Endocrine Notes

Updates for physicians on practices, advances and research from Cleveland Clinic's Department of Endocrinology, Diabetes and Metabolism
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**Endocrine Notes**

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*Endocrine Notes* is written for physicians and should be relied upon for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

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Dear Colleagues,

This issue of *Endocrine Notes* covers a variety of new evaluation and treatment strategies for endocrine patients.

A new use of thyrotropin-alpha in ablating remnant thyroid tissue in thyroid cancer patients following thyroidectomy is discussed on page 6. Instead of withdrawing patients from thyroid hormone, Dr. Skugor discussed how patients can receive I-131 after thyrotropin-alpha administration.

An ongoing study assessing the need for low iodine diets prior to thyroid ablation therapy for thyroid cancer patients is reviewed on page 15 with Dr. Zerikly.

Dr. Milas discusses the use of TSH on MRNA in following patients with thyroid cancer to help identify thyroid cancer recurrence and initial diagnosis of thyroid cancer (page 10). On page 14, Dr. Skugor and I review several medications that can cause abnormal thyroid function.

New findings of the ACCORD study, which showed increased mortality in the intensive glycemic control group for type 2 diabetes patients, are reviewed on page 4. Read about the role of gastric bypass surgery in managing type 2 diabetes and obesity on page 8. A study investigating a monoclonal antibody to T cells, teplizumab, in preventing type 1 diabetes is on page 13. Dr. Hoogwerf discusses a new insulin drip protocol designed for nursing floors that has recently been implemented at Cleveland Clinic (page 7).

On page 12, Dr. Diab reviews a new marker for fatty liver disease that can detect the disease noninvasively.

A recent study in hyperparathyroidism conducted here by Drs. Greene and Milas found that osteoporosis in men responds better to surgery than in women (page 16).

Dr. Hamrahian discusses his findings that free cortisol measurements are helpful in evaluation of adrenal function in critically ill patients on page 18.

We are pleased to continue our efforts to improve care for all endocrine patients. We hope you enjoy this issue of *Endocrine Notes*.

Sincerely,

Robert S. Zimmerman, MD
Interim Chairman
Department of Endocrinology, Diabetes and Metabolism

To refer patients to Cleveland Clinic’s Department of Endocrinology, Diabetes and Metabolism, please call 216.738.4567.
ACCORD Trial Assesses Glycemic Control Aggressiveness

“Results from ACCORD [Action to Control Cardiovascular Risk in Diabetes trial] will change the medical community’s approach to diabetes management,” says Cleveland Clinic endocrinologist Byron Hoogwerf, MD, a principal investigator for ACCORD.

The study was designed to resolve the controversy surrounding the benefits of intensive glycemic control, blood pressure control and management of diabetes-related hyperlipidemia in reducing cardiovascular risk, he explains. For example, although epidemiologic analyses suggest that each 1 percent increase in HbA1c increases the risk for cardiovascular disease by approximately 15 percent, “there was little confirmatory evidence from randomized trials on whether lowering glucose reduces this risk,” Dr. Hoogwerf notes.

Similarly, randomized trials demonstrate that lowering LDL cholesterol or reducing systolic blood pressure to <140 mm Hg reduces cardiovascular events in diabetic patients. However, data demonstrating benefit for lowering triglycerides is limited and does not include studies of patients on statins. Studies on increasing HDL cholesterol are sparse. While epidemiologic data suggest that lowering systolic blood pressure to 120 mm Hg or less may confer additional protective benefit, no large trial has ever tested this hypothesis.

ACCORD, concluding in 2009, will be an eight-year study of more than 10,000 patients with type 2 diabetes and existing heart disease or at least two cardiovascular risk factors. Patients were randomized to either intensive glucose management (HbA1c <6) or to standard glycemic control (HbA1c = 7–7.5). Outcomes include myocardial infarction, stroke and death from cardiovascular disease.

In addition to the different glycemic control approaches, participants were randomized to one of two additional arms, blood pressure management or lipid management. Within the blood pressure treatment group, patients were randomized to standard treatment (systolic blood pressure <140) or to intensive treatment (systolic blood pressure <120). Within the lipid management group, patients were randomized to receive statin therapy alone or statin therapy plus a fibrate.

The National Institutes of Health halted ACCORD’s intensive glucose management arm in February when preliminary data indicated a higher mortality rate in those patients compared with the standard glycemic group (14/1000/year vs. 11/1000/year). Patients in the intensive treatment group were switched over to the standard treatment group.
It is important to note, Dr. Hoogwerf stresses, that the overall mortality rate in ACCORD is below that seen in other comparable diabetes trial databases. “The reason for the small increase in death rates we observed in the intensive treatment group is definitely an area of interest,” he says. “We did note more hypoglycemia and weight gain among these patients, but it is unclear whether either of these factors contributed to the higher mortality.”

Despite the closing of the glucose treatment arm, Dr. Hoogwerf believes intensive glycemic control is still worth consideration in diabetes management. “The increased death rate appears to be related to treatment strategies and not necessarily to the glucose level achieved. Do not rush to judgment in backing off on glucose control,” he says. “We may need to pursue the benefits and learn how to balance the risk.”

ACCORD also raises other questions deserving further study, such as whether intensive glycemic control reduces the risk of nonfatal cardiovascular events. Researchers noted a 10 percent decrease in nonfatal myocardial infarction and stroke, Dr. Hoogwerf reports, but the difference was not significant.

