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Inside This Issue

Exenatide, a New Treatment for Type 2 Diabetes: What the Clinician Should Know

Glucagon-like peptide-1 (GLP-1) is an incretin hormone released by the gastrointestinal tract in response to nutrient ingestion. Although it has a short half-life in the circulation (secondary to its rapid inactivation by dipeptidyl peptidase IV [DPP IV]), it is a potent insulin secretagogue. GLP-1 also inhibits glucagon secretion and delays gastric emptying. Unlike other secretagogues, GLP-1 stimulates insulin secretion in a glucose-dependent fashion (ie, insulin secretion is stimulated only in the presence of hyperglycemia, therefore minimizing the risk of hypoglycemia). Adrian Vella, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, notes, "When combined with the ability to delay gastric emptying, GLP-1–based therapy seems an ideal remedy for postprandial hyperglycemia. In addition, short-term GLP-1 administration has been shown to restore insulin secretion in patients with type 2 diabetes for whom treatment with oral hypoglycemic agents has failed." Consequently, various compounds have been developed that act as GLP-1 receptor agonists or inhibit GLP-1 breakdown by DPP IV, thereby raising endogenous GLP-1 concentrations.

Exenatide (Byetta; Amylin Pharmaceuticals, Inc, San Diego, California) is the first GLP-1–based therapy to gain US Food and Drug Administration approval and has been marketed since June 1, 2005. It is a naturally occurring analogue of GLP-1 that acts as a GLP-1 receptor agonist. Because it is resistant to inactivation by DPP IV, it has a half-life of about 2 hours, as opposed to the 5 to 10 minutes of native GLP-1. Exenatide occurs naturally in the saliva of the Mexican beaded lizard *Heloderma horridum* and related species of large reptiles (eg, the iguana and Komodo dragon), where it may regulate satiety. Various trials in humans have demonstrated that this compound is a powerful insulin secretagogue. It also suppresses glucagon secretion and delays gastric emptying. There is evidence of decreased appetite with accompanying weight loss in patients treated with exenatide.

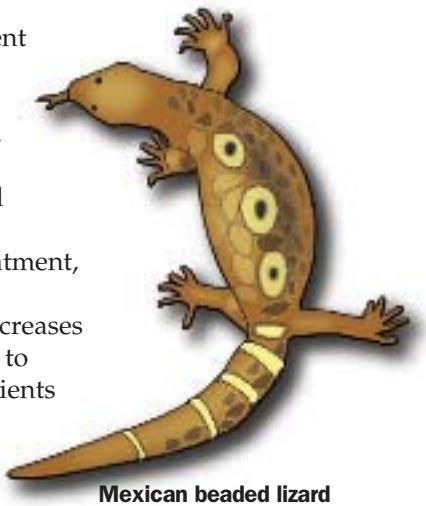
Adrian Vella, MD

Treatment with exenatide is recommended as adjunctive therapy for patients with type 2 diabetes mellitus who have not achieved adequate glycemic control with metformin, a sulfonylurea, or both. It is administered by subcutaneous injection 30 to 60 minutes before the morning and evening meals. The initial recommended starting dose is 5 μg administered subcutaneously twice daily, but this can be increased to 10 μg twice daily, depending on effect and how well the initial dose is tolerated.

Dr Vella cautions, "Adverse events are related to the drug's effects on gastrointestinal motility (or perhaps direct effects on the hypothalamus), with symptoms such as early satiety, epigastric fullness, gastrointestinal reflux, nausea, and vomiting. Most of these symptoms are mild and resolve over time, but this is not always the case. Patients with delayed gastric emptying may be more likely to develop these symptoms, and patients with known gastroparesis should not be treated with this compound." Drug interactions arise from the delayed absorption secondary to prolonged gastric emptying that this drug engenders. However, in clinical trials, no effect on lipid profiles or blood pressure was observed in patients treated with statins and antihypertensive agents, respectively.

