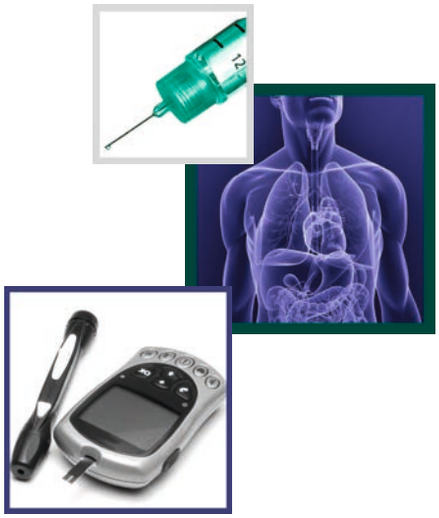
REVIEW



Early signs of diabetic nephropathy in childhood

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Practice Points

- Both childhood onset of Type 1 and Type 2 diabetes are clearly associated with an increased risk of kidney disease later in life.
- In subjects with Type 1 diabetes, screening for microalbuminuria should be performed annually from the age of 11 years in those subjects with 2 years of diabetes duration and from the age of 9 years in children with 5 years of diabetes duration.
- In subjects with Type 2 diabetes, screening for microalbuminuria should begin as early as the time of diagnosis.
- Microalbuminuria can be evaluated in 24-h urine collection, or in overnight timed urine collections as well as albumin–creatinine ratio or albumin concentration in an early morning spot urinary sample.
- Assessing albumin excretion rate in early morning urine is the easiest method to carry this out in an office setting, and it generally provides accurate information.
- A longitudinal assessment of glomerular filtration rate is highly recommended in order to detect variations in renal function and the associated risks.
- The normal level of glomerular filtration rate varies according to age, gender and body size.
- Preventive strategies include optimizing glycemic controlling, control blood pressure, controlling lipid levels, avoiding smoking, a healthy diet and physical activity.

SUMMARY Diabetes represents the single largest cause of end-stage kidney failure in adults. Although diabetic nephropathy is an uncommon cause of kidney failure during childhood, there is clear evidence that the underlying events increase to progressive kidney injury begin during childhood and accelerate during puberty. This is of paramount importance taking into consideration the significant worldwide increasing in the incidence of Type 1 and Type 2 diabetes in youths. The characterization of the natural history, identification of risk factors and subclinical signs of renal complications in childhood is essential for the implementation of preventive and therapeutic strategies, with the aim of changing the course of renal complications in young subjects with diabetes. In this report, an

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overview of the natural history, main histological alteration and risk factors associated with diabetic nephropathy are described. Finally, we focus on the screening guidelines suggested for youth with diabetes.

Background

Diabetes mellitus represents the single largest cause of end-stage kidney failure worldwide, in adults. Overt impaired renal function is characterized by a continuous increase in albumin excretion, leading to macroalbuminuria (albumin excretion rate >200 µg/min) and a consistent fall in glomerular filtration rate (GFR). This condition is rare during childhood. However, although this advance stage of diabetes nephropathy is uncommon in the pediatric population, it has been amply shown that the pathophysiologic events that will finally result in kidney damage are present early on in many patients, and are clearly manifested by the development of albuminuria. This is particularly important when we consider the burden of diabetes in childhood as well as the rising incidence of both Type 1 and 2 diabetes. Diabetes mellitus is one of the most common chronic disorders of childhood and adolescence worldwide [1]. Alarming reports have shown that the incidence of Type 1 diabetes is increasing at an annual rate of approximately 3–5%, particularly in children under the age of 5 years [1,2]. Although, in most Western countries Type 1 diabetes accounts for over 90% of cases of diabetes in children and adolescents, the increasing rates of childhood obesity worldwide has been associated with the rising prevalence of Type 2 diabetes. Thus, recent reports have documented that it is already more common than Type 1 diabetes in Japan and Taiwan and seems to account for 7–45% of all new diabetic patients in the USA [3–5]; whereas in Europe, the reported prevalence among new diabetics is still low, on the order of 0.5–1% [4,5]. In addition, youth-onset Type 2 diabetes may be associated with higher risks of adult morbidity and mortality than adult-onset disease [6], likely due to the longer duration of exposure to the diabetic milieu. Of note, several studies have shown that obesity, and especially birth weight and weight gain, during the first year of life might be significantly related to risk of Type 1 diabetes. In a recent systematic review and meta-analysis including 12 studies involving 2,398,150 people of whom 7491 had Type 1 diabetes, Harder *et al.* indicated that higher birth weight and increased early weight gain are risk factors for Type 1 diabetes, supposing therefore a possible role of obesity in the increased incidence of Type 1 diabetes [7]. Therefore, if early interventions are expected to be effective in slowing or arresting the development of diabetic nephropathy in adult patients, they may need to be initiated in childhood. Characterization of the natural history of kidney disease and of its related signs and risk factors is essential for the early implementation of preventive and therapeutic strategies, which could change the course of vascular complications and improve the prognosis of children, adolescents and young adults with diabetes.

Clinical course of diabetes nephropathy

In European populations, the risk of developing overt proteinuria and impaired kidney function in subjects with Type 1 and Type 2 diabetes has been reported to be similar [8]. Well-defined longitudinal data, in patients with Type 1 diabetes, describe that approximately 20–40% of patients eventually develop overt proteinuria after disease duration of at least 25 years [9]. Among them, 5–15% progress to renal failure, therefore causing increased morbidity and mortality, and it is disproportionately greater in patients having diabetes since the youngest ages [10]. Although during the last few decades the incidence of Type 2 diabetes in childhood has dramatically increased, large and well-defined studies describing the longitudinal changes occurring in the kidneys are still missing. Therefore, the complete natural history of Type 2 diabetes diagnosed childhood is mainly unknown. In addition, in contrast to subjects with Type 1 diabetes, the precise risk of nephropathy in young subjects with Type 2 diabetes is more difficult to estimate since our current knowledge of the onset and incidence of asymptomatic Type 2 diabetes itself is much less certain. Many affected individuals first present with overt diabetic complications later in life, after an unknown duration of Type 2 diabetes. Data available show that approximately 20% of those who develop overt diabetic nephropathy progress to kidney failure. Most of the information available is mainly obtained by studies on Pima Indian children with Type 2 diabetes, a well-defined ethnic group at an increased risk of developing Type 2 diabetes during childhood as well as in adulthood [11]. This population is also

