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Inside This Issue

Ts, Zs, and LSCs—Understanding Bone Mineral Density Reports

In the absence of established skeletal fragility, assessment of bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA) is the basis for the diagnosis of osteoporosis. The very low radiation exposure associated with DXA, coupled with extensive epidemiologic data and validation in clinical trials, has made it the standard clinical tool for the assessment of BMD. However, proper interpretation of the results from DXA requires a good understanding of the limitations of this technology.

Kurt A. Kennel, MD, and Michael K. O'Connor, PhD

Caveats When Using DXA for the Diagnosis of Osteoporosis

Modern DXA systems compare the results in a patient with a number of normal databases. Kurt A. Kennel, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, notes: "The T-score compares the patient's BMD with that of a young adult population, while the Z-score compares it with an age-matched population. In both cases, the score reflects how much the patient's BMD differs from the mean value for that database (in units of standard deviations). For the diagnosis of osteoporosis and assessment of fracture risk, the T-score should be used only in postmenopausal women (World Health Organization recommendation, found on the WHO Web site listed in the Table) and men older than 50 years. The diagnosis of osteoporosis in healthy premenopausal women or healthy men younger than 50 years should not be made on the basis of the BMD result alone. These patients should be compared with age- and sex-matched databases to derive Z-scores. Osteoporosis may be diagnosed if there is low BMD in the appropriate clinical setting (for example, glucocorticoid therapy, hypogonadism, fragility fracture, hyperparathyroidism)."

Technical Issues Important to Clinical Interpretation

Serial BMD measurements can be helpful in monitoring the response to therapy and in the detection of secondary causes of osteoporosis. Hence, an understanding of the validity and interpretation of serial measurement data is essential to avoid making unsupported clinical decisions.

Michael K. O'Connor, PhD, of the Department of Nuclear Medicine at Mayo Clinic in Rochester, says: "One of the most important numbers in a BMD report is the least significant change (LSC). This is defined as the smallest change that can occur in BMD that we are 95% sure is due to changes in the patient's BMD and not to machine or patient factors. The LSC varies with the type of machine, operator experience, the patient's position, the region of the body, and the patient's BMD. Because software upgrades by manufacturers may incorporate different reference populations to generate T- and Z-scores, only the LSC in absolute BMD (reported as grams per square centimeter) should be used for serial comparisons.

"At Mayo Clinic in Rochester, the average of 2 scans is determined during each assessment to reduce the LSC. Furthermore, an average LSC for all technicians and densitometers is used in the DXA laboratory to eliminate the need for

DXA: Online Resources for Clinicians and Patients

Patient education material regarding BMD by DXA: http://www.mayoclinic.com/health/bone-density-tests/WO00024

WHO Technical Report on Prevention and Manage-ment of Osteoporosis 2003: http://whqlibdoc.who.int/trs/WHO_TRS_921.pdf

US Surgeon General's Report on Bone Health and Osteoporosis 2004: http://www.surgeongeneral.gov/library/bonehealth/

Official positions on the use of DXA for the diagnosis and management of osteoporosis at the International Society for Clinical Densitometry Web site, www.iscd.org

patients to be scanned on the same machine by the same technician when serial assessments are performed. The LSC at each site and range of BMD is reported. Absolute changes in BMD greater than the LSC at the site of interest likely represent a real change in BMD at that site. Values less than the LSC should not be considered as small changes or 'trends.' "

Clinicians should ask themselves the following questions:

- What is the precision error (LSC) of the local DXA laboratory?
- Is the precision error (LSC) clearly stated in the DXA report where serial changes in BMD are being reported?

Degenerative changes resulting in periarticular osteosclerosis or exophytic bone and undetected compression in the lumbar spine may spuriously elevate the BMD measurement. However, a low T-score at 2 or more vertebrae, despite the presence of some degenerative joint disease, may still be of use to the clinician who can conclude the lumbar spine BMD is the same or worse than the measured value. However, LSC values are usually quoted for the entire spine, and the fewer vertebrae used in the analysis, the poorer the accuracy of serial measurements. If only 1 evaluable vertebra remains after excluding other vertebrae, diagnosis should be based on a different valid skeletal site (International Society for Clinical Densitometry 2005 recommendations, reached via the Web site listed in the Table).

