Obesity and osteoporosis are growing health concerns worldwide. Their interrelationship is of interest given that adipocytes and osteoblasts are both derived from pluripotent stromal cells. Factors favoring differentiation toward one lineage (for example, fat) could be predicted to have detrimental effects on tissues dependent on the other lineage (for example, bone). Kurt A. Kennel, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn., says: “Many endocrinologists first became aware of this relationship with reports of bone loss and fractures in patients with diabetes treated with rosiglitazone, which increases adipocyte and decreases osteoblast genesis. While a low body weight has long been associated with an increased risk of fractures, obesity was historically felt to be protective against fractures. This notion was

**Figure.** Clearly there is more to bone loss after bariatric surgery with a complex interplay of weight loss, nutrient deficiencies, hormonal changes at the level of the gut and pancreas, which involve adipocytokines, neurohormonal interactions, and signaling pathways in the bone microenvironment.
based primarily on the observation that obese individuals have higher bone density than do their lean counterparts. However, recent investigations reveal an increase in fracture risk at the ankle and humerus in women but not men with increased body mass index (BMI). Beyond BMI, body composition appears to matter, with greater degrees of visceral fat increasing, and lean body mass reducing, fracture risk in similarly obese subjects. Related, and of emerging interest, is the influence of marrow fat given its proximity to the bone microenvironment (Figure, see page 1).

How can this paradox of “more bone but more fractures” be explained? L. Joseph Melton III, M.D., of the Division of Epidemiology at Mayo Clinic in Rochester, Minn., answers: “One theory stems from the observation that increases in bone strength among obese individuals, as measured by high-resolution images evaluated with finite element analysis, are not proportional to the excess weight. This could lead to relative bone fragility compared with normal weight individuals. Also, for some fracture types (for example, the ankle and humerus fractures noted above), increased rates of falling in obesity and higher loads at impact may play a role. In contrast, there is a lower risk of hip fractures in obese subjects, which can be explained in part by the biomechanical role that adipose tissue over the hip plays in absorbing impact energy in a fall.”

Dr. Kennel adds: “Morbid obesity is increasingly being treated with bariatric surgery, and derangements of mineral metabolism leading to secondary hyperparathyroidism, bone loss and osteomalacia have long been observed after bariatric surgery. However, the fact that bone loss can occur even when mineral metabolism is optimized, and that it also follows medical weight loss, suggests that changes in neurohormonal, mechanical, nutritional and other factors must be involved (Figure). The fact that the higher levels of serum estrogens in obese men and postmenopausal women decline with weight loss is notable given the key role that sex hormones play in bone metabolism. Any weight loss, and especially surgical weight loss, is also associated with loss of skeletal muscle. That high protein intake and physical activity applied to a restricted energy diet preserved bone mass during weight loss relative to an equivalent energy restriction diet alone suggests that some of the factors favoring bone loss due to weight loss are modifiable.”

Dr. Melton notes: “Ultimately, the occurrence of fractures out of proportion to expectations is the strongest evidence of a clinically important relationship. We recently reported an increase in the incidence of fractures among Olmsted County residents undergoing bariatric surgery at Mayo Clinic compared with that expected for community residents of like age and sex generally. A strength of our study was that it was population-based with a long duration of follow-up, noting that the average time to first fracture was about five years following surgery. In contrast, a study from the U.K. found no increased incidence of fractures after bariatric surgery compared with BMI-matched nonoperated subjects, but this finding was limited by an average follow-up of just over two years. Another key difference between these studies was the choice of bariatric procedure: The majority of subjects in the U.K. study underwent laparoscopic adjustable gastric banding, a less aggressive surgical procedure resulting in less weight loss, and possibly less detrimental to bone, than the gastric bypass procedures currently favored in the U.S.

“Because there are many unanswered questions and few prospective or intervention trials, there are no uniform guidelines for including obesity as a unique risk factor for fracture or for applying osteoporosis guidelines differently to obese or post-bariatric surgery patients. Until such information becomes available, clinicians should be equally vigilant in applying current osteoporosis prevention and treatment guidelines to obese and non-obese patients, as well as to those who have undergone a bariatric surgery.”
Thyroid nodules are common, with palpable nodules found in 4 to 7 percent of the adult U.S. population and solitary or multiple nodules found at much higher rates during ultrasonographic screening. “Most of these nodules — about 90 percent — are entirely benign,” says Diana S. Dean, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn. “However, identifying the occasional thyroid cancer requires careful evaluation of every nodule we find, using a combination of clinical assessment, neck palpation (Figure 1), ultrasound imaging (Figure 2) and, in many cases, analysis of a biopsy specimen (Figure 3).”

Sometimes, thyroid nodules are noticed by the patient or a family member or are discovered during a routine physical examination. They rarely cause symptoms, unless they are large enough to interfere with swallowing. Thyroid cancer can invade and damage the recurrent laryngeal nerve, causing hoarseness. Such invasion and damage are infrequent.