known to present a relatively accelerated course of diabetic nephropathy, when compared with populations of European origin. This difference appears to be partially explained by the early onset of Type 2 diabetes, the former typically experience kidney failure in their 30s and 40s versus 50s and 60s in the latter group [12]. However, although contrasting results on the magnitude of the regression have been reported during the last few decades [13,14], since the initiation of more intensive therapies after the DCCT, a visible reduction in the incidence of kidney failure has been documented [15]. In this study, authors described the clinical care, metabolic results and outcomes in subjects from the DCCT and the longitudinal follow-up study, the EDIC study over a diabetes duration of 30 years, and compare these results with those of the Pittsburgh EDC study. In particular, the DCCT, is a multicenter, controlled clinical trial, in which a population of 1441 subjects with diabetes from 29 centers across Canada and the USA, was recruited between 1983 and 1989, and assigned to conventional or intensive therapy. The DCCT has been observational, and intensive therapy was recommended for all patients since 1993. In addition, the Pittsburgh EDC study is an observational study of patients with Type 1 diabetes from Allegheny County (PA, USA) representing a more population-based observational study with clinical data collected with methods similar to the DCCT/EDIC study during an overlapping period. Results from this study showed that, after having diabetes for 30 years, the cumulative incidences of nephropathy, as well as of proliferative retinopathy and cardiovascular disease (CVD), were 25, 50 and 14%, respectively, in the DCCT/EDIC conventional treatment group, which was similar to the EDC cohort with 47, 17 and 14% cumulative incidences, respectively [15]. By contrast, the DCCT intensive treatment had cumulative incidences of 9, 21 and 9% for nephropathy, proliferative retinopathy and CVD, respectively, displaying the powerful effect of intensive therapy over time [15]. In addition, recent data have shown that modern prevention has also reduced progression of nephropathy to end-stage renal disease due to Type 1 diabetes. In particular, it has been reported in a relatively recent study the estimation of age- and sex-standardized incidence of end-stage renal disease by type of diabetes and temporal trends, in population-based data obtained by renal registry analysis including persons aged 30–44, 45–54 or 55–64 years newly treated for end-stage renal disease during 1998–2002 in eight countries or regions of Europe, and Non-Indigenous Canadians and Australians. More specifically, a decrease from 60–85% (within 6–14 years) [16] to 30% (over 10 years) [12] of the rate of progression of microalbuminuria to overt proteinuria has been documented. By contrast, the number of end-stage renal disease patients due to Type 2 diabetes has shown a failure of the measures activated that aimed to control the disease-related complications [12], thus indicating that additional effort is needed to develop prevention strategies in this high-risk group. However, these results mainly refer to young adult subjects while, to date, confirmation is still needed in pediatric population-based data.

During the last five decades several studies have allowed us to characterize the natural history of diabetic nephropathy, helping to definine the risk factors and possible intervention strategies for diabetes-related kidney changes. Characteristically, function and morphology changes occurring in the kidney in patients with diabetes evolve through five stages [17,18].

The first stage, often at the time of diagnosis of diabetes, is characterized by reversible abnormalities including increase of both kidney sizes and GFR. Hyperfiltration is characteristically experienced by 20–40% and 30–40% of newly diagnosed Type 1 and Type 2 diabetes patients, respectively [16,19]. Nevertheless, in some instances, nephromegaly and raised GFR persist, whereas in others these findings may return after a few years.

The following second stage mainly occurs 2–5 years after diagnosis. This phase is clinically silent and is characterized by the occurrence of typical morphological changes, including mesangial matrix expansion and glomerular basement membrane thickening. In this stage, progression to the later stages of nephropathy can be prevented or delayed by the maintenance of excellent metabolic control [20]. Toward the end of this period, urinary albumin excretion will begin to rise, within the normal range, in a set of patients that will ultimately develop microalbuminuria. Of note is that although no universally accepted data are available, studies have pointed out the possibility of defining the risk of diabetic nephropathy according to the levels of or rate of the increase of albumin excretion during the first 5 years after the diagnosis [21,22]. In fact, an association between the

development of microalbuminuria and a higher albumin excretion rate level within 1–2.5 years after diabetes onset has been reported. In addition, an increase in the albumin excretion rate during the first 5 years after the diagnosis of diabetes has been shown to be a risk factor for the development of microalbuminuria [21,22]. Similarly, higher levels of albumin excretion, even if they are within the normal nonalbuminuric range (7.5–20 µg/min or 24-h >15 µg/min), were associated with a twofold increased risk of developing persistent microalbuminuria as well as predicting the onset of persistent microalbuminuria within 1.5–4 years [23,24]. Therefore, in a percentage of subjects with diabetes, and especially in the presence of risk factors associated to diabetic nephropathy, the alteration documented during the second stage persists and determines the progression to the following stage.

The third stage, also called incipient nephropathy, typically, develops approximately 7–10 years after diagnosis [16]. This stage is determined by the presence of microalbuminuria, defined as an albumin excretion rate of 30–300 mg in 24-h urine collection or 20–200 µg/min in a 24-h or timed urine collection, and by more profound structural changes. Although these two definitions are the most used in childhood, other definitions of microalbuminuria have also been reported such as: an albumin/creatinine ratio in spot urine of 2.5–25 mg/mmol and of 3.5–25 mg/mmol, in males and females, respectively, or an albumin/creatinine ratio of 30–300 mg/g in spot urine or an albumin concentration of 30–300 mg/l in an early morning urine sample [9,25–27].

