# Endocrine Notes

## In This Issue:

<table>
<thead>
<tr>
<th>Page</th>
<th>Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Cleveland Clinic Recruits Established Leader</td>
</tr>
<tr>
<td>6</td>
<td>Cleveland Clinic Establishes New Thyroid Center</td>
</tr>
<tr>
<td>8</td>
<td>The Risk of Developing CAD or CHF in DM2 Patients</td>
</tr>
<tr>
<td>9</td>
<td>Robotic Adrenalectomy Available</td>
</tr>
<tr>
<td>10</td>
<td>TSHR mRNA for Detecting Thyroid Cancer</td>
</tr>
<tr>
<td>12</td>
<td>Why Iodine Depletion IS Necessary</td>
</tr>
<tr>
<td>13</td>
<td>Diagnostic Characteristics of NSC Using LC-MS/MS</td>
</tr>
<tr>
<td>14</td>
<td>New Vitamin D-Based Multidimensional Nomogram</td>
</tr>
<tr>
<td>16</td>
<td>Gastric Bypass versus Gastric Restrictive Surgery</td>
</tr>
<tr>
<td>18</td>
<td>Does WC Predict Mortality?</td>
</tr>
<tr>
<td>20</td>
<td>Ultrasound Screening for Detecting Thyroid Cancer</td>
</tr>
<tr>
<td>21</td>
<td>Case Study: Painful Diabetic Neuropathy</td>
</tr>
<tr>
<td>22</td>
<td>Optimal Control in Patients with Acromegaly</td>
</tr>
<tr>
<td>24</td>
<td>Staff Directory</td>
</tr>
<tr>
<td>26</td>
<td>Clinical Trials</td>
</tr>
</tbody>
</table>

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# Endocrine Notes

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Dear Colleagues,

I am very pleased to present the 2009 Endocrine Notes. With the creation of the Endocrinology & Metabolism Institute in 2008, for the first time this publication represents the activities of all Cleveland Clinic departments involved in medical and surgical subspecialties primarily focused on the endocrine system.

The Endocrinology & Metabolism Institute is one of 16 new clinical institutes at Cleveland Clinic, formed by bundling multiple specialties together based on specific organ systems and disease states. With this new organization, we have an eclectic group of endocrinologists, endocrine surgeons, bariatric surgeons, bariatricians – and even a cardiologist – who staff three units: the Department of Endocrinology, Diabetes and Metabolism, the Department of Endocrine Surgery and the Bariatric and Metabolic Institute. Full integration of these seemingly disparate units was accomplished with ease because of the spirit of Cleveland Clinic’s philosophy of “acting as a unit” and “all for one and one for all.”

Moving forward, Endocrine Notes will include articles from our endocrinologists, endocrine surgeons or bariatric surgeons, as we dissolve traditional borders and collaborate with one another to improve care for all patients with endocrine difficulties.

In this issue, we introduce you to Dr. Laurence “Ned” Kennedy, the new chairman of our Department of Endocrinology, Diabetes and Metabolism (page 4). Dr. Kennedy, an established leader in the field of endocrinology, joined us from the University of Florida in Gainesville, where he most recently served as Professor and Chief of the Division of Endocrinology. We are very excited to now have Dr. Kennedy on board and working with our team to enhance many of our existing programs, as well as establishing a new Center for Diabetes that will open later this year. We also have been quite fortunate to have Dr. Robert Zimmerman lead the department during our search for a new chair.

You will also find articles on our most recent research findings, such as Dr. Zimmerman’s work on the risk of developing coronary artery disease or congestive heart failure and/or death in type 2 diabetes patients taking various anti-diabetic agents (page 8) and work by Dr. Sangeeta Kashyap on the acute effects of gastric bypass versus gastric restrictive surgery on β-cell function and insulinotropic hormones in severely obese patients with type 2 diabetes (page 16). We also highlight new services offered, such as robotic adrenalectomy (page 9) and our new thyroid center (page 6).

I hope that you enjoy this issue of Endocrine Notes and find the information interesting and useful in your practice. Please do not hesitate to contact me at 216.444.6568 or 800.223.2273 ext.46568 with questions or for more information on how we can help you as you care for your patients. Our entire staff remains committed to the core ideology of Cleveland Clinic: “Patients First.”

Sincerely,

James B. Young, MD  
Chairman, Endocrinology & Metabolism Institute  
Professor of Medicine and Executive Dean,  
Cleveland Clinic Lerner College of Medicine of Case Western Reserve University  
George and Linda Kaufman Chair  
Physician Director, Institutional Relations and Development

To refer patients to Cleveland Clinic’s Endocrinology & Metabolism Institute, please call 216.444.6568.
Officially joining the Department of Endocrinology, Diabetes and Metabolism on April 1, 2009, Dr. Kennedy came to Cleveland Clinic from the University of Florida in Gainesville, where he most recently served as Professor and Chief of the Division of Endocrinology.

“We are pleased to have such an established leader in the field of endocrinology join our team and continue to develop this talented department of physicians who excel at providing the highest-quality care to patients with a wide range of complex endocrine diseases,” says EMI Chairman James Young, MD.

Dr. Kennedy is a medical graduate of Queen’s University in Belfast, Northern Ireland. He completed his General (Internal) Medical Training as a resident at the teaching hospitals of Queen’s University. He completed a fellowship in endocrinology at the Royal Victoria Hospital, Belfast, followed by a research fellowship in the Endocrine Division of the University of Florida. He is a Fellow of the Royal College of Physicians of both London and Edinburgh.

For more than 30 years, Dr. Kennedy has been actively involved in clinical research in the fields of diabetes and pituitary disease. Particular areas of interest have been glycation of hemoglobin (HbA1c) and other proteins, and the link between glycemic control and the development of diabetes complications. Dr. Kennedy was an investigator in the United Kingdom Prospective Diabetes Study, has been a Primary Investigator in the NIH-sponsored BARI 2D study, and a sub-Primary Investigator in a NIH-funded study examining whether testosterone with or without growth hormone will improve bone structure in men deficient in testosterone and growth hormone, as well as additional trials involving acromegaly and Cushing’s disease.

Dr. Kennedy will now lead a department that is among the best treatment providers of diabetes and related conditions in the nation, which sees more than 17,000 patients each year. Its staff of 13 physicians offers expertise in every area of Endocrinology, from type 2 diabetes to thyroid cancer. Its members are involved in the teaching and training of a new generation of endocrinologists and also participate in a variety of research and scientific activities.

Dr. Kennedy’s vision for the Department of Endocrinology, Diabetes and Metabolism includes increasing its number of physicians and improving access and collaboration among endocrinologists, endocrine surgeons and bariatric
surgeons within the EMI. He also wants to enhance inpatient pre- and post-surgical diabetes care and has plans to grow its thyroid cancer and pituitary programs, the latter of which includes a newly established clinic to see pituitary patients at Cleveland Clinic in Florida, Weston, Fla.

