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**DIABETIC KIDNEY DISEASE IN PEDIATRIC PATIENTS. A CURRENT REVIEW**

Muntean C *et al*. DKD in pediatric patients

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Abstract
In the last decades, a significant increase in the incidence of diabetic kidney disease was observed concomitant with rising diabetes mellitus incidence. Kidney disease associated with diabetes mellitus in children and adolescents is represented by persistent albuminuria, arterial hypertension, progressive decline in glomerular filtration rate (eGFR) to end-stage renal disease (ESRD), and increased cardiovascular and all-cause morbidity and mortality of these conditions. In medical practice, the common and still the "gold standard" marker for prediction and detection of diabetic kidney involvement in pediatric diabetes is represented by microalbuminuria screening even if it has low specificity to detect early stages of diabetic kidney disease. There are some known limitations in albuminuria value as a predictor biomarker for diabetic kidney disease, as not all diabetic children with microalbuminuria or macroalbuminuria will develop ESRD. As tubular damage occurs before the glomerular injury, tubular biomarkers are superior to the glomerular ones, therefore they may serve for early detection of diabetic kidney disease in both type 1 diabetes mellitus and type 2 diabetes mellitus. Conventional and new biomarkers, to identify diabetic children and adolescents at risk of renal complications at an early stage as well as renoprotective strategies are necessary to delay the progression of kidney disease to ESKD. New biomarkers and therapeutic strategies are discussed as timely diagnosis and therapy are critical in the pediatric diabetic population.

Key Words: Diabetes; Kidney disease; Biomarkers; Microalbuminuria; Therapy; Children

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Core Tip: Several reviews in the literature contributed to the pathophysiology, diagnostics as well as therapeutic options for diabetic kidney disease in pediatric
patients. In this review, we reported the latest data regarding novel biomarkers and methods to identify diabetic children and adolescents at risk of renal complications at an early stage as well as renoprotective strategies to delay the progression of kidney disease to ESKD.

INTRODUCTION

Diabetes mellitus (DM), a chronic metabolic condition, is characterized by complete or insufficient insulin production. The main form of DM in childhood and adolescence is Type 1 diabetes mellitus (T1DM) compared to Type 2 diabetes mellitus (T2DM) which is more frequent in adulthood. Within the last twenty years, DM prevalence increased significantly worldwide. In the last decades, we have also assisted in an ascending trend in the prevalence of T2DM in childhood and youth, because of the outbreak in juvenile obesity prevalence [1]. T1DM and T2DM have similar symptoms upon diagnosis and both include polyuria, polydipsia, and polyphagia. While obesity and insulin resistance signs: acanthosis nigricans, and polycystic ovarian syndrome, are typical hallmarks of T2DM, loss of weight may be present in both types of DM [1].

Both T1DM and T2DM, with lasting inadequate glycemic control, are associated with long-term vascular complications [2] and a significant increase in mortality, especially in those who develop kidney disease [3].

While diabetes mellitus represents the main worldwide cause of end-stage kidney disease (ESKD) in adults this is uncommon during childhood [2,3].

Although specific kidney structural changes in DM patients, namely thickening of the glomerular basement membrane and mesangial expansion, appear soon after DM onset (1.5 to 5 years) they are in a clinically silent phase [4]. These structural changes of diabetic kidney injury progress at different rates among T1DM patients, and, this is, more evident in T2DM cases [4]. Clinical and biological abnormalities (micro/macroalbuminuria) and GFR decline will develop over a longer period (10 to 25 years) [3]. This emphasizes that diabetic kidney disease (DKD) starts early therefore an early diagnosis, intensive monitoring, and therapeutic interventions are necessary.
Albinurica and changes in GFR, which are late biomarkers, are the most used tools to assess kidney involvement. Diagnostic strategies for early diagnosis of kidney involvement are necessary.

1. METHOD

There are several reviews in the literature that contributed to the pathophysiology, diagnostics as well as therapeutic options for diabetic kidney disease in pediatric patients. In this work, the state-of-the-art on novel biomarkers and methods to identify diabetic children and adolescents at risk of renal complications at an early stage as well as renoprotective strategies to delay the progression of kidney disease to ESKD was carried out.