The blood pressure and lipid arms of the trial are continuing and present interesting possibilities of their own, he adds. “ACCORD is the first trial to combine simvastatin and fibrate in type 2 diabetic subjects at high risk for cardiovascular events,” he says. “There is tantalizing evidence so far that fibrate may have positive effects outside of its effects on triglycerides and HDL cholesterol.”

Similarly, the blood pressure management arm is breaking new ground by treating a systolic pressure of less than 120, previously the lowest level tested. “ACCORD should resolve the question of whether there is a threshold for treatment,” Dr. Hoogwerf says.

Although ACCORD has faced challenges, he believes the trial ultimately will help establish treatment goals for glucose, blood pressure, lipids and cholesterol for diabetic patients at high risk for cardiovascular events.

The American Diabetes Association (ADA) currently recommends that most people with diabetes achieve an HbA1c of <7 percent and has no plans to revise those guidelines at this time. ■

For more information, contact Byron Hoogwerf, MD, at 216.444.8347 or hoogweb@ccf.org.
Synthetic TSH Improves Quality of Life for $^{131}$I Ablation Patients

Cleveland Clinic endocrinologists have implemented a new approach to thyroid remnant ablation in patients with differentiated thyroid cancer that significantly improves patient quality of life in the post-operative/pre-ablation period. As an alternative to a four-to-six-week withdrawal of thyroid hormone to increase serum TSH concentrations, they now are using recombinant human thyroid stimulating hormone (thyrotropin-alpha, rh-TSH) prior to ablation.

“Post-surgical $^{131}$I ablation is an essential element of treatment for thyroid cancers larger than one centimeter to destroy remaining thyroid fragments and enhance later detection in the event of a cancer recurrence,” says Cleveland Clinic endocrinologist Mario Skugor, MD.

“Prior to ablation, increasing serum TSH concentrations optimizes radioiodine uptake for thyroid remnant ablation and diagnosis of metastatic disease,” he says. “However, withdrawal of thyroid hormone for this purpose is fraught with side effects.”

The hypothyroidism induced by withholding thyroid hormone is accompanied by a variety of unpleasant symptoms such as weight gain, chilliness, impaired cognition, depression, constipation and muscle cramps. Symptoms may prevent patients from driving and keep them home from work.

Compared with that scenario, rh-TSH increases TSH without thyroid hormone withdrawal and avoids the adverse events associated with discontinuing the hormone. Side effects of rh-TSH are mild and include nausea and headaches. “The key difference is that rh-TSH does not interrupt patients’ routines. They can live their normal lives, go to work and drive during that pre-ablation period,” Dr. Skugor says. “Their quality of life is much better than it is when thyroid hormone is withheld.”

At Cleveland Clinic, radioiodine ablation typically is performed four to six weeks after thyroidectomy. Three days prior to the procedure, thyrotropin-alpha is administered as two injections 24 hours apart, with ablation performed on the third day.

Based on multiple studies that demonstrated rh-TSH is safe and as effective as withdrawal of thyroid hormone for stimulating TSH production and yields equivalent results for radioiodine ablation, the U.S. Food and Drug Administration approved rh-TSH for this indication in June 2007. rh-TSH was approved first in 1998 for use in radioiodine scans for the diagnosis of thyroid cancer recurrence following thyroidectomy.

For more information, contact Mario Skugor, MD, at 216.445.0739 or skugorm@ccf.org.
Critically ill patients at Cleveland Clinic will benefit from implementation of a new clinical protocol for insulin infusion that improves glucose control in this population. The protocol is designed for use on regular nursing floors. A multidisciplinary team, led by endocrinologist Byron Hoogwerf, MD, developed the protocol to simplify insulin infusion in hyperglycemic patients such as those with diabetic ketoacidosis, nonketotic hyperosmolar coma and major infection, or in the perioperative period following major surgery.

Cleveland Clinic’s extensive experience with insulin infusion for cardiac surgery patients was the inspiration for the new protocol. “Clinical evidence from several institutions is pretty robust that intensive glucose control in critically ill patients reduces the risk of infection, shortens length of stay and improves survival,” Dr. Hoogwerf says. “Our experience in the Cardiothoracic ICU indicates that we can do this safely in intensive care units. Accomplishing this level of control on regular patient units has been complicated, however, by the lack of uniformity in approach, complexity of orders and the need for frequent changes in physician orders.”

Dr. Hoogwerf saw the need for an insulin administration protocol that would be easy to implement on the nursing floors and avoid the need for frequent revisions to physician orders while achieving stringent glucose control.

The team, including endocrinologists Leann Olansky, MD, and Department Interim Chairman Robert Zimmerman, MD; Jean-Pierre Yared, MD, medical director of the Cardiovascular Intensive Care Unit; and nurse educator Mary Beth Modic, RN, created a protocol that meets all of these requirements. It is based on a grid that establishes the insulin infusion rate depending on only body weight and glucose level at initiation, and then rate of change in glucose thereafter.

The process will begin with a physician order to “initiate insulin infusion protocol.” Once the order is written, “to start the insulin, the nurse needs to know only the patient’s glucose level and weight,” Dr. Hoogwerf explains. “Locate the intersection of those two numbers on the grid, and you know how much insulin to start.”

After initiation of insulin infusion, the nurse performs hourly blood glucose levels. At each one-hour interval, the insulin infusion rate is adjusted according to the grid based on the patient’s current glucose, the previous hour’s glucose level, the insulin infusion rate for the previous hour and whether the patient’s blood glucose is higher, lower or unchanged compared with the last hour’s level.

