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## Diabetic kidney disease in children and adolescents

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### Abstract

Diabetes, more frequently type 1 but increasingly also type 2, commonly occurs in childhood. While more advanced diabetic kidney disease (DKD), e.g. loss of glomerular filtration rate (GFR), does not occur until adulthood, kidney biopsies show DKD structural changes as early as 1.5–5 years after the onset of type 1 diabetes. Earliest clinical sign of DKD, e.g. increased urine albumin excretion, commonly appears during childhood and adolescence and presents an important opportunity to detect and intervene on early DKD, perhaps more successfully than later in the disease course. Longitudinal studies of type 1 diabetes have enriched our understanding of the DKD natural history and modifiable risk factors for DKD progression. These studies have also shown that presence of DKD marks a subset of people with diabetes who are at the highest risk of early mortality, supporting an enhanced focus on DKD detection, prevention, and treatment. Early studies suggest that youth-onset type 2 diabetes is associated with a higher prevalence of comorbidities and risk factors and follows a more aggressive natural history. A deeper understanding of the natural history, risk factors, underlying mechanisms and therapeutic options for DKD in young-onset type 2 diabetes awaits further studies.

### Keywords

diabetic kidney disease; type 1 diabetes; type 2 diabetes; microalbuminuria; macroalbuminuria; glomerular filtration rate; end-stage renal disease

### Introduction

Diabetes is one of the most common chronic diseases affecting children and adolescents. There are currently more than 190,000 people younger than 20 years of age with diabetes in the US[1] and this number is projected to increase two-folds or more by 2050.[2] Historically, type 1 diabetes has been the predominant form of disease in children and adolescents. However, over the past two decades, the rise in childhood obesity has led to an increasing incidence of type 2 diabetes among children and adolescents, which now parallels and at times exceeds that of type 1 diabetes among minority youth, particularly after the age of 15.[1]

It has long been known that diabetes is associated with a significant increase in mortality, largely as a result of its long term complications. More recently, this excess mortality has been found to be concentrated in the subset of people with diabetes who develop kidney disease, both in type 1 [3, 4] and type 2 [5] diabetes. These observations highlight the

importance of diabetic kidney disease (DKD) at least as a marker of a population at highest risk of mortality and perhaps as a risk factor directly contributing to excess mortality.

While more severe stages of DKD take decades to develop and are thus rarely observed in childhood, kidney biopsies as early as 1.5–5 years after diabetes onset show structural changes characteristic of DKD in both adults and children.[6–8] This suggests that the DKD course begins soon after diabetes onset and that this early interval may provide a critical time-frame for detection and intervention in the disease course, warranting intensive monitoring and modification of risk factors in children and adolescents. Perhaps more so than in adults, our current tools for early diagnosis of DKD in children and adolescents are few and flawed. Nonetheless, the heavy impact of childhood diabetes on morbidity and mortality later in life mandates our full use of all available tools and resources with a nuanced understanding of their strengths and limitations as well as a renewed effort towards development of new diagnostic tools and therapies.

This review will discuss the natural history and risk factors for development of DKD, the structural changes observed in DKD and the pathophysiological mechanisms causing those alterations. We will also discuss the differences in natural history and outcomes between type 1 and type 2 diabetes.

## Natural history

DKD natural history was classically described as an initial and progressive rise in urine albumin excretion, followed by progressive GFR loss and eventual development of end-stage renal disease (ESRD) over several decades (Figure 1). Microalbuminuria, defined as a urine albumin excretion of 30–299 mg/day (or an albumin to creatinine ratio of 30–299 mg/g creatinine in random samples) in at least 2 of 3 measurements, is the earliest sign of DKD and occurs in 26% of children and adolescents after 10 years and in 51% after 19 years of diabetes.[9] In the classic DKD presentation, once microalbuminuria develops, urine albumin excretion continues to rise, particularly in presence of uncontrolled risk factors. Macroalbuminuria, defined as a urine albumin excretion  $\geq 300$  mg/day (or albumin to creatinine ratio  $\geq 300$  mg/g creatinine), heralds the onset of overt DKD and is thought to inexorably lead to impaired GFR (defined as an estimated GFR  $<60$  ml/min/1.73m<sup>2</sup>) and eventually ESRD (Figure 1).

