Although there is general agreement that patients with a previous history of a hip or vertebral fracture or those with bone mineral density (BMD) T-scores less than or equal to -2.5 at the femoral neck, total hip or lumbar spine by dual energy X-ray absorptiometry (DXA) warrant initiation of drug therapy for osteoporosis, it is clear that approximately 60 percent of fragility fractures in women and approximately 80 percent of fragility fractures in men occur in patients with T-scores above this value. Not surprisingly, clinicians often see patients with T-scores above -2.5 who have had fragility fractures, leading to uncertainty as to the true extent of skeletal fragility present in these patients. Thus, there is a critical need for novel approaches to better identify patients with osteopenia (T-scores -2.5 to -1) who may be at increased fracture risk.

Over the past decade, a unique partnership involving the clinical research expertise of Sundeep Khosla, M.D., and colleagues at Mayo Clinic and the bioengineering capabilities of Tony M. Keaveny, Ph.D., and his group at the University of California, Berkeley has contributed to the development of one such approach. Dr. Khosla, an endocrinologist at Mayo Clinic in Rochester, Minnesota, explains: “This technology, VirtuOst, is now commercialized by O.N. Diagnostics, a company started by Dr. Keaveny. VirtuOst, which has been cleared by the Food and Drug Administration, utilizes clinical computerized tomography (CT) scans that may have been obtained for any purpose (such as standard abdominal imaging or CT colonography) to obtain noninvasive measures of bone strength by finite element analysis (FEA).

These bone strength measures at the spine or hip are highly correlated with the true breaking strength of bone in cadaveric studies.

“The figure depicts the process by which CT images are analyzed. Based on the empirical relationship between CT density and the yield

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**Figure.** The overall test provides measures of a DXA-equivalent bone mineral density (BMD) at the hip and trabecular BMD at the spine, and measures of bone strength at both sites. The input CT scan is processed to separate out the bones of interest to measure BMD. The same bones are then converted into engineering “finite element models” for virtual stress testing, using information on the biomechanical behavior of bone tissue and its relation to bone density from the CT scan. Strength measurements are computed for the femur in a sideways-fall configuration and for the spine for a compressive overload.
stress of bone, FEA is used to virtually load the bone to failure, thereby arriving at the FEA-based bone strength, in units of newtons (N).”

The use of FEA-derived bone strength at the spine or the hip has now been validated in a number of retrospective and prospective fracture-outcome studies whose outcomes were published in *Radiology* in 2016, *American Journal of Gastroenterology* in 2014, *Osteoporosis International* in 2012 and *Journal of Bone and Mineral Research* in 2010. Based on these studies, thresholds for fragile bone strength at the spine or the hip, separately in women and in men, have been derived.

Dr. Khosla highlights: “Collectively, these studies have demonstrated that using these thresholds, virtually all patients who fracture with BMD-defined osteoporosis are accurately identified. Moreover, these thresholds also identify a significant number of patients with fragility fractures who have osteopenia, demonstrating that the FEA-derived bone strength is capturing aspects of bone structure and strength not evident by conventional DXA.

To identify osteoporosis, this analysis provides a measurement of trabecular BMD at the spine that avoids artifacts inherent in DXA due to degenerative changes or aortic calcification; it also provides DXA-equivalent measurements of total hip and femoral neck BMD T-scores at the hip that are highly correlated with DXA.

Recently, the International Society for Clinical Densitometry has endorsed these BMD and bone strength measurements, and their validated thresholds, as a sufficient basis for identifying patients for initiation of pharmacological therapy.”

The Metabolic Bone Group at Mayo Clinic has gained experience in using FEA-derived bone strength as part of its practice in specific groups of patients. These uses include:

- Patients undergoing CT imaging for other purposes, for which the bone strength analysis can be an add-on, providing additional information regarding skeletal fragility. If the imaging includes the proximal femur, a DXA-equivalent T-score also is obtained.

- Patients with fragility fractures in the setting of a DXA BMD T-score of greater than -2.5. For these patients, a CT scan specifically for bone strength analysis can be obtained and the images processed for spine and hipbone strength. A finding of bone strength in the fragile range, despite a BMD by DXA that is not considered osteoporotic, can provide an explanation for the patient’s fragility fractures.