Exenatide does not cause hypoglycemia

because of the glucose-dependent nature of its effect on insulin secretion. However, when exenatide is used as an adjunct to sulfonylurea treatment, the incidence of hypoglycemia increases considerably; up to about 40% of patients self-reported hypoglycemia in this setting. In contrast, the incidence of hypoglycemia when exenatide was used with metformin did not differ from placebo. There are no data on its safety in pregnancy, and the compound has not been approved for use in combination with thiazolidinediones, with insulin, or as montherapy. The glucose-lowering effect of this medication translates into about a 1% decrease in hemoglobin A_{1c} (similar in magnitude to other classes of agents used to treat diabetes).



Mexican beaded lizard (*Heloderma horridum*)

When should GLP-1 receptor agonists be used? Who would benefit from treatment with exenatide as opposed to insulin? The answers to these questions are likely to be a subject of debate for some time to come. Dr Vella says, "Our current practice has been to use insulin with or without an insulin sensitizer when secondary failure has occurred. However, without extensive dietary modification, patients tend to gain weight and are at risk of hypoglycemia. The latter may affect the ability of patients to maintain their occupational status and lifestyle. Theoretically, GLP-1 receptor agonists are superior to conventional treatment in people who are at risk of hypoglycemia or who are unwilling or unable to check their blood glucose on a regular basis." Patients who are at risk of excessive weight gain with improved glycemic control may also benefit from exenatide use.

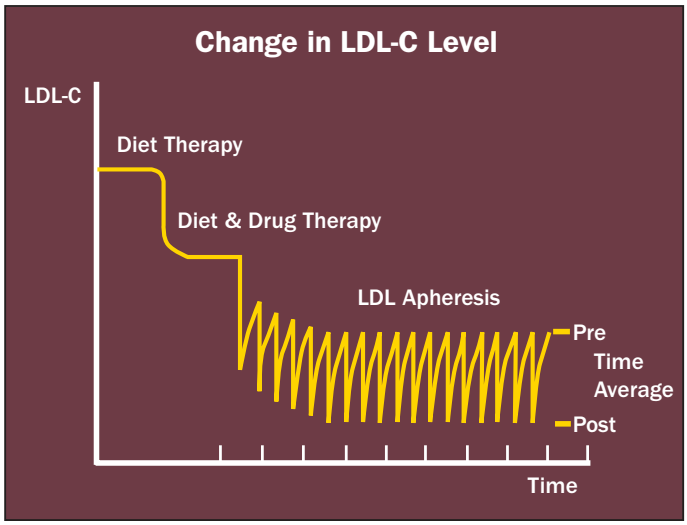
According to Dr Vella, "At present, we recommend that exenatide should not be used as a first-line agent for the management of diabetes or excess weight in diabetic patients, but it should be reserved for patients whose oral therapy with a sulfonylurea or metformin or a combination of the two has failed."

When Lipid-Lowering Agents Fail: Low-Density Lipoprotein Cholesterol Apheresis

"Low-density lipoprotein cholesterol apheresis is a treatment technique used to remove LDL-C from a patient's blood," says Ananda Basu, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester. Whole blood is pumped from a patient into an instrument that separates it into the cellular components and plasma. The cellular components are returned to the patient, while the plasma is pumped through a column that binds the LDL-C. The cleansed plasma is then returned to the patient. When the column becomes saturated, flow is switched to a second column while the first column is regenerated and made available to treat more plasma. The US Food and Drug Administration (FDA) has approved LDL-C apheresis for the following categories of indications:

- Category A: LDL-C ≥500 mg/dL in patients with homozygous familial hypercholesterolemia
- Category B: LDL-C ≥300 mg/dL despite maximum tolerated diet and drug therapy
- Category C: LDL-C ≥200 mg/dL in patients with coronary heart disease despite maximum tolerated diet and drug therapy
- Category D: None of the above; category used when the physician believes this procedure is

Ananda Basu, MD, and Jeffrey L. Winters, MD



appropriate despite the absence of Category A, B, or C criteria

"We use a dextran sulfate cellulose absorption system for LDL-C apheresis," says Jeffrey L. Winters, MD, of the Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester. This system has a high selectivity for apolipoprotein B–containing lipoproteins through an electrostatic interaction between apo B and dextran sulfate. It is effective in those patients with familial defective apo B-100 and removes LDL-C, lipoprotein (a), and very low-density lipoprotein (VLDL). This LDL-C apheresis system has also been used in cardiac transplant patients with graft atherosclerosis.