“I have been very impressed by the caliber of the people who make up this department, which influenced my decision to join Cleveland Clinic,” Dr. Kennedy says. “Dr. Robert Zimmerman has done an excellent job managing this department in the interim for the past two and a half years. I am excited to now be on board and working with this excellent team, and of course it is a privilege to be given the opportunity to lead a department at Cleveland Clinic.”

Another goal of Dr. Kennedy’s is establishing a Center for Diabetes, which will be headed by Robert Zimmerman, MD, as Director. The Center for Diabetes, which is scheduled to open soon, will unite various disciplines to provide the highest-quality treatment and education. The Center also will encourage diabetes patients to seek help from endocrinologists much sooner in their care than is currently the standard.

“There is a tendency for patients with diabetes to not be referred to endocrinologists until late in their disease. My aim is for us to see more newly diagnosed patients with type 2 diabetes, perhaps for a limited time, to make sure they are on the right track with their care and then return them to their primary care doctors,” Dr. Kennedy says. Various studies, he says, show that emphasizing good control of blood sugar is most effective in newly diagnosed patients.

“If you wait until the patient has had diabetes for 10 to 15 years, then putting emphasis on excessively tight blood sugar control could possibly do more harm than good,” he notes. “We need to turn people’s thinking around and get diabetes patients specialty care sooner.”

Dr. Kennedy has published more than 80 peer-reviewed articles and delivered invited lectures throughout the United States, as well as in Canada and Europe. He also serves as the Chairman of the Grant Review Committee of the American Diabetes Association and is on the editorial board of Diabetes Care.

For more information, contact Laurence Kennedy, MD, at 216.445.8645 or kennedl4@ccf.org.
Cleveland Clinic Establishes New Thyroid Center

A new multidisciplinary Thyroid Center has been created within Cleveland Clinic’s Endocrinology & Metabolism Institute to streamline care for patients with all types of thyroid disorders, including thyroid cancer, thyroid nodules, hyper- and hypothyroidism conditions such as Graves’ and Hashimoto’s diseases, medication-induced thyroid disorders, and hereditary neoplasias.

Established in November 2008, the Thyroid Center brings together endocrine surgeons, endocrinologists and their nursing staff under one roof to provide comprehensive and collaborative care, explains Mira Milas, MD, endocrine surgeon and director of the new center.

“The reorganization of Cleveland Clinic into an institute model, focused on organ and disease systems rather than physician specialties, has really allowed this multidisciplinary center to happen,” Dr. Milas says. “This is a center designed to provide the best care to patients with thyroid problems by ready access to many dedicated specialists and ongoing innovations. Our goal is to reach out to both patients and their referring physicians and bring new benefits to the care of thyroid conditions – from routine problems to the most complex.”

The Thyroid Center, which is co-directed by endocrinologists Mario Skugor, MD, and Christian Nasr, MD, eliminates the need for patients to travel to four or five separate locations for various medical appointments and testing. Patients with thyroid disorders are now triaged to improve both efficiency and the patient experience. The expertise of collaborators from a number of fields – pathology, radiology, genomic medicine, oncology, and other surgical specialties – is integral to the center.

Dr. Milas says establishment of the center is timely because thyroid cancer has the most rapidly rising incidence rate of any cancer to affect women, and also has rising mortality rates for cancers among men. Nationwide, the advantages of medical care in specialized, high-volume centers are increasingly being contemplated. Recent research highlights benefits for patients treated at high volume centers for thyroid and parathyroid surgery, in terms of fewer complications and improved outcomes.1,2,3

The Thyroid Center will now be home to the largest thyroid cancer surgical
“This is a center designed to provide the best care to patients with thyroid problems by ready access to many dedicated specialists and ongoing innovations. Our goal is to reach out to both patients and their referring physicians and bring new benefits to the care of thyroid conditions – from routine problems to the most complex.”

program in Ohio and the five surrounding states, having high patient volumes that include about 500 endocrine neck surgical procedures every year – many of which are for complex and reoperative surgeries.

The new center is dedicated to bringing new knowledge and advantages to both patients and physicians. It is one of only few centers nationwide to provide radiofrequency ablation of liver metastases from thyroid cancer and have robotic surgery expertise. It also has nationally and internationally recognized expertise in thyroid ultrasound, and novel diagnostic markers and genetic evaluations of thyroid cancer patients.

The Thyroid Center, which will move into a new home in September, hopes to enhance current programs in clinical, translational and outcomes research, as well as provide access to clinical trials for patients with thyroid cancer, Dr. Milas adds.

For more information, contact Mira Milas, MD, at 216.444.4985 or milasm@ccf.org.

History of Thyroid Disease Care at Cleveland Clinic

Our new Thyroid Center builds upon Cleveland Clinic’s history of innovation in thyroid care, which dates back to George Crile, Sr., MD, a founding member of Cleveland Clinic who was a pioneer in the area of thyroid surgery. With meticulous surgical technique, he was able to improve the safety of thyroid surgery, a previously high-risk procedure, and to develop the modified radical neck dissection, giving Cleveland Clinic international recognition as a center for patient referral. Dr. Crile performed more than 35,000 thyroidectomies and this was part of the early fame and success of Cleveland Clinic.

This legacy was continued by his son, George Crile, Jr., MD, who established a standard operation for patients with thyroid cancer, as well as breast cancer, by demonstrating that less radical and less disfiguring procedures gave excellent results. Caldwell Esselstyn, MD, subsequently set the standard for more than 30 years as a leader in endocrine surgery, with a nationally and internationally respected reputation in the areas of parathyroid and thyroid surgery.

Our new Thyroid Center will build upon ongoing growth in clinical, research, and education endeavors. Cleveland Clinic is ranked among the top 10 best centers for endocrine disease treatment in the country by U.S. News & World Report.

The Risk of Developing CAD or CHF and Overall Mortality in Type 2 Diabetes Patients Taking Oral Anti-Diabetic Agents

Controversy still surrounds the selection of oral anti-diabetic agents for the treatment of type 2 diabetes (DM2). There has been a discrepancy in the reported risk of coronary artery disease (CAD), congestive heart failure (CHF), and/or death in type 2 diabetics taking various anti-diabetic agents.

This inconsistency prompted Cleveland Clinic endocrinologists to investigate the risk of CAD, CHF and mortality using multivariable Cox models in a retrospective cohort of 20,450 DM2 patients from their electronic health record (EHR).

“We looked at all newly diagnosed and previously diagnosed type 2 diabetics throughout the Cleveland Clinic system over 18 years old who had a prescription for rosiglitazone, pioglitazone, metformin or sulfonylureas,” explains lead author Robert Zimmerman, MD.

