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Inside This Issue

Hyperinsulinemic Hypoglycemia After Bariatric Surgery, A Newly Recognized Complication

Since the 2005 report of hyperinsulinemic hypoglycemia—occurring in the absence of a discrete islet cell tumor—after Roux-en-Y gastric bypass (RYGB) surgery, more cases have been recognized and independently reported in the literature. Adrian Vella, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, says: "Understandably, given the relatively short time since the disorder's description, there is limited understanding of its natural history, the use of diagnostic tests, and ideal therapy for the disorder. The original description of noninsulinoma pancreatogenous hypoglycemia syndrome by my colleague F. John Service, MD, PhD, also an endocrinologist at Mayo Clinic in Rochester, included some patients with a history of other upper gastrointestinal tract surgery such as Billroth I or II, Nissen fundoplication, antrectomy, pyloroplasty, and vagotomy. It is unclear whether hypoglycemia after bariatric surgery represents the same or a slightly different disorder. Much has been made of elevated incretin hormone concentrations (eg, GLP-1) after RYGB surgery—with speculation that this may underlie the β-cell hypertrophy/hyperplasia seen in this situation."

The incidence of obesity is increasing in the United States, and because of its association with medical illnesses that may improve or resolve with considerable weight loss, various surgical strategies, most recently RYGB, have been used. There are several possible complications related to bariatric surgery that are well known, namely, surgical complications and malabsorption. The postprandial hyperinsulinemic hypoglycemia complication after RYGB occurs within weeks to months postoperatively. The frequency of this complication is unknown.

Dr Service cautions: "In our experience, various symptoms in patients who have had RYGB surgery have been attributed to hypoglycemia without clear evidence that a hypoglycemic disorder is present. In addition, not all seizures that occur in patients who have undergone an RYGB procedure are hypoglycemic in origin. Also, we have evaluated patients with a hypoglycemic disorder in the presence of RYGB who have a history of symptoms that predate the surgery, and some are found to have an insulinoma."

Adrian Vella, MD, and Geoffrey B. Thompson, MD

Dr Vella explains: "The diagnosis of hyperinsulinemic hypoglycemia after RYGB surgery depends on documentation of hypoglycemia with accompanying symptoms of neuroglycopenia. Reflectance meter glucose measurement is not reliable in this setting and often provides misleading information. The importance of low blood glucose values after an oral glucose tolerance test (OGTT) in this setting is unclear. However, many patients who have asymptomatic low blood glucose during an OGTT do not have a hypoglycemic disorder, and this may also occur in patients who have had RYGB surgery—who are likely to have accelerated gastric emptying. Indeed, consumption of refined carbohydrates is likely to produce ill-defined symptoms in most patients after they have had RYGB surgery. In the absence of a documented episode of hypoglycemia, a mixed-meal test is often used to screen for this disorder. It is important that the

meal used—in an attempt to provoke symptoms—is representative of the appropriate diet for such patients and avoids caloric liquids or other foods containing simple sugars."

If hyperinsulinemic hypoglycemia is documented and other explanations—such as medication or exogenous insulin or sulfonylurea use—are conclusively excluded, further evaluation is required. Increasing experience with this disorder suggests that a clear spectrum of severity ranges from occasional mild symptoms (that are easily recognized and treated by the patient) to severe hypoglycemic episodes that greatly alter quality of life. Geoffrey B. Thompson, MD, of the Department of Surgery at Mayo Clinic in Rochester, says: "The extent of evaluation and subsequent therapy depend on the frequency and severity of symptoms. It is clear that there is a spectrum of severity, and some patients who have the disorder have mild or occasional symptoms that can be managed conservatively. Such patients may not be well served by undergoing invasive diagnostic procedures. In our practice, surgery is a treatment of last resort—reserved solely for those with profound life-threatening and life-altering symptoms, including seizures, and inability to drive, maintain a job, or care for their children.


F. John Service, MD, PhD

"Imaging studies of the pancreas are usually not revealing in a patient with hyperinsulinemic hypoglycemia after RYGB surgery. For example, in a patient who has had RYGB surgery, endoscopic ultrasonography cannot adequately and safely visualize the pancreas. Technical considerations, including residual obesity and overlying bowel gas, usually limit the usefulness of transabdominal ultrasonography. The confirmatory and localization test of choice in this clinical setting is the selective arterial calcium stimulation test (SACST). The SACST is used to document an abnormal pancreatic islet response to calcium and to localize the primary region or regions of pancreatic insulin hypersecretion. Insulin concentrations in the right hepatic vein after intra-arterial injection of calcium into the gastroduodenal, superior mesenteric, and splenic arteries can help guide pancreatectomy if this is deemed necessary—a treatment decision that should be based on symptom frequency, severity, and refractoriness to nonsurgical therapy."

