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The theme of the Basu-Kudva-Basu laboratory continues in the long and rich tradition of clinical investigations directed at understanding the integrative physiology of glucose metabolism in humans with and without diabetes mellitus (DM). This line of investigation was pioneered by Robert A. Rizza, M.D., former chair of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, Minn., and past president of the American Diabetes Association. Ananda Basu, MBBS, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn., says: "While continuing to research novel aspects of type 2 diabetes and prediabetes, the group has come a full circle in an attempt to close the loop for type 1 diabetes from the inpatient clinical

research-based intravenous insulin Biostator experiments performed by Dr. Rizza in the late 1970s and early 1980s to current ambulatory translational near-term reality using subcutaneous glucose sensing and insulin delivery."

Is closed-loop control with artificial pancreas imminent in type 1 diabetes?

Yogish C. Kudva, MBBS, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn., says: "The short answer is a resounding yes! Building upon the almost 20 years of experience (under the tutelage of Dr. Rizza), the laboratory is focused on conducting experiments designed primarily to better understand the effects and effect sizes of day-to-day factors that influence glucose control and vari-

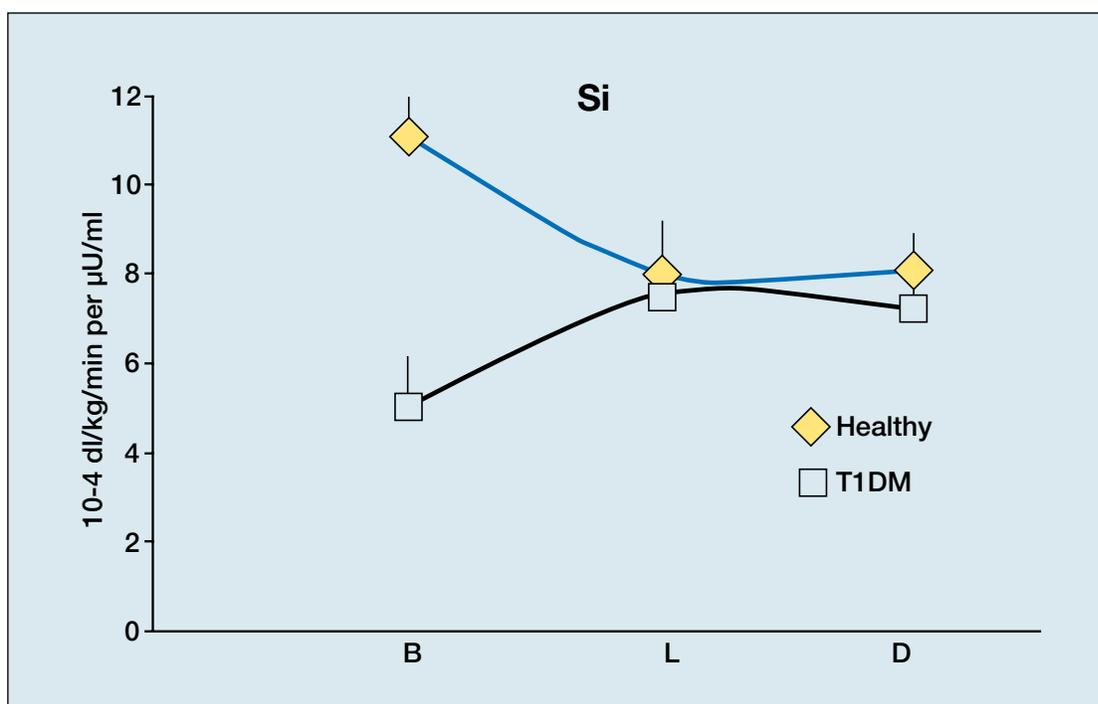


Figure 1. Shows diurnal patterns of Si (insulin sensitivity index) at breakfast (B), lunch (L) and dinner (D) in healthy subjects and in those with type 1 diabetes.



