

INSIDE THIS ISSUE

- 2 Evaluation of Diabetic Gastrointestinal Dysmotility
- 4 Glucocorticoid-Induced Diabetes Mellitus
- 5 Diabetic Nephropathy: Update on Diagnosis and Treatment

Diabetic Retinopathy

Diabetic retinopathy affects more than 5.3 million persons age 18 years and older in the United States. Steven A. Smith, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: "Epidemiologic studies looking at the major risk factors for diabetic retinopathy have shown a consistent association between retinopathy and duration of diabetes mellitus, degree of hyperglycemia, and presence of hypertension, hyperlipidemia, pregnancy, and renal disease. The less consistent risk factors for diabetic retinopathy are obesity, cigarette smoking, moderate alcohol consumption (more than 1 alcohol-containing beverage per day), and lack of physical activity."

John M. Pach, MD, of the Department of Ophthalmology at Mayo Clinic in Rochester, explains: "Most patients with diabetes mellitus have some degree of diabetic retinopathy after having diabetes for 20 years.

Diabetic retinopathy is divided into 2 types—nonproliferative and proliferative.

The term *proliferative retinopathy* [Figure 1] refers to retinal neovascularization from ischemia.

Nonproliferative changes [Figure 2] occur before the onset of neovascularization due to increased capillary permeability and ischemia. The typical fundus findings are

microaneurysms and hemorrhages. The retinal hemorrhages, depending on their location, take a dot-blot or flame-shaped appearance. As vascular permeability increases, retinal edema may ensue. Lipoproteins may precipitate out, giving the appearance of hard exudates. Infarctions of the nerve fiber layer may also occur, producing the appearance of cotton-wool spots. As the background retinopathy increases in severity, more numerous retinal hemorrhages are seen, along with irregularity of the veins or venous beading."

In patients with background diabetic retinopathy, the leading cause of decreased visual acuity is macular edema. Dr Pach notes: "Diabetic macular edema can be categorized as focal or diffuse. *Focal diabetic macular edema* refers to leakage primarily from microaneurysms. Diffuse diabetic macular edema is due to increased widespread leakage from the capillary bed. As retinal ischemia increases, vascular endothelial growth factor is upregulated, which promotes retinal neovascularization. Although neovascularization may occur in the iris or the trabecular meshwork and thus result in neovascular glaucoma, the primary location of the neovascularization is on the retinal surface.

"The natural history of retinal neovascularization is for continued growth and fibrosis. As the vitreous contracts, it may cause the sites of neovascularization to bleed. Typically, the hemorrhage occurs in the vitreous, causing such symptoms as floaters and the appearance of cobwebs. As the neovascularization progresses, fibrosis develops. The increasing retinal neovascularization and fibrosis may exert tractional forces on the retina. When this traction overcomes the adhesive force of the retina to the retinal pigment epithelium, a traction retinal detachment occurs. Once the macula is detached, visual acuity is poor."

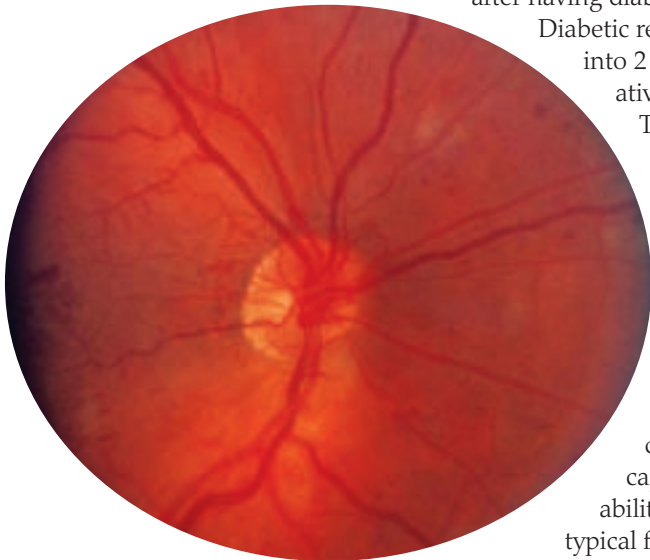


Figure 1. Proliferative retinopathy. Color fundus photograph of proliferative diabetic retinopathy shows neovascularization.