Dr Thompson adds: "If partial pancreatectomy is necessary, an experienced surgeon is needed to perform major surgery in less than ideal circumstances (ie, a prior RYGB procedure). The whole pancreas must be inspected because, in a few cases, single or multiple islet tumors (staining for insulin) have coexisted with islet hyperplasia and hypertrophy. This operation is not without serious risk for complications, both short-term (pancreatic fistula, abscess, bleeding, and pulmonary embolism) and long-term (diabetes, malabsorption, vitamin deficiency). To this end, our group usually attempts strategies such as dietary manipulation or α-glucosidase inhibitors (acarbose or miglitol) in an attempt to provide symptomatic benefit before considering surgery."

Dr Vella summarizes: "In the coming years, we hope to gain a better understanding of the prevalence, pathogenesis, and optimal diagnostic and therapeutic approaches for the patient with hyperinsulinemic hypoglycemia after RYGB surgery. It may subsequently be determined that only a small proportion of patients who undergo RYGB surgery become severely affected with postprandial hyperinsulinemic hypoglycemia."

Anabolic Steroids: What the Clinician Should Know

The emphasis on winning in sports and the lucrative incentives professional athletics offer have magnified the means an athlete might use to gain an edge over competitors. The popular sports media has alleged use of performance-enhancing agents by many recognized star performers. Paul C. Carpenter, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, says: "It is easily understandable why an athlete or others might experiment with substances or methods—apart from those of basic good training, equipment, and coaching—in an attempt to improve athletic performance or appear to have above-normal physiologic levels. The motivation to use such methods or substances may come from fellow athletes, coaches, trainers, business managers, the economic rewards of superior performance, self-image difficulties, and, unfortunately, from physicians treating these individuals. Many times the incentive is also driven by peer-social pressures

2006 International Olympic Committee Anti-Doping Rules

IN and OUT of competition

Prohibited substances:

- Anabolic androgenic steroids
- Hormones and related substances (eg, erythropoietin, growth hormone, insulin-like growth factor 1, human chorionic gonadotropin, insulin, corticotrophins)
- β_2-Agonists (eg, salmeterol, terbutaline, salbutamol)
- Antiestrogenic agents (eg, aromatase inhibitors, selective estrogen receptor modulators, clomiphene)
- Diuretics and masking agents (eg, 5α-reductase inhibitors, probenecid, plasma expanders)

Prohibited methods:

- Enhancement of oxygen transfer (eg, blood doping, oxygen transport and delivery boosters)
- Pharmacologic, chemical, physical manipulation
- Gene doping (eg, cells, genes, gene expression)

IN competition

Prohibited substances:

- Stimulants (eg, amphetamine, phentermine, ephedrine, cocaine)
- Narcotics
- Cannabinoids
- Glucocorticoids

and the push of societal body image."

In the past decade, it has become obvious that the use of performance-enhancing drugs has filtered down to those younger than college age. This includes both boys and girls. Use in this young age group has a number of physiologic and psychological consequences—not thought to be major problems in older peer drug users. This makes it important that clinicians are aware of the magnitude of the drug abuse and its symptoms or complications.

Other trends include the following:

- Between 18% and 25% of 12- to 21-year-olds report use of over-the-counter (OTC) performance-enhancing agents (eg, androstenedione, DHEA, creatine, ephedrine).
- In general, use of OTC and illicitly acquired drugs is higher in North American adolescents and teens than in their European and Asian counterparts.
- In college sports, performance-enhancing drug use is higher in National Collegiate Athletic Association Division I than in Division III schools.

Paul C. Carpenter, MD

- College athletes receive their anabolic steroids from a physician (other than the team physician) 32% of the time.
- Use of performance-enhancing drugs is also increasing in nonathletes to improve their nonsport occupational performance and physical appearance.
- Where to obtain performance-enhancing drugs is broad knowledge to 12% of preteens, 29% of adolescents, and 38% of college students.
- Two-thirds of those reporting use of performance-enhancing drugs are involved in organized sports—one-third are not involved in sports—possibly a comment on other societal issues that would prompt a juvenile to use performance-enhancing drugs.