DXA Does Not Stand Alone in Assessing Fracture Risk

The diagnostic threshold for osteoporosis (T-score ≤ −2.5) using BMD by DXA in postmenopausal women was chosen to identify women with a high risk for hip fracture. Dr Kennel cautions: "Just as the risk of a cardiovascular event is not determined by serum cholesterol alone, fracture risk assessment should be based on several clinical risk factors in addition to BMD. Notable examples include age, prior fragility fracture, parental history of hip fracture, history of smoking, chronic glucocorticoid use, history of falls, and low body weight (see serial comparison BMD report below)." While clinicians can look forward to a World Health Organization absolute fracture risk assessment method that may clarify this approach, it is essential to consider current DXA BMD measurements in the context of other risk factors when assessing the benefits and risks of interventions to reduce the possibility of fracture.

Serial Comparisons

Lumbar spine L2-L4 results:

11/26/2001 BMD: 0.775 g/cm^2, T-score: −3.0

11/18/2004 BMD: 0.709 g/cm^2, T-score: −3.5

04/07/2006 BMD: 0.813 g/cm^2, T-score: −2.7

Change – baseline: 4.9%/previous: 14.7%.

The LSC in BMD for the spine is 0.041 g/cm^2.

The absolute BMD change from previous, 0.104 g/cm^2, is greater than the LSC.

The absolute BMD change from baseline, 0.038g/cm^2, is less than the LSC.

Example of a Mayo Clinic BMD report clearly stating least significant change (LSC). This patient had osteomalacia (low T-scores do not always indicate osteoporosis) due to vitamin D deficiency, which was diagnosed and treated in 2005.

2006 Graduating Clinical Endocrinology Fellows

Left to right (and their upcoming appointments): Neena Natt, MD (program director); Lisa S. Chow, MD (University of Minnesota, Minneapolis); Helen Karakelides, MD (Mayo Clinic Rochester); Julie E. Hallanger-Johnson, MD (MeritCare, Fargo, North Dakota).

Thyroid Nodules: A Systematic and Cost-effective Approach

Thyroid nodules are commonly encountered in clinical practice. In the United States, approximately 300,000 new nodules are diagnosed each year. Their prevalence ranges from 4% by palpation to more than 60% by ultrasonography (US). Thyroid "incidentalomas," found in up to 40% of patients undergoing US evaluation for suspected parathyroid and carotid artery disease, add another level of complexity for the clinician.

M. Regina Castro, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, notes: "Although most thyroid nodules are benign, approximately 5% of all nodules may be malignant. Thus, a systematic evaluation is crucial both to reassure the majority of patients with benign disease who do not require surgery and to refer for surgical treatment the small minority of patients with malignant, suspicious, or large symptomatic nodules who will benefit from surgical excision."

Fine-needle aspiration (FNA) biopsy is a cost-effective and safe outpatient procedure with a diagnostic accuracy that approaches 95%. "Thyroid FNA has resulted in up to 75% reduction in the number of patients requiring surgery, while at least doubling the rate of malignancy found at the time of thyroidectomy," says Hossein Gharib, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester. However, the yield and accuracy of thyroid FNA depend on several factors, including whether the nodule sampled is, for example, a papillary carcinoma or a follicular neoplasm, the experience of the individual performing the procedure, and the cytopathologist interpreting the results. At Mayo Clinic in Rochester, approximately 1,000 thyroid FNA biopsies are performed each year. Obtaining an adequate specimen with enough cellularity to give a conclusive result is important, although the detection of malignancy following a nondiagnostic FNA is not much greater than that of a negative FNA (1.4% and 0.7%, respectively, at Mayo Clinic in Rochester). Nondiagnostic specimen rates in the literature average about 15% and may be greatly reduced by performing the FNA biopsy under US guidance. Dr Castro notes: "US guidance is valuable for small nodules (<1.5 cm) and essential for all nonpalpable nodules, helping to ensure proper needle placement for precise sampling and avoiding cystic areas in complex nodules which often yield inadequate specimens (Figure 1). In patients with multinodular goiters, US guidance is also helpful to select for biopsy those nodules more likely to be malignant (hypoechoic nodules with microcalcifications, irregular borders, increased vascular flow, greater height than width, or rapid growth). Nodule size, in the absence of other worrisome features, is not a good predictor of malignancy."