The third phase has also been shown to be reversible. In fact, regression to normoalbuminuria has been reported in 31–58% of adult patients with Type 1 diabetes [14,28] and in approximately 40–50% of adolescents with Type 1 diabetes [29–31]. Several factors strongly influence the evolution of microalbuminuria later on, after its determination. In particular, regression to normoalbuminuria has been associated with better metabolic control and a better lipid and blood pressure profile, as well as with non-modifiable factors, such as younger age and shorter duration of microalbuminuria [14,28]. By contrast, poor metabolic control early or later in the course of diabetes [29,32–34], as well as initial albumin excretion rate or substantial albumin excretion rate increase, initial systolic or mean blood pressure, and older age or longer diabetes duration, has been shown to be a strong predictor of progression [32,34]. However, in childhood in particular, a single measurement of albumin excretion is not considered to be appropriate to define the presence and progression of this early alteration of the kidney, the method of its determination in particular, has been considered to be of foremost importance. In fact, the data available to date show that the prognostic value of an elevated albumin excretion rate in a single (in particular random) urine sample is limited, and a single value in the microalbuminuria range only conveys a 40% chance of indicating persistent microalbuminuria in children and adolescents [35]. The persistence of elevated albumin excretion rate over time is strongly unstable, progressing to persistent microalbuminuria in 40–50% of these patients; by contrast the other 30–60% of cases show microalbuminuria only intermittently, and approximately 20% will never develop microalbuminuria again [36–39]. Nevertheless, in adolescents with transient microalbuminuria the clinical significance of intermittent microalbuminuria is largely unknown. Some of these patients may still progress to diabetic nephropathy in the presence of unfavorable conditions [40], or develop persistent microalbuminuria within 3 years [41]. By contrast, in some subjects, regression to normoalbuminuria is not achieved and if microalbuminuria (defined as an albumin excretion rate of 20–200 µg/min or 30–300 mg/24 h) is detected in a minimum of two out of three urine samples collected consecutively, preferably within a 3–6-month period, they progress to a phase termed persistent (permanent) microalbuminuria [25].

The fourth stage is marked by the onset of dipstick-positive albuminuria, commonly defined as macroalbuminuria. This stage is commonly associated with the presence of other microvascular complications, particularly retinopathy. Renal function begins to deteriorate during this stage, with initial normalization and then a decline in the previously elevated GFR, plus the development of systemic hypertension. Stages 3 and 4 are amenable to intervention to achieve meticulous diabetes control and amenable to the use of angiotensin-converting enzyme (ACE) inhibitors and other antihypertensive agents [20,42]. Interestingly, although no difference is documented on the rate of progression of microalbuminuria to macroalbuminuria between children and adults with Type 1 diabetes, in children macroalbuminuria occurs at an earlier age [28,43]. The ORPS cohort showed that the cumulative prevalence of macroalbuminuria

was 13.9% after 19 years of diabetes duration [30], which is similar to the 14.6% prevalence reported in a similar inception cohort in adults [28]. Therefore, these data strongly suggest that progression is related to the duration of diabetes regardless of the age at onset. Characteristically, in patients with Type 2 diabetes the overall risk for progression from normoalbuminuria to proteinuria is similar to that seen in Type 1 diabetes patients – approximately 10% in 10 years [44]. The UKPDS found that progression from normoalbuminuria to microalbuminuria occurred at a rate of 2% per year, from microalbuminuria to proteinuria at 2.8% per year and from proteinuria to serum creatinine level of 175 µmol/l or end-stage renal disease at 2.3% per year [45].

The final stage is end-stage renal disease, which usually takes 5–10 years to develop after the appearance of overt proteinuria (albumin/creatinine ratio ≥300 mg/g; albumin excretion rate of ≥200 µg/min). The outcome of patients with diabetes who enter dialysis and transplantation programs is poorer than the outcome of their nondiabetic peers [46]. In Pima Indian adolescents, there is a high prevalence of microalbuminuria (22%) and hypertension (18%) at diagnosis [45], with progression of renal impairment manifested by microalbuminuria in 60%, and proteinuria in 17% between 20 and 29 years of age. Of note is that subjects with an onset of diabetes before 20 years of age have a roughly fivefold increased incidence of end-stage renal disease between 25 and 54 years of age compared with a later onset of the disease [6]. The higher risk of a worse progression related to an early onset of Type 2 diabetes in childhood has been further confirmed in studies in the American and Japanese Population [47,48]. In Manitoba and Northwestern Ontario, follow-up data in youth diagnosed with Type 2 diabetes before the age of 17 years revealed high rates of mortality (9%), end-stage renal disease (6.3%), pregnancy loss (38%) and other complications only 15 years after diagnosis [47]. In addition, 60% of Japanese people who develop Type 2 diabetes before the age of 30 years, develop diabetic nephropathy at a mean age of 31 years with 23% developing end-stage renal disease at a mean age of 35 years [48]. Taken together, in adolescents with Type 2 diabetes it is well defined that microalbuminuria is not rare at the time of diagnosis, and the rate of progression of microalbuminuria and nephropathy seems to be rapid. After 5–10 years of diabetes, microalbuminuria and overt diabetic nephropathy is found in 18–72% and 5–27% of patients, respectively. Furthermore, contrary to the declining incidence of nephropathy in Type 1 diabetes patients, in those with Type 2 diabetes, the incidence remains persistently high [49]. In addition, in contrast to what shows in subjects with Type 1 diabetes, morphology of kidney disease in Type 2 diabetes is less uniform, with only approximately 40% of patients having microalbuminuria or proteinuria showing typical diabetic glomerulopathy, whereas the remaining patients have minimal structural changes or a combination of diabetic and hypertensive/atherosclerotic lesions [50,51].

In addition, to this often used classification, a report from the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative to improve the detection and management of chronic kidney disease (CKD) has been published. This guideline aimed to define CKD irrespective of the type of kidney disease (diagnosis) and proposed a five-stage classification system [52,53]. One of the advantages of this classification is the minor relevance associated to the time of events. In fact, using time as the driving factor is rather simplistic, as many of the hemodynamic, histopathologic and clinical aspects are not clearly time limited and may overlap [26,52].

According to these guidelines to improve the detection and management of CKD, the presence of CKD should be established based on the presence of kidney damage and level of kidney function (GFR), irrespective of diagnosis [52,53]. CKD is defined as either kidney damage or GFR <60 ml/min/1.73 m^2 for ≥3 months. Among individuals with CKD, the five stages are defined by the level of GFR, with higher stages representing lower GFR levels, as reported in **Table 1**. In particular, stage one is defined by the presence of kidney damage (defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests, or imaging studies) with a normal or increased GFR (≥90 ml/min/1.73 m^2). Similarly, stage two is defined by the presence of kidney damage with a mild decrease of GFR (60–89 ml/min/1.73 m^2). Stage three and four are defined by a moderate (30–59 ml/min/1.73 m^2) or severe (15–29 ml/min/1.73 m^2) reduction of of GFR, respectively. Finally stage five is defined by the development of kidney failure (GFR <15 ml/min/1.73 m^2 or dialysis) [26,52]. Of note, it is well known that the correct interpretation of GFR values in individual patients, especially in

Table 1. Stages of chronic kidney disease.