Ananda Basu, MBBS, M.D., Rita Basu, M.D., and Yogish C. Kudva, MBBS

ability in people with type 1 diabetes. A better understanding of these parameters can then inform and refine a closed-loop control algorithm that would eventually be individualized for each patient with type 1 diabetes.”

Some of the factors that the team is currently investigating, in collaboration with Claudio Cobelli, Ph.D., of the University of Padova, Italy, include:

- Is there a diurnal pattern to insulin action in people with type 1 diabetes? Dr. Ananda Basu answers: “In a series of complex and meticulously designed experiments, we have shown that there indeed appears to be a diurnal pattern to postprandial insulin action in type 1 diabetes that is opposite to that observed in healthy controls (Figure 1). We are now exploring possible causes for this difference that could generate new concepts and hypotheses on other circadian hormonal control of glucose metabolism.”
- What is the role of low- and moderate-intensity physical activity on postprandial glucose excursion and glucose variability? Dr. Kudva answers: “Applying state-of-the-art techniques and with collaboration from Dr. James Levine (Division of Endocrinology, Mayo Clinic in Arizona), it is evident that even low-intensity physical activity (that mimics activities of daily living) has a profound impact on postprandial glucose excursions in people with and without type 1 diabetes (Figure 2) and can also predict the rate of rise and fall of glucose after a meal. Furthermore, it appears that the timing of the physical activity in relation to the meal is a vital modulator of glucose variability. Additional experiments are being conducted that will help incorporate energy expenditure and physical activity into closed-loop control algorithms.”
- Role of glucagon on “hypoglycemia prevention and rescue” in type 1 diabetes. Rita Basu, M.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn., says: “Current experiments will determine whether hepatic glucagon sensitivity varies with ambient glucose concentration in people with type 1 diabetes. Such information is critical for the design of the control algorithm, especially for future bihormonal closed-loop control systems.”
- Dawn phenomenon in type 1 diabetes. Dr. Kudva explains: “The dawn phenomenon is not only an enigma but also a thorn in the physician’s armamentarium that challenges the diabetologist and adversely affects glucose control in type 1 diabetes. The team is applying cutting-edge methods to determine the cause, effect size and reproducibility of this phenomenon. A better understanding of all these issues is vital to achieve optimal overnight glucose control in closed-loop systems.”