More recent work has refined our understanding of the DKD natural history under current standards of care. First, longitudinal studies of type 1 diabetes have shown that while microalbuminuria does raise the odds of future DKD development, more adults[10–12] and children[13, 14] with microalbuminuria regress to normoalbuminuria (~30–40%) than progress to more advanced stages of DKD. In addition, microalbuminuria is not associated with an increased rate of GFR loss,[15] altogether suggesting that rather than being a committed marker of specific and irreversible DKD, microalbuminuria may represent reversible endothelial injury. Microalbuminuria regression to normoalbuminuria is more common with improved glycemic and blood pressure control, but is independent of renin angiotensin system (RAS) inhibition both in adults[12] and children.[13, 14] As such, the current KDOQI guidelines recommend treatment with RAS inhibitors only if

microalbuminuria co-exists with other DKD risk factors (e.g. hypertension, diabetic retinopathy, dyslipidemia, etc).[16]

Secondly, while the classic presentation of macroalbuminuria preceding the impairment of GFR is observed in a majority of cases in type 1 diabetes, in a sizable minority GFR loss occurs either after microalbuminuria (16%) or even in absence of any albuminuria (24%). [15] Thirdly, while macroalbuminuria is associated with a 50-fold greater risk of progression to impaired GFR,[17] 60% of people with macroalbuminuria maintained an estimated GFR  $>60$  ml/min/1.73m<sup>2</sup>, even after 15 years of follow-up (Afkarian et al, submitted). These observations suggested that macroalbuminuria was a sign of substantial renal injury but that it did not set an inexorable course to impaired GFR or ESRD in all cases. In addition, significant renal injury could occur in absence of macro-or even microalbuminuria.

Interpretation of albuminuria in children and adolescents requires two additional considerations. First, the vast majority (75–95%) of proteinuria in children and adolescents is due to benign causes such as transient and orthostatic proteinuria.[18–22] Transient proteinuria may be associated with exercise, fever, cold, stress, dehydration or seizure and is reported to occur in as many as 50–74% of cases of observed proteinuria in children and adolescents.[18, 20] Orthostatic proteinuria, another etiology of benign childhood proteinuria, is reported in 6–20% [23] of healthy children and adolescents and leads to no adverse outcomes after up to 50 years of follow-up.[24, 25] Luckily, transient and orthostatic proteinuria can be readily identified by repeat measurement of urine protein excretion in absence of the conditions causing transient proteinuria and in a first-void urine sample to exclude orthostatic proteinuria.[26]

The second challenge in accurate interpretation of albuminuria in children is the likely misclassification of albuminuria status by application of a single threshold of 30 mg/day (or 30 mg/g of creatinine) in children of different age, size, gender and race. In children and adolescents, excretion of creatinine [27, 28] and albumin [27, 29] increases with age. Creatinine excretion is higher in boys [27, 30] and albumin excretion is higher in African Americans compared to Caucasians.[31] Using the single threshold of 30 mg/g in spot urine samples is likely to overestimate albumin excretion in younger, smaller and female children whose daily creatinine excretion is more likely to be much less than 1 gram.

## Structural changes and their correlation with functional parameters

In biopsies performed in both adults and children with type 1 diabetes, the first observed alteration is the thickening of the glomerular [6] and tubular [8] basement membrane (GBM, TBM) at 1.5–2.5 years after diabetes onset, followed by mesangial matrix expansion with an increase in fractional volume of the mesangial matrix typically observed 5–7 years after diabetes onset.[7] Interstitial expansion is also observed, initially due to an increase in the cellular component and later on due to accumulation of fibrillar collagen in advanced DKD. [32] These various lesions progress at different rates within and between different patients with type 1 diabetes. However, by the time advanced DKD with renal insufficiency sets in, all patients display marked mesangial expansion and GBM thickening as well as interstitial expansion and fibrosis, tubular atrophy [33] and glomerulosclerosis.[34] Similar lesions are

observed in children and adults with type 1 diabetes and normoalbuminuric DKD.[35] Diabetic retinopathy (DR) is nearly universal at the time of macroalbuminuria[36] and its severity is proportional to the degree of structural abnormalities in early DKD in type 1 diabetes.[37]