Stage	Description	GFR (ml/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR	≥90
2	Kidney damage with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	<15 (or dialysis)

GFR: Glomerular filtration rate.

children and adolescents, requires a clear understanding that the normal level of GFR varies according to age, gender and body size. The normal GFR in young adults is approximately 120–130 ml/min/1.73 m^2, whereas the normal level of GFR is much lower than this in early infancy, even when corrected for body surface area, and subsequently increases in relationship to body size for up to 2 years [54]. Hence, the GFR ranges that are used to define the five CKD stages in Table 1 apply only to children 2 years of age and above. However, the normal range of GFRs at different ages are: 1 week (males and females) 41 ± 15 ml/min/1.73 m^2; 2–8 weeks (males and females) 66 ± 25 ml/min/1.73 m^2; >8 weeks (males and females) 96 ± 22 ml/min/1.73 m^2; 2–12 years (males and females) 133 ± 27 ml/min/1.73 m^2; 13–21 years (males) 140 ± 30 ml/min/1.73 m^2; and 13–21 years (females) 126 ± 22 ml/min/1.73 m^2 [26,52].

Main histological changes in the kidney in Type 1 & 2 diabetes

Therefore, most children with diabetes are in a clinically silent phase when histological changes are developing without evidence of kidney dysfunction [55,56]. Several groups have attempted to characterize structure changes in the kidney of youths with diabetes. However, most of the information available on kidney biopsy presents an important limitation related to the research based on clinical instead of protocol biopsies. In fact, since persons biopsied for clinical reasons often present atypically, their structural findings may frequently reflect nondiabetic diseases. In protocol biopsies, persons are not selected for atypical diabetes, so the frequency of nondiabetic disease as a cause of kidney damage may be less.

A complete characterization of the complex histological changes related to Type 1 and Type 2 diabetes have been reviewed by Najafian *et al.* and Diez-Sampedro *et al.*, in two recent reviews [57,58]. As described in these two reviews, several reports have documented that although similar, some renal lesions underlying renal dysfunction in subjects with Type 1 and Type 2 diabetes may differ. In fact, although tubular, interstitial and arteriolar lesions are ultimately present in Type 1 diabetes, as the disease progresses, the most important structural changes involve the glomerulus. By contrast, a substantial subset of Type 2 diabetic patients, despite the presence of microalbuminuria or proteinuria, have normal glomerular structure with or without tubule-interstitial and/or arteriolar abnormalities [57]. Of note, in both conditions, podocyte alterations have been shown to play a crucial role, representing a major current target for potential intervention [58].

In subjects with Type 1 diabetes, the morphologic lesions predominantly affect the glomeruli. These are characterized by thickening of the glomerular basement membrane, detected as early as 1.5–2.5 years after the onset of Type 1 diabetes, and mesangial expansion, that progressively became diffuse [57]. Substantial changes are also documentable for the podocytes, renal tubules, interstitium and arterioles, especially at later stages of disease. Glomerular basement membrane thickening is closely followed by thickening of the tubular basement membrane, implying that glomerular hemodynamic perturbations are not required for these changes to occur [57]. Thereafter, these structural changes do not necessarily develop at the same rate in individual patients. Afferent and efferent arteriolar hyalinosis may be present within a few years after diabetes onset and correlated significantly with the percentage of sclerosed glomeruli. Abnormalities of the glomerular–tubular junction are late manifestations of the disease, predominantly in patients with proteinuria, with focal adhesions, obstruction of the proximal tubular take-off from the glomerulus and detachment of the tubule from the glomerulus (a tubular glomerulus) [57].

These various lesions of diabetic nephropathology progress at varying rates within and between Type 1 diabetes patients, and, this is even more the case in Type 2 diabetes. In fact,

the situation in Type 2 diabetes is more complex, explaining most of the studies heterogeneity in renal structure among these patients. Often, only a minority had diabetic nephropathy patterns typical of those seen in Type 1 diabetes patients, the remaining patients had mild or absent diabetic glomerulopathy with or without tubule–interstitial, arteriolar and global glomerulosclerosis changes [57].

The podocyte has become a crucial focus as a target for interventions in CKD as well in diabetic nephropathy owing to its key roles in regulating glomerular permeability and maintaining glomerular structure through interactions with other glomerular parenchymal cells, including endothelial cells [58]. Although it is well known that podocyte foot process width increases and slit pore length per basement membrane surface area decreases with increasing urinary protein excretion in diabetes, recent studies have documented that podocyte shape changes, albeit subtle, are already present in normoalbuminuric young Type 1 diabetes subjects, perhaps consistent with an early role for this cell in the pathogenesis of diabetic glomerulopathy [58]. Of note is that detachment of podocyte from basement membrane worsens with increasing albuminuria and could be responsible for podocyte loss and decreased podocyte number. In addition, decreased podocyte number in patients with normal albumin excretion rate, thus suggesting that diabetes *per se*, may adversely affect podocyte reproduction, survival or both [58]. Low podocyte number and increased foot process width has also been described in proteinuric subjects with Type 2 diabetes. Of note is that evidence has suggested that podocytes probably have limited capacity to replicate. Podocyte loss, along with the increase in glomerular volume that may occur in diabetes, would require the residual podocytes to cover a larger area of glomerular basement membrane. This might facilitate podocyte detachment, resulting in bare glomerular basement membrane areas with consequent proteinuria. Moreover, these areas of detachment could initiate adhesions and potential starting points for glomerular–tubular junction and focal or global glomerular sclerosis [58].

Biochemical mechanisms associated to glucose toxicity

Several biochemical mechanisms accountable for the development of glucose-related toxicity have been proposed in the natural history of diabetic nephropathy, both in young subjects with Type 1 and Type 2 diabetes, presenting the last ones some supplementary particularities.