According to Dr Basu, "LDL-C apheresis is typically administered every 2 weeks, and each session lasts 2½ to 3½ hours. The frequency of apheresis may be modified on the basis of interindividual variability in LDL-C response. LDL-C apheresis is used in addition to maximally tolerated oral therapy between apheresis treatments to reduce the rate of interval rise in LDL-C. LDL-C apheresis is effective in lowering serum concentrations of LDL-C, lipoprotein (a), and VLDL approximately 70% to 80% from baseline. There are little or no effects on high-density lipoprotein cholesterol, albumin, or immunoglobulin levels."

Because heparin is used during apheresis, LDL-C apheresis is contraindicated in patients who have a heparin allergy or have had surgery recently. In addition, hypotension due to bradykinin release can occur in 1% to 2% of patients, and angiotensin-converting enzyme (ACE) inhibitors should be withdrawn 1 to 2 days before the procedure. Hemolysis and angina complicate 0.1% of all apheresis procedures.

In a 6-year study of patients with coronary artery disease, LDL-C apheresis resulted in regression of angiographic lesions, decreased the frequency of angina, and reduced coronary events. Potential future uses of LDL-C apheresis include treatment of peripheral vascular disease and corticosteroid-resistant nephrotic syndrome due to focal segmental glomerulosclerosis.

When considering patients for possible LDL-C apheresis at Mayo Clinic, Dr Basu advises that patients should:

- Meet FDA-approved categories for apheresis
- Be willing to travel for apheresis every 2 weeks
- Understand that they will be enrolled in a FDA-approved registry and that the Mayo Foundation Institutional Review Board has approved the protocol
- Be seen by selected physicians in the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic before commencement of apheresis
- Visit with the staff at the Therapeutic Apheresis Unit to work out a schedule and to check status of vascular access. A proportion (about 15%) of patients may need to have an arteriovenous fistula placed in the arm by a vascular surgeon before initiation
- Be followed at regular intervals in the Mayo Clinic Division of Endocrinology, Diabetes, Metabolism, and Nutrition

This patient undergoes LDL-C apheresis every 2 weeks at Mayo Clinic in Rochester.

Vitamin D Deficiency—A New Understanding

Daniel L. Hurley, MD, and Ravinder J. Singh, PhD

"Vitamin D deficiency has been an underrecognized problem in the past because of suboptimal assays and an inappropriately low 'normal range' for blood vitamin D concentrations. With modern assays, very low (eg, ≤15 ng/mL) serum 25-hydroxyvitamin D (25-OH-D) concentrations have been reported in 20% to 50% of housebound elderly residents, 44% of ambulatory elderly women, 30% of women older than 70 years with osteoporosis, 23% of patients presenting with hip fracture, and 57% of all hospitalized adults," says Daniel L. Hurley, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester.

Exposure to UV-B radiation (sun exposure or UV-B tanning) converts 7-dihydrocholesterol to vitamin D_3 in the skin. Dietary sources of vitamin D include plant-derived ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3) from animal and fish oils. Circulating vitamin D is then hydroxylated in the liver to 25-hydroxyvitamin D_2 (25-OH-D_2) and D_3 (25-OH-D_3). The most common causes of vitamin D deficiency are inadequate sun exposure and diminished intake of vitamin D–fortified foods. Dietary sources of vitamin D in nonfortified foods are limited and often do not provide the necessary daily requirement. Disease-related causes of vitamin D deficiency include gastrointestinal malabsorption, defective liver 25-hydroxylase activity, and renal insufficiency. Both aging and renal insufficiency (glomerular filtration rate <30 mL/min) are associated with diminished renal 1α-hydroxylase activity required to convert 25-OH-D to the more active 1,25-dihydroxyvitamin D [1,25-$(OH)_2$D].

