DIABETIC NEPHROPATHY

Dr Mohamad Ahangar Davoodi
Pediatric Endocrinologist
Department of Pediatric,
Arak University of Medical Sciences

PREVALENCE

- Diabetic nephropathy affects 20–30% of patients with T1DM and 15–20% of T2DM patients 20 yr after onset.
- The increased mortality risk in long-term T1DM may be due to nephropathy, which may account for approximately 50% of deaths.
- The risk of nephropathy increases with duration of diabetes (up until 25-30 yr duration, after which this complication rarely begins), degree of metabolic control, and genetic predisposition to essential hypertension.
- Overt DN is exceptionally rare before puberty and is uncommon even in teens with long-standing diabetes.

PATHOPHYSIOLOGICAL CHANGES IN DN

- glomerulopathy associated with diffuse or nodular glomerulosclerosis (Kimmelsteil-Wilson lesion).
- hyperplasia or hypertrophy of various cell types of the glomerulus and tubules, thickening of glomerular and tubular basement membranes, and expansion of tubulointerstitial and mesangial compartments.

PATHOPHYSIOLOGICAL CHANGES IN DN

- The development of proteinuria is associated with morphological changes in podocytes.
- important changes; including the tubules, interstitium, medulla, and papilla.
- hyperglycemia disturbs the homeostasis of blood flow and vascular permeability in the glomerulus.
- accumulation of advanced glycation end products (AGEs).
- Low-grade inflammation via activation of cytokines, such as TGF-ß.

Stage 1 (hyperfiltration stage):

- increase in glomerular filtration rate (GFR)
- increased capillary glomerular pressure.
- correlation between elevated GFR and later development of proteinuria

Stage 2 (silent stage):

- absence of overt evidence of renal dysfunction with maintenance of GFR and lack of albuminuria.
- Renal morphological studies demonstrate significant structural changes (basement membrane thickening and mesangial expansion)

Stage 3 (microalbuminuric stage):

- urinary albumin excretion rate 20 to 200 mcg/min or 30 to 300 mg/24 hours.
- Persistent microalbuminuria (two occasions 3 to 6 months apart).
- Microalbuminuria is considered as the earliest marker of the development of DN (early lesions in both glomerular and tubular structures).
- Microalbuminuria at the higher end of the normal range at the age of 10 to 16 years is associated with an increased risk of progression to microalbuminuria and future cardiovascular disease risk, independently of HbA1c.
- The reversal of microalbuminuria; glycemic control is appropriate; and systolic blood pressure, serum cholesterol, and triglyceride levels are in the normal range.

Stage 4 (macroalbuminuria stage):

- urinary albumin excretion rate greater than 300 mg/24 hours (200 mcg/min).
- strongly predictive of subsequent progress to renal failure, if left untreated.

Stage 5 (renal impairment):

- end-stage renal disease(uremia, the nephritic syndrome, and the need for renal replacement (transplantation or dialysis). can occur in up to 40% of T1D patients.

Screening for Microalbuminuria

- The earliest clinical marker of DN is microalbuminuria.
- Albumin/creatinine ratio (ACR) 2.5 to 25 mg/mmol or 30 to 300 mg/g (spot urine) in males and 3.5 to 25 mg/mmol or 42 to 300 mg/g in females (easiest method : First-voided urine in the morning)
- Or
- Albumin excretion rate (AER) between 20 and 200 mcg/min (30 and 300 mg/24 h) in 24 hours or timed urine collections.
- microalbuminuria is confirmed by finding two or all of three samples abnormal over a 3 to 6 month period.

TABLE 21.12 Screening Recommendations and Risk Factors for Vascular Complications in Children and Adolescents With Type 1 Diabetes Mellitus

	Initiation of Screening	Screening Methods	Risk Factors
Nephropathy	11 years with 2–5 years of diabetes	Urinary albumin/ creatinine ratio	Hyperglycemia High BP Lipid abnormalities Smoking
Nephropathy	At puberty or age ≥ 10 yr whichever comes first, if T1DM ≥ 5 yr	Annually	Albuminuria; urine albumin to creatinine ratio

Screening for Microalbuminuria

- false positive (increased ACR/AER) tests:

  strenuous exercise, infections, nondiabetic kidney disease (IgA or other types of nephritis, urinary tract infections), marked hyperglycemia, fever, and menstrual bleeding, marked hypertension, heart failure.

- Timed overnight or 24-hour collections are more burdensome and generally do not enhance accuracy or prediction of DN.