“Most nodules are incidental discoveries,” notes M. Regina Castro, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn., “and now many more such nodules are discovered because of the increased use of imaging performed for other reasons, including carotid ultrasonography, neck or chest computed tomography, magnetic resonance imaging, and even positron emission tomography.”

“Diagnosing a thyroid nodule accurately and promptly is important,” says Geoffrey B. Thompson, M.D., of the Department of Surgery at Mayo Clinic in Rochester, Minn., “because early diagnosis improves the likelihood that a cancer can be discovered while contained within the thyroid gland and amenable to surgery. Once soft tissue invasion has occurred or lymph nodes are extensively involved, the chance of surgical cure drops substantially, especially in older patients, and there is a much higher incidence of metastatic spread of these late-stage cancers.”

Prompt diagnosis is also important for the patient because the finding of a nodule often raises fears about cancer and a delay to diag-
nosis fuels the concern and anxiety. The most recent set of guidelines from the American Thyroid Association specifies that the evaluation of a thyroid nodule should include clinical assessment to determine the number, size and location of all nodules within the gland; measurement of serum thyrotropin (TSH) to exclude hyperthyroidism; an ultrasound to assess the nodule for features of malignancy; and fine-needle aspiration (FNA) of nodules that meet the appropriate size and ultrasound criteria,” says John C. Morris III, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn. However, he goes on to say, “not every nodule needs to be biopsied, so the clinical scenario and ultrasound features are important in selecting the appropriate nodule for biopsy. Typically, these steps involve several appointments for the patient and often take a number of days to weeks. To streamline the evaluation, we created the Thyroid Nodule Clinic, at which patients with thyroid nodules can have their assessment completed within a day or so.”

Opened in July 2009, the Thyroid Nodule Clinic provides a one-stop thyroid nodule evaluation that includes a focused clinical assessment, ultrasound evaluation and FNA — all typically performed within a 60-minute appointment. “The ultrasound allows us to select both palpable and impalpable nodules for biopsy and target the most suspicious nodule, which is not always the largest nodule,” says Dr. Dean. “Using ultrasound guidance for those biopsies, we have improved our diagnostic yield dramatically. We perform more than 800 biopsies every year in this way and can now expect a diagnosis in more than 95 percent of cases at the first attempt.”

Furthermore, because of the coordinated assessment provided through the Thyroid Nodule Clinic, FNA cytology reports are typically available within two hours, so the patient usually receives a definitive result of the entire assessment within four hours. Patients with a benign thyroid nodule can be reassured, and those with a malignant or suspicious nodule can be offered an appropriate surgical referral, often within 24 hours. Dr. Dean concludes: “We believe that the Thyroid Nodule Clinic improves our care of these patients while lowering costs, improving efficiency and providing a better service to the referring physician.”

Figure 3. Thyroid cytology of a specimen of papillary thyroid carcinoma showing papillary architecture and nuclear enlargement with crowding of classic papillary thyroid cancer (Papanicolaou stain, original magnification times 100).
Osteonecrosis of the Jaw (ONJ) Update

A decade has now passed since publication of the first reports of osteonecrosis of the jaw (ONJ) in bisphosphonate (BP) users. Since that time, an association between BP therapy and ONJ has been clearly shown with route of administration (for example, intravenous administration results in greater risk than does oral route), dose (potency) and duration-dependent effects. Bart L. Clarke, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn., says: “Typically patients being treated with BPs in adjuvant fashion to prevent skeletal-related events secondary to cancer or chemotherapy are most at risk of developing ONJ. However, not all patients receiving BP therapy for either cancer or osteoporosis suffer from ONJ, and specific comorbidities have been identified with dentoalveolar surgery, like a dental extraction, local dental suppuration (associated with a dental infection), periodontal disease, radiation therapy to the affected jaw site and systemic steroid therapy being the principal agents.”

James M. Van Ess, D.D.S., M.D., of the Division of Oral Diagnosis and Oral and Maxillofacial Surgery, at Mayo Clinic in Rochester, Minn., says: “The reported cumulative incidence of bisphosphonate-related ONJ ranges from 0.8 to 12 percent; whereas, the cumulative incidence due to orally administered bisphosphonates is much lower at 0.01 to 0.06 percent. Evidence is accumulating that oral BP use for longer than three years may be associated with increased risk of ONJ. These data indicate that ONJ in oral BP users is a relatively rare occurrence and, therefore, comforting to many patients. Nevertheless, ONJ when it occurs is difficult to resolve and can create significant clinical management challenges.”

Sreenivas Koka, D.D.S., M.S., Ph.D., M.B.A., previously at Mayo Clinic in Rochester, Minn., says: “Clinically, ONJ lesions present as white-yellowish areas of exposed bone, sometimes accompanied by pain and erythema of the mucosa or gingival tissue surrounding the lesion (Figure 1). In some patients, the lesions can go unnoticed, especially when the lesions are located on the mylohyoid ridge or in the retromolar region.