Over the last few decades, studies have demonstrated that intracellular hyperglycemia results in a relevant and pathological activation of four major metabolic pathways: increased glucose flux through the polyol–sorbitol pathway; the hexosamine pathway; formation of advanced glycation end products; and activation of protein kinase C [59,60]. Although, apparently different, further research has documented that a common hyperglycemic-dependent pathway is involved in each of these metabolic cascade. In fact, according to the unifying theory proposed by Brownlee and colleagues [59], under hyperglycemic conditions human cells develop an accumulation of glycolysis pathway intermediates as a consequence of the overproduction of reactive oxygen radicals generated in particular by mitochondrial uncoupling and the subsequent activation of poly(ADP-ribose) polymerase and the inhibition of the glycolysis enzyme D-glyceraldehyde-3-phosphate dehydrogenase. Therefore, as long as intracellular hyperglycemia persist, reactive oxygen radical production copiously increases inducing a direct reactive oxygen radicals-dependent toxic action on the cell. In addition to the direct toxic effect, the continuously produced glycolysis pathway intermediates are shunted through the four main biochemical pathways resulting in several cellular damages [59,60]. Although, in young subjects with Type 2 diabetes all these hyperglycemia-related pathways are also activated, especially in the presence of chronic increase of blood glucose, and most of the metabolic alterations associated to obesity could play an additional risk factor able to significantly increase the damages in kidney [61]. In fact, in young subjects Type 2 diabetes is mainly associated with obesity [61]. In addition, childhood obesity has been associated with several consequences, including hypertension, dyslipidemia, hormonal alterations, insulin resistance and fatty liver disease, which are well known risk factors for the development of diabetic nephropathy [61].

Risk factors for kidney disease in childhood diabetes

Several factors have been shown to stimulate and influence progression of the molecular pathway implicated in the natural history of kidney

disease in young subjects with diabetes. Most of the available information defining risk factors for diabetic nephropathy mainly relate to children and adolescents with Type 1 diabetes; while limited information are available in young subjects with Type 2 diabetes. However, studies in adults have identified several risk factors that appear to mimic those identified in subjects with Type 1 diabetes and could potentially be extended to the youngest age [62,63].

Identification of modifiable or not risk factors of microvascular complications is crucial for the early implementation of preventive and therapeutic strategies, which could change the course of vascular complications and improve the prognosis of children, adolescents and young adults with diabetes. Among the recognized risk factors associated with diabetic nephropathy, some are clearly not modifiable, such as duration of diabetes, puberty, age at onset, family history of diabetic complications, including genetic factors, and race/ethnicity **(Box 1)**. By contrast, glycemic (metabolic) control, higher blood pressure, smoking, hyperlipidemia, maternal diabetes, intrauterine exposure, pregnancy, infections, nutrition, obesity and social status are unquestionably modifiable and therefore notably need be identified in order to activate all highly effective interventions available to date **(Box 1)**.

Glycemic control

As was definitively established by data from the DCCT and the EDIC, glycemic control represents one of the most important factors related to the development and severity of complications in subjects with diabetes [64–66]. In the adolescent cohort of the DCCT, improved metabolic control, achieved by intensive insulin therapy, has been shown to reduce the occurrence of microalbuminuria and proteinuria by 39 and 54%, respectively [64,66]. In addition, the benefit of better metabolic control also extends beyond the period of its intense implementation and even if differences in metabolic control between the intensively and conventionally treated groups were abolished later on [65]. Similarly, in patients with early-onset Type 2 diabetes, HbA1c is a relevant risk factor for microalbuminuria being the incidence of diabetic nephropathy increased with the increasing mean HbA1c level in a dose-dependent manner [67,68].

Although there is strong evidence describing the role of metabolic control in limiting the development and progression of diabetic nephropathy, recent reports mainly in adults subjects, including the ACCORD [69], the ADVANCE [70] and the VADT [71] have provided a note of caution. In fact, results from these trials documented that high-risk patients with Type 2 diabetes have not shown a benefit from intensive control in reducing cardiovascular risk over a rather short-term follow-up period of up to 5 years, with some data indicating that intensive control accompanied by hypoglycemia is detrimental in patients with high cardiovascular risk. In addition, since none of the studies evaluate metabolic control in youth-onset Type 2 diabetes, a note of caution may be warranted about extrapolation of these findings to a youthful Type 2 diabetic population. Therefore, new data are needed in order to firmly define these aspects in the preventive strategies aimed to optimize the metabolic control in children and adolescents with Type 2 diabetes.

Plasma lipids & blood pressure

Dyslipidemia, as well as alteration in blood pressure and its circadian rhythm, has been shown to significantly influence the risk of diabetic nephropathy in young subjects with Type 1 or Type 2 diabetes.

In a recent report, high-density lipoprotein (HDL) concentrations have been documented as playing a relevant role in defining the risk of micro- and macro-albuminuria [72]. In a group of children and adolescents with persistent abnormal urinary albumin excretion during a follow-up period of 13.1 years, Salardi *et al.* clearly showed significantly persistent decreased HDL concentration compared with normoalbuminuric subjects [72].

In the DCCT and the EDIC, higher total and low-density lipoprotein (LDL) cholesterol as well higher triglyceride levels were associated with development of microalbuminuria [73]. Confirming results were reported in the adolescent cohort from the NFS, in which total cholesterol during puberty was significantly associated with albumin excretion and the development of microalbuminuria [74]. Similarly, in adolescents with recent-onset Type 2 diabetes and microalbuminuria, significantly higher LDL cholesterol and triglyceride levels have been documented compared with those with Type 2 diabetes and normoalbuminuria or healthy controls [67,75].

In adolescents with Type 1 diabetes, an increase of blood pressure has been found to precede or occur concomitant with the appearance of microalbuminuria [76]. In addition, data

from the adolescent cohort of the NFS, showed that increases in daytime diastolic blood pressure emerged to be predictive of the future development of microalbuminuria [77]. In addition, in young subjects with Type 1 diabetes, alteration in the nocturnal dipping phenomenon, mainly characterized by an increase of blood pressure during sleep, has been shown to precede the development of microalbuminuria and also to be related to more relevant morphological changes in the kidney [78,79]. Blood pressure abnormalities are often described in young patients with Type 2 diabetes and also related to the risk of diabetic nephropathy. In particular, both diastolic and systolic blood pressure, as monitored by the 24-h ambulatory blood pressure measurements, have a significant predictive effect on development of diabetic nephropathy [67]. In addition, higher daytime average systolic and diastolic blood pressure and higher daytime systolic and diastolic load have been shown in adolescents with Type 2 diabetes and microalbuminuria compared with age-matched peers without microalbuminuria or healthy subjects [75]. In addition, these alterations in blood pressure are associated with a higher nocturnal blood pressure and load [75]. These differences in ambulatory blood pressure measurements were found in the absence of significant differences in casual blood pressure, demonstrating that ambulatory blood pressure measurements may be a more sensitive tool than office blood pressure checks [75].