1. EPIDEMIOLOGY OF DM IN CHILDREN

From 2002 to 2015 Centers for Disease Control and Prevention (CDC) reported a 4.8% increase per year for T1DM and a 1.9% increase per year for T1DM in youths aged <20 years [5]. A very recent study, comprising 6 areas of the United States from 2001 to 2017, reported an important increase in estimated prevalence for both type 1 and type 2 diabetes (T1DM from 1.48 to 2.15 per 1000 youths <19 years, and for T2DM from 0.34 to 0.67 per 1000 youths among those aged 10-19 years) [6]. Up-to-date research that included a large cohort of Hungarian children and teenagers during the period 2001 to 2016 (covering 16-years), showed that T1DM is still the most common type and its prevalence is rising, with a significant male predominance (male/female ratio:1.25). Also, there is a high prevalence of T2DM, affecting more females every year (female/male ratio: 2.86) [7]. A Danish study showed no increase in T2DM prevalence in children and adolescents [8] while in the UK a rising incidence and prevalence of T2DM have been observed in youths, especially in some ethnicities [9].

Contributing risk factors to this major increase in incidence are obesity, race, and ethnicity, exposure to maternal obesity and diabetes as well as exposure to environmental contaminants [6].
There is an increased morbidity and mortality rate, mainly in T1DM and in those with early T2DM onset. According to Rhodes et al, a considerably lower life expectancy (8-15 years) was observed in the diabetic group compared to the general population of children without diabetes. A significantly shorter life expectancy was reported in children developing T1DM before 10 years of age (loss of 17.7 years for females vs 14 years for males) compared with those diagnosed at 25-30 years (loss of 10 years for females and 9.4 years for males). There is a double cardiovascular risk in pediatric diabetes that triggers early cardiovascular mortality and a fourfold higher mortality rate for all causes in youth. In a nationwide Swedish study of patients with T1DM, age before 10 years at diabetes onset was the most important risk factor for survival and cardiovascular disease (coronary heart disease, and acute myocardial infarction) in their early adult years, especially in females (2-3 fold higher vs males). DM represents the main cause of end-stage renal disease worldwide in adults. Diabetic nephropathy affects 20% (1 in 5) of adults with diabetes. Within the pediatric population, a significant increase in the incidence of diabetic kidney disease (DKD) was also observed, the prevalence rate being three times higher in 2013 compared to 2002 (1.16 to 3.44%). A 4-fold higher risk of kidney failure was found in a large cohort of youth with T2DM vs those with T1DM. Also, compared with the control group, those with youth-onset T2DM had a 16-fold higher risk of a kidney disorder, a 23-fold higher risk of severe renal injury, and a 39-fold increased risk of ESRD respectively. A multicenter study reported that more than a quarter (28%) of T2DM youth aged under 20 years developed microalbuminuria.

1. PATHOPHYSIOLOGY

Chronic hyperglycemia leads to the occurrence of diabetic nephropathy, retinopathy, and neuropathy as well as macrovascular complications (cardiovascular disease: stroke, coronary artery disease, peripheral vascular disease).
DKD recognizes four major pathogenic mechanisms: glomerular damage, tubular injury, inflammation, and oxidative stress \[^{21}\], as they are presented in Figure 1.

In DKD patients there are important alterations in tubules as well as in the interstitium. These findings may pave the way or they may appear concomitant with glomerular changes \[^{22}\].

This is sustained by tubular hypertrophy observed in the immediate future of hyperglycemia. Also, an increase in tubular basement membrane (TBM) thickening was found even among diabetic patients with normoalbuminuria. TBM is one of the earliest structural changes therefore it may represent a better severity marker of DKD than GBM alteration \[^{22}\].

Pathological glomerular changes in DKD are typical and consist of glomerular basement membrane (GBM) thickening, podocyte foot process widening, expansion of the mesangial matrix, and loss of endothelial fenestrations \[^{23}\].

There is a greater risk for complication occurrence in young with T2DM \[^{vs}\] adults with T1DM and T2DM \[^{1}\]. The main microvascular complication of diabetes is represented by diabetic kidney disease and later by diabetic nephropathy which finally leads to end-stage renal disease (ESRD). In time, with diabetes evolution, clinical and biological changes will be observed (Figure 2).

Diabetic kidney disease (DKD), one of the most important and frequent complications of DM, recognizes a wide spectrum of risk factors, some of them are modifiable, therefore DKD occurrence or evolution may be considerably influenced by strict control of these factors that are listed in Table 1.