In 2000, the lifetime prevalence of anabolic steroid use was at its highest level (4%) among 12th graders, which represented a marked increase from the previous decade. While other drug use either remained unchanged or decreased among 12th graders, anabolic steroids and other ergogenic aids were the only drug classes for which use increased markedly for lifetime, annual, and 30-day prevalence from 2000 to 2002. Although lifetime use of anabolic steroids among 10th graders remained steady during 2002, its lifetime prevalence more than doubled since 1993 and remains at the highest level since steroid use data were first assessed by the *Monitoring the Future* study. The proportion of female users has increased disproportionate to that of young male users (www.monitoringthefuture.org). There may be a downward trend in the use of performance-enhancing drugs among 8th graders since 2000—but it still remains above 1998 values, and many suspect the diversity of drugs used may be diluting the focused abuse reporting.

Dr Carpenter notes that "as physicians, we have a good understanding of the potential consequences of overreplacement with androgenic medications":

- Men have testis atrophy, oligospermia, baldness,

prostatism, and gynecomastia.
- Women have hirsutism, amenorrhea-infertility, clitoral hypertrophy, voice changes, and breast atrophy.
- Both sexes have acne, jaundice, tremor, edema, bad breath, reduced HDL-cholesterol, hypertension, peliosis hepatitis, hepatic adenomatosis, polycythemia, and thrombosis.

Additional health hazards include aggressive behavioral-psychological changes (eg, "roid rage"), biomechanical consequences (eg, tendon ruptures), hypertrophic cardiomyopathy, and impairment of exercise-induced growth of the cardiac capillary bed.

Anabolic steroids are not the only "hormone" agents being used as ergogenic aids; other examples include human growth hormone, erythropoietin, amphetamines, human chorionic gonadotropin, and insulin (capitalizing on its muscle anabolic actions). The supplement industry is also under scrutiny and the FDA intervened to ban distribution of ephedra when life-threatening consequences of its use were found. Other supplements may also have serious health hazards. In addition, the insurance industry has become interested in studies suggesting major reduction in life expectancy with prolonged use of anabolic steroids.

Dr Carpenter explains: "As health care providers, we have some opportunities to see patients who are using these ergogenic drugs." He offers these clues to recognition of performance-enhancing drug use:
- An adolescent with more than average gynecomastia.
- A high school football player with marked acne resistant to usual therapies.
- An athletic woman with secondary amenorrhea.
- A teenaged athlete with unusual tendon injuries (muscle development without parallel tendon mass increase).
- New type 2 diabetes mellitus in a trim teenager.
- New sexually aggressive behavior.
- Aberrant rage behaviors.

Through their physical examination and psychosocial assessment of suspected performance-enhancing drug users, health care professionals can play a role in identifying, counseling, and making appropriate referrals for patients, particularly youngsters, at risk. Dr Carpenter concludes: "Remaining alert to the possibility of this hidden medication use is important. Health care professionals, particularly endocrinologists, are the logical specialists to be approached when advice about these agents is needed. Maintaining knowledge of what is being used and abused is important in our practices."

Endocrine Education in the Simulation Center

"Doctor, the patient's blood pressure is 235/110! What should we do?"

Ideally, endocrine surgeons never hear a question like this in the operating room while attempting to resect a pheochromocytoma—typically preoperative α- and β-adrenergic blockade effectively minimizes intraoperative hypertension. However, it can happen every day in the Mayo Multidisciplinary Simulation Center at Mayo Clinic in Rochester, where physicians, nurse anesthetists, surgery residents, medical students, and nurses learn about treating this rare, but life-threatening problem. Located in the Stabile Building, the 10,000-square-foot Simulation Center includes exact replicas of operating, emergency, and intensive care unit rooms (Figure 1). In these examination, endoscopic, and surgical skills rooms, Mayo Clinic staff create controlled scenarios to engage all learners without fear of patient complications.

Figure 1. Scenes from the Mayo Clinic Simulation Center. A, An operating room scene. B, Vital sign monitor in the pheochromocytoma operating room scenario.