Box 1. Risk factors associated with diabetic nephropathy.

Not modifiable

- Duration of diabetes
- Puberty
- Age at onset
- Family history of diabetic complications
- Family history of insulin
- Resistance, Type 1 and 2 diabetes
- Genetic factors
- Race/ethnicity

Modifiable

- Glycemic (metabolic) control
- Higher blood pressure
- Smoking
- Hyperlipidemia
- Intrauterine exposure
- Obesity
- Pregnancy
- Social status

■ Cigarette smoking

According to findings in adulthood, smoking history has been recognized as a relevant and preventable predictor of renal disease [80]. Compared with smokers, nonsmokers had significantly reduced risk of developing microalbuminuria or established nephropathy both in childhood-onset and adult-onset patient groups [80]. In young subjects with diabetes, a correlation between cigarette smoking and albumin excretion rate, independent of age and other variables, has also been reported [81]. Compared to nonsmokers, young smokers with diabetes have also been documented to present a higher baseline GFR and a tendency for a larger decline in GFR later on [82].

■ Duration of disease & impact of puberty

Duration of diabetes is recognized as an important contributor to diabetic nephropathy and other diabetes-related complications in adults [83,84]. In people with childhood-onset Type 1 diabetes, microalbuminuria is often detected during puberty [85], with a cumulative prevalence of approximately 10–25% after 5–10 years of diabetes duration [29,30] and up to 50% after 19 years of diabetes duration [30]. Relevant differences have been reported between young patients with Type 1 and Type 2 diabetes. In fact, a significantly higher rate of microalbuminuria has been reported in youths with Type 2 diabetes compared with their peers with Type 1 diabetes (28 vs 6%), despite a shorter diabetes duration. Data evaluating differences in the incidence of nephropathy between individuals with Type 1 and Type 2 diabetes in Japanese patients with early-onset diabetes mellitus [86], showed that in those subjects with a diagnosis of the disease between 0–9 years, the incidence of nephropathy is 25.5 and 4.87 per 1000 person-years for children with Type 2 and Type 1 diabetes, respectively. While the incidence reported for those diagnosed at the age of 10–19 years was 12.44 and 6.63 per 1000 person-years, respectively. The higher incidence of nephropathy in patients with Type 2 diabetes held true even when accounting for duration of disease (after 5–9 years, the incidence in individuals with Type 1 and 2 diabetes was 0.75 and 8.26 per 1000 person-years, respectively). Altogether, the cumulative incidence of nephropathy after 30 years of post-pubertal diabetes was significantly higher for Type 2

(44.4%) than for Type 1 diabetes (20.2%) [86]. Relevant information describing the incidence of microalbuminuria in young subjects with Type 2 diabetes has been reported in studies on Pima Indian adolescents. In this population, microalbuminuria has been found in 27–40% within 5 years after diabetes diagnosis [75,87], and the incidence was estimated at 13/1000 person/year [88]. Similar data have also been reported in Australian adolescents (28%) [68]. In a nationwide population-based study in Sweden, 16% of Type 2 diabetes subjects with disease onset at 15–34 years of age had microalbuminuria after 9 years of follow-up [89].

Several reports have clearly documented that both pre- [30,90] and post-pubertal [35,36] duration of diabetes play a major role in the risk of vascular complication, although recent reports claimed that pre-pubertal duration could be a more accurate determinant of the development of microvascular complications.

Kostraba *et al.* analyzed data regarding the risk of diabetes-related mortality in a cohort of 1582 subjects (mean duration: 12.9 years) and showed that the contribution of the pre-pubertal years of diabetes to long-term prognosis may be minimal. This indicates that the post-pubertal duration of Type 1 diabetes may be a more accurate determinant of the microvascular risk [35]. Similar results were reported in a subsequent study evaluating the impact of age at onset on the development of end-stage renal disease due to diabetic nephropathy in a nationwide population-based Swedish cohort with childhood-onset Type 1 diabetes and with a median duration of disease of 21 years [36]. However, discordant results have been reported in more recent studies evaluating the ORPS cohort. This study showed that pre-pubertal more than post-pubertal duration of disease has been shown to have a major role. In fact, patients with Type 1 diabetes from early childhood, and especially those diagnosed under 5 years of age, seem to have slightly delayed onset of persistent microalbuminuria during the first 10–15 years of duration compared with patients diagnosed later in childhood or during puberty [30,90]. However, this initial protective effect of younger age at diagnosis disappears over time. After 15 years of diabetes duration, the risk of developing microalbuminuria is similar between subjects diagnosed with diabetes before 5 years of age and those diagnosed between 5 and 11 years of age or after the age of 11 years [30], suggesting that age at the onset of diabetes does not influence the overall risk of microalbuminuria. Age at onset is also important because several factors associated with growth in childhood, and especially puberty, have been shown to be important factors implicated in the development and progression of microvascular complications. Particularly, puberty influences the risk of developing diabetic nephropathy by inducing hyperglycemia, as a consequence of the physiological decrease in insulin sensitivity experienced at this age [64,65,91]. In addition , the hormonal and metabolic changes characteristic of this age, as well as described renal growth occurring during this period of life, represent important factors associated with the risk attributed to puberty [30,92]. However, an important difference has been described between male and female, in regards to age at onset of the disease. Of note, an increasing difference in renal outcome over time between men and women, but only in the groups with onset of diabetes at puberty or later has been reported in two different study populations (Swedish and Finnish) [93,94]. In contrast to pre-pubertal onset of diabetes, the progressively increasing difference in outcome between the genders does not occur. This would seem to be strong evidence for microvascular injury related to gender occurring at the time of diagnosis, if that is at puberty or later. The levels of male hormones and other factors that influence the development of nephropathy (i.e., glycemia, blood pressure and smoking) over many years of adult life seem likely to be little different between those who developed diabetes before puberty and after puberty. Thus, there is a clear implication that onset at puberty or later results in some form of renal and retinal injury that allows the development of microvascular disease many years afterwards.