Thomas J. Sebo, MD, M. Regina Castro, MD, and Hossein Gharib, MD

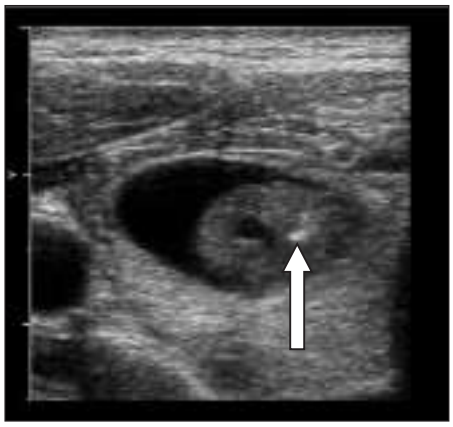

Figure 1. Ultrasound-guided FNA, showing needle tip (arrow) in the solid component of this complex nodule.

Nodules classified on FNA as nondiagnostic should be reaspirated, preferably under US guidance. Nodules repeatedly inadequate for cytologic evaluation may be followed closely, but surgical excision should be considered if US demonstrates worrisome features, if considerable interim growth is documented, or if the patient is at high risk for developing malignancy. It is important to consider the clinical findings of a thyroid nodule classified as nondiagnostic when determining the most appropriate form of management in a given patient, since some studies have shown that up to 10% of patients undergoing surgery for repeatedly nondiagnostic aspirates were found to have malignant nodules.

Dr Gharib highlights: "One of the most difficult management dilemmas for the endo-

crinologist is evaluating a patient with a thyroid nodule classified on FNA cytology as 'suspicious.'" This occurs in approximately 10% of all FNAs and includes specimens with features suggestive of, but not conclusive for, malignancy, such as follicular and Hürthle cell neoplasms, and samples with features worrisome for papillary and medullary carcinoma. Thomas J. Sebo, MD, of the Department of Laboratory Medicine and Pathology at Mayo Clinic in Rochester, says: "In follicular neoplasms, the smears are typically cellular with the presence of microfollicles (Figure 2). In these cases, the determination of malignancy requires identification of capsular or vascular invasion in the surgical specimen. There are no cytologic features to help distinguish follicular or Hürthle cell adenomas from their malignant counterparts." Thus, surgery is typically recommended to firmly establish the biological behavior of folliculogenic tumors. Only about 15% of smears considered suspicious for follicular and Hürthle cell neoplasms are identified as carcinomas at surgery (Table). Dr Sebo notes: "Many ancillary biomarkers, evaluated using methods such as immunoperoxidase techniques, flow cytometry, digital image analysis, and, most recently, reverse transcriptase–polymerase chain reaction analysis have been used in an attempt to further define a 'suspicious' folliculogenic lesion as malignant, but the results have been equivocal." Hence, at present, nodules with a suspicious cytologic appearance are referred for surgical excision. Other indications for surgery besides a "suspicious" or "positive for malignancy" cytology include rapid nodule growth, development of pressure symptoms (such as dysphagia), and, for some patients, cosmetic concerns.