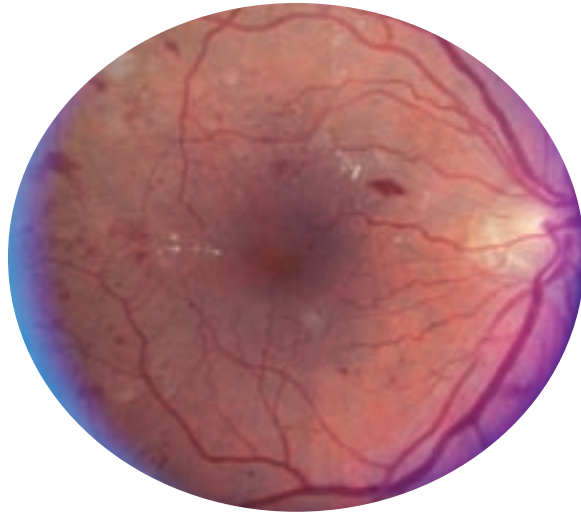


Figure 2. Nonproliferative retinopathy. Color fundus photograph of nonproliferative diabetic retinopathy shows retinal hemorrhages, yellow lipid exudates, and cotton-wool spots.

Eye-Directed Treatment

The mainstay of treatment for diabetic macular edema and proliferative diabetic retinopathy is laser photocoagulation. Dr Pach highlights: “Prompt treatment is recommended when eyes have high-risk characteristics of proliferative disease. Panretinal photocoagulation in eyes with high-risk characteristics decreases by approximately 60% the risk of severe visual loss. For an eye that does not have the high-risk characteristics, panretinal photocoagulation may still be recommended, depending on the condition of the other eye, as well as the documented progression of the retinopathy. Focal laser photocoagulation for clinically significant diabetic macular edema decreases the risk of moderate



John M. Pach, MD, and Steven A. Smith, MD

visual loss by 50%. Such photocoagulation is most effective in patients with focal or multifocal leakage primarily from microaneurysms.”

Dr Pach continues: “Diffuse macular edema, due to leaking primarily from parafoveal capillaries, may suggest an underlying systemic condition. Often, patients with this type of edema have hypertension, congestive heart failure, or renal disease as a contributing factor. Normalization of blood pressure or diuresis may improve diabetic macular edema.”

Control of Systemic Factors

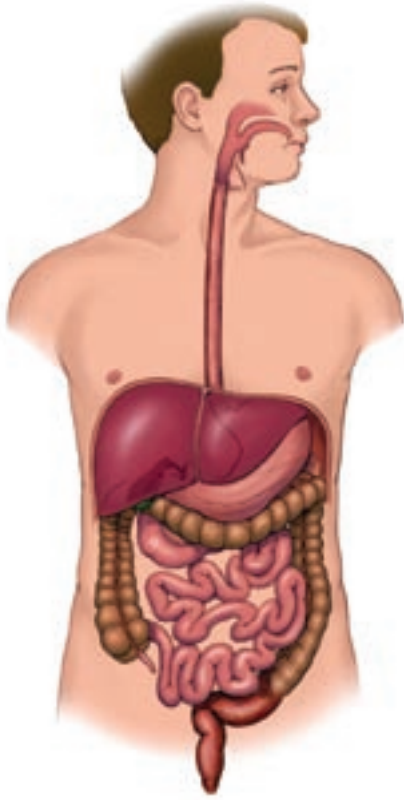
Dr Smith says: “There is strong evidence in the medical literature showing that the lowering of hemoglobin A_{1c} levels to approximately 7.0% is advantageous in reducing the onset and progression of diabetic retinopathy. Similarly, evidence shows that a decrease in systolic or diastolic blood pressure, or both, is advantageous in reducing the development and progression of diabetic retinopathy. Aggressive lowering of total cholesterol and triglyceride levels may cause regression of the exudates.”

Evaluation of Diabetic Gastrointestinal Dysmotility

Gastrointestinal symptoms are commonly reported in people with diabetes mellitus. Adrian Vella, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: “Approximately 75% of patients referred to a diabetes clinic have at least 1 gastrointestinal symptom. However, such symptoms should not be ascribed to diabetes without appropriate evaluation.” The most common gastrointestinal symptoms and complications related to diabetes are listed in Boxes 1 and 2. Gastrointestinal symptoms



Adrian Vella, MD, and Gianrico Farrugia, MD



may also be due to the increased prevalence of certain gastrointestinal diseases in patients with diabetes (Box 3).