The study, published in Acta Diabetol in March 2009, found no differences in CAD risk among the agents. The results did not identify an increased CAD risk with rosiglitazone in clinical practice, but did report a possible increased risk of adverse events in DM2 patients prescribed sulfonylureas.

More specifically, the study found a 24 percent risk reduction in developing CHF with metformin versus sulfonylurea (HR 0.76, 95 percent CI 0.64-0.91, P = 0.003) and mortality (HR 0.54, 95 percent CI 0.46-0.64). An increased risk of CHF with pioglitazone when compared to metformin was of borderline significance (HR 1.38, 95 percent CI 1.0 – 1.90, P = 0.05).

Pioglitazone was also associated with a lower risk of mortality when compared to sulfonylurea (HR 0.59, 95 percent CI 0.43-0.81). A 46 percent risk reduction with metformin versus sulfonylurea (HR 0.54, 95 percent CI 0.46-0.64, P<0.001) also was observed.

The results, Dr. Zimmerman says, suggest that the choice of initial diabetic agent does impart risk and influences outcomes independent of glycemic control, and that metformin may be a preferred first-line agent.

“A careful examination of the patient’s comorbidities should be conducted and these comorbidities should be considered when picking an oral diabetic agent to control glycemia,” Dr. Zimmerman says.

The study did not observe an increased risk of CAD associated with rosiglitizone that contrasts with other recently published work. Prospective studies to determine whether these agents have evidence of causing adverse cardiac outcomes and are associated with an increase in overall mortality would be beneficial, he says.

For more information, contact Robert Zimmerman, MD, at 216.444.9428 or zimmerr@ccf.org.
Robotic Adrenalectomy Latest Minimally Invasive Option Available

To provide an additional treatment option, the Endocrinology & Metabolism Institute is now offering robotic adrenalectomy at Cleveland Clinic.

Endocrine surgeon Eren Berber, MD, began offering the robotic procedure in November 2008 as another alternative for patients facing adrenal tumor removal.

“Robotic surgery is now one of three minimally invasive options available to patients as part of our adrenal surgery program,” Dr. Berber says. “We also are offering lateral transabdominal and posterior approaches. Having these three approaches enables us to treat a wide spectrum of adrenal tumors laparoscopically. Cleveland Clinic is one of the very few – if not the only – centers in the nation offering all three options for patients.”

Robotic adrenalectomy is conducted through four ports in the abdomen, which are 8 mm to 10 mm incisions. The surgical instruments (attached to the robotic arms), and one camera are placed through these ports. The surgeon, operating the robot from a computer console, detaches the adrenal gland from the surrounding tissues, ties off the blood vessels and removes the dissected adrenal gland.

Dr. Berber says robotic adrenalectomy is useful in cases involving more complicated or larger adrenal lesions.

“Robotic technology increases dexterity and allows us to make fine dissections,” Dr. Berber says. “It enables us to approach tumors that we wouldn’t have approached laparoscopically in the past.”

Advantages of robotic adrenalectomy include smaller incisions with minimal scarring, less trauma to the patient, less pain, shorter hospital stay, decreased use of pain medications, less bleeding, decreased risk of infection and quicker recovery. Outcomes are comparable to other minimally invasive approaches.

There are few contraindications to the robotic approach, Dr. Berber says. However, if patients are not candidates for robotic adrenalectomy, they may be candidates for another minimally invasive approach.

Cleveland Clinic endocrine surgeons perform about 30 adrenalectomies each year. Dr. Berber is currently training the program’s three other endocrine surgeons in the approach.

For more information, contact Eren Berber, MD, at 216.444.0555 or berbere@ccf.org.
Cleveland Clinic physicians and scientists have found TSHR mRNA is detectable in thyroid microcancers and is also useful for directing surgery in patients with thyroid follicular neoplasms (FN).

These findings are the result of two studies that were presented at the American Association of Endocrine Surgeons (AAES) annual meeting in May 2009 and the International Surgical Week in September 2009.

The first study at the AAES demonstrated that the thyroid cancer marker, TSHR mRNA, which is detectable in peripheral blood among patients with larger thyroid cancers, is also detectable in those whose thyroid cancers are just millimeters small. Manjula Gupta, PhD, medical director of the Endocrinology and Immunology Laboratories in the Department of Clinical Pathology, invented and developed this novel thyroid cancer marker, and Cleveland Clinic is the only institution to offer it for testing. It is available to patients and physicians nationwide. This novel finding is the first to show detectable traces of thyroid cancer in circulation when cancers are still small. Although this has been demonstrated for other cancers (breast, colon, melanoma), it has previously not been shown for thyroid cancer.

The team included Dr. Gupta and Rose Lounsbury from Clinical Pathology, and endocrine surgeons Mira Milas, MD, Tomislav Novosel, MD, Hadley Ritter, MD, Adrian Harvey, MD, Jamie Mitchell, MD, Eren Berber, MD, and Allan Siperstein, MD.
They studied 37 patients with papillary thyroid microcancer (PTMC; tumor size ≤ 1 cm) from a larger cohort of 159 patients with papillary and follicular thyroid cancers who had TSHR mRNA levels checked before surgery. Analysis found 59 percent of patients with PTMC had detectable (+) TSHR levels, which was not statistically different from the rate in patients with tumors > 1 cm (78 percent) but was significantly higher than the chance finding of detectable TSHR in patients with benign goiters who undergo surgery and have no cancer (15 percent, p<0.001).

All patients with (-) TSHR mRNA had classical PTMC. In contrast, (+) TSHR mRNA patients had fewer classical PTMC (67 percent) and manifested the subtypes of follicular variant, tall cell and Warthin (p = 0.001) that may have different clinical behavior. The factors that were found to be significantly associated with a chance of lymph node metastases found at initial surgery included tumor size between 5 and 10 mm, multifocality in tumors larger than 5 mm, and (+) TSHR mRNA in tumors larger than 5 mm or those who have a biopsy-proven cancer diagnosed before surgery.

“This is the first time that a circulating molecular marker for thyroid cancer has been detected in the smallest of thyroid cancers. It implies that thyroid cancer becomes a systemic disease long before we appreciate clinical signs or think of it in those terms,” Dr. Milas says. Although additional studies are needed, the finding of (+) TSHR mRNA in patients with microcancers may identify patients at higher risk for lymph node metastases who might benefit from additional therapy.

The second study addressed the role of TSHR mRNA in directing surgery for thyroid biopsies that are indeterminate or designated follicular neoplasms (FN). Only some of these will be thyroid cancers but this is not possible to predict from the biopsy alone. Twenty-six patients with FN underwent thyroidectomy by current standards of care. Clinical characteristics and pathology were reexamined to determine whether a previously proposed algorithm for managing thyroid FNs – based on ultrasound (US) features and TSHR mRNA detection – successfully predicts thyroid cancer (TC).