Children with T1DM may have damaged renal function at the disease onset, as acute complications through acute kidney injury (AKI) and renal tubular damage (RTD), as well as chronic complications by the diabetic nephropathy development \[^{24}\].

Genetic aspects

DKD is a multifactorial disorder, in its pathogenesis being implicated the genetic susceptibility, epigenetics, and environmental factors (such as lifestyle, diet, and medication). Also, oxidative stress, metabolic disturbance, activation of the renin-
angiotensin-aldosterone system (RAAS), and production of inflammatory factors, are involved in the development and progression of DKD [26]. Genetic and epigenetic studies were performed to understand the pathogenesis of the DKD and to identify genes that confer susceptibility to disease. Genetic studies of DKD investigated mainly the association between genomic DNA variants [for example, single nucleotide polymorphisms (SNP), copy number variants (CNV), etc.] and clinical phenotypes of DKD in both T1DM and T2DM [26]. Epigenetic modifications (histone modifications and DNA methylation) may play a critical role in DKD as it was shown that histone acetylation and methylation are involved in the regulation of inflammation and fibrosis in DD [27]. Epigenetics studies of DKD investigated the potentially inherited changes in gene expression that occur without changing the DNA nucleotide sequence. Candidate gene association studies, genome-wide association studies (GWAS), and epigenome-wide association studies (EWAS) were performed in DKD patients [28]. A large meta-analysis study conducted by Mooyaart et al identified 24 genetic variants in 16 genes (EPO, APOE, APOC1, ACE, ALR2, eNOS, HSPG2, VEGF, FRMD3, GREM1, ELMO1, CCR5 and CNDP1, CARS, UNC13B, and CPVL/CHN2) which are the most likely to be associated with diabetic nephropathy [29]. Recently, Tziastoudi et al conducted a systematic review and meta-analysis of genetic association studies in diabetic nephropathy in order to elucidate the contribution of genetic background in the development of this disease and observed an association with the genes revealed by Mooyaart et al and some additional genes (ACACB, ADIPOQ, AGT, AGTR1, AKR1B1, ATP1B2, ATP2A3, CGNL1, CNDP1, CYGB-PRCD, EDN1, ENPP1, FLT4, FTO, GLO1, HMGA2, IGF2/INS/TH cluster, interleukin genes (IL1B, IL8, IL10), KCNQ1, KNG, LOC101927627, MTHFR, NOS3, SETD7, SIRT1, SLC2A1, SLC2A2, SLC12A3, SLC19A3, TCF7L2, TGFBI, TIMP1, TTC39C, UNC13B, VEGFA, W1AP31, WWC1, XYL1) [30]. By GWAS studies were identified about 30 genes associated with the DKD (for example ELMO1, CNDP1, FRMD3, MMP9, UMOD, SLC12A3, etc) [25]. By EWAS studies several genes (for example TRPM6, AQP9, SLC22A12, HP, HYAL2, AGTX), were identified to have epigenetic effects on DKD [25]. The data presented above provide further evidence
for the contribution of genetic factors in DKD offering new perspectives in the discovery of new therapies for personalized medicine.

1. **DIAGNOSIS**

5.1 Glomerular filtration rate (GFR) abnormalities

Hyperfiltration, defined as an increase in GFR with more than 2 standard deviations (SD) than the mean GFR value, is related to an early increase in renal blood flow and high intraglomerular pressure [31]. In the first phases of DKD, hyperfiltration is observed in up to 40% of diabetic patients [32]. In both T1DM and T2DM, hyperfiltration has been linked to GFR loss [33, 34]. Hyperfiltration was noticed more frequently in females vs males in both T1DM and T2DM [32, 35]. The estimated glomerular filtration rate (eGFR) in children and adolescents with T1DM or T2DM should be screened at diagnosis and then annually [36].

These ongoing changes help us to assess diabetic kidney disease stages, which are presented in Table 2 [20, 21, 37].

Normal GFR values according to child age are listed in Table 3.

5.2 Seric and Urinary biomarkers for DKD

Common markers for kidney injury are creatinine, albuminuria, cystatin C, neutrophil gelatinase-associated lipocalin, and alfa-1-microglobulin in plasma and urine.