Finally, recent advances in preventive strategies have provided opportunities to influence the duration of diabetes. In fact, as summarized in two recent reviews [95,96], several studies aimed to restore insulin secretion by modulating immune assault on the pancreatic beta cell system have been performed and most are underway. Although not yet ready for clinical use, successful trials have been conducted in new-onset Type 1 diabetes that demonstrated the utility of three experimental agents with disparate modes of action (anti-T cell, anti-B cell and costimulation blockade) to preserve insulin secretion. By contrast, prevention studies have so far failed to produce positive results but have shown that

such studies are feasible and have identified new promising agents for study. All these new promising results will significantly change the effects of duration of the disease on the onset and progression of microvascular complications in subjects with diabetes.

■ Low birth weight

Birth weight correlates with the number of nephrons at birth [97]. It was therefore suggested that subjects with a low birth weight, and thereby with a congenitally reduced number of nephrons, are at an increased risk of postnatal development of glomerulosclerosis [98] and glomerular and systemic hypertension later in life, a relevant risk factor for diabetic nephropathy [99]. In addition, it has been hypothesized that the same factors affecting kidneys *in utero* also impact on pancreatic tissue development, thus predisposing infants of low birth weight to an increased risk of the subsequent development of diabetes and diabetic nephropathy, consistent with the so-called 'thrifty phenotype' hypothesis [100]. However, to date, discordant results have been reported regarding the effect of birth weight on the risk of diabetic nephropathy in Type 1 diabetes, while more convincing data are available in Type 2 diabetes. In fact, some studies have shown an association or a trend between birth weight and diabetic nephropathy in Type 1 diabetes [101,102]. By contrast, further reports failed to show such an association between birth weight and both the onset and progression of established diabetic nephropathy in Type 1 diabetes [103]. Pima Indian Type 2 diabetic patients with a birth weight below 2500 g, and also those with a birth weight over 4500 g, were found to be at an increased risk of proteinuria [104]. In detail, in this study when examined as a continuous variable by generalized additive logistic regression, birth weight had a U-shaped association with the prevalence of elevated urinary albuminuria, after adjustment for age, sex, duration of diabetes, glycosylated hemoglobin and blood pressure. The odds of elevated albuminuria in subjects of low birth weight was 2.3-times that in subjects of normal birth weight, and the odds in subjects of high birth weight was 3.2-times (95% CI: 0.75–13.4) as high [104].

■ Genetic & familial factors

Studies reporting significant differences in the risk of diabetic complications irrespective of glycemic control [105], as well as observations of familial clustering of diabetes and diabetic nephropathy [106,107], ethnic/race differences [108] and genome-wide scan analysis exploring candidate genes linked to the evolution of nephropathy [109], strongly support a relevant role of genes in diabetic nephropathy. Several candidate genes have been shown to be associated with the disease, but the results have not been consistent and most of the genes conferring risk to diabetic nephropathy remain to be identified. The few genome-wide association scans performed for diabetic nephropathy so far in combination with improved understanding of the human genome have identified novel risk loci (such as genes on chromosome 3q) and emphasized the importance of performing detailed genetic studies across diverse ethnic populations to fully unravel the genetic susceptibility to diabetic nephropathy [110].

■ Gender

Gender has been shown to play an important role in the risk of developing diabetic nephropathy and its effect appears to be mainly related to the hormonal milieu and differences in insulin sensitivity between males and females [111]. In particular, in contrast to what is described in adulthood, during adolescence the risk for microalbuminuria is higher in female than in male subjects with similar glycemic control [30].

Screening

As for most of the microvascular complications associated to diabetes, diabetic nephropathy is often asymptomatic during early stages, and once symptoms develop, it may be difficult to reverse. Therefore, several international societies (International Society for Paediatric and Adolescent Diabetes, American Diabetes Association and the US National Kidney Foundation) have proposed relevant guidelines aimed to detect kidney abnormalities related to diabetes early. Although very similar, they differ on some practical points, the discussion of which is not the aim of the present review. However, although differences may be highlighted, all these guidelines agree with the concept that repeated screenings for kidney alterations are currently strongly recommended to be activated and longitudinally repeated, and in particular highlight the importance of initiating during early adolescence [25]. In **Table 2**, information mainly from the International Society for Paediatric and Adolescent Diabetes has been

used. The identification of subjects at risk by screening for subclinical signs of complications is essential for the early implementation of more intensive preventive and therapeutic strategies that could change the course of vascular complications and improve the prognosis of people with diabetes. Of note, in a recent review the controversy associated to the screening for CKD in children have been pointed out [112]. In this review, Hogg clearly highlighted the importance of the inclusion of children and adolescents in the mandates for clinical laboratories to report eGFRs when serum creatinine is measured [112]. In addition, the author clearly showed that global consensus has not been reached regarding the cost benefit (or even absolute benefit) of urinary screening for proteinuria and other markers of CKD in children [112]. This important gap is mainly related to the lack of a consensus/ global response regarding screening procedures studies to permit the early identification of children with CKD.

In subjects with Type 1 diabetes, screening for microalbuminuria should be performed annually from the age of 11 years in those subjects with 2 years of diabetes duration and from the age of 9 years in those children with 5 years of diabetes duration [25]. Microalbuminuria could be evaluated in 24-h urine collection, or in overnight timed urine collections as well as albumin–creatinine ratio or albumin concentration on a early morning spot urinary sample [25]. However, in children and adolescents, the 24-h or timed urine collections are often difficult to collect. Assessing albumin excretion rate in early morning urines is the easiest method to carry out in an office setting, and it generally provides accurate information [25]. Screening before the age of 10 years is not generally recommended given the low prevalence of nephropathy in pre-pubertal children and should be repeated annually. Of note, according to the International Society for Paediatric and Adolescent Diabetes guidelines the presence of microalbuminuria need to be confirmed by finding two or all three samples abnormal over a period of 3–6 months in order to avoid confounding factors related to para-physiological increases of albumin excretion rate, which are relatively common in childhood [25]. Among them, exercise represents one of the most important as it is associated with increasing albumin excretion rate in nondiabetic individual as well as markedly pronounced effects in those subjects with diabetes. Even moderate exercise may interfere with the interpretation of data [41]. In addition, particularly in young subjects with short diabetes duration an accurate definition of persistently elevated albumin excretion rate values, requires a proper evaluation of other causes of albuminuria, such as immunoglobulin A or other types of nephritis common in childhood.