Dr. Khosla says: “As we gain more experience with this technology, bone strength analyses from CT imaging may prove to be useful in patients with osteopenia who have not yet fractured, but where fracture risk based on FRAX or other criteria appear to be increased or remain ambiguous. A subset of these patients may have compromised bone strength and thereby warrant consideration for drug therapy. Moreover, as we learn more about how bone strength and, in particular, the distribution of bone within the spine or hip change with various therapies for osteoporosis, this approach also may become useful in determining the best choice of therapy for particular patients with very low bone strength and perhaps for monitoring response to therapy. To the extent that certain medications may replace bone precisely where it is needed to maximize...
Hyperinsulinemic hypoglycemia is a disorder that can be very challenging to evaluate. Adrian Vella, M.D., an endocrinologist at Mayo Clinic in Rochester, Minnesota, says: “Once factitious disease has been excluded (that is, inappropriate use of hypoglycemic medication), insulinoma is the most likely cause of hypoglycemia. Non-invasive imaging studies such as abdominal ultrasound and computerized tomography with intravenous contrast can identify an insulinoma in approximately 75 percent of the cases. However, in the remaining instances, more invasive testing such as endoscopic ultrasound or selective arterial calcium stimulation test (SACST) is required. These tests alone or in combination have allowed virtually all insulinomas to be localized or regionalized preoperatively at Mayo Clinic since 1998.”

The SACST has been of increasing interest to internists and endocrinologists since the relatively recent description of two distinct syndromes characterized by hypoglycemia, an abnormal SACST and abnormal islet morphology. Noninsulinoma pancreaticogynemic hypoglycemia syndrome (NIPHS) is a rare disorder characterized by postprandial hypoglycemia. A similar presentation has been encountered after Roux-en-Y gastric bypass (RYGB) and Nissen fundoplication.

James C. Andrews, M.D., a radiologist at Mayo Clinic in Rochester, Minnesota, says: “The SACST was developed by the late John L. Doppman, M.D., from the National Institutes of Health in response to the observation that intravenously administered calcium stimulates insulin release from insulinoma, but not from normal beta cells. The test requires cannulation of the femoral vein and artery with passage of a sampling catheter to the right hepatic vein for sampling for insulin and sequentially under fluoroscopic guidance, a catheter placed into the splenic, superior mesenteric and gastroduodenal arteries to allow injection of calcium gluconate into these arteries (Figure 1). Two 2015 publications by our group in Surgery and the Journal of Clinical Endocrinology and Metabolism have highlighted the importance of the arterial anatomy and vascular supply (head, uncinate process and tail, respectively).

For more information
Endocrine disorders requiring surgical intervention are rare in childhood:

- Thyroid nodules have an incidence of 1,000 to 2,000 per 100,000 children.
- Primary hyperparathyroidism has an incidence of 2 to 5 children per 100,000.
- Adrenocortical tumors have an incidence of 2 children per 10,000,000.
- Most uncommon are pancreatic neuroendocrine tumors.

Studies to date have shown superior outcomes when such patients are managed in a tertiary referral center with the availability of a multidisciplinary team and higher volume surgeons.

Geoffrey B. Thompson, M.D., Endocrine Surgery section head at Mayo Clinic in Rochester, Minnesota, says: “The Mayo Clinic pediatric surgery experience over a 20-year period was published in the Journal of Clinical Endocrinology and Metabolism in 2014. This report included a total of 241 patients: 177 underwent thyroid surgery, 13 had a neck dissection, 24 had parathyroid surgery, 14 had an adrenalectomy, seven had a resection of a paraganglioma and six had a neuroendocrine pancreatic procedure. An average follow-up of 62 months was available.”

Aida N. Lteif, M.D., chair of Pediatric Endocrinology at Mayo Clinic in Rochester, Minnesota, explains: “The indications for thyroid surgery can be broadly divided into thyroidectomy for suspicious thyroid nodules and cancer, multinodular goiter, hyperthyroidism, and regional perfusion when interpreting results of the SACST. The anatomy of the celiac axis and superior mesenteric artery (SMA) is aberrant in approximately 40 percent of patients. Hence it is important to discuss the results obtained with the interventional radiologist performing the study. Such an approach significantly improves the sensitivity of localization for occult insulinoma.”

Dr. Vella adds: “Previously a positive response to the injection of calcium was defined as at least a doubling or a tripling of the insulin level at more than one time point after the injection. However, consideration of the absolute value of peak insulin concentrations also is important in light of the pulsatile nature of insulin secretion where underlying endogenous insulin pulsatility may mimic a response to calcium injection.

A recent analysis of our experience with SACST suggests that positive territories usually exhibit a greater than fourfold response from baseline concentrations (Figure 2) and the peak insulin concentrations observed with insulinoma are higher than those observed in subjects with NIPHS or post-RYGB hypoglycemia.”

Dr. Vella concludes: “Continuing experience with SACST at our institution has reinforced the utility of the test in the management of hypoglycemic disorders when performed selectively. Close communication between the endocrinologist and the interventional radiologist also is important to interpret the results correctly and manage the patient appropriately.”