The algorithm advises total thyroidectomy for patients with 1) positive TSHR mRNA; 2) negative TSHR mRNA but nodule size ≥ 3.5 cm and one concerning US feature; or 3) negative TSHR mRNA with nodule < 3.5 cm and two concerning US features. Concerning US features included hypervascularity of the nodule, irregular borders and microcalcifications.

Sensitivity (SN), specificity (SP), negative (NPV) and positive (PPV) predictive values, and accuracy (AC) were calculated.

The team, which was comprised of the same group as the first study, found that 13 patients (50 percent) had benign disease and 13 TC. TSHR mRNA alone predicted TC with SN 62 percent, SP 100 percent, NPV 72 percent, PPV 100 percent and AC 81 percent. TSHR mRNA and US algorithm predicted TC with SN 100 percent, SP 83 percent, NPV 100 percent, PPV 89 percent and AC 92 percent. Ten patients (39 percent) had potentially avoidable surgery for benign diseases: three follicular adenomas (sizes 1.8 to 2.3 cm) and seven asymptomatic goiters or small nodules. TSHR mRNA had no false positives; three of five false negatives were micropapillary TC. Histology revealed 46 percent papillary TC (mean size 0.9 cm) and 54 percent follicular TC (3.5 cm). All TC patients were captured by the combined TSHR mRNA and US algorithm.

“Our research validates the use of this blood test in patients whose biopsies do not clearly give a diagnosis of thyroid cancer to predict those who do, in fact, have thyroid cancer and ought to have surgery,” Dr. Milas says. “It also shows that some patients with undetectable TSHR mRNA could possibly avoid surgery.”

The TSHR mRNA test is now routinely available from Cleveland Clinic Reference Lab (800.628.6816) to patients nationwide.

For more information on either of these studies, contact Mira Milas, MD, at 216.444.4985 or milasm@ccf.org; or Manjula Gupta, PhD, at 216.444.2714 or guptam@ccf.org.
Cleveland Clinic endocrinology fellow Rahfa Kurdi Zerikly, MD, recently led a trial that analyzed the effectiveness of iodine depletion and found that depleted iodine state is advisable prior to RAI ablation therapy in thyroid cancer patients. “Putting a patient on a diet where you can’t have any salt is extremely difficult,” Dr. Zerikly says. Not only is it challenging, but previous research by the department found that a large share of patients can’t follow it, or follow it well enough. That prompted Dr. Zerikly to question whether iodine depletion is truly necessary.

Dr. Zerikly retrospectively studied 72 patients who underwent total thyroidectomy for thyroid cancer between 2003 and 2006. All patients had differentiated thyroid cancer by histology. None of the patients had distant metastases. All patients were instructed to follow 14 days of LID. Patients were subdivided into two groups; group 1 (n = 58), patients in whom low iodine state was achieved as defined by total 24-hour urine iodine of less than 100 µg; and group 2 (n = 14), patients in whom 24-hour urine iodine was higher than 100 µg.

Efficacy of remnant RAI ablation therapy was measured based on the results of the first withdrawal or the thyroglobulin stimulated whole body scan (WBS), or based on the thyroglobulin (TG) level obtained within six to 24 months post ablation therapy. Success of therapy was defined by the absence of focal uptake on WBS and/or TG levels of less than 2 µg/ml. In patients with positive TG antibodies, success rate was based on scan results only.

Her study, which was presented at the American Association of Clinical Endocrinologists meeting in May 2009, found that iodine depletion does make a difference. Patients in group 1 who achieved low iodine state had successful remnant RAI ablation therapy in 91.4 percent of cases; only five out of 58 (8.6 percent) patients failed therapy. In contrast, four of 14 (28.6 percent) of patients who failed to achieve low iodine state failed RAI ablation therapy (p < 0.05). All had 24-hour urine iodine greater than 160 µg/day.

Finding iodine depletion does make a difference means endocrinologists should measure 24-hour urine iodine levels and have patients who don’t achieve low iodine status redouble their diet efforts so therapy can be effective. That should help reduce the recurrence rate, which is estimated to be as high as 35 percent, with two-thirds occurring in the first decade after therapy.

Dr. Zerikly also concluded that it may be useful to develop a reliable test that can determine iodine state in a timely manner before RAI therapy is implemented, which may allow a delay in the scheduled therapy if low iodine state is not achieved by routine LID.

For more information, contact Rahfa Kurdi Zerikly, MD, at 216.444.8761 or kurdir@ccf.org.
Measurement of late-night salivary cortisol (NSC) has been increasingly used as a simple and effective screening test for Cushing syndrome (CS). But Cleveland Clinic endocrinologists questioned whether NSC is better than other available tests that have a sensitivity and specificity of around 80 percent – still leaving them with the wrong answer a fifth of the time.

Amir Hamrahian, MD, and Rahfa Kurdi Zerikly, MD, conducted a study designed to describe the diagnostic performance of a commercially available NSC assay using liquid chromatography-tandem mass spectrometry (LC-MS/MS).

The team identified 90 patients from The Pituitary and Adrenal Clinic Database between 2004-2007 who had one or more NSC determinations; 52 patients in whom CS was excluded or could not be confirmed (Group 1, G1), and 38 patients in whom CS was confirmed by either positive immunostaining for ACTH or development of adrenal insufficiency post-operatively (Group 2, G2). Subjects provided salivary samples collected at bedtime, with the majority being collected between 11 pm-midnight.

The study, which was the subject of a poster presentation at the Endocrine Society meeting in June 2009, found the highest combined sensitivity (90.5 percent) and specificity (90.6 percent) was achieved at a cutpoint of 118.2 ng/dL, as compared to the current recommended reference lab’s cutoff level of 100 ng/dL.

“So this is actually better than the other tests that have been available up to this point,” Dr. Zerikly says. “It’s an easier test to do. It’s also a less invasive test, so it’s less bothersome for the patient.”

The team concluded that commercially available LC-MS/MS assay to measure NSC is a simple and reliable screening test to rule out CS. Rarely, spuriously high values of NSC may occur in patients without CS. Clinicians should be aware of appropriate cutpoints for proper interpretation of NSC and use additional tests when necessary.

For more information, contact contact Rahfa Kurdi Zerikly, MD, at 216.444.8761 or kurdir@ccf.org, or Amir Hamrahian, MD, at 216.445.8538 or hamraha@ccf.org.
New Vitamin D-Based Multidimensional Nomogram Aids Diagnosis of Primary Hyperparathyroidism

The biochemical diagnosis of primary hyperparathyroidism (1°HPT) has traditionally been based on elevated calcium and elevated PTH values. But these classic criteria fail to diagnose the increasingly recognized subset of patients in whom calcium, PTH or both lie within the “normal” range.

