the help of their respective neutralizing antibodies, VEGF-B and IL-17A signaling were simultaneously blocked, reducing kidney damage and enhancing renal function. The success of the treatment was linked to both a diminished inflammatory response as well as a decreased lipid deposition, particularly the neutral lipids in the kidney. Additionally, by lowering collagen deposition and the expression of fibronectin and alpha smooth muscle actin (alpha-SMA) in kidney tissues, the treatment reduced renal fibrosis. In db/db mice, differentially expressed genes (DEGs) were significantly clustered into pathways related to lipid metabolism, inflammation, fibrosis, and DKD pathology, according to RNA-seq analysis, and 181 of those DEGs were significantly reversed by the combinatory treatment, pointing to the potential mechanism underlying the administration of anti-VEGF-B and anti-IL-17A antibodies in the treatment of DKD. Together, these findings show that aberrant lipid metabolism and inflammation play a significant role in the development of DKD, and that blocking both VEGF-B and IL-17A signaling together may be a promising DKD therapeutic approach.

6. MMP-9 (Matrix-Metalloproteinase-9)

Several experimental investigations have shown that glucose can raise the levels of pro-inflammatory transcription factors such NF-KB, AP-1, and EGR-1 in the presence of acute or chronic hyperglycemia. According to reports [148-151], the MMP-9 promoter region contains response elements to several transcription factors, upregulating MMP-9 transcription and activity. The majority of the patients exhibited elevated MMP-9 levels, most likely as a result of an acute rise in their BG levels in the context of severe illness. Blood glucose (BG) ranged from 121 mg/dL to 200 mg/dL in these patients. High MMP-9 levels have been found in patients with severe sepsis or septic shock because activated PMNs release MMP-9 at the site of infection, which damages surrounding tissue and feeds the vicious spiral of inflammation and tissue destruction [152-153]. According to a study [154], individuals with low blood sugar (9.0 mg/dL) or normal glycemia (80–120 mg/dL) nevertheless had elevated matrix metalloproteinase 9 (MMP 9) levels, suggesting that the increase in neutophil activation rather than acute or chronic hyperglycemia is likely the cause of the elevated MMP 9 levels in these two groups. This study assessed the levels of two biomarkers (IL-8 and ICAM-1), which are directly related to neutrophil function, together with MMP-9 levels. Due to its propensity to draw in, operate on, and degranulate neutrophils, IL-8, a member of the CXC chemokine family, has been linked to high levels and a role in the pathophysiology of sepsis [155-156]. Additionally, sepsis increases the production of ICAM-1 9 (a cell-surface glycoprotein), allowing neutrophils to bind and permeate through the endothelium [157]. The researchers postulated an antagonistic interaction between MMP-9, IL-8, and ICAM-1. A specific region of the IL-8 molecule's chemical structure is known to be disrupted by MMP-9, producing a variant IL-8 molecule that is 10–30 times more effective at activating neutrophils [158-159]. Further research is required to determine the genetic basis of the association between IL-8 and MMP-9. Because there are so few research documenting the association between MMP-9 and ICAM-1, it is more difficult to explain this relationship. These investigations discovered that while MMP-9 levels increase, ICAM-1 levels fall, possibly as a result of the direct impact of insulin on such biomarkers. It is reasonable to assume that early inhibition or elimination of this biomarker may have therapeutic significance given the pathogenic relationship between raised MMP-9 levels and elevated BG levels.

7. circANKRD36 (circular ankyrinrepeat domain 36)

Circular RNAs are a subclass of endogenous non-coding RNAs that have been linked to a variety of illnesses, including T2D. CircaNKRD36 interacts with miRNAs like hsa-miR-3614-3p, hsa-miR-498, and hsa-miR-501-5p to affect T2D and inflammation-related pathways. In peripheral blood leucocytes, the expression of circANKRD36 was elevated, and it was associated with long-term inflammation in T2D. As a result, circANKRD36 may be employed as a possible biomarker for T2D patients to screen for chronic inflammation. The ongoing study (clinicaltrials.gov : NCT05061459) seeks to determine the expression levels of circANKRD36 in the onset and progression of DN as well as the relationships among experimental circANKRD36 levels and pro-inflammatory cytokines (TNF-alpha and IL-6) in young people, adults, and older adults.

8. GLUT-1 (SLC2A1)

In the presence of excessive extracellular glucose, hyperglycemic cells are unable to downregulate glucose entry, which causes the intracellular activation of harmful metabolic pathways. The main glucose transporter, GLUT-1, is expressed more frequently in mesenchymal cells, which contributes to the development of diabetic nephropathy. This diabetes condition has been linked to variations in the GLUT-1 gene (SLC2A1). The objective of this ongoing investigation (clinicaltrials.gov: NCT01768611) is to determine if this

polymorphism in SLC2A1 confers vulnerability to diabetic nephropathy in T1D patients.