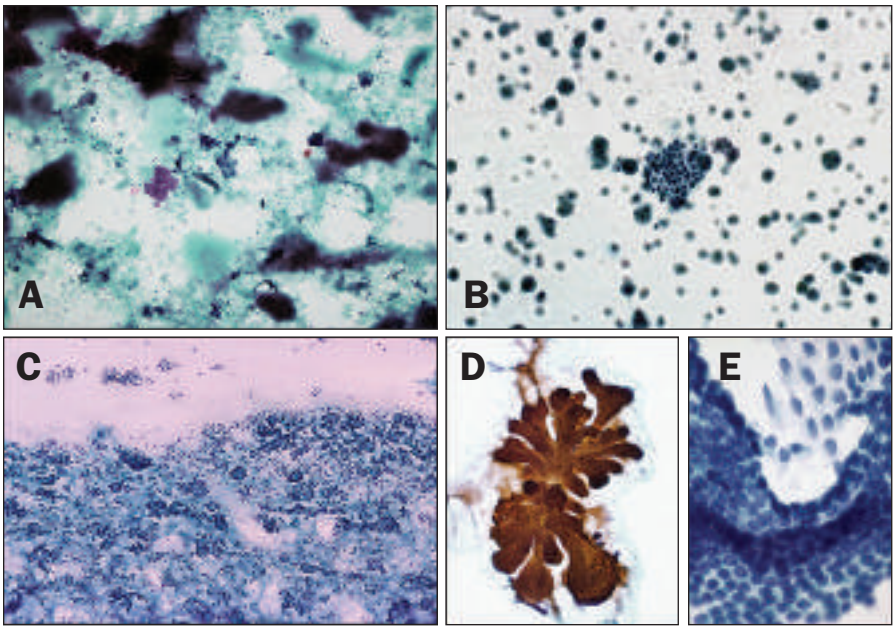

Figure 2. A, Benign thyroid nodule. Follicular cells are in relatively large sheets without microfollicle formation. Abundant colloid in the background (Papanicolaou stain, ×50). B, Nondiagnostic specimen shows foamy macrophages, both scattered and in clusters, reflective of cystic degeneration, likely in a benign thyroid nodule. The lack of follicular cells precludes classifying the aspirate as diagnostic and negative for malignancy (Papanicolaou stain, ×100). C, This specimen, suspicious for a follicular neoplasm, shows follicular cells increased in cellularity with a lack of cohesion. Many of the cells are in microfollicles, and colloid is reduced or absent. The constellation of findings suggests classifying the aspirate as suspicious (Papanicolaou stain, ×50). D and E, In these specimens, positive for malignancy (papillary thyroid carcinoma), the presence of well-defined papillary structures (D) and cells with nuclear enlargement, crowding, and sharp longitudinal grooves (E) earmarks this aspirate as definitely coming from a nodule of papillary thyroid carcinoma (Papanicolaou stain, ×100 [D] and ×400 [E]).

Suspicious FNA Results in 2,175 Smears With 73% Tissue Examination at Mayo Clinic, 1980-2001

Cytology *	Histology, no.	Malignant, no. (%)
Follicular neoplasm	561	83 (15)
Hürthle cell neoplasm	548	77 (14)
Papillary carcinoma	489	318 (65)
Total	1,598	478 (29)

Reproduced with permission from Castro MR, Gharib H. Continuing controversies in the management of thyroid nodules. *Ann Intern Med.* 2005;142:926-931.
* Specimen labeled by a cytopathologist as "suspicious for" follicular neoplasm, Hürthle cell neoplasm, or papillary thyroid carcinoma.

Intensive Diabetes Self-management Programs at Mayo Clinic

The primary goal of intensive diabetes management is to keep the blood glucose as near normal as possible without causing severe hypoglycemia. The key to achieving this goal is effective diabetes self-management. The Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester played a pioneering role in describing glucose profiles and devising complex insulin programs for patients with diabetes.

Yogish C. Kudva, MD, an endocrinologist at Mayo Clinic in Rochester, notes: "Our center contributed the largest cohort of patients to the Diabetes Control and Complications Trial, the landmark study that established the effectiveness of tight glycemic control in preventing microvascular and neurologic complications of type 1 diabetes. Over the years, the program has expanded to incorporate advances in diabetes management, particularly utilization of technology." Services currently offered include the following:

- A 3-day outpatient program in intensive diabetes management (called the "Diabetes Unit")
- Fast-track instruction in intensive diabetes management
- Insulin pump initiation program
- Upgrading an insulin pump program
- Insulin pump clinic

Diabetes Unit

"The Diabetes Unit is an intensive diabetes education and management program established in 1983 at Saint Marys Hospital as an inpatient program. The unit is now an outpatient program located on the 19th floor of the Mayo Building," according to Nancy M. Klobassa, a registered nurse and certified diabetes educator. The program has undergone some changes through the years, but the principles are largely unchanged.

The Diabetes Unit is a 3-day outpatient program held twice a month. The program meets Monday through Wednesday from 7:15 AM to 4:30 PM each day it is in session. Class size is limited to 5 patients, and family involvement is encouraged.

A team approach is used to help each patient work with specific lifestyle issues. The health care team consists of an endocrinologist, endocrinology clinical fellow, certified diabetes educator, dietitian, and behavioral medicine counselor. Breakfast and lunch are served in a special nutrition dining room at the Rochester Methodist Hospital. Patients are able to make meal choices under the direction of a dietitian.

The management of patients with diabetes at Mayo Clinic is a team effort and, in addition to the patient, includes physicians, certified diabetes nurse educators, and dietitians.