“When glucose approaches the normal range, instructions are to call the doctor for a decision regarding the transition of IV fluids or to subcutaneous insulin,” Dr. Hoogwerf says. Nurses also can call the doctor at any point there is a question or problem, he stresses.

In addition to the benefits in terms of improved patient outcomes, the protocol also has practical advantages, he notes. “From a process perspective, it simplifies continuity of care between nursing shifts, and eventually it will transfer easily to an electronic order entry system.”

Cleveland Clinic is implementing a pilot trial of the insulin infusion protocol on two nursing floors before the end of the year. In the longer term, Dr. Hoogwerf anticipates a comparative study of patient outcomes of the new protocol vs. prior methodology that will evaluate its safety, efficacy and clinical outcomes.

For more information, contact Byron Hoogwerf, MD, at 216.444.8347 or hoogweb@ccf.org.
STAMPEDE Trial: Analyzing Surgery for Diabetes

The landmark STAMPEDE (Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently) trial under way at Cleveland Clinic has the potential to transform treatment of type 2 diabetes from medical to surgical. Philip R. Schauer, MD, Director of Advanced Laparoscopic and Bariatric Surgery, endocrinologist Sangeeta Kashyap, MD, and cardiologist Deepak Bhatt, MD, are co-investigators for the five-year trial under the sponsorship of Ethicon Endo-Surgery and LifeScan.

STAMPEDE will be the first trial in the world to compare relative clinical outcomes between advanced medical therapy alone and advanced medical therapy combined with bariatric surgery in patients with type 2 diabetes and a body mass index (BMI) between 30 and 40 kg/m². Currently, NIH guidelines for bariatric surgery require the presence of morbid obesity alone (BMI greater than 40 kg/m²) or a BMI greater than 35 kg/m² plus at least two other co-morbidities.

“This is the first randomized controlled trial that will assess efficacy and durability of two bariatric procedures vs. medical therapy in treatment of type 2 diabetes in a lower weight population than that typically seen in a bariatric cohort,” says Dr. Kashyap. “These subjects are more typical of patients with diabetes in our community than those who often present for weight-loss surgery.”

STAMPEDE is an outgrowth of several studies that have reported a remission rate for diabetes of greater than 80 percent in patients who undergo gastric bypass, as measured by HbA1c of less than 6 percent for five years or more, Dr. Schauer explains. “We believe it is significant that many bariatric surgery patients reach normal blood glucose levels even before they are discharged,” he says. “This early effect — occurring before these patients have lost any significant weight — suggests that the bypass procedure itself has an effect on diabetes independent of weight loss.”

The most accepted hypothesis for the observed effects is based on hormonal changes in the gut. Surgically bypassing the duodenum causes alterations in gut hormones involved in regulation of plasma glucose homeostasis, most likely increasing production of a hormone that promotes pancreatic beta-cell insulin production and has a tropic effect on the cells themselves. After bypass surgery, the foregut is excluded from the food stream, and the distal small bowel receives the food stimulation, which may cause this alteration in gut hormones.

The leading hormonal candidates are glucagon-like peptide 1 (GLP-1), produced in the ileum, peptide YY and gastric inhibitory polypeptide (GIP). Post-bypass effects on these hormones have been demonstrated in laboratory animals but have yet to be proven in humans — something the STAMPEDE researchers hope to establish. Reduction in weight- and fat-derived toxic hormones also may be improved by altered nutrient-intestinal interactions following surgery.

STAMPEDE will randomize 150 patients to one of three arms: advanced medical therapy, including weight loss, diet, exercise, oral medications and insulin; Roux-en-Y gastric bypass; or laparoscopic sleeve gastrectomy, a procedure that reduces gastric volume by two-thirds by means of excision or stapling.

“If the theory that bypass resolves diabetes through the effect on the gut hormones, we should not see the same results with the sleeve procedure because it leaves the duodenum intact,” Dr. Schauer notes.

Primary outcome measure will be the success rate for biochemical resolution of diabetes at 12 months, as measured by HbA1c ≤ 6 percent. Over the course of five years, researchers also will evaluate changes in insulin secretion and resistance, obesity-related co-morbidities (blood pressure, dyslipidemia), quality of life and hospitalizations. The
implications of gastric bypass surgery for reducing end-organ effects such as retinopathy, kidney disease, stroke and neuropathy also will be part of the final analysis.

The STAMPEDE patient population is the most challenging of any represented in similar studies to date, Dr. Schauer reports. All patients enrolled in STAMPEDE have an HbA1c > 7.5, with the average being 9.0. Some patients have had diabetes for at least 10 years. “STAMPEDE will be one of the first studies to go beyond previously established thresholds with primary evidence,” Dr. Schauer states. “The potential is that bypass surgery can resolve advanced disease.”

Ultimately, STAMPEDE could provide the evidence needed for bariatric surgery to be considered a first-line treatment for diabetes.

For more information, contact Philip Schauer, MD, at 216.444.4794 or schauep@ccf.org; or Sangeeta Kashyap, MD, at 216.445.2679 or kashyas@ccf.org.

**Gastric bypass** combines a restrictive and a malabsorptive procedure. A small (15-30 cc) gastric pouch is created to restrict food intake and a Roux-en-Y gastrojejunostomy provides the mild malabsorptive component. One-third of study participants will be randomly assigned to receive this procedure.

