When Sundeep Khosla, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, hears discussions about the current institutional and national focus on team science, he allows himself a satisfying smile. As a clinical investigator who also pursues epidemiological and basic science studies focusing on the pathogenesis of osteoporosis and age-related bone loss, Dr. Khosla’s professional career has both depended on and fostered team science in his own program and at Mayo Clinic.

Role for estrogen in age-related bone loss in men

As a clinical investigator, Dr. Khosla is perhaps best recognized for his seminal studies in identifying the dominant role that estrogen plays in regulating bone metabolism in men. Dr. Khosla comments: “Since the 1940s, the prevailing dogma regarding hormonal regulation of bone metabolism in men was that this was predominantly and perhaps only by testosterone, whereas in women it was mainly by estrogen.”

In perhaps his best known series of research studies, Dr. Khosla established a new paradigm by demonstrating that estrogen, rather than testosterone, played the dominant role in regulating bone turnover and bone mass in men, completely reversing conventional thinking. In a study that is widely regarded as one of the most elegant clinical-investigative studies performed in the field of bone and mineral metabolism, Dr. Khosla used a factorial design to produce complete sex steroid deficiency in elderly men by pharmacological means and then replaced them with estrogen alone, with testosterone alone or with both hormones. As assessed by biochemical markers of bone turnover, the results clearly showed that estrogen was the dominant hormone regulating bone turnover.

Based on this and several other studies, Dr. Khosla hypothesized that age-related decreases in bioavailable sex steroids, and in particular in bioavailable estrogen levels, were important determinants of age-related bone loss in men.

Epidemiological and imaging studies on bone quality

In population-based epidemiological studies, Dr. Khosla collaborated with L. Joseph Melton III, M.D., of the Division of Epidemiology at Mayo Clinic in Rochester, and Shreyasee Amin, M.D., of the Division of Rheumatology at Mayo Clinic in Rochester, and was the first to apply high-resolution peripheral quantitative

Sundeep Khosla, M.D.
computerized tomography (HRpQCT) to assess changes in trabecular and cortical bone separately and to evaluate bone geometry and bone “quality.” In a series of population-based studies in men and women using both HRpQCT and central QCT, he demonstrated that the postulated threshold for skeletal estrogen deficiency in men was most evident in cortical bone and that age-related changes in trabecular structure may help explain the lower incidence of fractures and, in particular, wrist fractures in men as compared with women.

Dr. Khosla explains: “We have pursued studies to evaluate, in population-based case-control studies, the potential utility of using voxel-based finite element modeling and other, novel image analysis techniques, including the role of cortical porosity, in identifying vertebral or Colles’ fracture patients better than with dual energy X-ray absorptiometry.”

Mouse models for estrogen action on bone
In cellular and mouse studies, Dr. Khosla has worked with Merry Jo Oursler, Ph.D., and David G. Monroe, Ph.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, to conduct extensive studies in mice on the roles of the steroid receptor coactivators (SRCs)-1 and -2 in estrogen action on bone, on skeletal effects of estrogen mediated via classical vs. nonclassical signaling mechanisms, and on basic cellular models examining osteoblast differentiation and sex steroid effects on osteoblastic and bone marrow stromal cells. Dr. Khosla highlights: “We demonstrated that SRC-2 was a coactivator in bone for both estrogen receptor-alpha (ERα) and peroxisome proliferator-activated receptor-gamma (PPARγ), but loss of SRC-2 led to a high bone mass phenotype due to impaired skeletal PPARγ action having a dominant effect over impaired estrogen action. We are continuing this line of work, and using novel mouse models developed in our laboratory, we plan to define more precisely which cells in the bone microenvironment are primarily responsible for triggering the bone loss following estrogen withdrawal.”

Evolving Therapeutic Strategies for Patients With Differentiated Thyroid Cancer

Dilemma: How to manage incidental, low-risk differentiated thyroid cancers
Over the last 30 years, there has been a sharp rise in the incidence of thyroid cancer, with a large proportion of newly diagnosed cases representing incidental, small, papillary thyroid cancers (PTCs). Mabel Ryder, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: “The vast majority of these PTCs are indolent with excellent 20-year survival rates of over 95 percent. It is now becoming clear that treating such patients with total thyroidectomy, radioactive iodine (RAI) therapy and thyroid-stimulating hormone (TSH) suppression may induce greater harm than benefit in patients. The newly revised American Thyroid Association Guidelines for the Management of Thyroid Nodules and Differentiated Thyroid Cancer (expected to be published in late 2014) reflect the evolving needs in this area by supporting lobectomy for low-risk PTCs and a risk-adapted approach for postoperative management that encourages limited use of RAI, shortened and less profound TSH suppression therapy, and optimized surveillance testing for patients with excellent prognoses.” Moreover, the guidelines propose less aggressive approaches to biopsy and therapy of solitary thyroid nodules less than 1 centimeter and PTCs.
**Advanced-stage differentiated thyroid cancers**

