Endocrine University: Intensive Technology Training for Clinical Endocrinology Fellows

The Tenth Endocrine University (EU) was held on the Mayo Clinic campus in Rochester, Minnesota, on March 5 to 10, 2011. EU is an annual course sponsored by the American College of Endocrinology (ACE) and supported by the American Association of Clinical Endocrinologists and the Mayo Clinic Division of Endocrinology, Diabetes, Metabolism, and Nutrition. Hossein Gharib, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Minnesota and dean of EU, says: “The 2011 EU course was filled to capacity...
with a record number of trainees (243) from 130 clinical endocrinology programs in the United States. Course evaluations and verbal feedback indicate that this educational program continues to be extremely popular and highly successful. The first EU course was offered in April 2002 with financial support provided by ACE and educational grants from corporate partners and associates of ACE. Fellows pay a modest registration fee. All other expenses for lodging, food, and course materials are covered through ACE. Travel costs are offset by scholarship grants provided to those fellows selected to attend EU by their program directors.”

During the first 10 years of EU, a total of 2,011 clinical endocrinology fellows completed the program. Dr Gharib notes: “The EU curriculum is flexible and is modified on the basis of advances in endocrine science, changes in medical technology, and feedback from the fellows. The 2011 course was specially designed to help prepare senior clinical endocrinology fellows for clinical practice by enhancing their exposure to the key areas of thyroid ultrasonography and fine-needle aspiration biopsy; bone mineral density measurement; endocrine laboratory; invasive endocrine testing; genetic testing; insulin pump and sensor hands-on teaching; and practice management. Small-group ‘meet the expert’ sessions covered areas in pediatric and adult nutrition, bone and calcium disorders, diabetes mellitus, and thyroid disease.”

John C. Morris III, MD, chair of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Minnesota, says: “The EU program is a unique collaboration between an academic medical center and a national society. The EU curriculum is both extensive and intensive and is led by a faculty of 38 experts, with nearly half of the faculty from Mayo Clinic. This special week-long program is something that endocrine fellows will remember and rely on for many years to come.”

Dr Gharib concludes: “Our goal is to continue offering the yearly EU course, and we plan to conduct a survey of EU graduates to determine how we can more effectively help our newer colleagues enjoy and succeed in endocrine practice.”

Endocrine Laboratory Pearls: Vitamin D Tests

Over the past decade, awareness and interest in vitamin D testing have increased among physicians, patients, and researchers. Various new studies have been performed to determine the prevalence of vitamin D deficiency and its potential impact on health. The interest and research have resulted in large-scale national screening, and millions of vitamin D tests have been performed. However, 3 issues continue to baffle many physicians:

• Which test is best suited to assess a patient’s vitamin D status?
• What is the optimal blood level of vitamin D?
• What is the impact of different testing methods on the interpretation of vitamin D test results?
Ravinder J. Singh, PhD, in the Division of Clinical Biochemistry and Immunology and the Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester, Minnesota, explains: “Vitamin D is either created by UV light exposure in the skin or derived from nutritional sources (food or supplements). In the case of the former, it stems from cholesterol and is termed vitamin D$_3$. Animal-based nutritional sources provide the same, cholesterol-derived vitamin D$_3$. In contrast, vitamin D from plants is derived from ergosterol (the plant equivalent of cholesterol) and is termed vitamin D$_2$. Despite some debate, the consensus is that both forms of vitamin D are equipotent and the sum of their concentrations correlates with their biological effects.”

Dr Singh continues: “The amount of vitamin D in blood fluctuates with dietary intake and sun exposure, and most of it is rapidly stored in adipose tissue, from which it can be released on demand [Figure 1]. The circulating vitamin D fraction is converted in the liver to 25-hydroxyvitamin D (25(OH)D, or calcidiol). Serum levels of 25(OH)D are very stable and reflect the tissue-body stores of its precursor, vitamin D. As with vitamin D, 25(OH)D is not active biologically but serves as a readily accessible reservoir for on-demand conversion to the active metabolite, 1,25-dihydroxyvitamin D (1,25(OH)$_2$D, or calcitriol). Because of the on-demand nature of 1,25(OH)$_2$D synthesis, circulating levels of this final metabolite also are relatively poor markers of vitamin D body stores. Of the 3 main vitamin D metabolites that can be measured, 25(OH)D is the preferred one for assessing body stores of vitamin D.”