Renal structural lesions are much more heterogeneous in type 2 diabetes.[38, 39] Adults with type 2 diabetes and micro- or macroalbuminuria but GFR  $>60$  ml/min/1.73m<sup>2</sup> display typical DKD lesions in only 30% and 50% of cases, respectively, while the remainder show either atypical pathology (little or no diabetic glomerulopathy, with chronic tubulointerstitial fibrosis, arteriolar hyalinosis and glomerular sclerosis) or no significant pathology.[39] Interestingly, some degree of DR is present in all cases with typical DKD pathology while none of the cases with atypical pathology or non-significant injury have proliferative DR. [39] On the other hand, in type 2 diabetic patients with micro- or macroalbuminuria and impaired GFR ( $<60$  ml/min/1.73m<sup>2</sup>), typical glomerular lesions are reported in 83% and 100%, respectively. However, less than 40% of those with impaired GFR and normoalbuminuria show typical DKD glomerular lesions, while a majority show either severe renovascular and/or tubulointerstitial changes or no identified cause for kidney disease.[40]

In type 1 diabetes, mesangial expansion is significantly and inversely correlated with GFR, presumably due to consequent reduction in glomerular capillary filtration surface area,[7] a feature which is strongly correlated with GFR loss.[41] Mesangial expansion is also strongly correlated with albuminuria [7, 42] and hypertension.[43] GBM thickening closely correlates with albuminuria, but less so with GFR or hypertension.[44] Interstitial expansion and global sclerosis are correlated with albuminuria and hypertension and inversely correlated with GFR.[7] These associations are similar, though less precise, in type 2 diabetes, with albuminuria correlating closely with both GBM width and mesangial expansion, while risk of progressive GFR loss in type 2 patients with albuminuria is significantly correlated with the extent of mesangial matrix expansion.[45] Notably, unlike the structural studies in type 1 diabetes, all of those in type 2 diabetes were conducted in adults. In the light of rising incidence and poor prognosis of type 2 diabetes in children and adolescents, as discussed below, similar structural studies in this population have the potential to add much needed depth to our understanding of the disease process.

## Pathophysiology

Animal models have shown dysregulation of many pathways in DKD and these findings have largely been corroborated in human studies. The Diabetes Control and Complications Trial (DCCT) demonstrated that hyperglycemia is the primary trigger for dysregulation of all these pathways. Hyperglycemia leads to end-organ damage in several tissues, perhaps particularly those which are not able to down-regulate glucose entry in hyperglycemia.[46] In 2001, Brownlee presented a unifying hypothesis [47] which aimed to connect all the implicated pathogenic pathways to elevated intracellular glucose concentration (Figure 2). Drawing on several lines of evidence, including hyperglycemia-induced increase in intracellular superoxide, the Brownlee hypothesis posited that elevated intracellular superoxide inhibits a key glycolytic enzyme Glyceraldehyde 3-phosphate dehydrogenase

(GAPDH) thus blocking metabolism and disposal of excess intracellular glucose. The resulting accumulation of intracellular glucose and its glycolytic intermediates, Fructose-6-Phosphate and Glyceraldehyde-3-phosphate, then feed into and induce four primary pathways: the polyol, hexosamine and Protein Kinase C pathways and non-enzymatic generation of Advanced Glycation End-products (AGE). These pathways in turn activate many other pathogenic signaling cascades, most notably the TGF $\beta$  and RAS pathways, leading to distal effects such as excessive production and accumulation of extracellular matrix components which give rise to the DKD structural and functional alterations discussed in previous sections, e.g. expansion of the mesangial matrix and thickening of GBM.