Kidney function in pediatrics is assessed mainly by GFR estimation according to updated/bedside Schwarts equation eGFR=k x Height (cm)/Serum creatinine (mg/dL), k=0.413 [40].

In a recent study, 11.5% of Romanian children with T1DM had DKD, manifested as transitory microalbuminuria (7.7%) and incipient diabetic nephropathy (3.8%) [41]. In another research study, T1DM patients were found to have microalbuminuria in 30% of cases, representing the most common microvascular complication. In T1DM children the occurrence of microvascular complications was correlated with metabolic control, higher glycated hemoglobin A1c (HbA1c), albuminuria, systolic blood pressure, triglycerides, and total cholesterol [42].
Diabetes microvascular, as well as macrovascular complications, can lead to serious morbidity and mortality. Nephropathy (which is preceded by microalbuminuria), retinopathy, and neuropathy, represent diabetes microvascular complications. According to ISPAD Guideline, annual microalbuminuria or urinary protein screening should start from age of 11 years and after two years of diabetes evolution, and then annually. It was demonstrated that persistent microalbuminuria predicts the progression to end-stage renal disease and is linked with an increased risk of macrovascular complications occurrence.

In T1DM pediatric patients, the urine microalbumin to creatinine ratio (UACR) monitoring should start at puberty or 10 years of age (whichever is earlier), and when the child has had DM for 5 years this parameter should be checked annually. In T2DM the UACR should be checked at diagnosis and every year thereafter.

In medical practice, the common and still the “gold standard” marker for prediction and detection of diabetic kidney involvement in pediatric diabetes is represented by the microalbuminuria screening, even if it has a low specificity and sensitivity to detect early stages of diabetic kidney disease. Microalbuminuria screening should be done annually by timed overnight or 24-hour urine collections (albumin excretion rate) or first-morning urine albumin to creatinine ratio.

Definitions of albuminuria and its abnormalities are based on the International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines.

Normoalbuminuria is defined as a urine albumin level of ≤30 mg/L in all first-morning urine specimens, while microalbuminuria is characterized by the presence of an albumin limit of 30–300 mg or 20–200 μg/min in 24-hours urine collection or a value of 30–300 mg/L in at least 2 of 3 first-morning urine specimens respectively. Another parameter, namely urinary albumin to creatinine ratio (UACR) of 2.5–25 mg/mmol in males or 3.5–25 mg/mmol in females in at least 2 of 3 first-morning urine specimens quantifies the microalbuminuria. Macroalbuminuria is
defined as the presence of >300 mg/L albumins in at least 2 first-morning urine specimens \cite{37, 43}.

There are some limitations in albuminuria value as a biomarker for the prediction and detection of diabetic kidney disease, as not all diabetic children with micro or macroalbuminuria will present a decrease in kidney function. Also, there are a lot of factors that may influence albuminuria level, urine albumin to creatinine ratio, and estimated glomerular filtration rate (eGFR): fever, infection, diet, hydration status, hemodynamics, stress, physical activity, periods, and hyperglycemia. Furthermore, a significant proportion of cases with microalbuminuria (up to 40\%) may return to normoalbuminuria with strict glycemic and blood pressure control, therefore microalbuminuria can be transitory \cite{21}.

Microalbuminuria incidence in children with T1DM spans between 3\% to 30\% \cite{37}. A cross-sectional study that involved children with T1DM reported a 25\% frequency for microalbuminuria, while macroalbuminuria was found in 3.5\% of these cases. The results of the cited study revealed a significantly higher (3 times) prevalence of microalbuminuria in T2DM (68\%) compared to T1DM (24\%) diabetes patients \cite{37}.

This is of particular interest given that children with T1DM are already at risk for renal complications secondary to diabetic kidney disease over the long term.

A recent study reported early occurrence of microalbuminuria within 2 years of diagnosis of DM in 3.5\% (7 of 199) of patients, whereas in 2 of those with microalbuminuria it appeared within the first year of diagnosis (in 7 mo) \cite{37}.