At Cleveland Clinic, endocrine surgeons have created a new, vitamin-D based multidimensional nomogram that redefines diagnostic criteria for 1°HPT to capture these atypical patients.

“We wanted to know if we could make the diagnosis of hyperparathyroidism in this group of challenging patients who are not in the typical areas of the standard two-dimensional nomogram, by analyzing their vitamin D patterns,” says Cleveland Clinic endocrine surgeon Mira Milas, MD. “We made a three-dimensional graph of how PTH should behave depending on what the patients’ calcium and vitamin D levels are. As a result, we came up with a formula that works to make the diagnosis when patients don’t fall in the clear and easy diagnostic category.”

A team including Dr. Milas and Adrian Harvey, MD, from the Department of Endocrine Surgery, and Manjula Gupta, PhD, medical director of the Endocrinology and Immunology Laboratories in the Department of Clinical Pathology, created the new nomogram by comparing a group of 351 patients with surgically confirmed 1°HPT to a group of 221 healthy patients not suspected to have hyperparathyroidism or other diseases of calcium metabolism. Crucial to the research efforts were medical student Mengjun Hu, BS, and senior biostatistician Robert S. Butler, MS, from the Quantitative Health Sciences Institute.

Among 1°HPT patients, 104 (30 percent) did not meet classic criteria of elevated calcium and PTH values. Simultaneous calcium, intact PTH, and 25-hydroxy vitamin D levels were measured in both 1°HPT and healthy patient groups. Multivariate analysis was performed first on healthy patient data to identify those factors that significantly impacted PTH levels, essentially defining a new reference range for expected PTH values. A mathematical model was then developed, incorporating those new variables to determine whether this would capture patients with atypical 1°HPT.

Multivariate analysis of the healthy patient data revealed that calcium (p<0.015), vitamin D (p<0.0001) and age (p<0.0002) were independent predictors of PTH level. In the traditional nomogram, which plots calcium on the x-axis and PTH on the y-axis, the presence of classic disease can be visually apparent, but atypical 1°HPT patients resemble ‘normal’ patients,” says Dr. Harvey. “When additional variables are added, we were able to create a multidimensional nomogram that more clearly separates these atypical groups with boundaries of normal and abnormal PTH.” (Figure 1)

The formula developed by the Cleveland Clinic team, which predicts the upper limit of normal PTH, is most specifically calculated as follows: PTH (pg/ml) = 119.73 – (6.07 x calcium (mg/dL)) – (0.52 x vitamin D (ng/ml)) + (0.26 x patient age (yrs)). It is simplified as shown in Figure 2.

When applied to the team’s surgical group, this model successfully distinguished 96 percent (64/67) of patients with normocalcemic 1°HPT and 53 percent (21/40) of patients with 1°HPT who had inappropriately normal PTH.

“The practical implication of this formula is that it provides an added tool, lacking thus far, to clarify a diagnosis of 1°HPT in atypical patients. In clinic, we take our formula and insert the patient’s calcium level, vitamin D level and age,” Dr. Milas explains. “It returns a number for what the PTH lab test should be, given those other values. If the patient’s actual measured PTH is higher than the formula’s number, then we interpret that as supportive of the patient having 1°HPT. In previous years, patients with atypical clinical profiles for parathyroid disease might have endured more prolonged observation periods or multiple blood draws to accumulate enough data to feel confident in concluding 1°HPT is present.”
Figure 1
A multidimensional representation of PTH as a function of calcium and 25-hydroxy vitamin D levels. The patients represented by the pink and black datapoints represent those with atypical primary hyperparathyroidism, confirmed by surgery. They would have been harder to distinguish in a traditional 2-dimensional graph of PTH and calcium values.

For example, the equation would predict that a 54-year-old man with 9.5 mg/dL calcium and 20 ng/mL vitamin D should have a maximal PTH of 66 pg/mL; a higher measured PTH value would predict parathyroid disease. The formula requires that the measured calcium, vitamin D and PTH values be from a simultaneous blood draw, rather than separate measurements from days, weeks or months apart. It also may not be applicable to patients with renal failure/insufficiency or organ transplantation, as the formula is based on data from patients without these conditions.

The team’s findings, which were presented at the American Association of Endocrine Surgeons annual meeting in May 2009, show that in addition to calcium, vitamin D and age are independent predictors of PTH.

“Multidimensional modeling reliably predicted normocalcemic 1°HPT, but diagnosis remains more challenging in patients with normal PTH who may still require serial laboratory or other investigations before their diagnosis is convincing enough to advise surgery,” Dr. Milas says. “Our new model may allow for more rapid definitive diagnosis and treatment of 1°HPT in patients with atypical presentations.”

For more information, contact Mira Milas, MD, at 216.444.4985 or milasm@ccf.org; Adrian Harvey, MD, at 216.444.5914 or harveya@ccf.org; or Manjula Gupta, PhD, at 216.444.2714 or guptam@ccf.org.

Figure 2
Calculated PTH = 120 - 6*Calcium - \( \frac{1}{2} \) *Vitamin D + \( \frac{1}{4} \) *Age
Acute Effects of Gastric Bypass versus Gastric Restrictive Surgery on β-Cell Function and Insulinotropic Hormones in Severely Obese Patients with Type 2 Diabetes

Bariatric surgery improves hyperglycemia related to type 2 diabetes, but the mechanisms of action and the most effective type of surgery remains unclear. Cleveland Clinic endocrinologists recently conducted a mechanistic study to differentiate early β-cell function effects associated with Roux-en-Y gastric bypass (RYGB) from those induced by gastric restrictive (GR) surgery in patients with type 2 diabetes (T2DM).

“We speculated that both procedures would result in weight loss and improvement of diabetes, but the gastric bypass procedure would have specific effects to improve pancreatic β-cell function and insulin action that would have curative effects on diabetes,” says lead author Sangeeta Kashyap, MD, an endocrinologist with Cleveland Clinic’s Department of Endocrinology, Diabetes and Metabolism. “Our hypothesis was that the intestinal bypass procedure has specific effects on pancreatic β-cell recovery independent of weight loss – somehow making the β-cells enhance their ability to secrete insulin in response to altered nutrient intestinal interaction.”

The NIH-funded study, which was published in January 2009 in *Diabetes Care*, found that fasting hyperglycemia, β-cell function and insulin sensitivity were improved within four weeks after RYGB. The improvement in β-cell function was partly due to β-cell preservation and an enhanced incretin response. Similar improvements were not evident after GR surgery.