The program includes the following topics:

- Introduction to the intensive insulin program
- Concepts of dose adjustment and correctional bolus
- Introduction to meal planning, food exchanges, and carbohydrate counting
- Intensive insulin program sick-day management
- Use of food labels and strategies for special occasions
- Stress management
- Exercise guidelines
- Medical management and follow-up as appropriate (phone or return visits)

Fast-Track Instruction in Intensive Diabetes Management

The fast-track instruction is a 6-hour class, held 3 times per month, specifically for individuals already using an intensive insulin program. The primary focus of this class is to review the principles of intensive diabetes self-management. A certified diabetes nurse educator and registered dietitian provide the instruction.

Insulin Pump Initiation Program

The full-day insulin pump initiation program is held twice monthly. Appropriate candidates for the external pump are patients who are testing

Nancy M. Klobassa, RN, CDE, and Yogish C. Kudva, MD

their blood glucose 4 times daily and were previously instructed in intensive diabetes management. A prepump assessment with the endocrinologist and nurse educator is advised. The patient and endocrinologist can then decide if insulin pump therapy is appropriate. Nurse educators discuss therapy and provide hands-on insulin pump demonstrations. Highlights of this program include the following:

- Insulin pump therapy and hypoglycemia
- Insulin sensitivity factor and correction bolus
- Adjustment of basal insulin and bolus insulin
- Exercise and insulin pump therapy
- Carbohydrate counting
- Calculating the ratio of insulin to carbo-hydrates
- Phone call follow-up

Upgrading an Insulin Pump

Nancy Klobassa notes: "Since insulin pump models are continually being improved, instructions to upgrade insulin pumps are offered on a 1-on-1 basis." This is a 2-hour individual education session with the diabetes nurse educator to learn the pump functions and infusion set insertion of a new insulin pump model.

Insulin Pump Clinic

The insulin pump clinic is offered on 3 days every month. This is a team visit with a patient, an endocrinologist, and a certified diabetes educator with expertise in pump management. Information from the pump and glucose meter is downloaded and interpreted, and changes are made to the pump program during the same visit. This clinic is appropriate for patients who have recently completed the insulin pump class or for patients who are currently on insulin pump therapy. Participation in this clinic includes a visit at 2 to 4 weeks after starting insulin pump therapy and every 3 months thereafter.

Dr Kudva concludes: "Medical care and technology utilization in the management of diabetes mellitus have improved substantially, and we are excited to offer an intensive diabetes management program that is efficient, evidence-based, and responsive to patient needs."

Hypoglycemia—A Role for Arterial Stimulation Venous Sampling

The observation that intravenously administered calcium stimulates insulin release from insulinoma, but not in normal subjects, prompted the late Dr John Doppman from the National Institutes of Health to adapt the Imamura test, which involves venous sampling for gastrin in response to the arterial injection of secretin, for the identification of gastrinomas. Arterial stimulation venous sampling, when applied to the assessment of possible insulinoma, has been referred to also as the selective arterial calcium stimulation test (SACST). F. John Service, MD, PhD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, notes: "SACST is performed in patients with biochemical evidence of hyperinsulinism but with inconclusive noninvasive imaging (eg, abdominal CT, transabdominal ultrasound [US], and endoscopic US). SACST is not necessary if an insulinoma is clearly identified on CT or US."

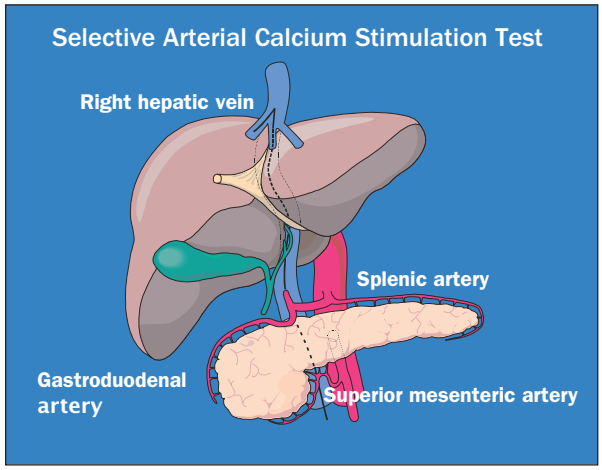

Figure 1. Graphic representation of the relationships among the 3 major arteries (gastroduodenal, superior mesenteric, and splenic) and regions of the pancreas supplied (head, uncinate, and tail, respectively).