While hyperglycemia is widely believed to be the inciting pathogenic stimulus, recently controversy has surrounded the role of intracellular superoxide in triggering the subsequent pathophysiologic mechanisms. The hyperglycemia-induced increase in intracellular superoxide is at the core of the Brownlee hypothesis. However, recent observations of reduced superoxide levels in kidneys of DKD animal models [48] have led to an alternative hypothesis. This hypothesis suggests that hyperglycemia reduces superoxide generation which in turn decreases activity of 5' AMP-activated protein Kinase (AMPK), a major energy-sensing enzyme, and PGC1, the master regulator of mitochondrial biogenesis. The resulting reduction in mitochondrial number and function promotes DKD progression. Pharmaceutical activation of AMPK and PGC1 $\alpha$  were shown to increase kidney superoxide content and diminish activity of the distal pathogenic mechanisms, manifested in reduction of albuminuria and lower expression of fibronectin, collagen and TGF- $\beta$  in the kidneys in several animal models of DKD.[48] Resolution of the controversy surrounding the effect of hyperglycemia on intracellular superoxide and its role in DKD pathogenesis awaits further studies.

Another question worthy of further study is scarcity of novel diagnostic and therapeutic tools in the face of acknowledged advances in our understanding of the underlying DKD pathophysiology based on experimental animal models. Since the discovery of the beneficial effect of intensive diabetes treatment and RAS inhibition on DKD, no new therapies have proven successful. Most recently, dual RAS inhibition and activation of Nrf antioxidant pathway failed to impact DKD progression, joining a cadre of prior failed trials using inhibitors of advanced glycation end-products, protein kinase C and aldose reductase. Given the strong association of mortality with DKD, understanding, and remedying, the causes for this delay in translation from pathophysiology to novel diagnostic and therapeutic options are of significant public health impact.

## Risk factors

The seminal DCCT/EDIC study included 195 participants who were 13–17 years old at enrollment, among whom intensive diabetes treatment was associated with 54% reduction in microalbuminuria and this benefit persisted during the EDIC study.[49] This established hyperglycemia, as measured by hemoglobin A1c, as the predominant risk factor for DKD. In addition female gender, diabetes duration, hypertension [50, 51], high normal urine albumin excretion [52] elevated LDL cholesterol, triglycerides,[53] high body mass index [54] and

smoking [55] have been reported as risk factors for development of microalbuminuria in children and adolescents. Role of pre-pubertal diabetes duration in development of microalbuminuria has been the subject of some debate, but overall the total disease duration, and not the duration before or after puberty, appears to determine cumulative microalbuminuria risk [50, 56] and DKD structural alterations in the kidney.[57] Hemoglobin A1c,[9] male sex,[58] smoking,[59] baseline albumin excretion,[9] and serum uric acid[60] have been reported as risk factors for progression to macroalbuminuria in children and adolescents. Given the significant heritability observed for DKD,[61] family history of kidney disease is also a significant risk factor for DKD development.

## Insulin resistance and type 2 diabetes in children and adolescents

In 2009, type 2 diabetes contributed to 23% of cases of diabetes among US children and adolescents, but was disproportionately more common among ethnic minorities. For example, among 15–19 year olds, type 2 diabetes caused 5.5% of diabetes among the non-Hispanic White, but 34–38% of diabetes in African-Americans, Hispanics and Asian Pacific Islanders and 80% of diabetes among American Indians.[1] Among youth diagnosed with type 1 diabetes, an additional 23% were insulin resistant with higher prevalence of obesity, again more commonly among ethnic minorities.[62]

Despite its lower overall prevalence compared to type 1 diabetes, the rise of type 2 diabetes in youth presents a grave public health problem for four reasons: youth with type 2 diabetes have a greater prevalence of risk factors for diabetic complications and mortality, show evidence of poor control of these risk factors, display more rapid progression of complications, higher rates of mortality and, most alarmingly, unabated progression of complications despite attempts to control risk factors.