The study examined 16 obese T2DM patients (9M/7F, 52±14 years, 47±9 kg/m2, HbA1c 7.2±1.1 percent) undergoing either RYGB (N=9) or GR (N=7) surgery. Patients were studied one to two weeks prior to surgery, and again at one and four weeks after surgery. Insulin secretion and sensitivity were assessed using a hyperglycemic clamp, and mixed meal tolerance test (MMTT). The clamp was always performed two to three days after the MMTT. Subjects were started on an 800-calorie liquid diet two weeks before surgery. Oral agents were discontinued 24 hours prior to the procedures. Sulfonylurea medications were discontinued after surgery, however, metformin and thiazolidinediones were continued as before surgery.

The authors reported that one week after surgery, weight loss was similar between the two surgery groups, fasting glucose was reduced in both groups (P < 0.01), and insulin clearance and insulin sensitivity increased only after RYGB, (P < 0.05). Four weeks after surgery, weight loss was similar for both groups, but fasting glucose was normalized only after RYGB. Insulin secretion in response to infused glucose was increased after GR, while insulin clearance was increased after RYGB (P < 0.05). Insulin sensitivity was improved solely after RYGB. In contrast, the β-cell responsitivity to glucose during meal ingestion was increased fivefold after RYGB (P < 0.05), and was accompanied by a more robust insulin and GLP-1 response.

This is the first study to distinguish the acute anti-diabetic effects of RYGB compared to GR surgery, Dr. Kashyap says. “Basically, what we found was that the Roux-en-Y gastric bypass surgery as compared to gastric restrictive procedures have a potent effect on two things: insulin sensitivity and insulin secretion, in terms of production,” she explains. “The effects of insulin secretion were twofold. When we gave patients IV glucose through the vein that bypasses the entire gastric tract, we found that the effects of the Roux-en-Y gastric bypass were that they preserved β-cell function.”

Dr. Kashyap says the study also included an unexpected finding. Typically, diabetes gets worse in patients following surgery due to inflammation, leading patients to require more insulin. “Surprisingly, after gastric bypass, people don’t require more medication. They require less medication,” she says. “Part of it is because when we gave IV glucose, which bypassed the entire GI tract, we found that the β-cells were resting. They were working less hard.
But when we gave patients a meal to look at the gut effects, we found that it stimulated production of insulin. So, it had two effects on the β-cells. One was preservative and the other was to enhance the function of the β-cells with meals. These were not characteristics that we found with the other type of surgery.

The study has clinical implications because some patients who are not diabetic and want bariatric surgery to lose the weight might benefit from a restrictive procedure that could result in weight loss, but a diabetic and prediabetic patient will probably be better off with the Roux-en-Y gastric bypass, she says.

Dr. Kashyap notes that this study was a small pilot study to examine early effects, but the STAMPEDE (Surgical Therapy and Medications Potentially Eradicate Diabetes Effectively) currently underway at Cleveland Clinic is examining the effectiveness and durability of advanced medical therapy versus bariatric surgery and therapy in treating patients with type 2 diabetes and will include long-term follow up.

For more information about the study, contact Sangeeta Kashyap, MD, at 216.445.2679 or kashyas@ccf.org.
Clinical Utility of Waist Circumference in Predicting All-Cause Mortality in a Preventive Cardiology Clinic Population

Obesity is a major risk factor for both Diabetes Mellitus (DM) and coronary artery disease (CAD). The important question of whether or not waist circumference (WC), a measure of abdominal obesity, is a better predictor of mortality than generalized obesity, as measured by body mass index (BMI), has not been adequately addressed in a clinical setting of patients at high risk for CAD.

A recent study by Cleveland Clinic endocrinologists published in Obesity provides insights into the answer. According to lead author Harpreet Bajaj, MD, MPH, Clinical fellow, Endocrinology & Metabolism Institute, "This study provides support to the usefulness of WC assessment in routine clinical practice and expands our current understanding of risk factors responsible for residual mortality in preventive cardiology clinic patients."

BMI has long been regarded as the "gold standard" for evaluation and management of obesity. The following categorization is widely used in medical practice: 18.5 to 24.9 kg/m² represents normal weight, 25 to 29.9 kg/m² is considered overweight, and a BMI of more than 30 kg/m² is considered obese. Most population studies regarding the relationship between BMI and mortality reflect a curvilinear relationship, however. This suggests decreased mortality in the overweight BMI range compared to underweight, as well as severely high BMI ranges. Underweight BMI has been linked to increased mortality in the elderly and also to a greater incidence of DM and CAD in some populations. These findings mean that obesity, as measured by BMI, may not be a homogenous entity.

Next, the authors compared single WC cutoffs (to subcategorize BMI) adopted by the NHLBI versus gender and BMI-specific WC classification proposed by Ardern et al.
from the National Health and Nutrition Examination Survey (NHANES) data. Approximately a 10 percent increase in correct risk classifications in both men and women was observed by using this newer BMI-specific WC classification. “Modifying the current NHLBI obesity classification to include BMI-specific WC cutoffs will improve the predictive ability of anthropometric measurements in obese patients’ risk assessment,” notes Dr. Bajaj. “Subjects are placed in more correct risk categories and, therefore, should get the treatment best suited for the actual risk category.

“A potential clinical implication of the findings in this study is that WC reduction, as an adjunct to medical management of cardiovascular risk factors, may provide further cardiovascular and survival benefits in high-risk patients,” Dr. Bajaj states. “Trials are currently underway to see if specifically targeting abdominal obesity, by intensive lifestyle interventions or medications, would lead to a reduction in cardiovascular events or mortality.”

For more information, contact Amir Hamrahian, MD, at 216.445.8538 or hamraha@ccf.org.

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Colorectal surgeon James M. Church, MD, gastroenterologist Carol Burke, MD, and endocrine surgeon Mira Milas, MD, are using ultrasound to screen for thyroid cancer in patients with familial adenomatous polyposis (FAP), one of the most common inherited colorectal cancer syndromes.

“While we have known about the high risk of thyroid cancer in people with familial adenomatous polyposis for some time, there are very few centers in the world with an organized approach to screening,” says Dr. Church, Director of the Sanford R. Weiss, MD, Center for Hereditary Colorectal Neoplasia Center at Cleveland Clinic. “We have started to send our FAP patients for routine thyroid ultrasounds. If a nodule is found, it is biopsied by fine-needle aspiration.”

Dr. Church says traditional screening via neck palpation is notoriously inaccurate, with up to 50 percent of masses undetected. “Ultrasound is cheap, effective, non-invasive and convenient.”

As of early May 2009, Dr. Milas says about 110 patients had been screened for thyroid cancer at the Weiss Center, which opened last fall. “Two patients had cancer and required total thyroidectomy, and 45 percent of patients were found to have benign thyroid nodules that were undiagnosed before,” says Dr. Milas, who directs the Thyroid Center. “The incidence of cancer among these FAP patients (1.8 percent) is higher than in the general population (0.2 percent).”