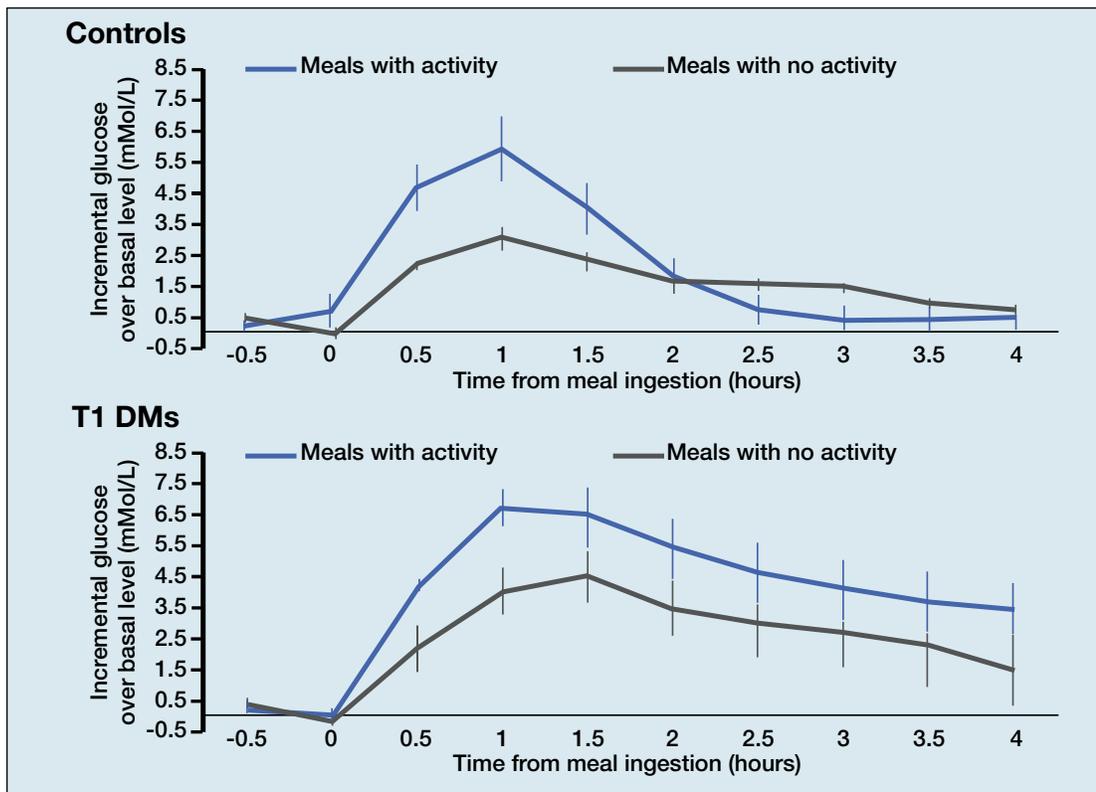


Figure 2. Shows postprandial glucose excursions in control subjects and in those with type 1 diabetes without and with low grade physical activity. Reproduced with permission, *Diabetes Care*, December 2012.

Can glucose sensing be improved?

The premise of an effective and safe closed-loop control system begins with accurate continuous glucose sensing within the interstitial fluid of the subcutaneous space. Dr. Ananda Basu comments: “However, the Achilles’ heel of the closed-loop effort has been limitations in, one, understanding the kinetics of glucose transport between the intravascular compartment and the subcutaneous tissue where the glucose sensors are lodged and, two, precision and accuracy of currently available glucose sensors. The investigative team led by Dr. Rita Basu is conducting pioneering experiments applying innovative isotope dilution techniques and methods to determine the

kinetics of glucose transport and the modulating effects of meals, activity and obesity. Defining these parameters will close a vital gap in the physiology of glucose transport and will clearly help refine and improve closed-loop control algorithms that currently account for the kinetic delay by applying an ‘arbitrary’ time lag in the algorithm. Furthermore, the team, led by Dr. Kudva, in collaboration with Dr. Steve Koester, an electrical engineer at the University of Minnesota, is also exploring novel varactors derived from carbon that could be used as innovative glucose sensors addressing several of the shortcomings with current sensing approaches.”

Major Progress in Understanding Osteoclast Function

Osteoclasts are large multinucleated cells that are responsible for bone degradation (resorption) in all vertebrate animals. Merry Jo Oursler, Ph.D., of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minn., explains: “The rate at which bone is lost depends mostly on the number of osteoclasts in contact with the bone. In young adults, the amount of bone lost through osteoclast activity is replaced by new bone formation. This ‘coupling’ of bone resorption to bone formation breaks down with aging. With age, increased osteoclast activity causes osteoporosis that can lead to debilitating fractures. Our interests are to uncover the mechanisms that regulate bone resorption, how bone resorption is coupled to formation, and how these mechanisms break down with aging. Our expectation is that resolving these questions will lead to more-effective therapies to prevent debilitating bone loss associated with aging. Below are listed our current projects.”

Mechanisms of osteoclast fusion

The question relates to the role of the anti-adhesive protein PODXL in regulating osteoclast fusion and function. Dr. Oursler

reports: “We have found that downregulation of PODXL expression is required for osteoclast fusion. Mice lacking PODXL in osteoclast lineage cells have a high bone mass in spite of an increase in the number of osteoclasts. Our studies have found that a low level of PODXL is required for proper osteoclast function through regulation of osteoclast cytoskeletal control of bone attachment and resorption. We are currently resolving the roles of PODXL in osteoclast differentiation and function.”

