DEFINITIONS

- Metabolic disorder of multiple causes characterized by chronic hyperglycemia and disorders of carbohydrate, fat, and protein metabolism
- Results from defects in insulin secretion (type 1), insulin action (type 2), or combination of these factors
- World Health Organization and American Diabetes Association diagnostic criteria:
  - Fasting plasma glucose ≥126 mg/dL (≥7.0 mmol/L) or fasting whole-blood glucose level ≥110 mg/dL (≥6.1 mmol/L), or a
  - 2-hour post–glucose-load plasma glucose ≥200 mg/dL (≥11.1 mmol/L; 180 mg/dL [10.0 mmol/L] if whole blood), or a
  - Random plasma glucose >200 mg/dL (>11.1 mmol/L) on >1 occasion
  - “Prediabetic” stage: fasting plasma glucose between 100 and 126 mg/dL (5.6 and 7.0 mmol/L) increasingly recognized as risk factor for end-organ complications; evidence supports lifestyle interventions to prevent or delay onset of diabetes

INCIDENCE

- 18.2 million people in United States have diabetes (National Health and Nutrition Examination Survey 1999 to 2000), and up to one third of these cases are undiagnosed
- Approximately 1 in 400 to 500 children and adolescents have type 1 diabetes
- With increases in obesity rates in adolescents, type 2 diabetes becoming common, especially in minority groups
- 8.7% of adults have diabetes; rate increases to 18% of adults aged ≥60 years
- By 2030, anticipate 366 million cases of type 2 diabetes worldwide and 30 million US cases

RISK FACTORS FOR DEVELOPMENT

**Type 1 diabetes**

- Defined by autoimmunity; autoantigens include islet-cell proteins, glutamic acid decarboxylase, insulin, and proinsulin
- Viral infections may initiate a poorly understood immune response, which induces β-cell damage
- Genetics/family history:
  - Lifetime risk for 1 monozygotic twin is 20% to 30% if the other has diabetes
  - 18 different risk alleles have been identified

**Type 2 diabetes**

- Environment:
  - Most patients are overweight or obese, suggesting role for environmental factors, especially “Westernization” of diet with highly processed foods high in fat and simple sugars
- Genetics/family history:
  - High degrees of concordance within families and between twins
  - Single gene mutations have been identified for multiple mature-onset diabetes of the young (MODY) phenotypes

ADDITIONAL READING

DIABETIC NEPHROPATHY (DN): GENERAL

Definition
- Progressive decline in glomerular filtration rate (GFR) in context of long-standing diabetes, usually accompanied by nephrotic-range proteinuria and other end-organ complications, such as retinopathy

Stages
- Normoalbuminuria with elevated GFR (within 5 to 10 years):
  - Usually associated with glomerular and tubular hypertrophy and enlarged kidneys on ultrasound evaluation
  - Hyperfiltration may be maladaptive
- Microalbuminuria/incipient diabetic nephropathy (within 5 to 15 years):
  - Defined as 30 to 300 mg albumin/g creatinine
  - May be measured quantitatively or semi-quantitatively with dipsticks
- Macroalbuminuria/overt proteinuria (10 to 20 years):
  - Defined as >300 mg albumin/g creatinine
  - Decline in GFR (15 to 25 years)
  - End-stage renal disease (ESRD) within 5 years of developing nephrotic-range proteinuria

Epidemiology
- DN remains leading cause of ESRD in United States:
  - In 2002, 45% of incident ESRD due to DN, resulting from increased prevalence of type 2 diabetes
  - 41% of prevalent ESRD from DN
- Incidence of DN in type 1 diabetic patients has been declining, which may be related to early and aggressive control of blood glucose and blood pressure
- Incidence of diabetic nephropathy from type 2 diabetes is variable, but probably increasing due to increased rates of obesity, metabolic syndrome, and type 2 diabetes

ADDITIONAL READING

DN PATHOLOGY

General
- Diabetic kidneys generally increased in size (between 10% and 30% above age-, sex-, and race-matched controls) on ultrasound and gross pathologic evaluation due to glomerular and tubular hypertrophy, rather than hyperplasia

Indications for Biopsy
- Accelerated disease kinetics compared with earlier description in “Diabetic Nephropathy: General” section
- Absence of extrarenal end-organ damage
- Concomitant nondiabetic lesions are rare, although higher incidences have been reported in selected populations characterized by atypical clinical presentations
Glomerular