Etiologic Factors of Gastrointestinal Symptoms in Diabetes Mellitus

Gianrico Farrugia, MD, of the Division of Gastroenterology and Hepatology at Mayo Clinic in Rochester, says: "The etiologic characteristics of gastrointestinal symptoms in patients with diabetes are multifactorial. Similar to damage caused by peripheral neuropathy, there is evidence that damage to the extrinsic innervation of the gastrointestinal tract occurs in diabetes. However, many patients have gastrointestinal symptoms without extrinsic neuropathy. There is increasing evidence of damage to the enteric nervous system in diabetic gastroenteropathy. Neuronal nitric oxide expression in enteric neurons is markedly decreased early in the course of diabetic gastroenteropathy. Although neuronal apoptosis is increased, most of the decrease in neuronal nitric oxide is not accompanied by neuronal loss; neuronal nitric oxide expression can be restored by decreasing oxidative stress and by using insulin.

"The interstitial cells of Cajal (ICC), together with enteric nerves and smooth muscle cells, are required for normal gastrointestinal motility. The ICC pace smooth-muscle function, amplify neuronal signals, act as mechanosensors, and set the smooth muscle membrane potential. Both

Box 1. Gastrointestinal Symptoms in Diabetes Mellitus

- Heartburn
- Nausea
- Vomiting
- Abdominal pain
- Diarrhea
- Constipation
- Fecal incontinence

Box 2. Gastrointestinal Complications of Diabetes Mellitus

- Esophageal dysmotility
- Gastroparesis
- Decreased accommodation/rapid gastric emptying
- Bacterial overgrowth
- Diabetic diarrhea
- Colonic dysmotility
- Anorectal dysfunction

Box 3. Diseases of the Gastrointestinal Tract Associated With Diabetes Mellitus

- Celiac disease
- Microscopic colitis
- Fatty liver
- Hepatitis C

human studies and animal models show loss of ICC in gastroparesis and diabetes-associated constipation. Reversal of this deficit in animals normalizes gastric emptying, suggesting that the loss of ICC is central to the development of motor abnormalities."

Evaluation and Diagnosis

Dr Vella explains: "In all evaluations of gastrointestinal symptoms that may be attributable to diabetes, a thorough history and physical examination should be the starting point. Nausea, vomiting, early satiety, and abdominal pain are the commonest symptoms in patients with gastroparesis. Evaluation should include an assessment of medications that may be contributing to symptoms, a complete blood cell count, the serum thyrotropin concentration, and

a metabolic panel. A test for blood amylase concentration and a pregnancy test may be relevant. Mechanical causes need to be excluded with endoscopy of the upper gastrointestinal tract or an upper-gastrointestinal series; if results are normal, then a gastric-emptying study should be obtained. Gastroduodenal manometry may also be necessary. If the history and the findings on the physical examination suggest general autonomic dysfunction (eg, abnormal pupil responses, abnormal sweating, urinary retention, or impotence), strong consideration should be given to autonomic nervous system evaluation, including cardiovascular responses to posture, thermoregulatory, and nerve conduction testing.”

For symptomatic diarrhea, drug-related causes need to be excluded (Box 4). Dr Farrugia notes: “Bacterial overgrowth associated with small-bowel dysmotility, microscopic colitis, and celiac disease is more common in patients with diabetes than in other patient groups, and the initial presentation may be diarrhea. Therefore, blood tissue transglutaminase concentration, small-bowel biopsy (if tissue transglutaminase level is abnormal), small-bowel aspirate for bacterial culture (or equivalent testing), and random colonic biopsies may be required. Sphincter tone should be assessed by anorectal manometry.

“If the presenting symptom is constipation, a medication and exercise history should be obtained, as well as serum calcium and thyro-

Box 4. Causes of Diarrhea in Diabetes Mellitus

- Medications (eg, metformin, acarbose, miglitol)
- Artificial sweeteners
- Rapid intestinal transit
- Bacterial overgrowth
- Celiac disease
- Pancreatic insufficiency
- Microscopic colitis
- Sphincter dysfunction
- Diarrhea not associated with diabetes

pin concentrations. Patients who are due for colon cancer screening should be evaluated with colonoscopy. Colonic transit tests and anorectal manometry with balloon expulsion help differentiate between normal transit constipation (most common), slow transit constipation, and pelvic floor dysfunction.”

Treatment options for patients with diabetic gastrointestinal dysmotility will be reviewed in Volume 4, Issue 3, of Mayo Clinic *Endocrinology Update*.