Mechanisms by which osteoclasts control bone formation

Osteoclasts secrete several factors that recruit osteoblast precursors and promote their differentiation and bone formation. Dr. Oursler explains: “We have determined that osteoclasts secrete sphingosine-1-phosphate (S1P), bone morphogenetic protein 6 (BMP6) and Wnt10b. S1P recruits osteoblast precursors to the bone surface and both BMP6 and Wnt10b stimulate osteoblast differentiation and promote mineralization. We are examining how gene expression of these factors is modulated during osteoclast differentiation and how they function to promote bone formation.”



Merry Jo Oursler, Ph.D., (on left) and her research team (from left) Christine M. Hachfeld, Larry G. Pederson, Ming Ruan, MD, and Megan M. Weivoda, PhD.

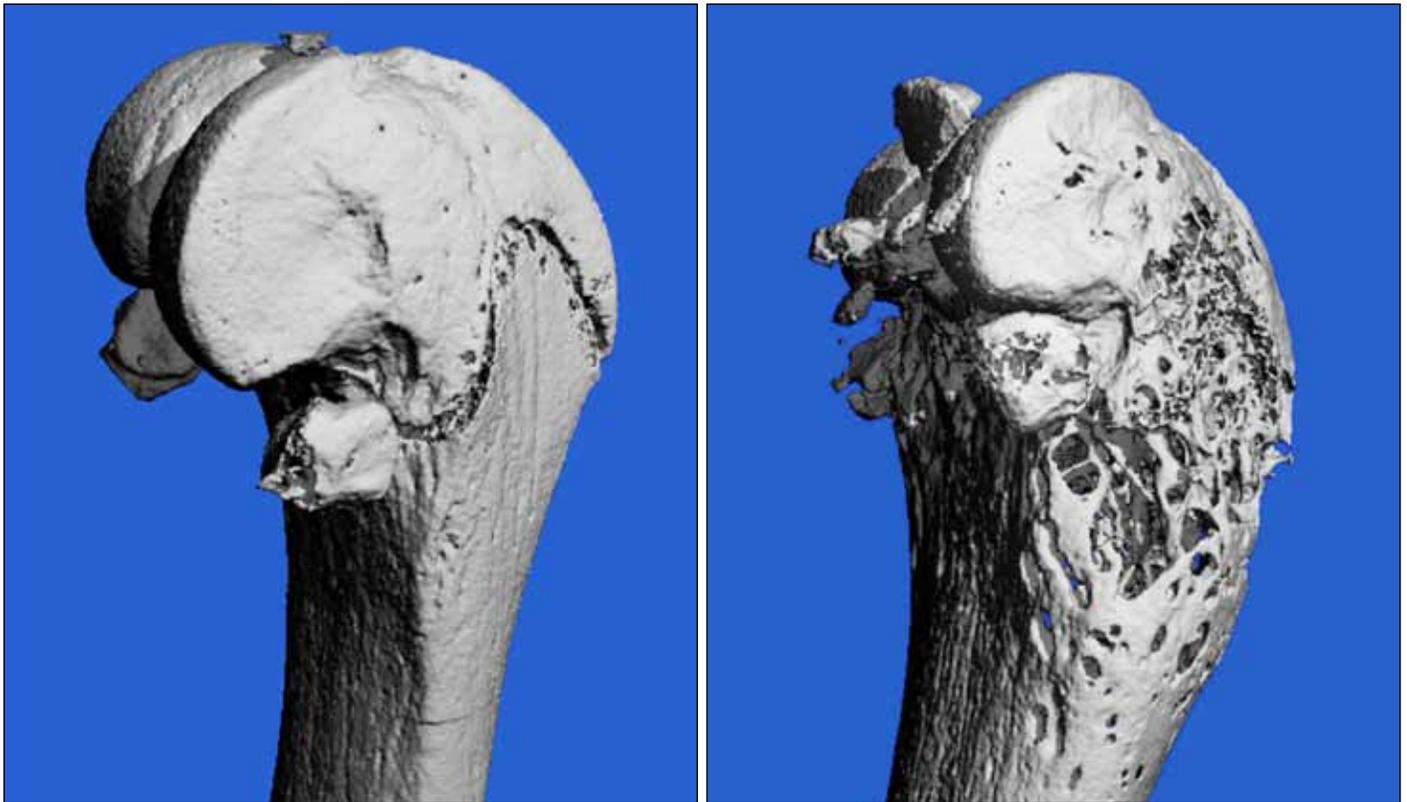


Figure. Shows that loss of β -catenin during osteoclast differentiation increases bone loss, resulting in large holes in the cortical bone (right image).