In subjects with childhood-onset Type 2 diabetes, screening for microalbuminuria should begin as early as the time of diagnosis [9,27,113]. This is of paramount importance owing to the insidious onset of metabolic syndrome and transition to Type 2 diabetes and the considerable number of patients with microalbuminuria present at diagnosis [68,114,115]. Screening should also continue annually thereafter, as for adult patients [9,27,113]. GFR should be assessed as described for patients with Type 1 diabetes [27,116].

Although indications for ambulatory blood pressure measurement in the clinical practice are still ill defined, the clear association between impaired blood pressure regulation and the risk of diabetic nephropathy show the need for regular measurements **(Table 2)** [117]. Blood pressure should be measured at least annually and determined using an appropriately sized cuff with the patient relaxed and seated. Confirmation of

Table 2. Screening recommendations for diabetic nephropathy in subjects with Type 1 and 2 diabetes.

Children and adolescents	Frequency and methods			
	When to start	**Nephropathy**	**Blood pressure**	**Lipids**
Type 1 diabetes	At the age of 11 years with 2-year Type 1 diabetes duration or from the age of 9 years with 5-year diabetes duration	Annual evaluation of Albumin:creatinine ratio in a spot urine sample or albumin excretion rate in 24-h or overnight urine collection	Annually using an appropriately sized cuff and age-appropriate percentile charts. Confirmation of hypertension may be assisted by 24-h ambulatory blood pressure measurements	In subjects older than 12 years and without family history of diabetes, soon after diagnosis and every 5 years thereafter. If dyslipidemia is documented annual monitoring is recommended
Type 2 diabetes	At diagnosis			

hypertension may be assisted by 24-h ambulatory blood pressure measurements and, if elevated blood pressure is confirmed, nondiabetes-associated causes of hypertension should be excluded. It is of paramount importance that, in children and adolescents, blood pressure values should be compared with age-appropriate percentile charts [118]: hypertension is defined as an average systolic or diastolic blood pressure ≥95th percentile for age, gender and height percentile and 'high-normal ('prehypertension') blood pressure defined as an average systolic or diastolic blood pressure ≥90th but ≤95th percentile for age, gender and height percentile, both measured on at least 3 separate days. These levels correspond to ≤140/90 and 130/80 mmHg in adults, respectively. According to guidelines, blood pressure should be maintained at <95th percentile for age in all children with hypertension [118].

According to the International Society for Paediatric and Adolescent Diabetes and American Diabetes Association guidelines, screening for fasting blood lipids should be performed soon after diagnosis in all children with Type 1 diabetes older than 12 years and repeated every 5 years, if normal results are obtained **(Table 2)** [25,27,116]. If there is a family history of hypercholesterolemia or early CVD, or if the family history is unknown, screening should start at 2 years of age. In this group, if values fall to within the accepted risk levels (LDL-C ≤100 mg/dl), a lipid profile should be repeated every 5 years. In prepubertal children, if the family history is not of concern, initial lipid screening should be performed at puberty (≥12 years) [25,27,116]. Screening for dyslipidemia by complete lipid profile evaluation, as well as all other risk factors for cardiovascular disease [27,113,116] are also recommended at diagnosis of Type 2 diabetes and repeated every 2–5 years, depending on other risk factors [27,116]. By contrast, if dyslipidemia is documented annual monitoring is recommended [27].

Pharmaceutical intervention

Clear guidelines for ACE inhibitor treatment in adult subjects with microalbuminuria, both normo- and hyper-tensive, are available [27]. ACE inhibitors reduce progression and increase regression to normoalbuminuria, with a long-lasting (8-year) effect. ACE inhibitors are the treatment of choice in adults with microalbuminuria, to date there is no universal recommendation for the use of these agents in children and adolescents. Small studies performed in youths with Type 1 diabetes and microalbuminuria have confirmed the efficacy of ACE inhibitors [119]. However, from these studies it is difficult to draw definitive conclusions especially in the long term. Results from new undergoing studies [120], will surely offer relevant information on the effectiveness and safety of ACE inhibitor therapeutic opportunities in young subjects with diabetes.

Most relevant areas of controversy & growing points

Although in adults with diabetes and diabetic nephropathy, treatment with antihypertensive drugs and statins is increasingly common, there are no definitive indications for treatment with these drugs in children and adolescents with early signs of complications. Ongoing studies characterizing these relevant gaps in childhood will be available soon. In addition, there is growing interest in the development of new preventive and therapeutic strategies targeting specific pathways implicated in the pathogenesis of microvascular complications. These include inhibitors of aldose reductase, inhibitors of protein kinase C, antagonists of advanced glycation end-products, glycosaminoglycans, inhibitors of growth factors and antioxidants. To date, there are no definitive data to recommend the use of these new potential therapies but the overall objective of targeting specific metabolic and hemodynamic pathways implicated in the pathogenesis of diabetic microvascular complications could lead to validation of these classes of drugs and discovery of novel pharmaceuticals.

Conclusion

Both childhood onset of Type 1 and 2 diabetes are clearly associated to an increased risk of development and progression of kidney disease later on in life. The health and social burden of diabetes nephropathy are exponentially increased by the constant and alarming increase of the incidence of both Type 1 and 2 diabetes. Although diabetic kidney alterations are often asymptomatic during their early stages, there is clear evidence that their pathogenesis and early signs develop during childhood and accelerate during puberty. Therefore, pediatric health care professionals ought to understand about natural history, risk factors and methods for screening of diabetic nephropathy. Identification of risk factors and subclinical signs of complications need

to be achieved early during adolescence and, in the case of Type 2 diabetes, at diagnosis, and represent essential tools for the early implementation of preventive and therapeutic strategies. Finally, characterization of new and effective therapeutic possibilities for preventing both the onset and progression of diabetic nephropathy in children could robustly change the burden and the natural course of kidney disease in children and adolescents with Type 1 and 2 diabetes.

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