**Laparoscopic sleeve gastrectomy** is a restrictive procedure that removes 75 percent of the stomach, leaving a narrow gastric sleeve. One-third of study participants will be randomly assigned to receive this procedure.
Current methods for diagnosis and monitoring thyroid cancer, which predominantly include fine needle aspiration biopsy, measurement of serum thyroglobulin, neck ultrasound and radioactive iodine whole body scans, are affected by a number of limitations that have prompted a search for new disease markers. Among these, a molecularly based assay using quantitative RT-PCR to detect circulating thyroid cancer cells by measuring thyrotropin receptor (TSHR) mRNA in peripheral blood is showing promise as a valuable addition to patient care.

The assay was developed at Cleveland Clinic by Manjula Gupta, PhD, medical director of the endocrinology and immunology laboratories in the Department of Clinical Pathology, who recognized the importance of primer selection for standardizing the assay and enhancing its reliability.

“The ability to shed tumor cells into circulation is a characteristic of malignant lesions. Since these circulating cancer cells express tissue (thyroid) specific mRNAs, they can be detected in blood by a highly sensitive RT-PCR technique,” says Dr. Gupta.

“We focused on TSHR mRNA for detecting thyroid cancer and demonstrated that the specificity of this marker depends on primer selection that avoids the splice variants and ectopic transcription, thus reducing the ‘signal to noise ratio’."

Together with members of Cleveland Clinic’s Endocrinology and Metabolism Institute, Dr. Gupta has conducted multiple clinical studies since 1999 to assess the performance of the quantitative TSHR mRNA assay for diagnosing thyroid cancer and its recurrence. The results of those investigations indicate TSHR mRNA is a sensitive and specific test for discriminating between patients with thyroid cancer and healthy controls or individuals with benign thyroid disease.

In one study, TSHR mRNA demonstrated a sensitivity of 72 percent and a specificity of 83 percent for diagnosing thyroid cancer in patients with a new thyroid nodule, and it offered 100 percent sensitivity and 98 percent specificity in
detecting recurrent or residual cancer (see table). In addition, the combination of TSHR mRNA with ultrasound was able to capture 100 percent of cancer patients with surgically confirmed follicular cancer who had an indeterminate fine needle aspiration biopsy.

“The cytology is indeterminate in 20 percent to 40 percent of patients who undergo fine needle aspiration biopsy, depending on the patient population or physician’s referral practice,” says Mira Milas, MD, Cleveland Clinic endocrine surgeon.

“Our studies indicate measurement of serum TSHR mRNA combined with ultrasound offers a promising, noninvasive approach for establishing whether nodular thyroid disease in these patients is benign or malignant and allowing the majority who will have a benign condition to avoid surgery.”

Another investigation demonstrated the effectiveness of TSHR mRNA in the long-term postoperative follow-up of patients with differentiated thyroid cancer. In that prospective study, 34 patients were followed for a median of 22 months after total thyroidectomy with or without postoperative radioactive iodine ablation. TSHR mRNA measurements agreed with serum thyroglobulin in 57 percent of measurements, but offered greater accuracy 27 percent of the time. In addition, TSHR mRNA had almost 80 percent concordance with whole body scans, ultrasound and clinician assessment for correctly identifying patients remaining disease-free and those with a recurrence. Notably, in 9 percent of patients, elevated TSHR mRNA was the first sign of cancer recurrence.

Unlike thyroglobulin, levels of TSHR mRNA were unaffected by TSH or circulating thyroglobulin antibodies. The combination of serum thyroglobulin measurement with TSHR mRNA offered a sensitivity of 90 percent and specificity of 93 percent for detecting thyroid cancer recurrence during routine long-term follow-up.

“As shown in our study and by others, about one-fourth of patients being monitored for recurrence after treatment for thyroid cancer have circulating antibodies that interfere with the interpretation of the thyroglobulin assay. This subgroup represents an important clinical scenario where quantitative serum TSHR mRNA can have a valuable role,” Dr. Milas says.

“Now, further effort is needed to confirm our encouraging experience and then to develop algorithms for using new molecular markers in the clinical care of thyroid cancer patients.”

Cleveland Clinic will offer testing of blood samples for quantitative TSHR mRNA as part of a routine panel of thyroid cancer markers in August 2008.

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

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*25% of patients are positive for Tg autoantibody that interferes and limits the use of serum Tg. TSHR mRNA may have predicted or obviated the need of WBS in these patients.
Marker Holds Promise for Detecting NASH Noninvasively

Nonalcoholic fatty liver disease (NAFLD) is insidious, rarely showing overt symptoms until it progresses and damage is done. Its prevalence is rising with increasing obesity rates. Today, the only reliable way to diagnose and stage the disease is a costly and invasive liver biopsy. A simple serum marker, however, could potentially allow physicians to detect the disease easily and stage its severity, ranging from simple fatty liver to serious nonalcoholic steatohepatitis (NASH), which may ultimately progress to cirrhosis.

Cleveland Clinic has been investigating just such a noninvasive serum marker, cytokeratin 18 (CK-18) fragments. These fragments are the products of hepatocyte cell death, which is thought to play an important role in the progression of the disease. Cleveland Clinic gastroenterologist Ariel Feldstein, MD, led a multicenter study that found serum levels of CK-18 could reliably stage and grade NAFLD.

Cleveland Clinic endocrinology fellow Dima L. Diab, MD, has taken the research an important step further by investigating this potential marker in bariatric surgery patients. The aim is to determine whether CK-18 can detect disease and differentiate simple fatty liver disease from NASH in these patients. For them, detecting NASH is important because even though bariatric surgery improves many of the metabolic complications of obesity, including NAFLD, disease progression may occur in some patients despite surgical weight loss.