Figure 1. Clinical presentation of a large (American Association of Oral and Maxillofacial Surgeons Stage 2) lesion showing erythematous oral mucosa and exposed bone associated with palatal exostosis.
Figure 2. Clinical presentation of small ONJ lesion showing small amount of exposed bone and erythematous gingiva three months after dental molar extraction.

of the mandible. This area is relatively easily traumatized, and the bony protuberance of the mylohyoid ridge and thin covering mucosa are contributing factors. Otherwise, sites of recent dental extraction or exostosis with thin covering mucosa (tori) are also common locations for ONJ to develop. In general, suppressed bone turnover in BP users renders these sites unable to mount the necessary osseous healing response to trauma or extraction and ONJ ensues. In the case of dental extractions, molar teeth (Figure 2) provide the greatest wound-healing challenge due to the large size of the extraction site and hence are the most common sites of ONJ, which is far less commonly seen with extractions of anterior teeth.

Dr. Van Ess adds: “Patients undergoing dentoalveolar surgery such as extractions, and who are receiving IV bisphosphonates, are five to 10 times more likely to develop ONJ than are patients who are not having any surgery. As the highest reported incidence of ONJ is in this specific patient population, our patients needing extractions are reassured that the risk of developing ONJ is low, especially when taken in the oral form. Dental implant therapy in osteoporosis-directed oral BP users is as safe a treatment option as in non-BP users, with ONJ being very rare and dental implant survival rates statistically similar in the two groups.”

Clinical management of patients with ONJ lesions is best undertaken using the American Association of Oral and Maxillofacial Surgeons or American Dental Association staging systems. Depending upon the size of the lesion and associated findings, management protocols range from use of topical analgesics and antibacterial mouthwashes in minor cases to systemic antibiotic therapy for larger lesions. In advanced cases, surgical therapy provided by an experienced oral surgeon may be considered.

The clinical utility of serum carboxy-terminal collagen crosslinks (CTX) testing to identify patients at risk of developing ONJ has received considerable attention. Dr. Clarke comments: “Current evidence indicates that, by itself, serum CTX testing has little support either as an ONJ risk management tool or as an ONJ predictor tool. Therefore, patients and clinicians should avoid the expense and effort in obtaining this test until the time when CTX testing has been proven to have clinical relevance. At present, CTX testing is not recommended, as it provides meaningless information that is of low patient-centric value.”
Anna A. Kundel, M.D., and her program director, Clive S. Grant, M.D. Dr. Kundel’s new appointment is in the Department of Endocrine Surgery at the NYU Langone Medical Center, New York.

Mabel Ryder, M.D., joined the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn., during 2013. Her main area of interest is thyroid cancer.

Wiebke Arlt, M.D., D.Sc., FRCP, FMedSci, professor of medicine and head of the Centre for Endocrinology, Diabetes and Metabolism at the University of Birmingham, U.K., and members of the Pituitary, Gonad and Adrenal Core Group. Seated, left to right: Dana Erickson, M.D., Wiebke Arlt, M.D., Irina Bancos, M.D. Standing, left to right: Stefan K. Grebe, M.D., Ph.D., Paul C. Carpenter, M.D., Johannes D. Veldhuis, M.D., Alice Y. Chang, M.D., Todd B. Nippoldt, M.D., Neena Natt, M.D., Ravinder J. Singh, Ph.D., and Adrian Vella, M.D.
Education Opportunities

17th Annual Mayo Clinic Endocrine Course

Designed for endocrinologists and interested internists and surgeons, the 17th Mayo Clinic Endocrine Update will address gaps in medical knowledge and barriers in clinical practice in order to improve the outcomes of patients with endocrine and metabolic disorders. This course will span the full range of endocrinology, through lectures, debates, panel discussions, clinicopathologic sessions, “clinical pearls” sessions, informal breakfast round-table discussions and small-group discussions with experts. Attendees will have plenty of opportunity for interaction with the course faculty, who are selected from Mayo Clinic for their expertise and clinical acumen. The course will be held at The Westin Kierland Resort & Spa in Scottsdale. For more information about this course, please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.

14th Annual Mayo Clinic Nutrition and Wellness in Health and Disease
Sept. 18-19, 2014, San Francisco

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 — will provide a full-spectrum, in-depth overview of situations that clinicians encounter in the ambulatory setting, including obesity in adults and children, weight management strategies, healthy diets, obesity-associated medical conditions, bariatric surgery and pre- and post-surgery medical management, dietary supplements, effective ways to provide coaching, principles of adult learning, nutrition for selected groups (patients with diabetes mellitus, women with cardiac disease and individuals who are malnourished), in addition to physical activity and wellness. Current clinical topics will be highlighted through presentations, interactive case studies and panel discussions. The course will be held at The Marriott Marquis in San Francisco. For more information about this course, please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.