Stefan K. Grebe, MD, a colleague of Dr Singh in the Division of Clinical Biochemistry and Immunology and the Department of Laboratory Medicine and Pathology at Mayo Clinic in Minnesota, highlights one of the major challenges with 25(OH)D testing: “What reference ranges should be used for interpreting 25(OH)D results? Since 2004, the Mayo Medical Laboratories have been using its listed reference ranges [Table]. These reference ranges are based on evidence in the medical literature and are in agreement with the clinical assessments of endocrinologists at Mayo Clinic. There is consensus in the literature that 25(OH)D serum concentrations less than 10 ng/mL are associated with a high risk of osteomalacia or rickets and should be considered as severe

Table. The 25 Hydroxyvitamin D (25(OH)D) Reference Ranges Used at Mayo Medical Laboratories

<table>
<thead>
<tr>
<th>Reference Range, ng/mL</th>
<th>Results</th>
</tr>
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<tbody>
<tr>
<td>&lt;10</td>
<td>Severe 25(OH)D deficiency$^a$</td>
</tr>
<tr>
<td>10-25</td>
<td>Mild to moderate 25(OH)D deficiency$^b$</td>
</tr>
<tr>
<td>26-80</td>
<td>Optimum 25(OH)D level$^c$</td>
</tr>
<tr>
<td>&gt;80</td>
<td>Toxicity possible$^d$</td>
</tr>
</tbody>
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$^a$ May be associated with osteomalacia or rickets.
$^b$ May be associated with increased risk of osteoporosis or secondary hyperparathyroidism.
$^c$ Optimum level in the general US population.
$^d$ The lowest reported level associated with toxicity in patients without primary hyperparathyroidism and with normal renal function is 80 ng/mL.
deficiency. The recent comprehensive Institute of Medicine report has recommended a 25(OH)D blood level of 12 ng/mL as the minimum population requirement. There is also consensus that blood concentrations of 25(OH)D on the other end of the spectrum, or greater than 80 to 100 ng/mL, are associated with increased risk of toxicity (hypercalcemia) and should be avoided. The middle ground, however, continues to be contested.”

Dr Grebe elaborates: “Studies of skeletal health in institutionalized elderly populations and surrogate markers of vitamin D biological effects (eg, intestinal calcium absorption, suppression of parathyroid hormone levels) suggest that the minimal desirable blood level of 25(OH)D for bone health should be somewhere between 20 and 35 ng/mL. For the multitude of biological effects of vitamin D on other organ systems, there are few, if any, definitive data that could allow us to derive sensible cutoffs. The Institute of Medicine report concludes that careful further investigations and interventional trials are needed to determine optimum levels of 25(OH)D for various diseases that have been associated with low vitamin D levels (eg, cancer, cardiovascular disease, diabetes mellitus, various autoimmune diseases, infections) in order to avoid problems with either undertreatment or overtreatment.”

Across clinical laboratories, markedly different methods are used for vitamin D testing. Dr Singh strongly believes that liquid chromatography tandem mass spectrometry (LC-MS/MS) is superior to most competitive immunoassays and receptor-binding assays. LC-MS/MS is capable of quantifying vitamin D2 and D3 metabolites separately, which can be invaluable in assessing issues of supplement malabsorption and patient compliance with treatment. Furthermore, LC-MS/MS is the recognized analytical criterion standard technology. Yet, some LC-MS/MS methods can be laborious and complex compared with automated immunoassays. Consequently, only 10% to 15% of all clinical laboratories use liquid chromatography–based methods at the international level.

Under optimal conditions, LC-MS/MS, immunoassays, and receptor-binding assays should differ little from each other for measuring the total 25(OH)D level (the sum of 25(OH)D2 and 25(OH)D3), but whenever a laboratory changes from one assay to another, the differences in results can be important clinically. Figure 2 highlights the differences that could be observed in various methods against the mean of all the methods. Although there is excellent agreement between LC-MS/MS and the all-method mean—reemphasizing the criterion-standard nature of LC-MS/MS—the results of individual immunoassays can easily deviate by 20% or more from those of LC-MS/MS. In particular, some immunoassays are reported to have inconsistent recoveries of 25(OH)D2, and thus may show large differences from LC-MS/MS and immunoassays methods with good recovery for patients taking vitamin D2 therapy. Therefore, it is recommended that serial testing be performed with the same assay whenever possible and that LC-MS/MS be used if vitamin D2 is given.
The decline in estrogen levels that begins with the menopausal transition is well recognized as an important contributor to postmenopausal bone loss. However, other hormonal changes also occur with menopause, including reductions in circulating levels of progesterone, androgens, and inhibins A and B. Matthew T. Drake, MD, PhD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: “Follicle-stimulating hormone (FSH) has received the most recent interest among potential candidate factors (other than estrogen) for mediating menopausal bone loss. Indeed, in perimenopausal women, increases in bone resorption markers best correlate not with serum estradiol levels, but with FSH levels. Further, the Study of Women’s Health Across the Nation showed that losses in spine and hip bone mineral density during the menopausal transition correlated most strongly with the interaction between the initial FSH level and longitudinal FSH changes, rather than with estradiol or androgen levels.”