David R. Farley, MD, of the Department of Surgery and codirector of the Mayo Multidisciplinary Simulation Center, says: "The mannequins, models, anesthesia machines, and hot dogs may not fare well, but rest assured, learners leave the center better prepared to tackle the toughest medical problems. Making mistakes in the Simulation Center is an opportunity to learn. Adult learning theory suggests that hands-on learning for approximately 15 minutes in a stressful environment (simulated operating room or hospital room) followed by a 30- to 45-minute 'debriefing session' is optimal for retaining knowledge and achieving understanding."

Kellie L. Mathis, MD, and David R. Farley, MD

Dr Farley explains: "Many diseases of the endocrine glands are rare, and our 74 general surgery residents may not have the opportunity to experience the related patient care issues and intraoperative decision making in patients with endocrine gland disease. Many trainees across the country will never see a patient with a pheochromocytoma or care for someone with medullary thyroid cancer. While Mayo Clinic trainees collectively have great exposure to these disease processes, patients don't come to us in an orderly fashion, and duty hour regulations limit resident time in the hospital."

With the help of his colleagues in surgery and endocrinology, Dr Farley has created learning scenarios in endocrine surgery that revolve around parathyroid, thyroid, pancreas, and adrenal diseases with specific technical and decision-making learning objectives. Dr Farley says: "Opting to close the wound or proceed to take out another parathyroid gland in a patient with primary hyperparathyroidism is a common issue today with the use of intraoperative parathyroid hormone (PTH) monitoring. While giving the trainees a simple technical task to complete on a mannequin (closing a fake wound made of cloth that looks like muscle, fat, and skin), we communicate with them via speaker phone (seen through a 2-way mirror) as though we were the pathologist or PTH technician and expect them to decipher the facts and act accordingly. Very few interns can handle the questions effectively. After 5 years of training, our chief residents hold up quite well to the stress and respond appropriately and safely."

Additional scenarios like the one involving a pheochromocytoma include having residents counsel a "patient"—actually an actor coached to portray a patient with thyroid cancer, Graves' disease, or multinodular goiter—about treatment options. Residents also have the opportunity to make decisions about surgical management and pancreatic margins in a mannequin with an islet cell tumor, perform fine-needle aspiration with ultrasonographic guidance, and handle questions from a pathologist regarding a follicular neoplasm of the thyroid. All 15-minute sessions are videotaped and available immediately for learners and Mayo staff to critique mistakes and reinforce accurate decisions and actions.

Including nurses, medical students, and anesthesia personnel lends a sense of reality to each scenario, enhances learning in teamwork and systems-based practice, and generates opportunities for real practice improvement. Kellie L. Mathis, MD, a third-year surgical resident at Mayo Clinic in Rochester, notes: "The pancreas operating room scenario is an excellent one—sewing the pancreas (a hot dog) to the small bowel (layered cloth to simulate the jejunum) (Figure 2) is very lifelike and perhaps more difficult than the real thing."

A safe environment where residents are free to make mistakes and see the consequences of those mistakes without harming patients is the thrust of early success with simulation. The simulated scenarios support standardized learning, and all residents are given the opportunity to work through rare case scenarios that they may not otherwise experience during their training. The scenarios can be tailored to the level of the learner, and the resident is provided with immediate feedback during the debriefing session. Behavior is changed and patient safety is improved.

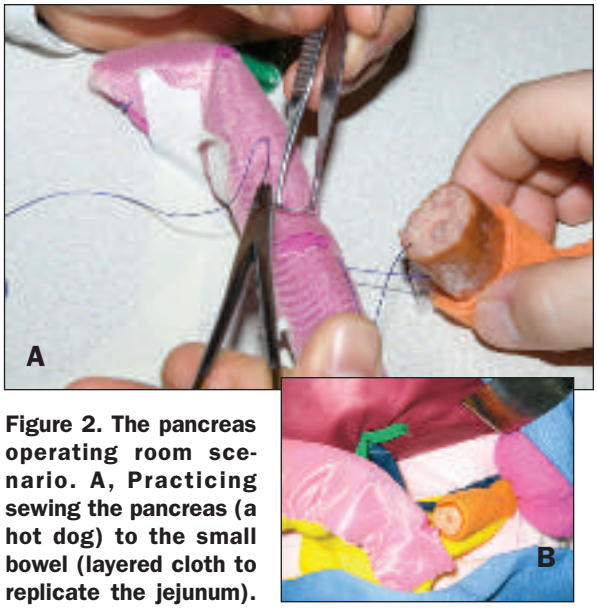

Figure 2. The pancreas operating room scenario. A, Practicing sewing the pancreas (a hot dog) to the small bowel (layered cloth to replicate the jejunum). B, Operative simulation with pancreas and small bowel in anatomic positions.