For more information


The Mayo Clinic Pediatric Endocrine Surgery Experience
prophylactic surgery in patients with multiple endocrine neoplasia, type 2A (MEN 2A) or type 2B (MEN 2B). Twenty-six patients were under 10 years, and four were under 5 years of age. Of 22 patients with hereditary medullary thyroid cancer (MTC), 18 had MEN 2A while four patients had familial MTC. The majority of thyroidectomies performed had benign disease (follicular adenoma, Graves’ disease and C-cell hyperplasia). On final pathology, 45 patients had a diagnosis of thyroid cancer — papillary thyroid cancer (PTC) or MTC.

Zahraa AlHilli, M.B., B.Ch., BAO, an endocrine surgery fellow at Mayo Clinic in Rochester, Minnesota, adds: “The unique frozen section practice at Mayo Clinic allows for intraoperative assessment of all specimens, which spares patients the need for a completion thyroidectomy. None of our patients required re-operation. In patients who underwent a neck dissection, only one child was under the age of 10 years. Indications for surgery included 12 patients with recurrent or persistent PTC in the lateral neck nodes and one patient with recurrent MTC associated with MEN 2A. The morbidity rates in our thyroidectomy and neck dissection population were low and comparable to those in our adult population. Permanent hypoparathyroidism was noted in 2.3 percent, cervical hematoma in 0.6 percent and unintentional recurrent laryngeal nerve (RLN) paralysis in 0 percent.”

Peter J. Tebben, M.D., a pediatric endocrinologist at Mayo Clinic in Rochester, Minnesota, says: “Parathyroid surgery is the second most common type of endocrine surgery that is performed in our pediatric population. Out of 24 patients treated at Mayo Clinic in 20 years, 20 had primary hyperparathyroidism as the cause of their hypercalcemia and the remaining had tertiary hyperparathyroidism post-renal transplant. Children more commonly present with more aggressive sequelae than adults. Rather than having hypercalcemia identified on routine laboratory evaluation, children commonly present with nephrolithiasis and fatigue as their main symptom. Less commonly, other nonspecific symptoms include depression, panic attacks, irregular heartbeat, headaches or gastrointestinal symptoms such as nausea, vomiting, constipation and abdominal pain. Sporadic single gland disease is most commonly found at surgery. Multigland disease is usually associated with familial syndromes that include familial hyperparathyroidism, MEN 1 and MEN 2A. Our parathyroid cohort additionally included patients with tertiary hyperparathyroidism after renal transplantation for end-stage renal failure, one patient with familial hypophosphatemic rickets and one with familial hypocalciuric hypercalcemia.”

Dr. Thompson adds: “Subcutaneous autotransplantation to the anterior chest wall is routinely carried out in patients treated with subtotal parathyroidectomy. Tissue is removed the following day at the bedside if the serum
A Case From the Endocrine Teaching Clinics: An Unusual Cause of a Pituitary Mass

A 43-year-old man presented for evaluation of an incidentally discovered pituitary mass. His past medical history was notable for alveolar soft part sarcoma of the thigh resected 19 years previously. After a disease-free period of 16 years, the patient developed bilateral lung metastases, which were treated surgically. One year ago, he developed a metastasis in the pancreatic tail, which was resected, and another metastasis in the left kidney, treated with radiofrequency ablation. As a part of cancer surveillance, a brain MRI was obtained and it showed right-sided pituitary enlargement with mild extension into the suprasellar cistern and deviation of the infundibulum to the left. The patient had no symptoms suggestive of pituitary dysfunction except for minimal fatigue. He did not have headaches or visual symptoms.

Despite his asymptomatic state, laboratory testing demonstrated secondary adrenal insufficiency and hypogonadotropic hypogonadism (Table). Visual field testing was normal. The patient was initiated on glucocorticoid and testosterone replacements.

<table>
<thead>
<tr>
<th>Blood hormone, unit of measure</th>
<th>Result</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning cortisol, µg/dL</td>
<td>1.3</td>
<td>7-25</td>
</tr>
<tr>
<td>ACTH, pg/mL</td>
<td>13</td>
<td>10-60</td>
</tr>
<tr>
<td>LH, IU/L</td>
<td>&lt; 0.3</td>
<td>1.8-8.6</td>
</tr>
<tr>
<td>Total testosterone, ng/dL</td>
<td>8.3</td>
<td>240-950</td>
</tr>
<tr>
<td>Prolactin, ng/mL</td>
<td>30</td>
<td>4-15</td>
</tr>
<tr>
<td>TSH, mIU/L</td>
<td>0.2</td>
<td>0.3-4.2</td>
</tr>
<tr>
<td>Free thyroxine, ng/dL</td>
<td>0.9</td>
<td>0.9-1.7</td>
</tr>
<tr>
<td>IGF-1, ng/mL</td>
<td>127</td>
<td>64-210</td>
</tr>
</tbody>
</table>

Table. Hormonal evaluation at initial presentation with a pituitary mass.
Hypopituitarism is very uncommon with primary pituitary tumors and in view of his history of metastatic alveolar soft part sarcoma, a pituitary metastasis was suspected. Complete surgical resection of the pituitary mass was not considered feasible, and the tumor was treated with Gamma Knife radiosurgery. Six months after radiosurgery, the pituitary-directed head MRI showed heterogeneous hypoenhancement of the central pituitary gland consistent with post-radiation changes (Figure).