Whether FSH has direct effects on bone, however, continues to be unclear. Dr Drake explains: “Evidence both for and against direct FSH effects in bone has been provided from rodent studies. One study found that mice lacking the FSH receptor were hypogonadal but had normal bone mass. Further, they found that in these mice, osteoclasts and their precursors had FSH receptors, and FSH increased osteoclast formation and function in vitro. These findings led the authors to conclude that high circulating FSH levels caused hypogonadal bone loss. In contrast, another group of investigators found that the same FSH receptor–null mice had reduced bone mass and that bilateral ovariectomy reduced their elevated circulating testosterone levels and decreased bone mass to levels indistinguishable from those in ovariectomized normal controls. Accordingly, these investigators came to the opposite conclusion—namely, that sex steroids (and not FSH) were responsible for regulating bone turnover in these mice.”

Given the correlative human data and the conflicting mouse data regarding a potential role for FSH in mediating bone resorption, Dr Drake, in collaboration with Sundeep Khosla, MD, at Mayo Clinic in Minnesota, used a direct interventional human study to test whether FSH suppression in postmenopausal women reduced bone resorption marker levels. Dr Drake highlights the study: “Because of the myriad of hormonal changes in the perimenopausal and early menopausal years, we studied women well past the menopausal transition, in whom hormonal levels other than FSH would be stable and low. To suppress FSH levels, the experimental group received a gonadotropin-releasing hormone (GnRH) agonist while endogenous estrogen levels were controlled by aromatase inhibitor treatment of all patients. In GnRH-treated patients, FSH levels dropped rapidly into the premenopausal range, where they remained throughout the 4 months of the study [Figure 1]. In contrast, FSH levels stayed elevated in control subjects. Despite the groups having markedly different circulating FSH levels, however, bone resorption (as assessed by serum carboxy-terminal telopeptide of type I collagen levels) was not different between the groups when assessed at the study end point [Figure 2]. In fact, both the control subjects and the GnRH-treated patients had slightly increased bone resorption, likely due to the concomitant suppression of endogenous estrogen by aromatase inhibitor therapy in both groups.”

Dr Drake concludes: “Taken together, these findings clearly demonstrate that in postmenopausal women, FSH suppression does not affect postmenopausal bone resorption.”
Gastroparesis is a syndrome characterized by delayed gastric emptying in the absence of mechanical obstruction. The cardinal symptoms include postprandial fullness (early satiety), nausea, vomiting, and bloating. Between 5% and 12% of patients with diabetes mellitus (DM) report symptoms of gastroparesis. In addition, many persons with DM have asymptomatic gastric retention. It has been suggested that asymptomatic gastric retention may affect glycemic control.

Adil E. Bharucha, MBBS, MD, of the Division of Gastroenterology and Hepatology at Mayo Clinic in Rochester, Minnesota, explains: “While most of the attention with regard to the effect of DM on the gut has focused on delayed gastric emptying, 28 patients (22%) in a Mayo Clinic cohort of 128 patients with DM had rapid gastric emptying of solids, 54 (42%) had normal, and 46 (36%) had delayed. Other than weight loss being more common among those with delayed gastric emptying, symptoms are often indistinguishable between rapid and delayed gastric emptying.”

**Pathophysiology**

Gianrico Farrugia, MD, of the Division of Gastroenterology and Hepatology at Mayo Clinic in Minnesota, says: “In patients with DM, gastric motor dysfunction may result from autonomic neuropathy, enteric neuropathy involving excitatory and inhibitory nerves, abnormalities of the pacemaker cells, abnormalities of the interstitial cells of Cajal (ICC), acute fluctuations in blood glucose levels, incretin-based medications used to normalize postprandial blood glucose concentration, and psychosomatic factors.”