Bisphosphonate-Associated Jaw Osteonecrosis

Osteonecrosis of the jaw has recently been recognized as an uncommon but severe adverse event associated with oral or intravenous bisphosphonate therapy. Letters, case reports, and small case series have been published in the oncology, dental, maxillofacial surgery, and general medical literature during the past 4 years. Patients with jaw osteonecrosis typically present with jaw pain—more often in the mandible than the maxilla—and associated exposed bone (Figure 1).

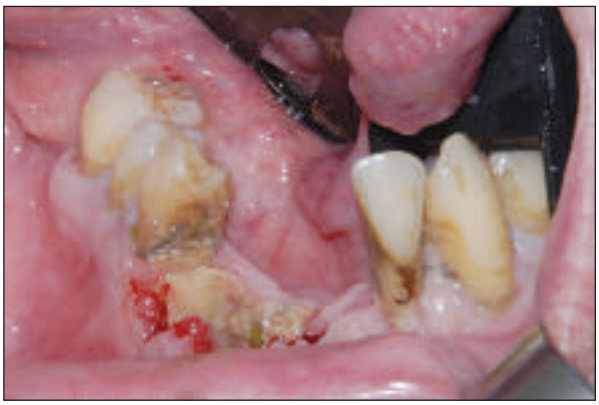

Figure 1. Osteonecrosis of the jaw in a patient who had poor oral hygiene and generalized periodontal disease and recently underwent routine dental extractions in the mandible. This patient had undergone monthly intravenous bisphosphonate therapy for treatment of multiple myeloma during the previous 12 months.

Clinical Setting

Sixty percent of jaw osteonecrosis cases occur after dental extraction, root canal surgery, dental implantation, or other dentoalveolar surgery, whereas the remainder of cases appear to occur spontaneously. To date, 94% of cases have occurred in patients treated with intravenous bisphosphonates, and 85% of these patients were being treated for cancer with 1 or more of the potent nitrogen-containing intravenous bisphosphonates, usually once a month for several years. The highest risk of jaw osteonecrosis appears to be associated with frequent, typically monthly, infusions of intravenous zoledronic acid, which has been widely used in patients with multiple myeloma and breast and prostate cancer.

Presentation

Sreenivas Koka, DDS, PhD, of the Department of Prosthodontics at Mayo Clinic in Rochester, explains: "Jaw osteonecrosis usually appears as an intraoral lesion with areas of exposed yellowish-white hard bone, sometimes associated with extraoral or intraoral sinus tracts, and which demonstrate a delayed healing response—that is, for more than 8 weeks, bone remains exposed rather than being covered with gingival or mucosal tissue. Painful ulcers may be present in the soft tissues adjacent to the bony margins of the lesion. Dental x-ray films are typically not revealing in early cases, but advanced cases may present with areas of moth-eaten radiolucencies, with or without radiopaque bone sequestra (Figure 2). Dental or surgical trauma sites are commonly associated with development of jaw osteonecrosis. In advanced cases, pathologic jaw fractures may occur, or part of the mandible or maxilla may need to be removed."

Sreenivas Koka, DDS, PhD, and Bart L. Clarke, MD

Risk Factors and Prevalence

Bart L. Clarke, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, says: "The main risk factors include cancer, frequent intravenous infusions of nitrogen-containing bisphosphonates, and dentoalveolar trauma. Most reported cases of jaw osteonecrosis have occurred with intravenous zoledronic acid or pamidronate. Risk factors have not been identified for patients receiving oral bisphosphonates such as alendronate, risedronate, and ibandronate for postmenopausal osteoporosis without cancer, because only a small number of cases has been published. Most of these cases were associated with alendronate therapy, likely because of its wider use than other oral bisphosphonates.

"Unless the number of cases has been greatly underreported, the prevalence of oral bisphosphonate-associated jaw osteonecrosis appears to be quite rare—estimated in 1 European database to be on the order of 0.00038% (3.8 cases per million persons treated). Intravenous bisphosphonate-associated jaw osteonecrosis in cancer patients is much more common, with prevalence estimates ranging between 0.8% and 10%, with most studies reporting estimates in the range of 1% to 4%."