Changes in osteoclast control bone formation with aging

Although numerous therapies exist to prevent osteolysis and bone loss, there is still a paucity of anabolic therapies. Dr. Oursler says: “A new and promising anabolic therapy is an antibody that neutralizes sclerostin and thereby enhances Wnt stimulation of bone formation. We have discovered that early osteoclast precursors secrete sclerostin, which inhibits Wnt effects on osteoblasts. During osteoclast differentiation, sclerostin expression is suppressed, allowing coupling of bone resorption to subsequent bone formation. Osteoclasts from aged, but not young, mice secrete sclerostin, and this could uncouple bone formation from bone resorption. We are examining the role of osteoclast sclerostin in the uncoupling that develops with aging.”

Role of Wnt signaling in regulating osteoclast differentiation and functions

Data that have not been extensively explored show that anti-sclerostin therapy also decreases osteoclast numbers and reduces bone resorption. Dr. Oursler notes: “The mechanisms responsible for this anti-

resorptive phenotype are unknown. Our data support that Wnts directly inhibit osteoclast formation, and we are investigating how Wnts suppress osteoclast differentiation. In a mouse model for targeting genes, we deleted the Wnt signaling intermediate beta catenin (β -catenin) in osteoclast precursors to block canonical Wnt signaling during osteoclast differentiation. MicroCT scanning revealed that bone resorption was so extensive in bones from mice lacking β -catenin that there were holes in the cortical bone by 17 weeks of age (Figure). We have found that Wnts can also activate an alternate pathway not influenced by sclerostin and the outcome of activation of this alternate pathway is to promote osteoclast differentiation and increase bone resorption. Thus, Wnt signaling can either suppress bone resorption by reducing osteoclast differentiation or promote bone resorption by stimulating differentiation, depending on which pathway is activated. We are investigating the balance of these suppressive and stimulatory effects of Wnts on osteoclast differentiation. Our expectation is that this will allow for better targeted therapies to build bone while preventing bone loss.”

Online Endocrine Surgery Curriculum



David R. Farley, M.D.

David R. Farley, M.D., of the Section of Endocrine Surgery, Department of Surgery, at Mayo Clinic in Rochester, Minn., says: "Recent data suggest many current surgical trainees will likely do fewer operations in their training, see fewer patients, and be placed under the gun less often than their surgical teachers and mentors were during their respective surgical residencies. Will less repetition and less practice result in less mastery? Surgery program directors around the country support duty-hour regulations with clear benefits to well-being, family and lifestyle concerns. However, many program directors and surgical educators are nervous the final training product of duty-hour-limited surgical programs may be inferior to graduating chief residents in the past."

Dr. Farley was the director of the General Surgery (GS) Residency Program at Mayo Clinic in Rochester, Minn., for 15 years; more than 300 surgical trainees arrived and departed under his watch, and he is anxious but optimistic about future graduates. Dr. Farley explains: "Although I see a very real possibility of less experience, less depth and less repetitions for surgeons in training, I see great opportunities for improvement. Mayo Clinic has an exceptional GS training program, which includes separate rotations with our four endocrine surgeons. Mayo GS trainees typically graduate in five years having seen, helped and performed more than 15 parathyroidectomies, 20 thyroidectomies and five adrenalectomies; such volume puts each over the 90th percentile for endocrine surgery experience among U.S. general surgery graduates. A single Mayo endocrine surgery fellow spends an additional full year with endocrine surgeons, endocrinologists, radiologists and pathologists and will participate in more than 200 endocrine operations."