Dr Farrugia continues: “Human and small-animal studies suggest that the most common gastric cellular defects in gastroparesis are loss of ICC, presence of immune cell infiltrate, and loss of expression of neuronal nitric oxide (nNOS). Enteric loss of nNOS occurs early after development of DM and appears to be independent of the development of gastroparesis. ICC generate...
slow waves that control smooth muscle contractility, participate in neurotransmission and mechanotransduction, and maintain the smooth muscle membrane potential gradient. In DM-related gastroparesis, insulinopenia, insulinlike growth factor 1 deficiency, and oxidative stress may predispose to ICC damage. In nonobese diabetic mice, mechanisms that normally counteract increased oxidative stress (eg, impaired upregulation of macrophage hemeoxygenase-1 [HO-1], loss of ICC) are compromised and gastric emptying is delayed [Figure]. Upregulation of HO-1 by hemin increases ICC and nNOS and normalizes delayed gastric emptying in mouse models of type 1 and type 2 DM.”

Management
Symptoms are managed through dietary measures, glycemic control improvements, and medications. Dr Bharucha notes: “Metoclopramide has antiemetic and prokinetic actions and is effective for short-term treatment of gastroparesis; however, long-term utility is unproven. Metoclopramide increases blood prolactin concentration and carries a US Food and Drug Administration (FDA) black box warning about the risk of tardive dyskinesia. Erythromycin stimulates motilin receptors to accelerate gastric emptying. However, due to tachyphylaxis, effectiveness declines within days.”

Dr Bharucha explains further: “Patients who have refractory vomiting or abdominal fullness, or both, may require a gastrostomy for decompression or a jejunostomy for enteral nutrition, or both. Except in patients with profound malnutrition, enteral feeding is preferable to and avoids clinically important complications associated with parenteral nutrition. Predominantly uncontrolled studies suggest that the only FDA-approved gastric electrical stimulation device stimulates the stomach at a high frequency and improves symptoms, particularly vomiting. However, because this device does not improve gastric emptying, the mechanisms of action are unclear. A gastrectomy is performed only as a last resort in carefully evaluated patients with profound gastric stasis.”

Dr Farrugia adds: “Motivated by the encouraging effects of hemin on gastric emptying in nonobese diabetic mice, we showed, for the first time, that HO-1 can be pharmacologically upregulated in humans. Intravenous hemin, which is approved for treating acute porphyria, increased plasma HO-1 protein concentrations 4- to 5-fold and HO-1 activity about 15-fold relative to baseline at 24 and 48 hours in healthy subjects.”

Dr Bharucha highlights: “On the basis of these exciting observations, we are recruiting patients with diabetic gastroparesis for a study comparing the effects of intravenous hemin (10 infusions over 8 weeks) and placebo. Gastric emptying will be assessed through breath tests. Patients who have moderately severe symptoms and delayed gastric emptying (ie, <40% emptying at 2 hours or <90% emptying at 4 hours, or both, by scintigraphy) with no structural cause for symptoms by endoscopy within the past 12 months are eligible to participate in the study. Other inclusion criteria are adequate platelet (>50,000/μL) and absolute neutrophil (>500/μL) counts and adequate hepatic and renal functions (serum creatinine ≤1.5 times the upper limit of the reference range). Patients with enteral feeding tubes or a gastrostomy are eligible also. Patients who are taking narcotics, anticholinergic agents, anticoagulants (eg, warfarin), or erythromycin are not eligible to participate.”

If interested in entering a patient in this study, clinicians should contact the study coordinator, Erica Veil, (phone: 507-538-3883; e-mail: veil.erica@mayo.edu) or Dr Bharucha (phone: 507-284-2687; e-mail: bharucha.adil@mayo.edu).

Diabetes With Normal Gastric Emptying

**Figure.** Proposed pathophysiology of abnormal gastric emptying in patients with diabetes mellitus. CO indicates carbon monoxide; HO-1, hemeoxygenase-1; ICC, interstitial cells of Cajal.
Upcoming Education Opportunity

15th Mayo Clinic Endocrine Course
April 16-21, 2012, Palma, Mallorca, Spain.

This course, created for endocrinologists and interested internists and surgeons, will present the latest material on the diagnosis and treatment of endocrine disorders. The course will span the full spectrum of endocrinology. For more information about this course, please visit http://www.mayo.edu/cme/endocrinology. The course program will be available in October 2011.

2011 Graduating Clinical Endocrinology Fellows

Left to right (and upcoming appointment): Neena Natt, MD, Program Director, Clinical Fellowship in Endocrinology, Diabetes, Metabolism, and Nutrition; Michael R. Nannenga, MD (Holston Medical Group, Kingsport, Tennessee); Kalpana Muthusamy, MBBS (Olmsted Medical Center, Rochester, Minnesota); Paul Aoun, DO, PhD (Palm Beach Diabetes & Endocrine Specialists, West Palm Beach, Florida); and Galina Smushkin, MD (Immanuel St. Joseph's Hospital, Mayo Clinic Health System, Mankato, Minnesota).

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