Clinical Presentation of Vitamin D Deficiency

Vitamin D promotes intestinal calcium absorption, bone matrix mineralization, and normal muscle function. Consequences of vitamin D deficiency include secondary hyperparathyroidism (HPT), osteoporosis, osteomalacia (rickets in children), and myopathy. Clinical symptoms of vitamin D deficiency include muscle fatigue and weakness, diffuse myalgias, abnormal gait, and bone pain. Dr Hurley notes, "The clinical recognition of vitamin D deficiency may be difficult. Vitamin D deficiency should be considered in patients who present with diminished bone density, skeletal fracture, fibromyalgia-like symptoms, and unexplained fatigue or muscle weakness. An elevated serum bone (or, less specific, total) alkaline phosphatase is an early biochemical finding in patients with vitamin D deficiency." The biochemical changes that may be seen at different stages of vitamin D deficiency are shown in the table.

Measurement of Vitamin D

Serum 25-OH-D has a half-life of about 1 month and is produced in proportion to the amount of sun exposure and vitamin D ingested. Thus, serum 25-OH-D is the preferred test to measure nutritional status and body stores of vitamin D. Serum levels of 1,25-$(OH)_2$D may be normal in patients with vitamin D deficiency due to secondary HPT and is of little help in the diagnosis of vitamin D deficiency. Serum 25-OH-D concentrations less than 25 ng/mL are associated with an increased risk of secondary HPT, bone loss, and fractures. At Mayo Clinic, the 25-OH-D analysis is performed using liquid chromatography–tandem mass spectrometry (LC-MS/MS).

"Deuterated stable isotope of 25-OH-D is added to a 0.2-mL serum sample as an internal standard. 25-OH-D_2, 25-OH-D_3, and the internal standard are extracted using acetonitrile precipitation. The extracts are then further purified online and analyzed by LC-MS/MS using multiple reaction monitoring as shown in the figure. Serum levels of 25-OH-D_2 and 25-OH-D_3 are quantified and reported both individually and as a sum (total 25-OH-D_2 and 25-OH-D_3)," says Ravinder J. Singh, PhD, of the Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester. The Mayo Medical Laboratory vitamin D assay report lists total serum 25-OH-D reference ranges as follows:

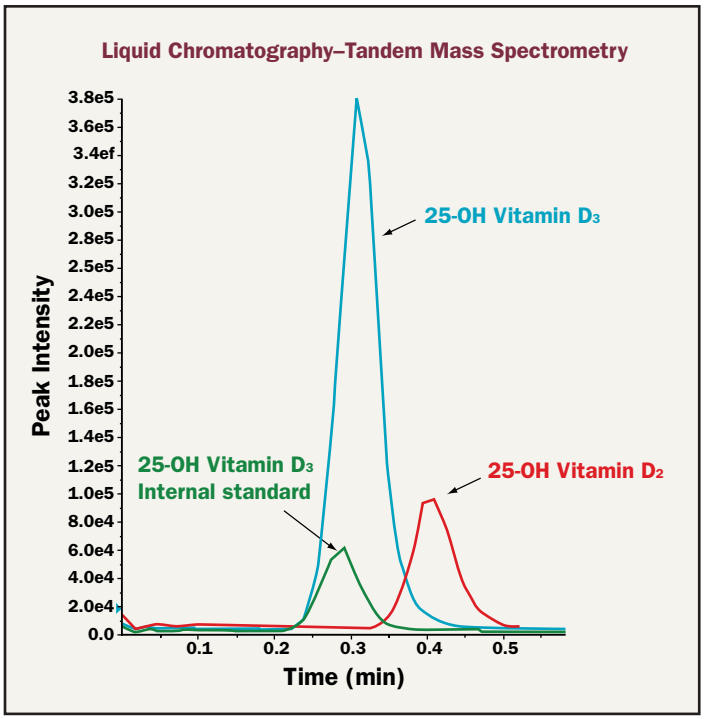
- <10 ng/mL: severe deficiency (may be associated with osteomalacia or rickets)
- 10-25 ng/mL: mild to moderate deficiency (may be associated with increased risk of osteoporosis or secondary HPT)
- 25-80 ng/mL: optimum levels in the normal population

• >80 ng/mL: toxicity possible

These reference ranges represent clinical decision values that apply to males and females of all ages, rather than population-based reference values. Population-based reference ranges for 25-OH-D vary widely, depending on ethnic background, age, geographic location of the studied populations, and the sampling season. A total serum 25-OH-D concentration of 80 ng/mL is the lowest reported level associated with toxicity in patients without primary HPT who have normal renal function. Most patients with toxicity have total serum 25-OH-D concentrations higher than 150 ng/mL. Patients with renal failure can have very high 25-OH-D levels without any signs of toxicity because renal conversion to the active hormone 1,25-$(OH)_2D$ is impaired or absent.