In contrast, 10 to 20 percent of patients present with or develop advanced, metastatic RAI-refractory (RAIR) thyroid cancer. Keith C. Bible, M.D., Ph.D., of the Division of Medical Oncology at Mayo Clinic in Rochester, notes that: “Data from the Surveillance, Epidemiology, and End Results (SEER) database estimates that 1,800 people die of thyroid cancer annually, with the majority of deaths from patients with RAIR disease. Moreover, death rates from thyroid cancer, while overall low, have appeared to increase over the past 30 years, indicating a strong need for more effective therapies for high-risk patients.”

**FDA-approved sorafenib for advanced differentiated thyroid cancers**

Current approaches in the treatment of advanced RAIR thyroid cancers involve drugs that target not only the cancer cell, but also the tumor microenvironment. Dr. Bible notes: “Sorafenib, an orally bioavailable multitkianase inhibitor that primarily targets vascular endothelial growth factor receptor (VEGFR), is the first FDA-approved tyrosine kinase inhibitor (TKI) for advanced RAIR thyroid cancer. In the phase III DECISION trial that led to Food and Drug Administration (FDA) approval, progression-free survival was 10.8 months vs. 5.8 for sorafenib- vs. placebo-treated patients, respectively. However, overall survival was no different between the groups, and sorafenib-treated patients had increased therapy-related toxicities and lower quality of life. A major challenge faced by endocrinologists and medical oncologists is thus now in determining when the optimal time is to initiate kinase inhibitor therapy in patients who are often asymptomatic from their disease.”

**Alternative therapeutic strategies for RAIR differentiated thyroid cancers**

**Tyrosine kinase inhibitors in RAIR differentiated thyroid cancers**

TKIs that target oncogenes or their downstream signaling pathways or both to reverse tumor progression or restore radiiodine sensitivity in RAIR disease have yielded promising, albeit mixed, results. Dr. Ryder explains: “Dabrafenib or vemurafenib, for example, inhibit mutant BRAF-V600E, a common oncogenic event in advanced PTCs, and have estimated partial response rates of approximately 30 percent, significantly lower than observed for BRAF-mutant metastatic melanoma, and also lower than response rates reported for several VEGFR-inhibitory kinase inhibitors. Published preclinical data suggests that thyroid cancer cells, unlike melanomas, have intrinsic resistance to the anti-tumor effects of BRAF-V600E inhibition that may be mediated by compensatory activation of additional, but potentially targetable kinases, such as HER2 or HER3.”

A recent promising alternative strategy is to use a short-term inhibition of phospho-MEK to attempt to restore RAI uptake in RAIR disease. Dr. Bible notes: “In a small study published in *The New England Journal of Medicine* in 2013, some patients with advanced RAIR thyroid cancer treated with selumetinib for five weeks experienced restored RAI uptake and restored sensitivity to RAI therapy in RAS-, but not BRAF-, mutant thyroid cancers. This small but potentially paradigm-shifting study suggests that RAI therapy, in the context of mitogen-activated protein kinase (MAPK) pathway inhibition, may have therapeutic benefits in selected patients with advanced-stage disease. Moreover, short-term kinase inhibition therapy has the advantage of minimizing morbidity as well as the potential development of acquired resistance associated with chronic kinase inhibitor use. Efforts remain underway to enhance RAI sensitivity in BRAF-mutant PTCs, which account for disproportionately higher deaths from thyroid cancer.”

**Targeting stromal-derived TAMs**

Allan B. Dietz, Ph.D., of the Division of Transfusion Medicine at Mayo Clinic in Rochester, says: “Targeting stromal cells, in particular tumor-associated macrophages (TAMs), in advanced thyroid cancers has been
little-studied but yet represents a potentially promising emerging therapeutic strategy. Dr. Ryder demonstrated for the first time in a large number of human thyroid cancers that TAMs heavily infiltrate poorly differentiated thyroid cancers (PDTCs) and anaplastic thyroid cancers. Moreover, in PDTCs, increased TAMs correlated with increased invasion and decreased overall survival. Using preclinical models of BRAF-induced thyroid cancers, Dr. Ryder demonstrated that recruitment of TAMs in early- and advanced-stage thyroid cancers could be genetically as well as pharmacologically inhibited, and that this impairs PTC initiation as well as facilitates PTC regression.” Dr. Ryder comments: “My focus now is on characterizing the immune phenotype of patients with advanced thyroid cancers in order to better understand immune response in advanced-stage thyroid cancers. In addition, I am examining how TAMs may influence resistance to existing therapeutics, and whether combination strategies to target TAMs, as well as the tumor cells, may improve disease response rates.”