Glucocorticoid-Induced Diabetes Mellitus

The mechanism of glucocorticoid-induced diabetes mellitus is multifactorial. Pankaj Shah, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: “Glucocorticoids induce hepatic and extrahepatic insulin resistance. Glucocorticoid treatment impairs both glucose transport in fat and muscle cells and the ability of glucose to stimulate its own utilization (glucose effectiveness), as well as reducing glucose clearance. These agents have direct harmful effects on insulin-secreting beta cells of the pancreatic islets by inducing apoptosis. In addition, hyperglycemia induced by glucocorticoids is associated with reduced GLUT-2 expression and a decrease in glucose transport into the beta cells. Also, glucocorticoids can increase appetite and weight.”

Glucocorticoid use is associated with increased concentrations of fasting and postmeal insulin and glucagon. Dr Shah notes: “As long as compensatory insulin release is adequate for the prevailing glucose concentration, hyperglycemia does not occur because the higher insulin level adequately suppresses glucose production and stimulates glucose utilization. The risk of glucocorticoid-induced diabetes increases with the glucocorticoid dosage, duration of therapy, advanced patient age, family history of diabetes mellitus, obesity, certain ethnicity/race,



Pankaj Shah, MD

and high blood glucose concentrations before glucocorticoid therapy. The glycemic effect of glucocorticoid use also depends on the route of administration and the type of glucocorticoid.”

Therapeutic Considerations

Management strategies for glucocorticoid-induced diabetes or for the glucocorticoid-induced worsening of diabetes mellitus have not been systematically studied in prospective trials. Dr Shah outlines: “We advise all patients to avoid both overeating and consuming concentrated sweets (eg, fruit juices and other drinks with simple carbohydrates, cakes, cookies, pies, or donuts). Restricting fatty foods is also helpful in restricting calories. We emphasize that *sugar-free* does not always mean carbohydrate-free, *fat-free* does not necessarily

suggest that a food is low in sugar or low in calories, and a *diabetic* label does not always mean that a food is low in calories. Low-calorie sweeteners often help improve the taste of sodas, baked goods, and candies. Other effective tips include increasing consumption of fiber to approximately 25 to 30 g per day. The importance of physical activity is always stressed.

“Our general approach to pharmacologic therapy is outlined in the Table. The most important goal of therapy for hyperglycemia induced by glucocorticoids is to prevent acute hyperglycemic complications, as well as serious adverse effects from therapy. It is generally believed that a glucose concentration less than 180 mg/dL for most of the day will prevent infections associated with hyperglycemia.”

Table. Approach to the Treatment of Patients With Glucocorticoid-Induced Hyperglycemia

- **All patients**
 - Diet: Avoid overeating and consuming concentrated simple carbohydrates
 - Exercise: Regular but as tolerated and the maximum possible for up to 150 min per week
 - Self-monitoring of blood glucose concentrations: Frequency depends on type and stability of the treatment regimen
- **Patients with mild hyperglycemia (all blood glucose concentrations <200 mg/dL)**
 - First-line treatment: metformin^a (at the maximum tolerated dose, up to 2 g/day)
 - Second-line treatment: sulfonylureas,^{a,b} meglitinides,^{a,b} or thiazolidinediones^{a,c}
 - Third-line treatment: single-dose neutral protamine Hagedorn (NPH) insulin
- **Patients with fasting glucose concentration in goal but other glucose concentrations ≥200 mg/dL^{d,e}**
 - NPH insulin or premixed (with rapid-acting insulin) insulin once a day; start at a generous dose (eg, 0.2-0.4 units/kg per day)
 - May need another dose of rapid-acting insulin with evening meal if bedtime blood glucose concentrations are high
- **Patients with fasting and daytime blood glucose concentrations ≥200 mg/dL^e**
 - Treat these patients like any patient who newly requires insulin but at a much higher starting dosage (eg, 0.6-0.8 units/kg per day)
 - Patients often require a much larger proportion of their insulin as prandial doses

^a May be contraindicated in patients with other comorbidities.

^b Hypoglycemia is a real danger with this treatment, especially for sick patients whose food intake and physical activity are erratic.

^c Weight gain and fluid retention may be problematic; long-term use of these agents may have an impact on bone health.

^d These patients should take no NPH insulin at bedtime if fasting blood glucose concentrations are under control.