Treatment of Vitamin D Deficiency

Secondary HPT is very rare when serum 25-OH-D concentrations are 30 ng/mL or higher, suggesting that this level should be the minimal goal of vitamin D therapy. However, marked variability for vitamin D assays has been demonstrated between laboratory measurements. As a result, a "universal" definition of an "optimal" serum 25-OH-D concentration is not possible, and whether an individual 25-OH-D level is low or normal may be a function of the laboratory method used. Thus, serum parathyroid hormone (PTH) and bone alkaline phosphatase measurements may be indicated in patients to ensure appropriate "hormone feedback" by documenting normal blood levels, and thus adequate vitamin D stores.



25-hydroxyvitamin D (25-OH-D) assay by liquid chromatography and tandem mass (LC-MS/MS) spectrometry. The total 25-OH-D level reported from a blood sample is determined by the amount of 25-OH-D_2 (ergocalciferol) and 25-OH-D_3 (cholecalciferol) present in the blood sample. LC-MS/MS spectrometry reports both the total 25-OH-D concentration and individual D_2 and D_3 concentrations. This is accomplished by separating 25-OH-D_2 (red line) and 25-OH-D_3 (blue line) using an internal standard (green line) and quantifying the amount of vitamin D_2 and vitamin D_3 by measuring the area under the curve of each peak concentration. For example, a patient with short bowel syndrome and malabsorption is taking one 50,000-IU capsule of ergocalciferol (vitamin D_2) by mouth once a week. The vitamin D assay reports 25-OH-D_2 <4 ng/mL; 25-OH-D_3 at 23 ng/mL; and total 25-OH-D at 23 ng/mL (optimal range, 25-80 ng/mL). Thus, the patient is absorbing none of the oral ergocalciferol (vitamin D_2), and the total 25-OH-D concentration is attributable to sunlight conversion of skin cholesterol to vitamin D_3.

Assessing Vitamin D Deficiency Biochemical Changes

	25-OH-D	sCa	sPhos	uCa	PTH	BAP
Early (hypervitaminosis D)	↓	↓–N	N	↓	N–↑	N–↑
Mid (secondary HPT)	↓↓	N	↓–N	↓↓	↑↑	↑↑
Late (osteomalacia)	↓↓↓	↓	↓	↓↓↓	↑↑↑	↑↑↑

Key: ↑↓, below or above normal (N) range; 25-OH-D, 25-hydroxyvitamin D; sCa, fasting serum calcium; sPhos, fasting serum phosphorus; uCa, urinary calcium; PTH, parathyroid hormone; BAP, bone alkaline phosphatase.

The Recommended Daily Intake for vitamin D is 400 IU, but this amount was clinically established in the 1940s and is inadequate for many persons. A total daily vitamin D intake of 1,000 IU has been recommended to meet bodily needs, and an intake of 1,000 to 2,000 IU has been reported to be safe, without causing hypercalciuria and hypercalcemia. Vitamin D can be provided as a daily multivitamin (400 IU) and as daily (400 to 1,000 IU) or intermittent (50,000 IU once weekly to once monthly) supplementation of vitamin D_2 or D_3 based on individual need and response to therapy. Poor clinical improvement, persistently low 25-OH-D levels, and lack of reduction in blood concentrations of PTH and bone alkaline phosphatase may indicate patient noncompliance, malabsorption, resistance to 25-OH-D, or other contributing factors.

Cushing's Syndrome: The Role of Inferior Petrosal Sinus Sampling and Internal Jugular Vein Sampling

Dana Erickson, MD

Distinguishing between the causes of adrenocorticotropic hormone (ACTH)–dependent Cushing's syndrome is essential to direct appropriate treatment. The hypersecretion of ACTH that causes Cushing's syndrome is usually from a pituitary source, but in up to 20% of patients, it is from an ectopic source.