Conclusion

The landscape of thyroid cancer management is rapidly evolving with a more minimalistic, individualized approach for low-risk patients, and more targeted and evidence-based therapeutic approaches for advanced-stage disease. Dr. Ryder concludes: “A multidisciplinary team approach involving endocrinologists, surgeons, radiologists, and oncologists remains the key for the optimal care of patients across the spectrum of low-risk to advanced-stage disease.”

For more information


Expanded Endoscopic Pituitary Surgery

A major advance in neurosurgery has been the development of new endoscopic techniques for skull base tumors. Skull base tumors pose significant challenges due to their close proximity to important neurovascular structures and potential extension into neural canals or the cavernous sinus. Surgical resection can be associated with significant morbidity, including damage to the optic nerve and leakage of cerebrospinal fluid.

Jamie J. Van Gompel, M.D., of the Department of Neurologic Surgery at Mayo Clinic in Rochester, Minnesota, says, “Everything we do centers around maximal safe resection of tumors, limiting comorbidity to patients and trying to get them back to the normal work or family life they previously had.” Mayo’s experience with skull base lesions ranges from rare types — esthesioneuroblastomas, chordomas and chondrosarcomas — to the more common meningiomas, pituitary tumors, cranioopharyngiomas and sinonasal malignancies.

Dana Erickson, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, says: “All of our patients with pituitary tumors who go to surgery undergo either the endoscopic-microscope approach or the expanded endoscopic approach.”

Dr. Van Gompel adds: “The advantage of the expanded endoscopic approach is that we can now visualize areas in the sella that we could not see previously, enhancing the opportunity for a complete pituitary tumor resection. Unlike the microscope, which focuses light...
narrowly on the tumor — it is like looking through a keyhole in a door — the endoscope works more like a flashlight, bringing the light and visualization to the tumor. The surgery is usually performed by both a neurosurgeon and an otorhinolaryngologist. There are two expert sets of eyes, and often intraoperative discussion about what’s best for the patient. In addition, endoscopes offer different angles of vision, and once the bulk of a pituitary tumor is resected, the endoscope can be advanced into the sella and we can look around the corner.” This technique is of particular value in patients with large tumors with significant suprasellar or cavernous extension.

Dr. Erickson comments: “For our patients with hormone-secreting tumors, like corticotroph tumors causing Cushing’s syndrome or somatotroph tumors causing acromegaly, complete resection at the first operation is key to successful long-term cure.”

Dr. Van Gompel adds: “The expanded use of the endoscope has been made possible by technological advances in neurosurgical techniques, improvements in light intensity and high-definition imaging.”

Conclusion
Dr. Erickson concludes: “The range of experience and expertise at Mayo Clinic allows patients to receive care appropriate to their individual needs. The development of endoscopic techniques for the management of sellar and parasellar tumors has been a major advance in our pituitary practice.”

An endoscopic endonasal approach to the resection of sellar and parasellar tumors allows visualization of areas in the sella that could not be seen previously and enhances the opportunity for a complete pituitary tumor resection.

Use of Smartphone App to Prepare Patients for Bariatric Surgery

Although we have recently seen a stabilization of the overall prevalence of obesity in the United States, the number of individuals with a body mass index (BMI) of 40 or greater (class III obesity) continues to grow. Manpreet S. Mundi, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: “Fortunately, we now have multiple options to offer patients seeking assistance with weight loss. Within the last few years we have seen two new drugs approved for long-term treatment of obesity — lorcaserin (Belviq) and the combination preparation of phentermine and topiramate extended-release (Qsymia) — and the emergence of endoscopic interventions to manage weight. Recent randomized, controlled trials have further solidified bariatric surgery as the most effective means of achieving adequate and sustained weight loss, with a concomitant improvement in related comorbidities, particularly type 2 diabetes mellitus.

“Regardless of the intervention used, however, successful weight management depends on an adequate understanding of nutrition and physical activity fundamentals, coupled with mechanisms to assist patients in developing and maintaining a high level of engagement in
lifestyle modification. Unfortunately, the comprehensive nature of weight management often necessitates tremendous resource utilization. Given the high level of scrutiny to control healthcare costs, it can be difficult to reconcile obtaining the required resources with those available.”