Dr. Farley continues: "The problem boils down to how do you train young physicians to become outstanding surgeons in less time?" Clearly using the time spent in the hospital, operating room, clinic, intensive care unit and emergency room more efficiently is important. Additionally, time spent at home or at leisure

could be utilized. If teaching and learning became enhanced, greater gains would be possible in less time. If learners came to the operating room better prepared, this would be ideal.

Dr. Farley has created more than 1,100 video clips that are compiled into 18 separate modules on how to perform general surgery operations. Taking whiteboard audiovisual clips that explain relevant anatomy and operative technique and sequentially inserting actual operative clips with voice-over allows surgeons in training to grasp the issues and problems and then watch the procedure unfold. The thyroid, parathyroid and adrenal surgery "How to" modules each take about 25 minutes to watch. They are available online 24/7 for all Mayo surgery residents. Dr. Farley's expectation is that after watching the video, trainees will take a multiple choice exam on the subject and procedure. They must obtain 100 percent correct prior to being allowed to assist in any procedure involving Dr. Farley, who explains: "Our patients deserve a competent trainee assisting with the procedure, and our trainees deserve to be well prepared and taught before embarking on a stressful procedure with real ramifications."

Early feedback would suggest the pilot project is working well. Dr. Farley highlights: "Trainees love the videos and ask for other staff to generate the same how-to curriculum. As a staff person, I see a more engaged and capable learner. I get less blank stares when asking a question or pondering what the next step might be." And what if the trainee doesn't get 100 percent on the quiz? Dr. Farley answers: "It hasn't happened yet. The answers are on the video, and trainees can repeat the exam. I just want them more knowledgeable when they operate on our patients."

Preliminary work with online surgical games suggest developing a more interactive curriculum works even better, and Dr. Farley and his research team are developing games to challenge learners in thyroidectomy, parathyroidectomy and laparoscopic adrenalectomy. Dr. Farley concludes: "It is a great time to be a surgical educator and, I hope, to be a surgical resident."

2013 Graduating Clinical Endocrinology Fellows



Left to right (and upcoming appointment): Adina F. Turcu, M.D., (University of Michigan, Ann Arbor, Mich.); Catalina Norman, M.D., Ph.D., (Medical Associates of Cape Cod, Endocrine Practice, Hyannis, Mass.); Kurt A. Kennel, M.D., (training program director, Clinical Fellowship in Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, Minn.); Nicola Gathaiya, M.D., (CoxHealth, Springfield, Mo.) and Jennie H. Law, M.D., (Northside Hospital, Canton, Ga.).

2013 Isley Lecturer



Henry N. Ginsberg, M.D., Irving Professor of Medicine, director, Irving Institute for Clinical and Translational Research, Columbia University, New York, presented the 2013 William L. Isley Lecture at Mayo Clinic in Rochester, Minn., in February 2013. Dr. Ginsberg (center) is pictured with John M. Miles, M.D., (l–eft) and William F. Young Jr., M.D., (right).

2013 Samuel F. Haines Lecturer



Elizabeth N. Pearce, M.D., M.Sc., Boston University School of Medicine, and members of the Mayo Clinic Thyroid Core Group. Seated, left to right: Hossein Gharib, M.D.; Elizabeth N. Pearce, M.D., M.Sc.; Rebecca S. Bahn, M.D. Standing, left to right: Vahab Fatourehchi, M.D.; Diana S. Dean, M.D.; Norman L. Eberhardt, Ph.D.; Ian D. Hay, M.D., Ph.D.; Stefan K. Grebe, M.D., Ph.D.; M. Regina Castro, M.D.; Marius N. Stan, M.D.; Michael D. Brennan, M.D.; and John C. Morris III, M.D.

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Education Opportunities

13th Annual Mayo Clinic Nutrition and Wellness in Health and Disease

Nov. 4-5, 2013, 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 — 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 malnourished individuals), 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 Westin Michigan Avenue in Chicago. For more information about this course, please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.

17th Annual Mayo Clinic Endocrine Course

Feb. 26-March 1, 2014, Scottsdale, Ariz.

Designed for endocrinologists and interested internists and surgeons, the 17th Annual Mayo Clinic Endocrine Course 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.

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