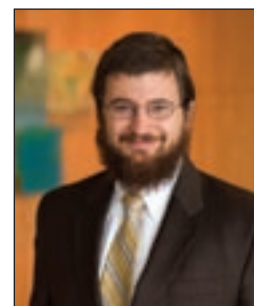
^e Avoid “sliding scale only” protocols with these agents; patients should not take rapid-acting insulin at bedtime unless blood glucose concentrations are very high (eg, >350 mg/dL).

Diabetic Nephropathy: Update on Diagnosis and Treatment

The annual costs (direct and indirect) related to diabetic nephropathy in the United States total \$174 billion. Dr Axel Pflueger, of the Division of Nephrology and Hypertension at Mayo Clinic in Rochester, Minnesota, says: "Patients with diabetes are the fastest-growing group of renal dialysis and transplant recipients. Diabetic nephropathy is associated with a high cardiovascular mortality rate. About 40% of patients with diabetes will have diabetic nephropathy if they do not die prematurely of cardiovascular disease. Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) worldwide. However, the growth in the number of patients with ESRD exceeds the kidney donor pool. Screening for diabetic nephropathy is imperative and should be started early."

The cumulative incidence of increased urinary albumin excretion is 50% over a lifetime of diabetes mellitus (both type 1 and type 2). Dr Pflueger explains: "The course of urinary albumin excretion follows 1 of 3 paths: it returns to normal in one-third of cases; its increased level persists in one-third; and it progresses to

frank proteinuria in one-third. Almost all patients with diabetes who have nephrotic-range proteinuria (>3 g protein/24 hr) will eventually have ESRD if they do not die prematurely of cardiovascular disease. Diabetic nephropathy



Axel Pflueger, MD, PhD

has several phenotypes, and many diabetic patients present with a decreased glomerular filtration rate and minimal or absent albuminuria, in contrast to the classic presentation of diabetic nephropathy." The 5 stages of diabetic nephropathy are shown in the Figure.

Dr Pflueger emphasizes: "Studies show that intensified therapy for diabetic nephropathy decreases progression and cardiovascular death. The primary intervention is treatment with an angiotensin-converting enzyme inhibitor or an angiotensin II receptor blocker, or both, with