Of special concern among patients with FAP, says Dr. Church, is this higher risk for papillary thyroid cancer. Papillary thyroid cancer forms in follicular cells and grows in small, finger-like shapes. It grows slowly, is more prevalent in women, and is the most common type of thyroid cancer. Papillary thyroid cancer is the only one reported to be at higher-risk for FAP patients.

A critical element involved in this screening is studying the biology of the thyroid cancer as it relates to the known germline mutations for FAP.

Another key to the success of the project overall, according to Dr. Church is the groundwork laid by Dr. Burke, who heads the FAP division of the Weiss Center. Her efforts to identify at-risk FAP patients have helped the FAP database grow to thousands of individuals, says Dr. Church. “We started the database in 1979. It was one of the earliest ones in the world, and now it’s one of the biggest.”

Both Drs. Church and Milas are optimistic that ultrasound screening will be a valuable surveillance method to help detect thyroid cancers that would otherwise have gone undiagnosed, but say more study is yet needed. They appreciate the team effort required to conduct such an inter-departmental study, especially aided by the Weiss Center’s Awad Jarrar, MD, Lisa LaGuardia, BSN, Margaret O’Malley, and Courtney Clough from Endocrine Surgery, who actively coordinate the thyroid ultrasound screening efforts.

“No one knows how often FAP patients should be screened for thyroid cancer,” Dr. Church says. “The first thing to do is study the prevalence, then the incidence. We have a lot more work to do to get enough patients enrolled to be comprehensive, but the potential is enormous.”

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Painful Diabetic Neuropathy

by Leann Olansky, MD

OVERVIEW: Diabetic retinopathy is a major cause for vision loss in adults. Diabetic kidney disease is responsible for half of the patients that need dialysis or kidney transplant. Diabetic neuropathy does not get much attention except for those patients that suffer from it. It is estimated that half the patients with diabetes for five years or more have some evidence for nerve damage, but many patient are not aware that diabetes may be the cause for their painful feet or numb and tingling hands or feet. For some patients, it may just be that their feet feel cold, but when they touch their feet, the hand does not confirm that the feet really are cold. Balance problems also can be due to neuropathy. Scientists disagree about how elevated glucose causes neuropathy but studies have shown that blood glucose closer to normal seems to delay or prevent the development. Once neuropathy develops, there is no known treatment to reverse it, but there are treatments that reduce the painful aspects.

PRESENTATION: A 68-year-old woman with a history of type 2 diabetes came to clinic complaining of pain in her feet, legs and thighs. The pain was sharp, aching and continuous – affecting her sleep and disrupting life activities. She described a heaviness of her legs when walking one block. Nothing she could do improved her pain. She had no numbness or tingling and felt she had no weakness. She had reduced her activities because her feet hurt so much.

TREATMENT: While there are no treatments currently available to reverse the nerve damage caused by diabetes, there are several U.S. FDA-approved medications for the relief of pain from diabetic neuropathy. The first she was tried on, pregabalin (Lyrica®) 100 mg twice a day, virtually eliminated her pain but made her too sleepy to function. A reduced dose of 50 mg twice a day incompletely controlled her pain. A second agent, duloxetine HCI (Cymbalta®), was less effective than the first, but caused no sleepiness. Addition of a topical lidocaine patch to each leg with Cymbalta controlled her pain, allowing her to reclaim her life. Her blood glucose control improved with relief of her pain.

DISCUSSION: Diabetic neuropathy is frequently overlooked by physicians caring for patients with diabetes. It is important for patients to mention their pain when seeing their physicians as there are medications that can help. Patients are different in their responses, so more than one therapy should be tried if the first is not effective or if the symptoms make it impossible to take. Sometimes combinations of several agents will be effective at lower doses to reduce side effects. Controlling the pain of neuropathy can improve the quality of life for patients with diabetes and this may translate into diabetes that is better controlled.

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What is the Optimal Control in Patients with Acromegaly and How Should We Treat Them?

by Amir Hamrahian, MD, and Laurence Kennedy, MD

There is clear evidence that uncontrolled acromegaly with elevated growth hormone (GH) and insulin-like growth factor (IGF-1) levels leads to a wide range of cardiovascular, respiratory and musculoskeletal complications, as well as to metabolic disorders such as impaired glucose tolerance and diabetes mellitus.

In addition, symptoms related to tumor mass effect, such as headache and visual field defect, may occur. While there is debate about optimal GH levels during therapy, achieving a random GH < 2.5 ng/mL measured by standard radio-immuno assay is associated with mortality close to levels expected in the general population1. Although there are more publications about the effect of lowering GH on mortality in patients with acromegaly, there is accumulating data about the importance of normalization of IGF-1 on mortality1. There is significant variation in published approaches to GH measurement, ranging from a single random value to the mean of six to eight values over several hours.

At Cleveland Clinic, we favor measuring three GH values at 30-minute intervals, preferably in a fasting state. With the availability of newer, more sensitive GH assays, our goal is to achieve a mean GH < 1 ng/mL during therapy, along with normalization of IGF-1. We use an oral glucose tolerance test (OGTT) in circumstances where there is discrepancy between GH and IGF-1 values, with a goal of achieving GH level < 1 ng/mL during the test. We feel that there is a need for long-term outcome data before adopting more restrictive cut-off values using newer GH assays during OGTT. It is important to emphasize that in cases where GH and IGF-1 results are discordant, the degree of abnormality and patient's clinical status need to be considered before initiating further therapy. It also is important to realize that GH measurement is inaccurate in patients being treated with pegvisomant, a GH antagonist that cross-reacts in commercially available GH assays.

There is ongoing debate about the role of medical therapy in the treatment of patients with acromegaly. Several publications have reported mild to moderate tumor shrinkage using somatostatin analogues in patients with acromegaly2-3. It is interesting that medical therapy, even in those with some degree of visual field defect, is being proposed by some European endocrinologists, a view that Cleveland Clinic endocrinologists would not endorse. Medical therapy may be an attractive first-line therapy in patients with no neurological deficits such as visual field defect but clear evidence of cavernous sinus invasion in whom surgery will likely not achieve long-term remission or cure (figure 1), and a case can also be made in the small minority of patients with no visible pituitary adenoma. But it needs to be emphasized that the effect of the somatostatin analogues on tumor mass in acromegaly is much less than the effect of dopamine agonists in patients with prolactinoma. One should also should keep in mind the high cost of long-term medical therapy in patients with acromegaly.