In a recent study, Hursh et al showed that more than 64\% of children hospitalized for DKD developed AKI. The same authors showed that a decreased serum bicarbonate level (< 10 mEq/L) and an increased heart rate are associated with a higher risk of severe AKI \cite{24}. Higher morbidity and mortality rate is encountered in diabetic children that developed AKI along with a higher risk of chronic kidney disease, a finding that is particularly important in these patients who are already at risk for diabetic kidney disease \cite{24}.
It is already known that patients with DM may present with kidney damage (decrease in GFR) but without micro or macroalbuminuria [44]. Therefore, other biomarkers that precede albuminuria should be considered more reliable to predict renal lesions, especially in the early stages; but most of these biomarkers still need validation in clinical practice [45].

As tubular damage occurs before the glomerular injury, tubular biomarkers are superior to the glomerular ones, namely microalbuminuria, therefore they may serve for early detection of DKD in both T1DM and T2DM [46].

Tubulointerstitial damage may be suggested by the urinary albumin-to-creatinine to total protein-to-creatinine (UACR/UPCR) ratio of 0.40, with high sensitivity and specificity [47].

In patients without glomerular involvement, low-molecular-weight (LMW) proteinuria or non-albumin proteinuria (NAP) represent an adequate marker of tubular dysfunction [48]. Urinary LMW proteins are absorbed in the proximal tubules so healthy individuals excrete up to 20 mg of LMW proteins/day in urine [48]. Alpha-1 microglobulin, beta-2 microglobulins (b2m), immunoglobulin light chains, retinol-binding protein, cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG), kidney injury molecule 1 (KIM-1), and liver-type fatty acid-binding protein (L-FABP), etc are included in the LMW protein group [48].

In the early period of diabetes, an increase in urinary tubular biomarkers suggests that kidney injury is present [49].

A recent study showed the association of proximal tubule (alpha-1 microglobulin and kidney injury molecule-1) and podocyte [nephrin, vascular endothelial growth factor (VEGF)] damage biomarkers, in T2DM even in the normoalbuminuric stage, so they may serve to early diabetic kidney disease diagnosis [49].

Urinary NGAL level increases before the onset of microalbuminuria, in the very early phase of the kidney disease [50]. Alongside urinary biomarkers of tubular health (NGAL), the oxidative stress biomarker (Pentosidine) may be used in the early detection of diabetic nephropathy, before the microalbuminuric phase, as they correlate
with albumin excretion and loss of nocturnal dipping of systolic blood pressure (SBP) and mean arterial blood pressure respectively [50].

Klotho, a transmembrane protein, is composed of a large extracellular and a small intracellular domain. Klotho is highly expressed in the renal tissue, especially in the distal tubules. The extracellular domain is cleaved by membrane proteases and discharged in the bloodstream, urine, and cerebrospinal fluid as soluble Klotho (s-Klotho) [52, 53]. A faster decline in eGFR was observed in diabetic kidney disease patients with low levels of serum s-Klotho concentrations [54], this being in opposition with the results of another study where s-Klotho levels did not correlate with eGFR [52].

Bob F et al found a direct correlation of s-Klotho levels with the rate of eGFR decline and with the serum levels of tubular injury marker KIM-1 [52]. A recent study found an inverse correlation between the Klotho and the HbA1c levels in T1DM children suggesting its possible role in chronic complications of diabetes occurrence [55].

Early stages prediction and recognition of diabetic kidney disease before microalbuminuria occurrence have a pivotal role to provide timely management. In this process, the assessment of more sensitive and specific biomarkers is essential.

A new study showed that serum Cystatin C (CysC) may be used as a biomarker for DKD at an early stage in T1DM children with disease duration not exceeding 5 years before albuminuria detection [21].

The same study found a significantly lower eGFR-CysC value in diabetic children compared to controls. Also, significantly higher urinary Cyclophilin-A (CypA) and urinary CypA/Creatinine ratios were found in T1DM children with microalbuminuria compared to the control group or normoalbuminuric subjects [21].

Salem et al observed a better diagnostic value with the highest sensitivity (93.5%), specificity (71.4%), and accuracy (86.7%) to predict microalbuminuria in T1DM children by the combined use of serum CysC and urinary CypA than that of urinary CypA alone [21]. CypA, an endogenous cytosolic protein, is expressed mainly by the proximal tubular epithelial cells. A kidney injury is followed by an increase in urinary CypA concentration [21]. CypA level proved an encouraging biomarker for the early stage of
diabetic nephropathy in adults with T2DM and it correlates with the progression of diabetic nephropathy. Novel biomarkers (Table 4) were proposed as early predictors of DKD.