Dr. Diab and her colleagues looked at baseline levels in a cohort of approximately 100 bariatric surgery patients to see whether marker levels correlated with pathology results of liver biopsies performed at the time of surgery. “The initial preoperative findings are very promising,” she notes.

Marker levels differentiated NASH well. At 275 U/L, the sensitivity for NASH was 77 percent and the specificity 100 percent. Moreover, the likelihood of NASH rather than simple steatosis increased 2.45 times for every 50 U/L increase in plasma levels of CK-18. Dr. Diab presented these results last fall at the American College of Gastroenterology’s annual meeting.

Dr. Diab also hopes to study the marker’s utility for follow up and is seeking approval for postoperative liver biopsies at one year after surgery to see if marker levels still correlate with pathologic findings.

“We believe it’s a very reliable, noninvasive test to assess for NASH and severity of NAFLD prior to surgery, and also for monitoring disease status after surgery. This could be of great clinical utility, and we hope that this test becomes commercially available in the near future,” says Dr. Diab.

For more information, contact Robert Zimmerman, MD, at 216.444.9428 or zimmerr@ccf.org.
Advances in understanding the pathophysiology of diabetes as an autoimmune disorder have led to the development of immunotherapeutic approaches with the potential to revolutionize diabetes management. One such compound is teplizumab, a humanized Fc-engineered monoclonal antibody that is proven to suspend the autoimmune response.

Cleveland Clinic’s Diabetes Center is participating in the Protégé study, a global phase II/III trial of teplizumab in type 1 diabetics. “The hypothesis is that by intervening in the autoimmune response, teplizumab can preserve the beta cells,” explains Cleveland Clinic clinical research coordinator Jackie Payne, RN.

“The proposed effect is to permanently modify T regulatory cells and alter their ability to regulate the generation of antibodies that damage insulin-producing cells, called beta cells” says endocrinologist Byron Hoogwerf, MD, the principal investigator at Cleveland Clinic.

Thus the study is predicated on the hypothesis that the development of type 1 diabetes involves injury to the pancreatic beta cells, possibly by an environmental agent such as a virus. This insult to the beta cells causes a T-lymphocyte-dependent autoimmune attack on them, which, over time, destroys their insulin-producing capability and leads to the development of diabetes.

Derived from an immunosuppressive drug used in kidney transplantation patients, teplizumab exerts its protective effect by bonding to T cells before they attack the beta cells. “This modified form of the drug has a lower side effect profile than the one used in transplant recipients,” notes Dr. Hoogwerf.

“If teplizumab is effective, it may reduce an individual’s insulin requirements and make blood glucose levels easier to control by preserving beta cells and insulin production,” explains Cleveland Clinic research coordinator Susan Thomas, RN, MSN, CCRP. “It is potentially a cure for diabetes.”

Dr. Hoogwerf adds, “Even protecting some beta cell function makes type 1 diabetes much easier to manage, so there may be benefits even if a ‘cure’ is not achievable.”

Protégé will enroll up to 530 patients at 85 locations worldwide. Cleveland Clinic will enroll five patients between ages 18 and 35 who are newly diagnosed (within 12 weeks) with type 1 diabetes. The trial will evaluate teplizumab’s effectiveness, tolerance and safety profile in three different dosing regimens in children and adults. Patients will receive a daily IV infusion of teplizumab for 14 days followed by a two-week booster six months later.

In phase II clinical trials, a single brief course of teplizumab administered within six weeks following diagnosis improved c-peptide (the connecting peptide of proinsulin and a measure of endogenous insulin production) responses, reduced HbA1c levels and lowered insulin requirements for at least two years.

Patients in Protégé will monitor their blood sugar closely so that their insulin dose can be adjusted as needed. “The ultimate goal,” Payne notes, “is to reduce the severity of the disease by maintaining relatively normal blood sugar levels and reduce the short- and long-term complications of diabetes.”

The most challenging aspect of teplizumab’s safety profile is a hypersensitivity reaction that occurs early on during treatment, the coordinators report. The drug also may result in a decreased white blood count; both effects are brief and self-limiting.

The trial is supported by MacroGenics, Inc., a Maryland-based biotechnology company, and the Juvenile Diabetes Research Foundation.

For more information, contact Byron Hoogwerf, MD, at 216.444.8347 or hoogweb@ccf.org; Susan Thomas, RN, MSN, CCRP, at 216.444.5930 or thomass4@ccf.org; or Jackie Payne, RN, at 216.444.3694 or paynej3@ccf.org.
Medication-induced hypo- or hyperthyroidism can have a significant impact on patient care, reports endocrinologist Robert Zimmerman, MD, Interim Chairman of Cleveland Clinic’s Department of Endocrinology, Diabetes and Metabolism. “There are a number of commonly prescribed medications that can affect thyroid function and can make patient management challenging.”

A team approach that involves an endocrinologist in collaboration with the referring physician yields the best results in these patients so that thyroid abnormalities are controlled while treatment for the underlying condition is continued under appropriate medical supervision.

Amiodarone, an iodine-rich drug commonly prescribed for ventricular tachycardia or ventricular fibrillation, is the most frequently encountered cause of medication-induced thyroid disorders. Standard amiodarone therapy of 200 mg per day delivers a dose of iodine that is more than 200 times the daily iodine requirement. At this dosage, an incidence of thyroid disorders as high as 14 percent has been reported; with lower-dose therapy, the incidence is less than 4 percent. Amiodarone-induced thyroid abnormalities range from abnormal thyroid function test findings to amiodarone-induced hypothyroidism or thyrotoxicosis. Any of these problems may occur in normal thyroid glands or in those with pre-existing, subclinical abnormalities.