Dana Erickson, MD, of the Mayo Clinic Division of Endocrinology, Diabetes, Metabolism, and Nutrition in Rochester, notes, "Several reports have shown that the results of conventional endocrine and radiologic testing are often inconclusive in determining the source of ACTH in patients with Cushing's syndrome." Clinical history, dynamic biochemical tests (eg, dexamethasone suppression test, corticotropin-releasing hormone [CRH] stimulation test), MRI of the pituitary gland, and CT or MRI of the chest and abdomen aid in distinguishing between pituitary and ectopic ACTH production. However, not infrequently, the results of these studies are indeterminate. According to Dr Erickson, "In such cases, direct sampling of the pituitary venous effluent in the inferior petrosal sinus (IPS) for ACTH before and after CRH stimulation can help resolve the uncertainty by accurately revealing the location of ACTH production."

David F. Kallmes, MD, of the Department of Radiology at Mayo Clinic in Rochester, explains, "IPS sampling (IPSS) is based on the fact that pituitary venous blood drains into the cavernous sinuses, then into the inferior petrosal venous sinuses, and then into bilateral internal jugular veins. As a result of this, patients with pituitary-dependent Cushing's syndrome have central-to-peripheral venous gradient of ACTH concentration between one or both inferior petrosal sinuses and the peripherally measured ACTH." CRH is used during IPSS to overcome problems with pulsatile and spontaneous secretion of ACTH. The sensitivity and specificity of IPSS with CRH are 82% to 100% and 90% to 100%, respectively.

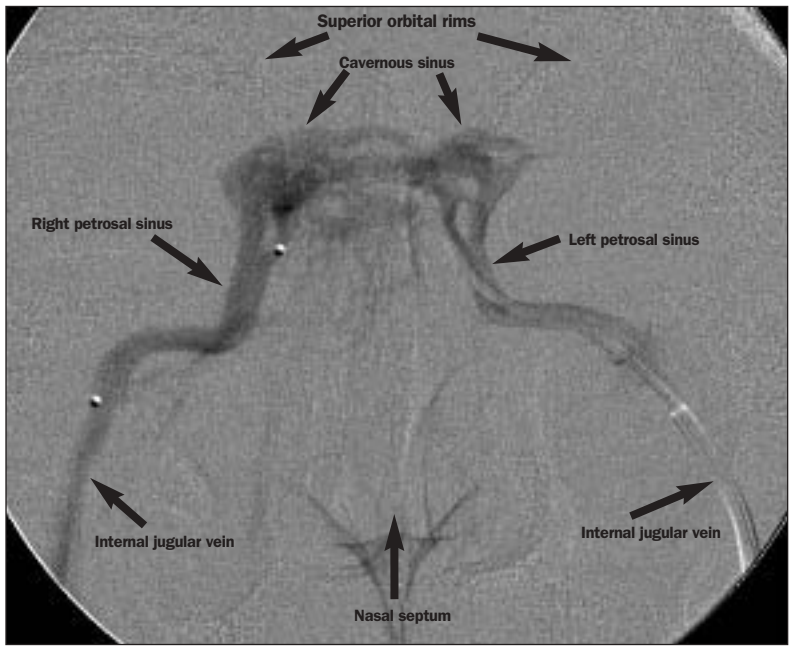
Harry Cloft, MD, PhD, of the Department of Radiology at Mayo Clinic in Rochester, says, "Catheterization of femoral veins is performed, and catheters are inserted into both inferior petrosal veins. It is extremely important that the radiologist is experienced so the proper location of the catheter is assured. A third intravenous catheter is placed in the peripheral vein. Blood samples for ACTH are drawn simultaneously from both IPS and peripheral vein. Plasma ACTH is measured 5 minutes and 1 minute before CRH stimulation and then 2, 5, and 10 minutes after CRH administration (1 μg/kg; maximum, 100 μg). Digital subtraction venography is performed at the end of IPSS to document the catheter position. A successful IPS catheterization is confirmed if the catheters do not move into other anatomic locations." An IPSS ratio of baseline central-to-peripheral ACTH of 2.0 or higher or post-CRH central-to-peripheral

David F. Kallmes, MD, and Harry Cloft, MD, PhD

ACTH ratio of 3.0 or higher is diagnostic of a pituitary source of ACTH.

