

CORE CURRICULUM IN NEPHROLOGY

Diabetes and the Kidney

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DIABETES

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

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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

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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

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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

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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

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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 A_{1c} (HgbA_{1c}) <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

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STRATEGIES FOR PREVENTING/SLOWING DN PROGRESSION

Glucose Control

- Multiple intervention trials show benefit of maintaining $HgbA_{1c} < 7.0\%$
- 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

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RENAL REPLACEMENT THERAPY IN DN

- 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, pre-access 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

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