“Treatment of amiodarone-induced hypothyroidism is relatively straightforward, consisting of thyroid hormone replacement therapy while continuing amiodarone,” Dr. Zimmerman says. Occasionally, discontinuation of amiodarone is feasible, which eventually causes a return to a normal thyroid condition.

Managing amiodarone-induced thyrotoxicosis is more complex and depends on the underlying disorder. When it is related to excess iodine-induced thyroid hormone synthesis in an abnormal thyroid gland (Type 1), treatment requires administration of thionamides and potassium perchlorate. Several months of treatment may be required before symptoms resolve.

Thyrotoxicosis caused by destructive thyroiditis (Type 2) is best treated by corticosteroid therapy. Corticosteroids are valuable in this case for their activity related to membrane stabilization and their anti-inflammatory properties, as well as their capacity to block conversion of T4 to T3.

Thyroid abnormalities also can develop as a consequence of interferon treatment such as for hepatitis C or multiple sclerosis, with reports of prevalence ranging as high as 35 percent. “These patients may have some evidence of hyperthyroidism that is exacerbated with interferon, although prior thyroid dysfunction is not a contraindication to treatment with interferon,” Dr. Zimmerman notes.

Interferon-induced hypothyroidism can be treated with levothyroxine therapy while continuing interferon. This hypothyroidism often is limited to the duration of the interferon therapy and resolves after therapy is discontinued. In these patients, thyroid hormone replacement may be terminated. In the event that the thyroid disorder is permanent, such as in patients with positive antibodies, levothyroxine therapy may need to be continued.

For patients with thyrotoxicosis, treatment with glucocorticosteroids can be effective, similar to the situation with Type 2 amiodarone-induced thyrotoxicosis.

Sunitinib and interleukin are newer drugs that also appear to be associated with a risk of thyroid abnormalities, reports Cleveland Clinic endocrinologist Mario Skugor, MD. “With these drugs the patient may undergo a phase of hyperthyroidism at the outset, which is followed by hypothyroidism,” he says.

Risk factors for medication-induced thyroid disease include multi-nodular goiter for amiodarone-induced conditions and positive thyroid antibodies for interferon-related disorders. A history of interferon-induced thyroid abnormalities also may be a risk factor.

For more information or to refer patients, please contact Robert Zimmerman, MD, at 216.444.9428 or zimmerr@ccf.org; or Mario Skugor, MD, at 216.445.0739 or skugorm@ccf.org.
Is Iodine Depletion Necessary?

Trial to access whether requiring thyroid cancer patients to follow a low-iodine diet prior to radioactive ablation is effective

It’s so logical that it’s standard practice: deplete iodine through diet and you will improve radioactive iodine uptake in thyroid cancer patients. But does it really improve the results of surgery and ablative therapy? Surprisingly, we don’t know the answer to this simple, critical question. Cleveland Clinic endocrinology fellow Rahfa Kurdi Zerikly, MD, is leading a trial to analyze the effectiveness of iodine depletion.

The question is critical, she points out, because the annual incidence of well-differentiated thyroid cancer has risen nearly 50 percent since 1973, one of the most rapid increases among malignancies tracked by the Surveillance Epidemiology and End Results (SEER) database. Making sure that therapy is as effective as it can be could spare patients distress, prevent recurrence, reduce healthcare costs and potentially obviate the pretreatment diet and urine collection that are so burdensome for patients.

“So many enjoyable foods and dietary staples — even tap water — are prohibited on this diet, that most patients don’t like it,” Dr. Zerikly notes. “I don’t think anybody would like it.”

Not only that, a large share of patients can’t follow it, or follow it well enough, according to previous research by the department. They instructed 46 patients to follow a low-iodine diet, based on a printed guide and information on the department’s website, for two weeks before their whole body scan and the radioactive ablation therapy. After those two weeks and before ablation therapy, the investigators measured the patients’ 24-hour urine iodine levels. The mark of diet success was a level of 100 μg/d or less. But only 59 percent of patients achieved it; 41 percent did not, and 9 percent actually had a high iodine load — greater than 460 μg/d.

“So the question was, should we have the patients diet or not? Maybe we should get these results back and not proceed with the ablation until we make sure the patient is in low iodine status,” says Dr. Zerikly.

Now, she has accrued 90 patients in the study and will compare the outcomes of treatment between patients who were iodine depleted before ablation and those who were not. She and her collaborators will judge the success of therapy based on serum thyroglobulin levels and repeat scans at six and 12 months after treatment.

Although there is some literature on iodine depletion in well-differentiated thyroid cancer, the data haven’t been convincing, she says, so this trial is sorely needed to help decide the best approach. Finding iodine depletion does make a difference will mean 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. On the other hand, finding diet doesn’t make a difference could make the therapy easier for patients and spur endocrinologists to find new ways to increase treatment efficacy.

For more information, contact Rahfa Kurdi Zerikly, MD, at 216.444.8761 or kurdir@ccf.org.
Study of Hyperparathyroidism-Related Male Bone Disease Extends Important Messages to Clinicians on Patient Screening

Endocrinologists recognize that primary hyperparathyroidism is a strong risk factor for bone disease. Results of a study undertaken by members of the endocrine surgery section of Cleveland Clinic, however, indicate this association has been underappreciated in men. They found that men were much less likely than women to undergo bone density screening. Encouragingly, the research does show a narrowing of the gap between genders in screening patterns, but it also documents that osteoporosis screening continues to be significantly underperformed in all patients with primary hyperparathyroidism.