- Glomerular basement membrane thickening:
  - May occur as early as 2 years after diabetes diagnosis
  - Irregular by electron microscopy, usually no glomerular basement membrane deposits
  - Subendothelial “hyaline caps” associated with progressive glomerular disease
- Podocyte numbers may decrease, with individual podocyte foot processes broadening to cover expanded surface area
- Mesangial matrix expansion (diffuse diabetic glomerulosclerosis) is most common lesion; hyalinization of parietal surface of Bowman capsule (capsular drop lesions) seen less commonly
- Kimmelstiel-Wilson nodules (nodular diabetic glomerulosclerosis): eosinophilic, at glomerular periphery
- Arteriolar hyalinosis; involves afferent and efferent arterioles, efferent hyalinization is relatively specific for DN

Tubulointerstitial

- Early cellular component, with tubular hypertrophy and decrease in ratio of capillaries to tubules
- Tubulointerstitial lesions (interstitial fibrosis and tubular atrophy) have been described, which correlates with degree of renal dysfunction and, by extrapolation, progression to ESRD

ADDITIONAL READING


RECOMMENDATIONS FOR DN SCREENING

Timing of Initial Screen

Type 1 diabetic patients

- In patients with appropriate glycemic control, initially screen 5 years after diabetes diagnosis
- Patients with risk factors for DN progression (see next section) should be screened earlier
- Onset of puberty is independent risk factor for DN, so adolescents should be screened at time of puberty

Type 2 diabetic patients

- At diagnosis, up to 7% of type 2 diabetic patients already have DN, which may reflect delay in diabetes diagnosis by 4 to 7 years
- Therefore, initially screen for DN upon diabetes diagnosis

Negative initial screen

- If initial screen is negative, annual screening should be followed

Urine Microalbuminuria

- Most accepted screening test
- Methods of microalbuminuria screening (composite based on American Diabetes Association and National Kidney Foundation guidelines):
  - Analysis of untimed “spot” samples is acceptable; first-morning-void specimens are preferred
  - Albumin excretion from 24-hour urine collection also acceptable, but cumbersome and often inaccurate due to inadequate collection
  - Patients can be screened with microalbuminuria dipsticks, but require subsequent
quantitative assay for correlation after positive dipstick reading

- Albuminuria screening should not be performed when patients have acute conditions that may independently increase urinary albumin excretion, such as:
  - Urinary tract infection
  - Acute illness, especially with fever
  - Recent heavy exercise
  - Hypertensive urgency/emergency
  - Hyperglycemia

**GFR Estimates**

- Useful for staging and therapeutic plans
- Creatinine clearance from 24-hour urine collection has been standard until recently; however, as with quantitative albuminuria, timed collections are cumbersome and often inaccurate
- GFR estimate from equations is preferred alternative, and current recommendations are that equations based on Modification of Diet in Renal Disease (MDRD) study should be used rather than Cockcroft-Gault equation; however, MDRD equation may underestimate GFR in normal range
- Because equations are based on serum creatinine values, calibration of serum creatinine assays to national reference standard is important

**ADDITIONAL READING**


**RISK FACTORS FOR DN PROGRESSION**

**Hyperglycemia**

- Diabetes Control and Complications Trial (DCCT):
  - Intensive glucose control decreased incidence of microalbuminuria and macroalbuminuria among type 1 diabetic patients
- Epidemiology of Diabetes Intervention and Complications (EDIC):
  - Follow-up of DCCT cohort that showed that initial tight glucose control had sustained benefit on incidence of microalbuminuria years later
- UK Prospective Diabetes Study Group (UKPDS):
  - In type 2 diabetic patients, hemoglobin A1c (HgbA1c) <7.0% associated with decreased risk for microvascular complications and progression of diabetic nephropathy

**Hypertension**

- Common in diabetic patients, even without documented renal disease; prevalence increases with declining GFR
- Systolic blood pressure predicts DN progression
- UKPDS: Reduced risk for microalbuminuria in type 2 diabetic patients with blood pressure <140/80 mm Hg
Proteinuria

- In type 1 diabetes, increased baseline urinary albumin excretion, even within normal range, is risk for micro- and macroalbuminuria in type 1 diabetes
- In type 2 diabetic patients, initial hyperfiltration predicted micro- and macroalbuminuria, which was followed by gradual GFR decline
- Conversely, some studies have shown that microalbuminuria is poor predictor of DN progression in diabetes types 1 and 2
- Macroalbuminuria is strong predictor of DN progression in diabetes types 1 and 2