Paul A. Lorentz, R.N., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, explains: “Fortunately, mobile technology, with its rapid and widespread adoption by the general population, offers a unique platform to provide valuable resources in a cost-considerate manner (Figure 1). Recent research suggests that traditional weight-loss programs can be enhanced by mobile technology such as text messages, social media and virtual coaching. Much of this research suggests that patients are generally accepting of and often prefer mobile platforms for intervention delivery.”

Dr. Mundi continues: “However, we feel that this is simply the tip of the iceberg. In addition to cost-effectively educating patients, mobile
technology can also engage and intervene with patient populations in real time, while in their natural environment. Using the concepts of ecological momentary assessment (EMA) and ecological momentary intervention (EMI), terms first coined by Stone and Shiffman in 1994, a powerful, synergistic behavior modification platform can be created. In fact, one of the main benefits is that the interventions can be facile and simple, but significant enough to increase self-awareness and mindfulness, such as asking patients to photo capture diet choices through a smartphone app (Figure 2). Similarly, because mobile technology supports real-time data gathering, the significant recall bias prevalent in traditional, self-report formats is drastically reduced, allowing for a more objective clinical assessment.

Lorentz explains: “Building upon these principles, our group has developed smartphone apps to assist patients preparing for bariatric surgery and those who have undergone bariatric surgery. The apps educate our patients through the use of video-based education modules (Figure 3) that are paired with short assessments, ensuring mastery or identifying deficiencies in a particular topic.”

Through the use of algorithmic EMA/EMI text messaging, the apps allow for robust, real-time data collection, while simultaneously providing an intervention. Dr. Mundi highlights: “We recently completed a trial, assessing the acceptability and feasibility of using this mobile technology in our clinical practice. Overall, the subjects expressed very high satisfaction, with most feeling that the app fit into their routine easily, while containing an appropriate amount of messaging. Patients also reported that the app was quite helpful in their preparation for bariatric surgery.

“Our feasibility trial also provided us with some intriguing data. To ensure that the EMA messaging was ‘real time,’ unanswered messages were programmed to expire within 60 minutes. Interestingly, we learned that the EMA response rate, arguably a correlate of patient engagement, was highest right after patients completed their initial appointment. The response rate started and continued to decrease for eight to 10 weeks after the patient’s initial appointment. Interestingly, the EMA response rate started to increase as patients were preparing to return for their follow-up appointments. This certainly points out a clinical need to identify methods, mobile and otherwise, that can increase and sustain patient engagement throughout the pre-surgical period. Although this study was simply a feasibility trial, we did note that patients using the apps tended to lose slightly more weight prior to surgery.”

Dr. Mundi concludes: “Clearly, mobile technology has a role to play in the delivery of efficient and effective health care. It’s also likely that what we’ve found to be beneficial in our bariatric surgery practice will be diffusible to many areas of specialty practice with similar needs (patient education, engagement, connection, cost containment). What remains to be answered is how the role of mobile technology will evolve, and how to best utilize the same, augmenting traditional care models with its known attributes (low-cost, dynamic, real-time interaction, and so on) while not compromising the quality of patient care and related outcomes.”
Education Opportunities

For more information about these courses, please call 800-323-2688 (toll-free) or visit www.Mayo.edu/cme/endocrinology.

Mayo Clinic Nutrition and Wellness in Health and Disease
Sept. 18-19, 2014, in 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, ambulatory nutrition topics in the news, and a healthy-cooking demonstration, in addition to physical activity and wellness. Current clinical topics will be highlighted through presentations with teaching pearls, interactive case studies and panel discussions. The course will be held at Marriott Marquis in San Francisco.

18th Annual Mayo Clinic Endocrine Update
Feb. 16-20, 2015, in Riviera Maya/Cancun, Mexico

Designed for endocrinologists and interested internists and surgeons, the 18th Annual 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 Fairmont Mayakoba in Quintana Roo, Mexico. To ensure accommodations at the discounted rate, please make your reservations directly with the hotel by calling 800-441-1414 (toll-free). Identify yourself as a participant of the Mayo Clinic Endocrine Update.

2014 Graduating Endocrine Surgery Fellow

Geoffrey B. Thompson, M.D., program director, poses with graduating fellow Benzon M. Dy, M.D. Dr. Dy’s new appointment is in the Winchester Surgical Clinic in Winchester, Virginia.

Mayo Clinic
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