The importance of this observation relates to additional study findings showing a high prevalence of bone disease among men and women with primary hyperparathyroidism and differences between genders in bone disease responses to parathyroidectomy, says Andrew Greene, MD, endocrine surgery research fellow.

“Primary hyperparathyroidism is a major health concern for men and women, with about 100,000 new cases being diagnosed annually in the United States,” he says. “Until recently, most of the attention on hyperparathyroid-mediated bone disease has focused on women, but we’ve identified that men with hyperparathyroidism likely have much higher rates of bone disease than previously recognized,” he notes.

“Coupling that finding with the consequences of osteoporotic fractures, which include an almost three times higher rate of fracture-related mortality among older men compared with women, underscores the importance of improving screening practices for hyperparathyroidism and bone disease to positively impact health for all patients.”

Cleveland Clinic endocrine surgeon Mira Milas, MD, was impressed by a difference in bone density screening patterns between men and women referred for parathyroidectomy when she joined the staff in 2002. Her observation prompted a new department protocol advocating routine bone density screening in all patients with parathyroid disease prior to surgery. In order to understand trends in bone screening practices and to characterize the scope of bone disease among men, a study was undertaken using Cleveland Clinic’s prospectively maintained database of patients undergoing parathyroidectomy for primary hyperparathyroidism.

The study reviewed 1,000 patients with primary sporadic hyperparathyroidism operated on between 2000 and 2006 and included 243 men and 757 women.

The proportion of men with a preoperative DXA was only 12 percent in 2000 compared with 32 percent of women. While the screening rate in men rose steadily over the study period and reached 42 percent in 2005, the other side of the coin is that the majority of men and women were still not being screened by their referring physicians.

At the end of the study, when the bone density screening rate was comparable in men and women, it became apparent that the prevalence of bone disease was almost as high in men as in women. In 2000, bone disease was identified in only 8 percent of referred men compared with 26 percent in 2005.

“Given the high prevalence of bone disease and the fact that our analyses showed that neither clinical parameters, such as age or body mass index, nor laboratory measurements, such as calcium, PTH, or vitamin D, predicted bone disease, we believe that DXA screening should be universal and routine in all men with primary hyperparathyroidism,” says Dr. Milas.

“Even if patients qualify for surgery based upon other indications unrelated to bone disease, DXA screening is still important, because it gives a more comprehensive
understanding of their disease. And this will allow patients to make a more informed decision about surgery. A patient told only that his or her calcium is elevated may not agree to undergo an operation, but the prospect of a crippling hip fracture is likely to get their attention. It may change their outlook on treatment options,” adds Dr. Greene.

A gender-related difference in screening patterns also was identified in an analysis of postoperative surveillance data. Among men and women who had preoperative bone scans, women were much more likely than men to undergo postoperative bone density follow-up even though there was no significant difference between genders in their preoperative lowest T-score.

Interestingly, postoperative bone density data showed bone disease responded better to surgery in men than in women. On average, men had significantly greater gains in bone density than women, while women were four times more likely than men to continue to lose bone.

“To our knowledge, ours is the first study to report such a significant gender disparity in bone density outcomes after parathyroidectomy. The finding that parathyroidectomy does not always cure bone disease, especially in women, reinforces the importance of postoperative screening. Without DXA surveillance, a need for medical management of bone disease may go unrecognized,” says Dr. Greene.

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Comparison of DXA screening and bone disease prevalence among women and men referred for parathyroidectomy in the years 2000 and 2005. Among both men and women, the percentage of patients with DXA scans rose between 2000 and 2005. During this period, there was a substantial increase in the percent of men undergoing DXA scanning (from 12 percent to 42 percent). Aggressive screening increased the apparent prevalence of bone disease among men from deceptively low levels in 2000 to levels approaching those observed in the female cohort in 2005.
Adrenal Insufficiency in ICU Patients

Adrenal insufficiency in critically ill patients is a life-threatening problem that requires urgent intervention. Awareness of the clinical signs of adrenal insufficiency and the exercise of sound clinical judgment can significantly impact outcome in these patients, says Cleveland Clinic endocrinologist Amir Hamrahian, MD.

“The overall estimated incidence of adrenal insufficiency in critically ill patients is less than 10 percent and the reported higher values in up to 65 percent of patients with septic shock is exaggerated and based on inappropriate biochemical evaluation,” he states. “Physicians should have a high suspicion in hypotensive patients who do not respond to IV fluids or vaso-pressors, in those who have eosinophilia, persistent low-grade fever, hyperpigmented skin, hyponatremia or hyperkalemia.”

For critically ill patients with suspected adrenal insufficiency based on their clinical picture, Dr. Hamrahian recommends measuring total cortisol levels during a standard ACTH stimulation test. Baseline total cortisol in ICU patients should be 15 ug/dL or more and 20 ug/dL or higher at 30 minutes after ACTH stimulation. Dr. Hamrahian cautions, however, that patients in the ICU often have low serum cortisol-binding protein levels (transcortin and albumin), resulting in falsely low total cortisol levels. Dr. Hamrahian and colleagues have shown that an albumin concentration less than 2.5 ug/dL is a reasonable cut-off value to identify patients with significantly low cortisol-binding proteins. Based on a recent review, a cortisol level as low as 9.5 ug/dL before and 15.5 ug/dL after cortrosyn stimulation may indicate normal adrenal function in patients with significant hypoproteinemia.