Table 1: Main studies published on biomarkers and diabetic kidney disease (DKD) between 2018 to 2022

S.No.	Author, Reference	Sample size and population	Study design	DKD stage	Biomarkers
	Gohda T et al. [119]	n = 314 T2D	Cross-sectional	Normoalbuminuria	Serum Osteoprotegerin (OPG) Plasma brain natriuretic peptide (BND) Cardio-ankle vascular index (CAVI) Tubular damage- urinary L-type fatty acid binding protein (L-FABP) Inflammatory- serum tumor necrosis factor (TNFα) and its receptors (TNFRs).
	Griffin TP et al. [120]	n = 192 (n = 100 DKD, n= 92 Diabetes Mellitus without DKD)	Cross-sectional	Low eGFR	Plasma dephosphorylated uncarboxylated matrix Gla-Protein (dp-ucMGP)
	Rubeaan KA et al. [121]	n = 200 T2D	Cross-sectional	Normoalbuminuria Low eGFR	IL-18 VCAM-1 P-selectin
	Qin Y et al. [122]	n = 1053 T2D	Cross-sectional	Normoalbuminuria DKD	Transferrin (TF) Immunoglobulin G (IgG) Retinol-binding protein (RBP) B- galactosidase (GAL) N-acetyl-betaglucosaminidase (NAG) B2-microglobulin (β2MG)
	Carlsson AC et al. [123]	n = 813 T2D	Cross-sectional	Microalbuminuria Low eGFR	Growth differentiation factor 15 (GDF-15)
	Siddiqui K et al. [124]	n = 92 T2D with or without DKD	Cross-sectional	Normal eGFR Low eGFR	Urinary N-acetyl-beta-d-glucosaminidase (NAG) Neutrophil gelatinase-associated lipocalin (NGAL)
	Hussain S et al. [125]	n = 90 DM	Cross-sectional	Normoalbuminuria Microalbuminuria Macroalbuminuria	Gelectin-3 Growth differentiation factor 15(GDF-15)
	Kurita N et al. [126]	n = 1576 T1D,T2D	Cross-sectional	Low eGFR	Urinary C-megalin
	Lupusoru G et al. [127]	n = 75 DM and DKD	Cross-sectional	Low eGFR	Serum soluble urokinase plasminogen activator receptor (suPAR)
	Tan Y M et al. [128]	n = 90 (n=30 healthy controls, n=30 DM and normal renal function, n=30 early DKD	Cross-sectional	Normal albuminuria Low eGFR	Uremic solutes and oxidative stress markers (glutamine, phenylacetylglutamine, 3-indoxysulphate, acetylphenylalanine, xanthine, dimethyluric acid, asymmetric dimethylarginine)

	Gonzalez-Salvatierra et al. [129]	n = 217 (n=142 T2D, n=75 healthy controls	Cross-sectional	Normal eGFR Mildly decreased eGFR	Osteoglycin (OGN)
	Johnson MJ et al. [130]	n = 70 (n=50 T1D, n=20 high BMI without T1D)	Cross-sectional	High GFR Lower renal vascular resistance (RVR)	Chitinase-3-like protein (YKL-40) Kidney injury molecule-1 (KIM-1)
	Lee JH et al. [131]	n = 116 (childhood onset T1D patients)	Prospective	Low eGFR	Serum neutrophil gelatinase-associated lipocalin (sNGAL)
	Zhu H et al. [132]	n = 90 (n=30 healthy controls, n=30 T2DM, n=30 DKD)	Cross-sectional	Low eGFR	Impaired amino acid metabolism (N-acetylaspartic acid, L-valine, isoleucine, asparagines, betaine, and L-methionine)
	Wu R et al. [133]	n = 728 (n=286 DKD, n=442 non DKD)	Cross-sectional	Low eGFR	Serum myoglobin (Mb)

Conclusion

Despite efforts to develop consensus guidelines for the management of diabetes in children and adolescents, there is still a dearth of data on the effectiveness of current diabetic therapeutics. Due to the brief duration of their condition, children rarely have overt nephropathy. However, the right therapies need to be adopted in early life if the emergence of late difficulties is to be avoided. The trials showed that significantly fewer microvascular complications are related with better glycemic control attained by intensive diabetes care in children and adolescents. However, to achieve the best possible glucose control, it is very helpful to know the initial status of childhood diabetes before quality control parameters are defined. Ambulatory blood pressure monitoring is the standard method for evaluating blood pressure control and should be done in all diabetes patients for prompt therapeutic intervention to prevent kidney and cardiovascular complications in the future. Children and teenagers with T1D and T2D should have their eGFR checked at the time of diagnosis and then yearly after that. The evaluation of DKD phases is aided by these continuing modifications. Controlling weight can be accomplished through exercise, calorie restriction, angiotensin-converting enzyme inhibitor therapy, and bariatric surgery. Before clinical trials are planned, confirmation of the apparent substantial impact of SUA on renal function must be attained via more follow-up investigations. In terms of the future burden of associated vascular complications, efforts to prevent or delay T2D in children could have a significant influence on public health.

The genetic component of DKD opens up new avenues for the development of customized medicine treatments. In order to provide timely care, early stage prediction and detection of DKD before MA occurrence are crucial. Thus, finding new diagnostic/prognostic biomarkers for DKD is necessary given the shortcomings of the existing markers. Therefore, it is crucial to evaluate more precise and sensitive biomarkers. In DKD, urinary biomarkers are significant because they can identify the nephron's site of injury, its loss or impaired function, and the key pathophysiological pathways. The search for biomarkers for DKD has a lot of potential thanks to novel omic methods and the integration of various omics data.

Declarations

1. Ethics approval and consent to participate

Not applicable

2. Consent for publication

Not applicable

3. Availability of data and material

All data generated or analyzed during this study are included in this published article.

4. Competing interests

The authors declare that they have no competing interests.

5. Funding

No funding from any sources was received to conduct the study.

6. Authors' contributions

SAG drafted the manuscript. AKQ and OBI revised the manuscript and contributed important knowledge. MC contributed the illustrations and OBI interpreted the patient data and supervised the study. All the authors read and approved the final manuscript.

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