First, compared with type 1 diabetes, young-onset type 2 diabetes is more frequently associated with several cardiovascular and mortality risk factors, even at diabetes onset. Hypertension is present in 24% of youth with type 2 vs. 6% of those with type 1 diabetes. [63] Dyslipidemia is also more common among youth with type 2 diabetes: an LDL >130 is present in 24% of children and adolescents with type 2 vs. 19% of type 1 diabetes; an HDL <40 is present in 44% vs. 12% of youth with type 2 and type 1 diabetes, respectively. [64] Children and adolescents with type 2 diabetes were also much more commonly obese (79%) than those with type 1 diabetes (13%).[65] Even more ominous is the considerable prevalence of early markers of cardiovascular disease at, or soon after, diabetes onset in youth with type 2 diabetes: microalbuminuria was observed in 22% vs. 9% of children and adolescent with type 2 vs type 1 diabetes.[66] Left ventricular hypertrophy was found in 22% of youth with type 2 diabetes up to 3 years after diagnosis.[67]

Secondly, risk factors appear to be less well controlled in children and adolescents with type 2 diabetes, compared to children with type 1 diabetes or adults. Poor glycemic control, defined as an HbA1c  $\geq$  9.5%, was reported in 27% of youth with type 2 diabetes, compared to 17% of those with type 1 diabetes and more commonly observed among ethnic minorities. [68] Only 32% of youth with type 2 diabetes, who had hypertension, were aware of their



diagnosis and only 6.6% received treatment.[63] Among youth with dyslipidemia, an even smaller fraction (1%) received treatment.[64]

Thirdly, youth with type 2 diabetes see earlier and more rapid progression of DKD, not only compared to youth with type 1 diabetes [69–71] but also adults with type 2 diabetes.[72] In countries where incidence of DKD among youth with type 1 diabetes has declined in the past two decades, DKD due to type 2 diabetes has not.[69] This more rapid progression of DKD in type 2 diabetes is at least partly due to coexistence of other risk factors, including insulin resistance.[73] Consistent with higher burden of comorbidities and complications, young-onset type 2 diabetes was found to be associated with greater risk of mortality at a younger age and with significantly shorter disease duration than type 1 diabetes, despite comparable glycemic control.[74] Consequently, the US youth with type 2 diabetes have a 15 year shorter remaining life expectancy and markedly reduced quality of life due to development of severe and morbid diabetic complication by their 40's.[75]

Perhaps most concerning were the recent reports from the Treatment Options for type 2 Diabetes in Adolescents and Youth (TODAY) study, suggesting that young-onset type 2 diabetes and its complications may be much more aggressive and treatment-resistant than its adult counterpart. TODAY was a multicenter trial of 699 adolescents 10–17 years old, with less than 2 years of type 2 diabetes, BMI 85<sup>th</sup> percentile, HbA1c 8% on metformin, controlled blood pressure and creatinine clearance >70ml/min, who were randomized to metformin alone, metformin and rosiglitazone or metformin and intensive lifestyle management.[76] Despite good compliance with medications, after a median of 1 year, 46% of participants failed glycemic control and had to start insulin. This was associated by a much more rapid loss of  $\beta$ -cell function in this cohort than seen in adults.[77] After 4 years of follow-up, prevalence of microalbuminuria and hypertension rose by 3-fold. Hypertension was associated with male gender and increase in BMI and appeared resistant to treatment, requiring multiple medications in more than one-third of participants initially treated with one agent.[78] Dyslipidemia, defined as an LDL 130 mg/dL or use of LDL-lowering therapy, increased from 4.5 to 10.7% over 3 years of follow-up while elevated inflammatory markers (hsCRP, PAI-1 and homocysteine) continued to increase over time and were not affected by lipid-lowering therapy.[79]

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## Multiple choice questions

1. A 15 year old boy with 10 years of type 1 diabetes has a urine albumin excretion of 280 mg/day based on a timed mid-day urine sample. What is the next best step?
  - a. Start an angiotensin converting enzyme inhibiting agent
  - b. Obtain a repeat urine sample to confirm microalbuminuria (random albumin/creatinine ratio is adequate)
  - c. Obtain a repeat first-void urine sample to exclude orthostatic proteinuria