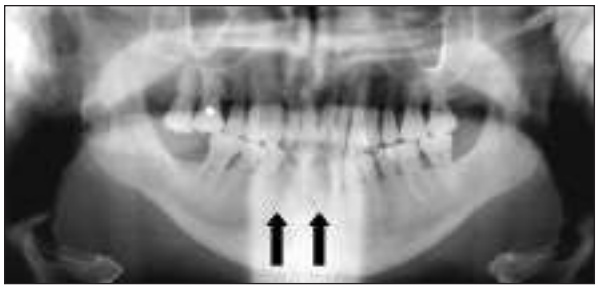

Figure 2. Dental radiograph showing nonhealing of the extraction sites (arrows) in the anterior mandible—findings consistent with jaw osteonecrosis in this patient who was treated with monthly intravenous bisphosphonate therapy.

Pathophysiology

There is no established pathophysiologic mechanism by which oral or intravenous bisphosphonates cause jaw osteonecrosis; it is hypothesized that suppressed bone turnover caused by potent bisphosphonate therapy leads to accumulation of fatigue damage in the form of microcracks, which may lead to microfractures. Also, bisphosphonates are potent inhibitors of angiogenesis, leading to a decreased ability to heal. Dental trauma or infection increases the demand for bone microdamage repair, which may lead to localized osteonecrosis, although it is not yet clear how this occurs.

Deepak Kademani, DMD, MD

Prevention

Deepak Kademani, DMD, MD, of the Department of Oral and Maxillofacial Surgery at Mayo Clinic in Rochester, says: "No randomized clinical trials have been published describing interventions to prevent or treat jaw osteonecrosis. Patients should have potentially traumatic dental treatment, such as tooth extractions, root canals, or dental implantations, before starting oral or intravenous bisphosphonate therapy. The optimal time for withdrawal of bisphosphonates before dental surgery in patients already taking bisphosphonate therapy is not yet established, but most specialists advocate withdrawal of therapy 1 to 3 months before dental surgery. However, the benefit from this form of 'drug holiday' is as yet unproven, particularly since bisphosphonates have a long half-life of several years in the skeleton."

Treatment

No effective therapy has been established for jaw osteonecrosis in patients receiving oral or intravenous bisphosphonate therapy. Some dental specialists recommend supportive management, starting with withdrawal of oral or intravenous bisphosphonate therapy, avoidance of further dentoalveolar trauma, appropriate use of oral antibiotic rinses, and allowing adequate time for healing. In some instances, surgery to debride dead bone may exacerbate the condition; however, debridement and local pedicled soft tissue flaps have been reported to stimulate healing in selected patients.

Recommendations

Until further relevant clinical data become available, it is reasonable to begin or continue oral or intravenous bisphosphonate therapy in patients with appropriate indications, unless jaw osteonecrosis is present or develops. Physicians should review with each patient the decision to continue treatment with frequent infusions of potent intravenous bisphosphonates. Patients contemplating starting therapy with oral or intravenous bisphosphonate for prevention or treatment of postmenopausal or glucocorticoid-induced osteoporosis should be informed of the rare risk of jaw osteonecrosis with oral bisphosphonates and the relatively infrequent risk of jaw osteonecrosis with intravenous bisphosphonates. Patients should undergo dental evaluation and treatment before starting intravenous bisphosphonate therapy and be regularly evaluated to ensure optimal oral health. It is appropriate to encourage patients who express concern about jaw osteonecrosis and who are taking, or about to start taking, oral bisphosphonates to visit a dentist for more information.

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

11th Mayo Clinic Endocrine Course, April 17-19, 2008, Mallorca, Spain. This course, created for endocrinologists and interested internists and surgeons, will span the full spectrum of endocrinology through short lectures, case-based debates, clinicopathologic sessions, clinical pearls sessions, and round table discussions with experts.

Mayo Clinic Nutrition in Health and Disease, November 8-9, 2007, Hilton San Francisco Financial District. This course, designed for physicians, dietitians, nurses, and pharmacists, will provide a full-spectrum, in-depth overview of challenging nutritional issues that clinicians encounter in the ambulatory and hospital settings.

2007 Graduating Clinical Endocrinology Fellows

Left to right (and their upcoming appointments): Neena Natt, MD (program director); Mihaela Cosma, MD (Walla Walla Clinic, Walla Walla, Washington); Marius Stan, MD (Mayo Clinic, Rochester, Minnesota); and Andrea Tom, MD (Santa Clara Valley Medical Center, San Jose, California).

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