We routinely treat our patients with a three- to four-week course of short-acting somatostatin analogues prior to surgery. Most patients report significant improvement in their symptoms and such short-term therapy may improve anesthesia care in these patients. However, well-designed studies to assess whether surgical outcomes of patients with invasive tumors can be improved by using somatostatin analogues prior to surgery are needed. On the other hand, tumor debulking in patients with invasive disease does lower GH and IGF-1 levels and improve the likelihood of remission with medical therapy. Availability of a dedicated and experienced pituitary neurosurgeon with at least 50 pituitary operations per year is a must.

REFERENCES:
While dopamine agonists have been successfully used in a small group of patients with acromegaly, our experience with them has been disappointing and we only consider them as a first-line therapy in patients with mild elevation of GH/IGF-1 levels, especially if there is evidence for GH and prolactin co-secretion.

Somatostatin analogues will reduce IGF-1 levels to normal in approximately 60 to 70 percent of acromegalic patients, while pegvisomant has been shown to achieve this goal in more than 90 percent.

In our opinion, radiotherapy should only be used in those who cannot achieve safe GH and IGF-1 levels after surgery and/or medical therapy, including patients who cannot tolerate or afford long-term medical therapy (figure 2). It may take many years for radiotherapy to reduce GH and IGF-1 levels to normal. The majority of patients who receive an effective dose of radiotherapy eventually develop panhypopituitarism and there is no good evidence that Gamma Knife radiotherapy protects against such complication. Conventional fractionated radiotherapy is associated with increased cerebrovascular accidents and may be associated with increased mortality4. For optimal outcome, a skilled multi-specialty team, consisting of an experienced neurosurgeon, an endocrinologist with pituitary expertise and a radiation oncologist, is essential.

Dr. Amir Hamrahian is the director of clinical research at the Cleveland Clinic’s Endocrinology & Metabolism Institute, who has special interest in pituitary and adrenal disorders. He is part of multi-disciplinary team caring for patients with pituitary disorders at Cleveland Clinic.

Dr. Laurence Kennedy is Chair of the Cleveland Clinic’s Endocrine, Diabetes and Metabolism Department. He has had a long-standing interest in pituitary disease and has published clinical observations and clinical research related to pituitary conditions stretching back over 30 years.

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Figure 1. A patient with acromegaly secondary to a large invasive pituitary adenoma invading the left cavernous and sphenoid sinuses (arrows). There is no pressure on optic chiasm. Due to the invasive nature of the tumor, even the best neurosurgeons would not be able to achieve a biochemical cure, although a significant decrease in GH/IGF-1 levels can be achieved.

Figure 2. Algorithm for treatment of patients with acromegaly

Dr. Amir Hamrahian is the director of clinical research at the Cleveland Clinic’s Endocrinology & Metabolism Institute, who has special interest in pituitary and adrenal disorders. He is part of multi-disciplinary team caring for patients with pituitary disorders at Cleveland Clinic.

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<table>
<thead>
<tr>
<th>TITLE</th>
<th>PI</th>
<th>CONTACT/NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>International Metabolic Study (KIMS®)</td>
<td>Amir Hamrahian, MD</td>
<td>Melanie Williams</td>
</tr>
<tr>
<td>Protocol # C1073-400 - An Open Label Study of the Efficacy and Safety of CORLUX (mifepristone) in the Treatment of the Signs and Symptoms of Endogenous Cushing's Syndrome</td>
<td>Amir Hamrahian, MD</td>
<td>Melanie Williams</td>
</tr>
<tr>
<td>The Effect of Vitamin D3 Supplementation on Glucose Control in Patients with Type 2 Diabetes Mellitus who are Vitamin D Insufficient</td>
<td>Mario Skugor, MD</td>
<td>Melanie Williams</td>
</tr>
<tr>
<td>A Phase 2/3, Randomized, Double-Blind, Multicenter, Multinational, 4-Arm, Controlled, Dose-Ranging Study to Evaluate Efficacy and Safety of Teplizumab (MGA031), a Humanized, FcR Non-Binding, Anti-CD3 Monoclonal Antibody, in Children and Adults with Recent-Onset Type 1 Diabetes Mellitus</td>
<td>Robert Zimmerman, MD</td>
<td>Melanie Williams</td>
</tr>
<tr>
<td>PYR-210 - A Randomized, Double-Blind, Placebo-Controlled, Multi-Center, Phase 2b Study to Evaluate the Safety and Efficacy of Pyridorin™ (pyridoxamine dihydrochloride) in Patients With nephropathy Due to Type 2 Diabetes</td>
<td>Leann Olansky, MD</td>
<td>Melanie Williams</td>
</tr>
<tr>
<td>TECOS: A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin in Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control on Mono- or Dual Combination Oral Antihyperglycemic Therapy</td>
<td>Robert Zimmerman, MD</td>
<td>Melanie Williams</td>
</tr>
<tr>
<td>The Global Hypopituitary Control and Complications Study (HypoCCS)</td>
<td>Amir Hamrahian, MD</td>
<td>Melanie Williams</td>
</tr>
<tr>
<td>The Role of Short-Term Intensive Insulin Therapy on Endothelial Dysfunction in African Americans with Type 2 Diabetes Mellitus</td>
<td>Sangeeta Kashyap, MD</td>
<td>Melanie Williams</td>
</tr>
<tr>
<td>ACROSTUDY - A Multicenter, Post Marketing Surveillance Study of Somavert Therapy in Patients with Acromegaly in the USA and Europe</td>
<td>Amir Hamrahian, MD</td>
<td>Melanie Williams</td>
</tr>
<tr>
<td>Pelvic Floor Disorders in Bariatric Surgery Patients</td>
<td>Stacy Brethauer, MD</td>
<td>Sharon O’Keefe</td>
</tr>
<tr>
<td>A Prospective Randomized Controlled Trial Comparing Advanced Practice Medical Management vs. Advanced Practice Medical Management Plus Bariatric Surgery in The Treatment of Type 2 Diabetes Mellitus</td>
<td>Philip Shauer, MD</td>
<td>Chytaine Hall</td>
</tr>
<tr>
<td>Prospective Randomized Comparison of Bilateral vs. Focal neck Exploration for Sporadic Hyperparathyroidism</td>
<td>Allan Siperstein, MD</td>
<td>Linda Heil</td>
</tr>
</tbody>
</table>
Critical Care Transport

Cleveland Clinic is able to go to new lengths to transport patients in critical condition with the addition of fixed-wing aircraft. The aircraft became available for critical care use on July 1, 2008. These aircraft will be able to reach patients in need wherever they are, including overseas. Specialty care teams are onboard to provide care for infants, children and adults. The teams consist of physicians, nurse practitioners, critical care nurses and paramedics. The planes are equipped with the technology to directly communicate with the referring physician or with physicians in any specialty at Cleveland Clinic to ensure the best possible care during transport. These aircraft join our team of critical care transportation fleet, which includes mobile intensive care units and helicopters.

For more information, visit our website at clevelandclinic.org/criticalcaretransport
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