5. A 16 year old Hispanic girl with recently diagnosed type 2 diabetes presents with poorly controlled diabetes (A1c 9.8), hypertension (BP 163/98), dyslipidemia (LDL 189), obesity (BMI 38) and an elevated urine albumin excretion (130 mg/g). Which of the following statements is incorrect?
- Her albuminuria must be benign or due to other causes of kidney disease because it takes at least 1 year to even see the first structural changes of diabetes and several more years to develop albuminuria.
  - Given her young age, her hypertension requires workup to exclude causes of secondary hypertension
  - She is at high risk for development and rapid progression of overt DKD despite her short diabetes duration because of many coexisting risk factors, including insulin resistance, hypertension, poor glycemic control and dyslipidemia.
  - She is at high risk of glycemic failure on oral agents and requiring transition to insulin.
  - Her presentation is consistent with early DKD as young onset type 2 diabetes is often associated with microalbuminuria and other risk factors at diagnosis.
  - In this young person with high risk of early mortality, weight loss is one of the most significant risk factors to modify.

**Answers:**

- e
- b
- g
- e
- a

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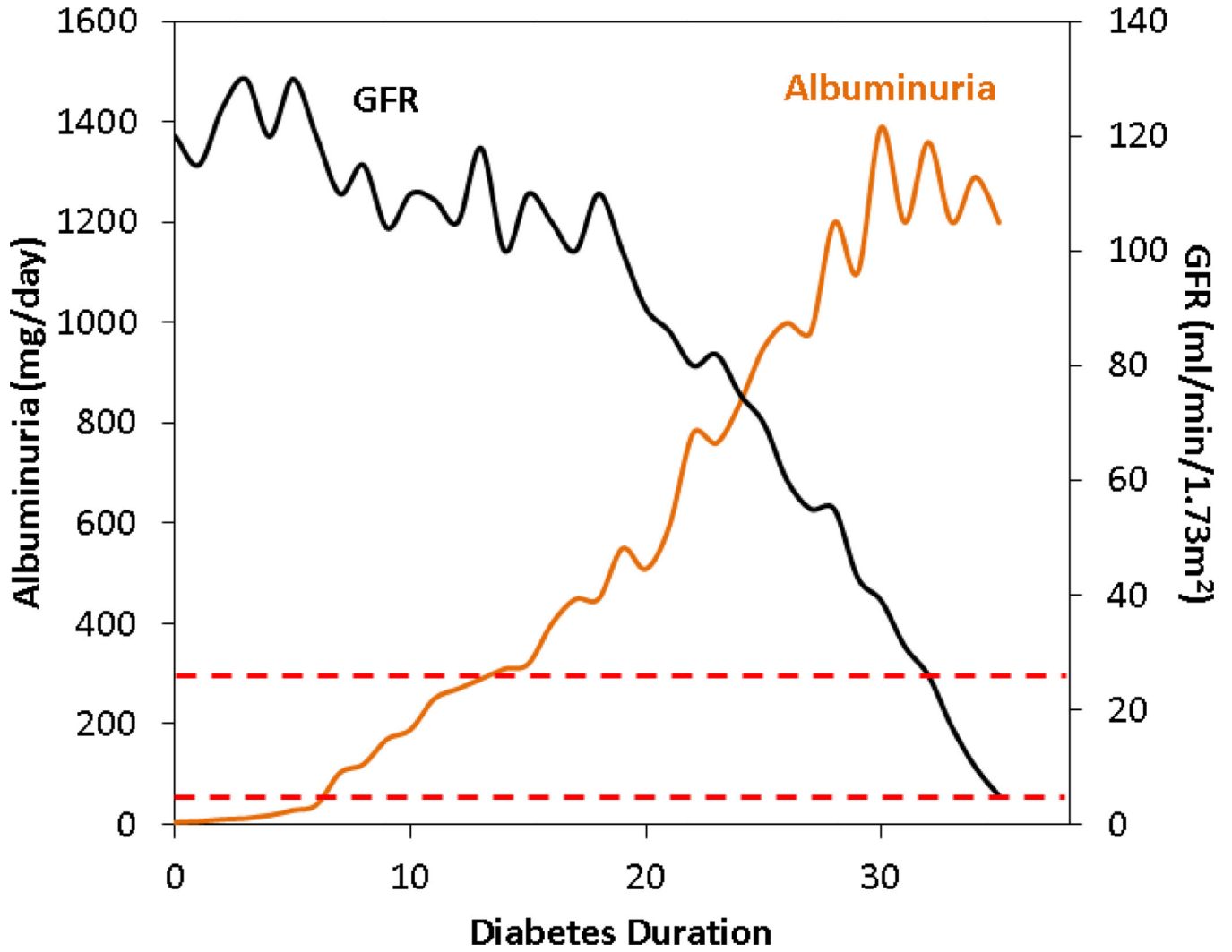
## Glossary