Drainage of the pituitary gland has a tendency to lateralize, and therefore, the site of pituitary microadenomas can be predicted by using the interpetrosal gradient of ACTH. An interpetrosal gradient of more than 1.4 is correlated with the surgical location of the pituitary lesion in 70% of cases.

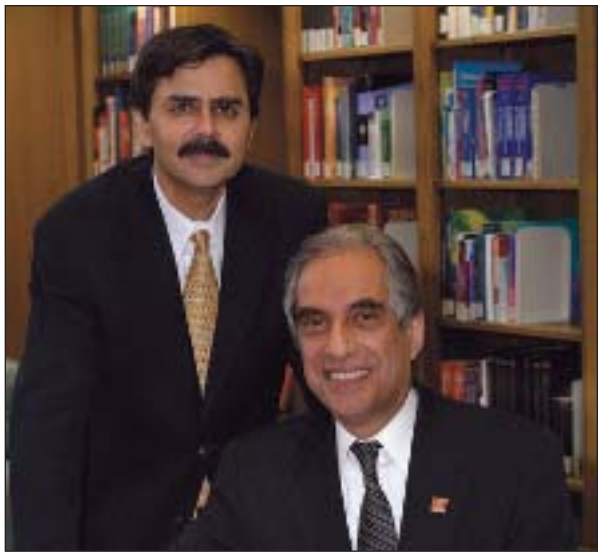
False-negative results can occur when there is an anomalous petrosal sinus on the same side as a pituitary microadenoma or if the catheter is displaced after the procedure. False-positive results have occurred in patients with periodic hormonogenesis and in patients with ectopic CRH syndrome. IPSS is invasive, and several severe complications have been reported in the literature. According to Dr Erickson, "In an effort to decrease the risk of central ACTH sampling, we performed internal jugular vein sampling (IJVS) for ACTH in 55 patients with ACTH-dependent Cushing's syndrome. Samples for ACTH levels from the IJV were obtained at the same time as for IPSS through microcatheters. Using a central-to-peripheral ACTH ratio for IJVS of 1.6 or higher at baseline or a post-CRH central-to-peripheral ACTH ratio of 2.5 or higher, we found the sensitivity and specificity of IJVS to be 87.5% and 75%, respectively. Since IJVS characteristics are inferior to those of IPSS, we use IJVS when IPSS is not technically feasible. In centers where there is not sufficient expertise with IPSS, IJVS could be performed, but again, positioning of the sampling catheters along the medial wall of the IJV is crucial to minimize the viscous blood streaming effect and to avoid sampling from the lateral aspect of IJV."



Anatomic relationships between cavernous sinuses, petrosal veins, and jugular veins are shown in this radiograph done during IPSS.

Chairs of National Endocrine Meetings

Sundeep Khosla, MD, is chair of the Annual Meeting Steering Committee for the 2006 Endocrine Society Annual Meeting. More than 6,000 attendees from more than 70 countries convene to learn the latest advances in endocrine research and clinical care. Hossein Gharib, MD, is dean of the American College of Endocrinology (ACE) Endocrine University held every March at Mayo Clinic in Rochester. The ACE Endocrine University curriculum provides endocrine-specific technology training (eg, thyroid ultrasonography, bone densitometry, office laboratory, insulin pumps) for endocrinology fellows in their last year of training.



Sundeep Khosla, MD, and Hossein Gharib, MD

Education Opportunities

Please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.html for more information about these courses or to register.

Mayo Clinic Nutrition in Health and Disease

This course will be held September 28-29, 2006, at the Minneapolis Marriott City Center in Minneapolis, Minnesota. The course will cover ambulatory and hospital nutrition topics.

10th Mayo Clinic Endocrine Course

The 10th Mayo Clinic Endocrine Course will be held March 19-23, 2007, on the Big Island of Hawaii. This course, created for endocrinologists and interested internists and surgeons, will present the latest material on the diagnosis and treatment of endocrine disorders. This 5-day course (7:30 AM to 12:30 PM daily) will span the full spectrum of endocrinology through short lectures, case-based debates, clinicopathologic sessions, clinical pearls sessions, and small group discussions with experts. The digital audience response system will be used extensively, and there will be many opportunities for interaction with the course faculty. An optional session on thyroid ultrasonography also will be offered.

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