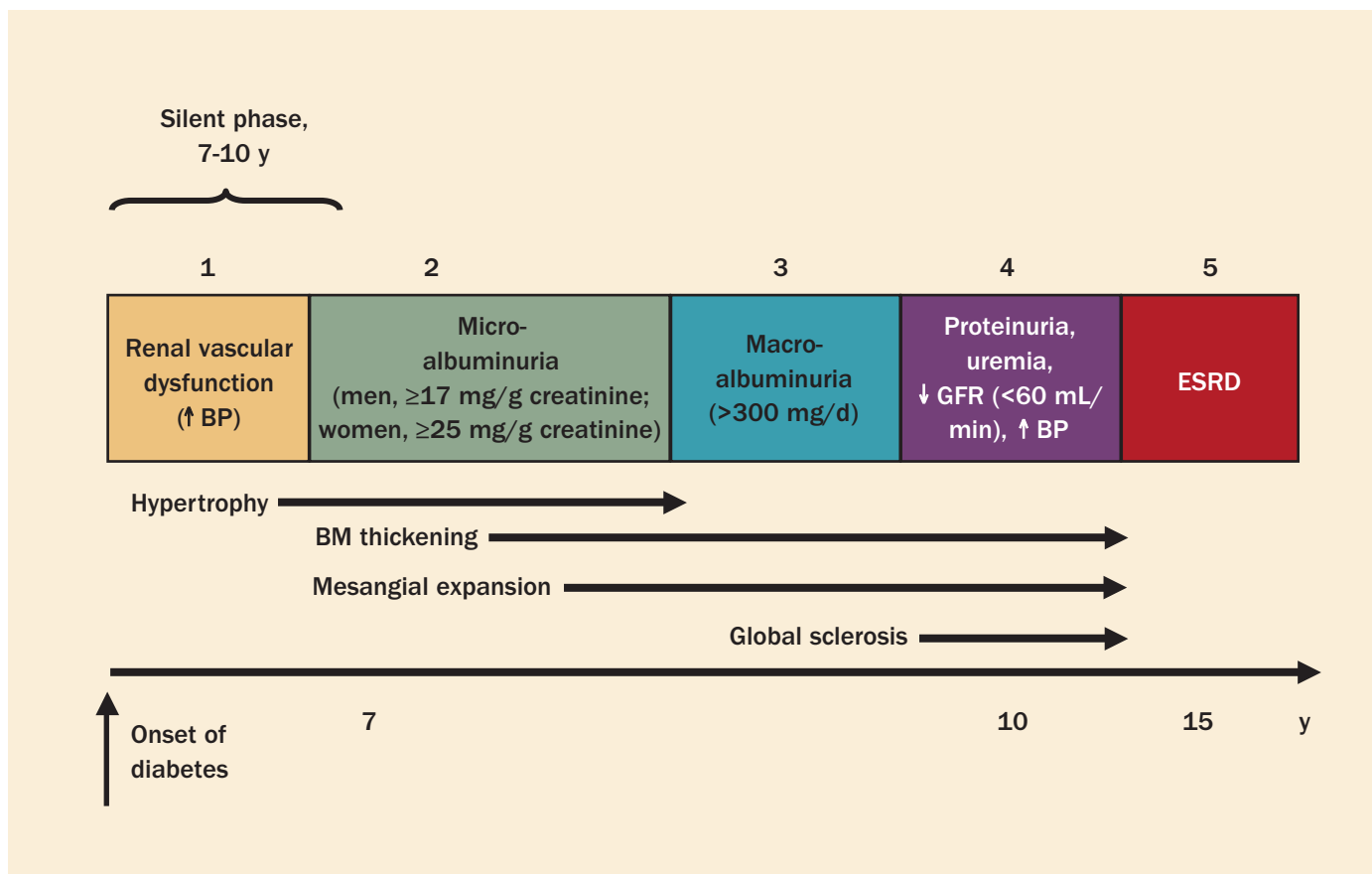


Figure. The 5 Stages of Diabetic Nephropathy.

Abbreviations: BM, basement membrane; BP, blood pressure; ESRD, end-stage renal disease; GFR, glomerular filtration rate.

proteinuria treatment goals of less than 17 mg/g creatinine in men and less than 25 mg/g creatinine in women. The renal function goal is to limit the glomerular filtration rate decline to less than 2 mL/min per year.”

Adjunctive cardiorenal protective therapy is also key to successful outcomes. Dr Pflueger highlights: “The target for hypertension management should be blood pressure less than 130/80 mm Hg. Dietary protein should be restricted to 0.6 to 0.8 g/kg per day; dietary salt should be restricted to less than 2 g per day. Glycemic control should be optimized, with a target hemoglobin A_{1c} value of 7.0% or less. Anemia should be corrected, with a target hemoglobin concentration of 11 to 12 g/dL. If the concentration of calcium-to-phosphate product is increased, it should be corrected. The target value for low-density lipoprotein cholesterol should be less than 100 mg/dL. Antiplatelet therapy with aspirin is indicated, and smoking cessation is mandatory. Body weight

goal should be at the calculated ideal body weight. Patients should be advised to avoid nonsteroidal anti-inflammatory drugs and other potential nephrotoxic substances, and medication use should be reviewed for dosing appropriate to kidney function. Furthermore, preventive-prophylactic measures for the prevention of acute kidney injury, such as contrast medium-induced acute kidney injury, should be implemented. The importance of regular cardiovascular exercise should be emphasized, with a target of a 45-minute duration 4 or 5 times weekly.”

Future pharmacologic therapeutic options may include pyridoxamine dihydrochloride, 25-hydroxyvitamin D, statins, aliskiren, AST-120, protein kinase C inhibitors (eg, ruboxistaurin), pirfenidone, connective tissue growth factor inhibitor FG-3019, and lactobacillus. However, trials are ongoing, and most of these agents are not yet available for evidence-based therapy.

2009 Graduating Clinical Endocrinology Fellows



Left to right (and upcoming appointment): Elizabeth G. Chittilapilly Haglind, MD (HealthEast Care System, St. Paul, Minnesota); Airani Sathananthan, MD (Western University of Health Sciences, Pomona, California); Kimberly A. Placzowski, MD (Aurora Clinic, Sheboygan, Wisconsin); Sumit Bhagra, MBBS (Mayo Health System, Austin and Albert Lea, Minnesota); A. Reagan Schiefer, MD (Premier Medical Group, Jackson, Mississippi); and Neena Natt, MD, Program Director, Clinical Fellowship in Endocrinology, Diabetes, Metabolism, and Nutrition.

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