<b>AGE</b>	Advanced Glycation End-products
<b>eNOS</b>	endothelial Nitric Oxide Synthase
<b>ET-1</b>	Endothelin 1
<b>GAPDH</b>	Glyceraldehyde 3-phosphate dehydrogenase
<b>GSH</b>	reduced form of Glutathione
<b>GSSG</b>	oxidized glutathione
<b>PAI</b>	Plasminogen Activator Inhibitor
<b>PARP</b>	Poly (ADP ribose) polymerase
<b>PKC</b>	Protein Kinase C
<b>RAGE</b>	Receptor for AGE
<b>ROS</b>	Reactive Oxygen Species
<b>VEGF</b>	Vascular Endothelial Growth Factor.

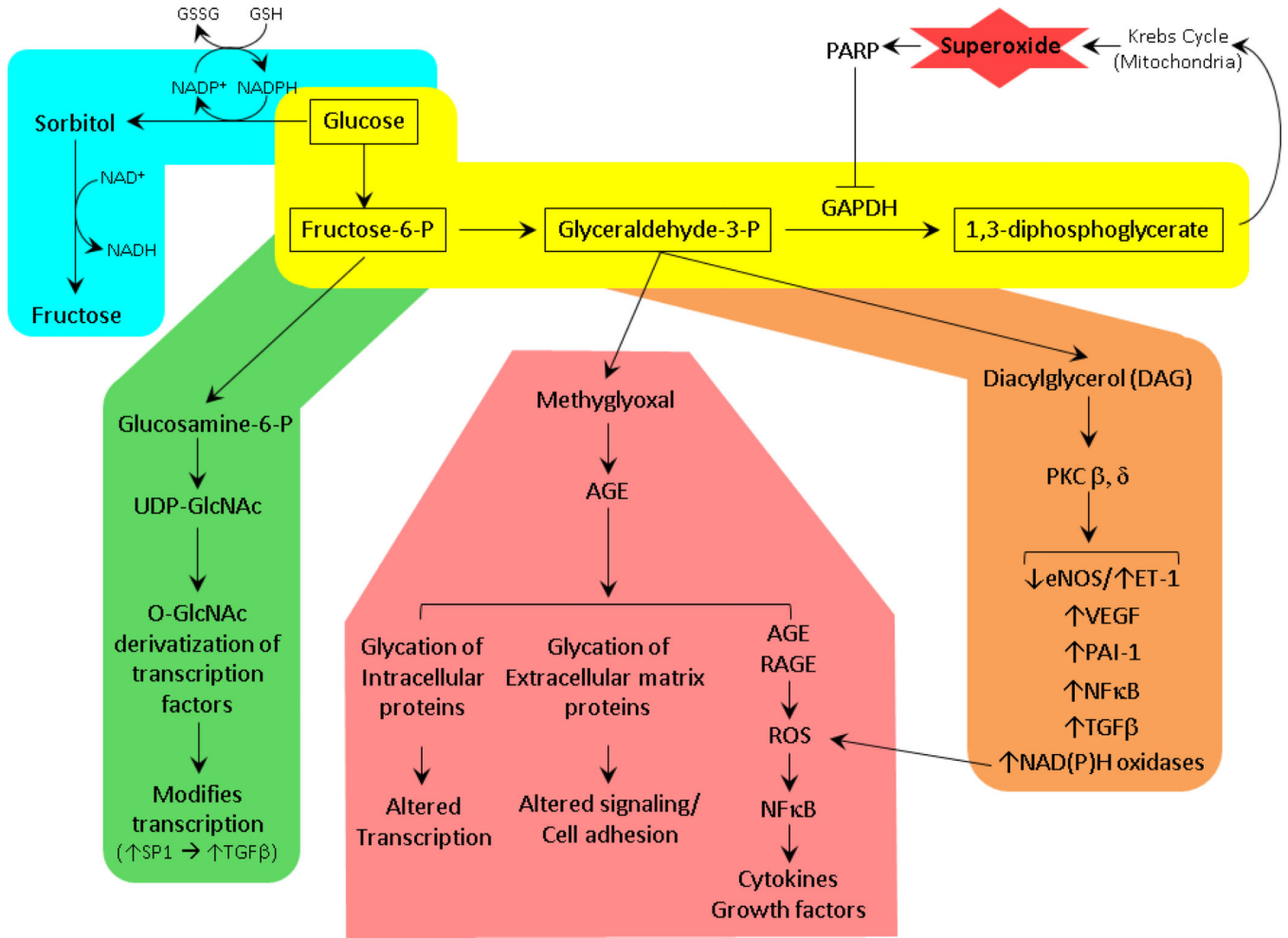


### Key summary points

- In 2009, diabetes affected more than 190,000 children and adolescents in the US, where its prevalence is projected to increase two-folds or more by 2050.
- Majority (75–95%) of proteinuria in children and adolescents is due to benign causes (orthostatic and transient proteinuria), which have to be ruled out before further evaluation for micro- or macroalbuminuria.
- Using random albumin or protein to creatinine ratio may overestimate albuminuria in younger, smaller and female children, where timed urine albumin excretion may be more appropriate.
- Microalbuminuria, defined as a urine albumin excretion of 30–299 mg/day (or albumin to creatinine ratio 30–299 mg/g), is the earliest available sign of predisposition to DKD. Microalbuminuria can regress, remain unchanged or progress to macroalbuminuria.
- Risk factors for microalbuminuria are high A1c, blood pressure, LDL, triglycerides, high normal urine albumin excretion, obesity and smoking. Microalbuminuria is more likely to regress with improved control of risk factors (A1c, blood pressure, smoking cessation).
- Macroalbuminuria, a urine albumin excretion  $\geq$  300 mg/day or albumin to creatinine ratio  $\geq$  300 mg/g, signals more severe kidney injury, but is also more likely to progress slowly with control of risk factors (A1c, blood pressure, smoking).