Free cortisol is a more accurate tool for evaluation of adrenal function in ICU patients, but currently is not available for routine clinical use in many local labs and requires long (seven to 10 days) turnaround times. A random and postcortrosyn-free cortisol level less than 1.8 and 3.1 ug/dL are suggestive of adrenal insufficiency and such patients should be treated with hydrocortisone until more data is available.

“Alternatively, calculating free cortisol by Coolens’ method seems to be an accurate estimate of free cortisol levels in critically ill patients, even in those with hypoalbuminemia,” Dr. Hamrahian notes. “However, such calculation requires transcortin levels, which again needs to be sent to central labs in most places.”

Salivary cortisol has been suggested as a potential, more convenient alternative to serum-free cortisol measurement. This technique is still investigational, “and will likely not replace serum cortisol measurements in critically ill patients,” Dr. Hamrahian comments.

Delta cortisol (the difference between the baseline and the maximum cortisol value at 30 or 60 minutes during the ACTH stimulation test) is used in some centers as the basis for treatment for suspected adrenal insufficiency. Although delta cortisol does have some prognostic value in patients with septic shock, it is not a good indicator of adrenal function for most ICU patients, Dr. Hamrahian reports. “Delta value does not assess the integrity of the hypothalamic-pituitary-adrenal axis, and does not measure adrenal function,” he explains.

When testing confirms the presence of adrenal insufficiency, the patient should be started on 50 mg hydrocortisone every six to eight hours. Treatment should continue for two to three days, at which time the patient’s hemodynamic status is expected to be improved. At that point, the dose should be reduced to 25 mg every six hours, with further taper based on the patient’s clinical condition.

For patients with hypotension and lack of response to IV fluids and pressors, but borderline cortisol levels, a trial of therapy with hydrocortisone is reasonable. “It is appropriate to give these patients hydrocortisone [150 to 200 mg/day] for one to two days and observe their clinical response,” he says. “If they do not respond, therapy should be discontinued.”

Following discharge from the ICU, patients should be re-evaluated to assess the integrity of the H-P axis before subjecting them to lifelong corticosteroid therapy. “A variety of factors, including inflammatory response during critical illness, can result in adrenal insufficiency, which can be reversible once the patient is recovered,” Dr. Hamrahian explains.

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

Aventis: A Study on Insulin Treatment in African American Patients with Type 2 Diabetes
The purpose of this study is for glycemic control in African American patients. African American volunteers are needed who are between the ages of 40 and 70 years old and have type 2 diabetes, with an HbA1c level greater than or equal to 8.5 who are on insulin or oral agents and who do not currently smoke.

Frantz Biomarkers
The purpose of this study is for the detection of early stage ovarian cancer. The objective is to establish sensitivity and specificity of the plasmalogen assay as an aid in the diagnosis of ovarian cancer. Volunteers are needed who have type 1 or type 2 diabetes with no history of ovarian cancer.

For more information on these trials, please call Melanie Williams at 216.444.5410.

STAMPEDE (Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently)
This is a three-arm randomized, controlled, single-center study evaluating medical therapy, Roux-en-Y gastric bypass and sleeve gastrectomy for the treatment of type 2 diabetes.

For more information on this trial, please call Philip Schauer, MD, at 216.444.4794 or research coordinator Chytaine Hall at 216.445.3983.

Outcomes Data Available
The latest outcomes data from Cleveland Clinic's Endocrinology & Metabolism Institute are now available. To view this outcomes book, as well as outcomes data for many other Cleveland Clinic institutes, visit clevelandclinic.org/quality/outcomes.

Upcoming CME Events 2008-2009

September 10–12, 2008
3rd Annual Obesity Summit

Sept. 26–28, 2008
11th Annual Endocrinology and Metabolism Board Review

April 3, 2009
4th Annual Contemporary Issues in Pituitary Disease: Case-based Management Update

May 2009 (Date TBD)
14th Annual Diabetes Day

These events will be held at the InterContinental Hotel & Bank of America Conference Center on Cleveland Clinic's main campus.

Call 216.444.5696 or 800.238.6750 or visit clevelandclinicemeded.com for more information.
Cleveland Clinic’s endocrinology services are ranked sixth in the nation by *U.S. News & World Report*’s annual America’s Best Hospitals survey.

Introducing The Future of Healthcare
Innovative new buildings improve patient access, experience.

This fall, Cleveland Clinic is introducing the future of healthcare with the opening of the Sydell and Arnold Miller Family Pavilion and the Glickman Tower.

These buildings, which represent the largest construction and philanthropy project in Cleveland Clinic history, embody the pioneering spirit and commitment to quality that define Cleveland Clinic. These structures are a tangible expression of institutes, our new model of care that organizes patient services by organ and disease.

At 1 million square feet, the Miller Family Pavilion is the country’s largest single-use facility for heart and vascular care. The 12-story Glickman Tower, new home to the Glickman Urological & Kidney Institute, is the tallest building on Cleveland Clinic’s main campus. Both will help us improve patient experience by increasing our capacity and by consolidating services, so patients can stay in one location for their care.

With 278 private patient rooms, more than 90 ICU beds and a combined total of nearly 200 exam rooms and more than 90 procedure rooms, patients will have faster access to Cleveland Clinic cardiac and urological services.

For details, including a virtual tour, please visit meetthebuildings.com.