James C. Andrews, MD

F. John Service, MD, PhD

Technique

"In brief, the femoral vein and artery are cannulated, and catheters are passed to the right hepatic vein for sampling for insulin and sequentially under fluoroscopic guidance into the splenic, superior mesenteric, and gastroduodenal arteries," says James C. Andrews, MD, of the Department of Radiology at Mayo Clinic in Rochester (Figure 1). A baseline sample for insulin is obtained before injection of calcium gluconate, 0.025 mEq/kg body weight, into each artery. Additional samples for insulin are obtained at 20, 40, and 60 seconds after each injection. Alternate sites of injection are dictated by anomalies of the arterial circulation. Should a hepatic lesion be suspected as the source of hyperinsulinism, the hepatic artery should also be injected.

Interpretation

Dr Service notes: "A positive response to the injection of calcium is defined as at least a doubling and, better yet, a tripling of the insulin level at more than 1 time point after the injection and is indicative of hyperfunctioning β cells (either insulinoma or islet hypertrophy) in the vascular territory of the artery studied" (Figure 2). Although overlap across vascular territories can occur, these can be identified from the angiographic findings. In general, the body and tail of the pancreas are within the splenic distribution, the head and secondarily the uncinate process are within the gastroduodenal distribution, and the uncinate process and secondarily the head are within the superior mesenteric distribution. This test serves not only as a means to regionalize (to 1 or more arterial distributions) the site of hyperfunctioning β cells, but also as a dynamic test to confirm the presence of hyperfunctioning β cells. In patients with clinical features of the noninsulinoma pancreatogenous hypoglycemia syndrome or who have postgastric bypass hypoglycemia, it is an essential procedure to document and regionalize the hyperfunctioning β cells.

More than 100 SACSTs have been performed at Mayo Clinic in Rochester in the past decade. In addition to the preinjection venous sampling for insulin, an arterial sample is also obtained before each calcium injection. When the basal arterial insulin concentration exceeds the hepatic venous level, the source of insulin may be extrapancreatic, ie, from another organ or by self-administration. In addition, the insulin responses to the calcium injection are flat in persons with a nonpancreatic cause for hypoglycemia, eg, insulin autoimmune hypoglycemia, non–islet cell tumor hypoglycemia, and hypoglycemia from renal failure. Dr Andrews cautions: "Variations in arterial anatomy may lead to errors in interpretation. There is great patient-to-patient variation in the area of the pancreas supplied by the branches of the superior mesenteric artery, and it is critical that the hepatic vein insulin levels be interpreted along with a careful analysis of the diagnostic angiogram."

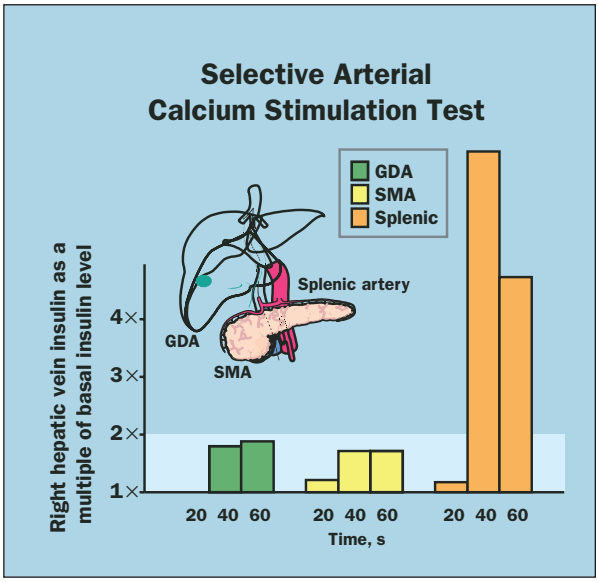

Figure 2. Results from SACST show a less than 2-fold rise in right hepatic vein insulin levels when calcium is infused into the gastroduodenal artery (GDA) and superior mesenteric artery (SMA). The more than 2-fold increase in right hepatic vein insulin concentrations when calcium is infused into the splenic artery (data shown in orange) is diagnostic of an insulinoma in the tail of the pancreas.

Education Opportunities

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

10th Mayo Clinic Endocrine Course

The 10th Mayo Clinic Endocrine Course will be held March 18-23, 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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Mayo Clinic Rochester
800-533-1564

Mayo Clinic Arizona
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