Metastases to the pituitary gland are rare and usually present with symptoms of pituitary dysfunction, visual disturbances, cranial nerve deficits or headaches, as documented in studies published in the Journal of Neuro-Oncology in 2015 and The Endocrinologist in 2002. In a Mayo Clinic series of 52 patients with intrasellar metastases diagnosed between 1950 and 1996, there were 29 women and 23 men with an mean age of 60 years. Breast and lung carcinomas were the most frequent primary tumors (37 percent and 23 percent, respectively). The primary tumor was unknown in 12 percent of patients. In the patients with a known primary tumor, it was diagnosed after the pituitary metastasis was discovered in 20 percent. The mode of discovery of pituitary metastases was symptom based (visual impairment, diabetes insipidus, hypopituitarism) in 75 percent of patients. Of the patients in whom prolactin was measured, 63 percent had hyperprolactinemia. Pituitary surgery and radiotherapy were performed in 42 percent and 63 percent of patients, respectively. Mean survival was 17 months (range, 0-240 months). Overall mortality at one year was 67 percent.

Histologic confirmation of metastatic disease is usually performed; however, when the imaging characteristics are suggestive of metastasis in a patient with a known metastatic disease at other sites, biopsy is not necessary, especially if it will not change subsequent management.

Little evidence exists in regards to the best treatment approach for pituitary metastases. Because of the poor prognosis associated with sellar metastases, the most reasonable therapeutic approaches are palliative radiotherapy, pituitary target hormone replacement therapy when indicated and primary tumor-directed chemotherapy. Surgical debulking of the sellar metastasis may be beneficial in patients with visual field defects caused by compression of the optic chiasm. Total resection of the pituitary tumor can be difficult because of invasion of surrounding structures and increased vascularity. Recovery of pituitary function is unlikely to occur after surgery, but visual symptoms may improve. Radiosurgery also can be performed after initial surgical debulking in an attempt to stop local tumor regrowth. Management of patients with pituitary metastasis should be individualized after consideration of presenting symptoms, imaging characteristics, goals of treatment and patient’s preferences.

For more information

Education Opportunities

16th Annual Mayo Clinic Nutrition and Wellness in Health and Disease 2016
Sept. 30-Oct. 1, 2016, at InterContinental Hotel, Chicago

Nutrition, physical activity and other healthy lifestyle behaviors are vital components in the promotion of health and the treatment of disease. This course — designed for physicians, advanced practice clinicians, dietitians, nurses, and health and wellness staff — provides a full-spectrum, in-depth overview of situations and topics that clinicians encounter in the ambulatory setting, including obesity in adults and children, individual and group-based weight management strategies, prevention of common medical conditions through healthy lifestyles, nutrition topics in the news, behavior modification, and resilience, plus physical activity and wellness focus on clinicians. A culinary demonstration highlights techniques to prepare healthy, great-tasting food. Presentations offer practical clinical management pearls, interactive case studies and panel discussions. The course will be held at InterContinental Hotel, Chicago. For more information, visit https://ce.mayo.edu/nutrition/content/mayo-clinic-nutrition-and-wellness-health-and-disease-2016 or call 800-323-2688 (toll-free). Course hashtag: #MayoNutrCME

20th Annual Mayo Clinic Endocrine Update
Jan. 30-Feb. 3, 2017, at The Ritz-Carlton, South Beach, Miami Beach, Fla.

Designed for endocrinologists and interested internists and surgeons, this course addresses gaps in medical knowledge and barriers in clinical practice to improve the outcomes of patients with endocrine and metabolic disorders. Topics span the full range of endocrinology through lectures, debates, panel discussions, clinicopathologic sessions, clinical pearls sessions, informal breakfast roundtable discussions and small-group discussions with experts. Attendees have plenty of opportunity for interaction with the course faculty, who are selected for their expertise and clinical acumen. For more information, visit https://ce.mayo.edu/internal-medicine/content/20th-annual-mayo-clinic-endocrine-update-2017 or call 800-323-2688 (toll-free).