Urinary biomarkers in DKD are crucial as they can indicate the site of injury within the nephron (structural biomarkers), as well as the loss of/reduced function of the nephron (functional biomarkers) and the main pathophysiological pathways (pathophysiological biomarkers). The proposed functional and/or structural tubular biomarkers might be valuable in the timely detection of DKD.

5.3 Blood Pressure in diabetic children

Another important sign of diabetes-related nephropathy is blood pressure (BP) measurement. In pediatric T2DM the guidelines recommend blood pressure (BP) and UACR evaluation at diagnosis and annually thereafter.

An important and modifiable risk factor for the development of diabetic kidney disease is hypertension. Arterial hypertension (ATH) is an important and frequent risk factor for the appearance of cardiovascular disease in T1DM patients. High blood pressure triggers the development and progression of microvascular complications, namely nephropathy, and retinopathy.

Ambulatory blood pressure measurement (ABPM) is superior to office BP measurements in predicting future cardiovascular events and targeting organ damage. In their study, Shalaby et al showed an abnormal BP profile for systolic and diastolic BP, with significant loss of nocturnal dipping. A significantly higher frequency of non-dipping patterns was observed in T1DM patients with microalbuminuria.

A recent study that comprises 3529 children and adolescents with T1DM revealed impaired blood pressure regulation with elevated/higher systolic BP, nocturnal diastolic blood pressure (DBP), mean arterial pressure (MAP), and diastolic dipping but lower nocturnal systolic dipping.

Lurbe et al showed that an increase in nocturnal systolic blood pressure precedes the microalbuminuria occurrence within T1DM children.
The non-dipper pattern for SBD is one of the earliest abnormalities in the blood pressure profile detected for children with T1DM. Also, non-dipping status has been associated with kidney damage (renal morphological changes) and hyperfiltration in adolescents with T1DM as well [65]. Also, the non-dipping status seems to be an early predictor of later nephropathy [65].

Teenagers with T1DM are at risk for hyperfiltration and higher UACR (urinary albumin-to-creatinine ratio), which are biomarkers for early/incipient nephropathy [35]. A recent meta-analysis found that almost 25% of T2DM patients have arterial hypertension, the male gender being more frequently affected, and that 1 in 4 or 5 children have albuminuria [60].

Mamilly et al found an increased urinary NGAL/Creatinine (a marker of tubular injury) and pentosidin/Creatinine (a marker of oxidative stress) in subjects with T1DM compared to control even in the absence of microalbuminuria [51]. The same study reported a high incidence of abnormal BP dipping, this being important as dipping abnormalities may serve as a predictor for vascular complications, especially kidney injury in diabetic individuals [51]. The same study proved that urine NGAL correlates with loss of nocturnal dipping of SBP [51].

Based on these, ABPM represents the gold standard to assess BP regulation and should be used in all diabetic patients for timely therapeutic intervention to prevent renal and cardiovascular diabetic complications later in life.

1. PROPHYLACTIC AND THERAPEUTIC STRATEGIES FOR DIABETIC KIDNEY DISEASE

The well-known strategies, namely: rigorous glycemic control, strict blood pressure control, and modulation of obesity still represent the most important tools to prevent and slow down the progression of diabetic nephropathy/the deterioration of renal function. These therapies proved to be effective mainly by targeting the modifiable risk factors for diabetic nephropathy, which are listed in Table 1.
A recent systematic review confirmed that early high doses of D vitamin supplementation in combination with renin-angiotensin-aldosterone system (RAAS) blockers may slow the onset or progression of DKD [66]. Standard and some novel proposed therapies in early-stage or late-stage development of diabetic nephropathy are presented in Table 5 [20, 66, 67].

CONCLUSION
Diabetic kidney disease, the most significant and frequent burden of this metabolic disorder, is still discovered late as microalbuminuria is the most used biomarker for predicting kidney involvement. Novel biomarkers proved valuable tools in the detection of kidney damage in early phases as well as reliable predictors for DKD progression, therefore effective therapies may be proposed. Early stages prediction and recognition of diabetic kidney disease in children and adolescents before microalbuminuria occurrence have a pivotal role to prevent the development of and/or progression to irreversible kidney damage and to provide timely management and appropriate treatment by using conventional and novel therapies that may slow the onset or progression of DKD.
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