- Significant DKD can be present even in absence of elevated urine albumin excretion, emphasizing the need for optimal risk factor control even in absence of albuminuria.
- Earliest DKD structural changes in the kidneys appear as early as 1.5–5 years after type 1 diabetes onset.
- Historically, type 1 diabetes was the predominant form of diabetes in children and adolescents. With the rise of childhood obesity, prevalence of type 2 diabetes has increased to 23% of cases of diabetes in the US children and adolescents, and 34–80% of diabetes among US ethnic minorities.
- Young onset type 2 diabetes is associated with more co-morbidities and risk factors, faster progression of DKD and other complications and higher mortality than type 1 diabetes and may be more aggressive and treatment resistant than type 2 diabetes in adults.



**Figure 1.** The classic course of diabetic kidney disease (DKD) natural history. Classic DKD is thought to begin with rise of urine albumin excretion, initially to microalbuminuria (lower dashed red line), then proceed to macroalbuminuria (upper dashed line), with glomerular filtration rate (GFR) dropping only after macroalbuminuria.



**Figure 2.** Schematic of the unifying theory connecting hyperglycemia to distal pathophysiologic mechanisms via elevated intracellular superoxide. Hyperglycemia increases mitochondrial superoxide generation which activates PARP. PARP inhibits GAPDH by ADP-ribosylating it. Inhibition of GAPDH leads to buildup of preceding glycolytic intermediates which feed into and activate the four primary (diabetic kidney disease) DKD pathophysiologic pathways, the polyol (blue), the Hexosamine (green), the AGE (pink) and PKC (orange). These pathways in turn trigger several distal cascades, upregulating expression of effector proteins such as components of the renin-angiotensin system and TGF-β