Antihypertensive therapy

- Effective antihypertensive therapy in patients with nephropathy prolongs the time to end-stage renal disease.
- Hypertension in children is defined as blood pressure equal to or above the 95th percentile for age, sex, and height, whereas in adolescents (age 13 years), it is defined as systolic blood pressure 130 and/or diastolic blood pressure 80.
- Elevated blood pressure (previously known as prehypertension) is defined as blood pressure over the 90th percentile for age, sex, and height, or from the age of 13 years, as blood pressure between 120 to 129/80 mmHg.
- should have elevated blood pressure confirmed on 3 separate days.
- Confirmation of hypertension may be assisted by 24-hour ambulatory blood pressure measurements.

Antihypertensive therapy

- lifestyle interventions encompassing dietary modifications and moderate to vigorous physical activity at least 3 to 5 days per week (30–60 minutes per session).
- If target BP is not reached within 3 to 6 months of initiating lifestyle intervention, pharmacological treatment.
- Pharmacological treatment of hypertension in children and adolescents should be initiated with an angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), longacting calcium channel blocker, or a thiazide diuretic.

Antihypertensive therapy

- ACE inhibitors are recommended for use in children and adolescents with hypertension and albuminuria
- ARB can be used if the ACE inhibitor is not tolerated because of side effects (cough, hyperkalemia, headache, and impotence).
- The goal of treatment is blood pressure consistently under the 90th percentile for age, sex, and height.
- reduce progression from microalbuminuria to macroalbuminuria and increase the regression rate to normoalbuminuria.

TABLE 21.13 Recommended Threshold Values for Intervention and Primary Prevention of Microvascular and Cardiovascular Disease in Children and Adolescents With Type 1 Diabetes

Threshold Value	Intervention
BP >90th percentile for age, gender and height	Lifestyle intervention: exercise, less screen time and diet
BP >90th percentile despite lifestyle intervention	ACE inhibitor or other BP lowering agent If microalbuminuria is present: ACE inhibitor or ARB
BP >95th percentile for age, gender and height	Lifestyle intervention and ACE inhibitor or other BP lowering agent If microalbuminuria is present: ACE inhibitor or ARB
LDL cholesterol >2.6 mmol/L (100 mg/dL)	Dietary and lifestyle intervention
LDL cholesterol >3.4 mmol/L (130 mg/dL) and one or more CVD risk factors	Statins

ACE, Angiotensin-converting enzyme; *ARB*, angiotensin II receptor blocker; *BP*, blood pressure; *CVD*, cardiovascular disease; LDL, low-density lipoprotein.
(Modified from Donaghue, K.C., et al. (2018). ISPAD Clinical Practice

<table>
<tr><td>Target HbA1c</td><td colspan="4">HbA1c <53 mmol/mol (<7.0%)
This target must be individualized with the goal of achieving a value as close to normal as possible while avoiding severe hypoglycemia, frequent mild to moderate hypoglycemia, and excessive stress/burden for the child with diabetes and their family.
Factors that must be considered when setting an individualized target include, but are not limited to:
Access to technology, including pumps and CGM
Ability to articulate symptoms of hypoglycemia and hyperglycemia
History of severe hypoglycemia/hypoglycemic unawareness
History of compliance with therapy
Whether child is a high or low glycator
Whether child has continued endogenous insulin production (e.g. in the new onset or “honeymoon” period of diabetes)</td></tr>
<tr><td rowspan="4">Glycemic Targets</td><td></td><td>NICE goal A1c ≤48 mmol/mol (≤6.5%) [107]</td><td>ISPAD goal A1c <53 mmol/mol (<7%)</td><td>ADA goal A1c <58 mmol/mol (<7.5%)[121]</td></tr>
<tr><td>Pre-meal</td><td>4.0-7.0 mmol/L (70-126 mg/dl)</td><td>4.0-7.0 mmol/L (70-130 mg/dl)</td><td>5.0-7.2 mmol/l (90-130 mg/dl)</td></tr>
<tr><td>Post-meal</td><td>5.0-9.0 mmol/L (90-162 mg/dl)</td><td>5.0-10.0 mmol/L (90-180 mg/dl)</td><td></td></tr>
<tr><td>Pre-bed</td><td>4.0-7.0 mmol/L (70-126 mg/dl)</td><td>4.4-7.8 mmol/L (80-140 mg/dl)</td><td>5.0-8.3 mmol/L (90-150 mg/dl)</td></tr>
</table>

Preventation of DN

(1) meticulous control of hyperglycemia

(2) aggressive control of systemic blood pressure

(3) Angiotensin-Converting Enzyme Inhibitors (thus decreasing transglomerular capillary pressure)

(4) dietary protein restriction (because high protein intake increases the renal perfusion rate).

- Previous extensive therapy of diabetes (Tight glycemic control) has a persistent benefit for 7-8 yr and may delay or prevent the development of diabetic nephropathy.

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