Family History/Genetic Predisposition

- Substantial evidence for familial predisposition to DN in diabetes types 1 and 2
- Studies containing large numbers of well-phenotyped patients are underway to identify DN susceptibility genes

Male Sex

- Independent risk for DN progression, although mechanism is unclear

Risks for CKD Progression, May Apply to DN

- Hyperlipidemia
- Tobacco use:
  - Risk for microalbuminuria in diabetes types 1 and 2
  - Longitudinal studies show relationship with CKD progression
- Decreased birth weight:
  - Associated with decreased nephron number, earlier onset, and more rapid progression of nephropathy

ADDITIONAL READING


**STRATEGIES FOR PREVENTING/SLOWING DN PROGRESSION**

**Glucose Control**
- Multiple intervention trials show benefit of maintaining HgbA1c <7.0%
- Multiple agents may be effective:
  - Insulin—DCCT and EDIC:
    - Of the diabetes regimens, best evidence for preventing nephropathy with insulin
  - EDIC study demonstrated sustained benefit of glucose control in decreasing micro- and macroalbuminuria, as well as new development of hypertension
- Thiazolidinediones:
  - May be beneficial for decreasing albuminuria in type 2 diabetic patients
  - May cause fluid retention in subjects with decreased left ventricular ejection fraction
- Metformin:
  - Excellent for glucose and lipid control
  - Use with caution in diabetic subjects with chronic kidney disease because of case reports of metformin-induced fatal metabolic acidosis
- Insulin half-life is prolonged with decreased GFR, so dosing of all agents should be adjusted in renal dysfunction to avoid hypoglycemia

**Blood Pressure Control**
- 130/80 mm Hg is reasonable goal, but may require 3 to 4 drugs
- Substantial data showing benefit of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) for DN progression:
  - Recent comparison of ACE inhibitors and ARBs suggests that these agents have equivalent long-term benefits in early DN (GFR ≥70 mL/min [≥1.17 mL/s])
  - In ACE inhibitor– and ARB-treated patients, serum potassium and creatinine should be closely monitored for 2 to 3 months; if documented stable renal function, annual monitoring of electrolytes is appropriate
  - If patients start on nonsteroidal anti-inflammatory drugs, develop a state of hypoperfusion, or demonstrate progressive GFR decline from DN, more frequent monitoring of electrolytes and creatinine is appropriate
  - Serum creatinine increase of 30% above baseline (after institution of blood pressure control) that subsequently stabilizes in a period of 2 to 3 months predicts improved long-term outcome
  - UKPDS—β-blocker as effective as ACE inhibitor

**Lipids**
- Treatment with statins to achieve low-density lipoprotein cholesterol <100 mg/dL (<2.59 mmol/L), or <70 mg/dL (<1.81 mmol/L) for patients with cardiovascular disease history

**Dietary Protein Restriction**
- Controversial
- Difficult to achieve without comprehensive dietary team
Weight Loss

- Improves insulin sensitivity, potentially slows DN progression

Smoking Cessation

ADDITIONAL READING


RENAAL study

- Diabetic patients are fastest growing proportion of ESRD population
- Mortality rate for diabetic ESRD patients remains very high, mainly related to cardiovascular disease
Hemodialysis versus peritoneal dialysis:
- Relative mortality data remain controversial
- No clear benefit of 1 modality versus another

Hemodialysis:
- Long-term economic and morbidity benefits of native vein arteriovenous fistula > graft > catheter
- Diabetic patients have significantly worse vascular access–related outcomes:
  - Significantly greater primary arteriovenous fistula rates have been achieved in diabetic patients with coordinated approach
  - Requires appropriate referral, preaccess planning (vein preservation, venous mapping), and collaboration with skilled surgeon
  - Centers for Medicare and Medicaid Services has launched “Fistula First” campaign to achieve Kidney Disease Outcomes Quality Initiative recommendation of arteriovenous fistulas in 50% of incident dialysis patients
- Achievement of national guidelines for access outcomes often requires a multidisciplinary team approach

Transplantation
- Patients with DN progression should receive education regarding benefits of transplantation and timely referral for evaluation
- Survival rates and quality of life for transplantation recipients superior to that for other forms of renal replacement therapy
- Kidneys from living-unrelated donors have similar functional outcomes to deceased donor organs:
  - Increased potential pool of donors may assist with current long waiting times
- Economic benefits to kidney transplantation
- Pancreas transplant for type 1 diabetes
- Potential for resolution of diabetic nephropathy, retinopathy, and improvement in cardiovascular outcomes

Potential for recurrent DN with poor glycemic control

ADDITIONAL READING