Endocrine Notes

Updates for physicians on practices, advances and research from Cleveland Clinic's Endocrinology & Metabolism Institute
Endocrine Notes updates physicians on clinical practices, advances and research from Cleveland Clinic’s Endocrinology & Metabolism Institute. It is written for physicians and should be relied on 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,

I am pleased to present the 2012 edition of Endocrine Notes, in which you can read about the latest clinical innovations, emerging research and new treatment modalities within Cleveland Clinic’s Endocrinology & Metabolism Institute.

The Endocrinology & Metabolism Institute is a part of Cleveland Clinic’s group practice model that brings related specialties together to provide integrated, patient-centered care. Collaboration among endocrinology, endocrine surgery, bariatrics, including bariatric surgery, and cardiology allows us to offer exceptional integrative, multidisciplinary patient care and novel discoveries.

In this issue, you will learn more about our leading-edge innovation and research, including:

- Details of a Cleveland Clinic study that identified increased mortality risk with sulfonylureas vs. metformin, while also demonstrating that glimepiride may be the preferred sulfonylurea for patients with underlying coronary artery disease.
- A mathematical model developed by our endocrine surgeons that can help differentiate normocalcemic primary hyperparathyroidism and secondary hyperparathyroidism.
- Five inferior petrosal sinus sampling (IPSS) pillars to adhere to when ordering and interpreting IPSS in patients with ACTH-dependent Cushing syndrome.
- Robotic bilateral posterior adrenalectomy for ACTH-independent macronodular adrenal hyperplasia causing subclinical Cushing syndrome.
- Highlights of our study that sheds light on the importance of screening for thyroid cancer in patients diagnosed with Cowden syndrome, including an online calculator that estimates a patient’s risk for PTEN mutation and the need for genetics consultation.
- Our study that found gastric bypass improves glucose homeostasis by attenuating the effect of ghrelin on B-cell function.
- A proposed clinical algorithm targeting the management of residual diabetes following bariatric surgery.
- Our groundbreaking study, known as STAMPEDE, that continues to provide a wealth of information about our field, including the story we bring you here about how the benefits of bariatric surgery in type 2 diabetes extend to the improvement and prevention of nephropathy.

Throughout the Endocrinology & Metabolism Institute, our staff remains committed to Cleveland Clinic’s core ideology: Patients First. Our institute comprises:

- The Department of Endocrinology, Diabetes and Metabolism, which manages specialized centers of care for patients with diabetes, thyroid disorders and pituitary disorders.
- The Department of Endocrine Surgery, which performs the highest number of surgical procedures in the region.
- The Bariatric & Metabolic Institute, which has been designated as a Bariatric Surgery Center of Excellence by the American Society for Metabolic and Bariatric Surgery.

Your comments and questions about Endocrine Notes articles are always welcome. Please feel free to contact me at 216.444.6568 or 800.223.2273, ext. 46568.

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
Cleveland Clinic Study Identifies Increased Mortality Risk with Sulfonylureas vs. Metformin

Kevin M. Pantalone, DO, and Robert Zimmerman, MD

But Glimepiride May Be Safest Sulfonylurea

In Cleveland Clinic’s Department of Endocrinology, Diabetes and Metabolism, we have identified an increased risk of overall mortality in patients with type 2 diabetes mellitus treated with sulfonylurea vs. metformin monotherapy. In patients who do receive a sulfonylurea, our research found that glimepiride may be the preferred agent in patients with underlying coronary artery disease (CAD).

We recently conducted a retrospective cohort study of nearly 24,000 patients with type 2 diabetes who were seen at Cleveland Clinic, to assess the risk of overall mortality in patients taking the most commonly prescribed sulfonylureas or metformin. In the entire population of our study, which analyzed patients seen across eight years, glipizide, glyburide and glimepiride were all associated with a statistically significant >50 percent increase in mortality risk vs. metformin. However, in those patients with documented CAD, a statistically significant increase in overall mortality risk was observed with glipizide (41 percent) and glyburide (38 percent) vs. metformin — but not with glimepiride.

These results suggest that metformin is associated with a substantial reduction in mortality risk vs. sulfonylureas; thus, in the absence of contraindications, metformin should be the preferred first-line agent. In addition, these study results suggest that when a sulfonylurea is required to treat patients with type 2 diabetes, particularly those with underlying CAD, glimepiride may be the preferred/safer agent among the most commonly used generic sulfonylureas available in the United States (glipizide, glyburide and glimepiride).

We presented the results of our study at The Endocrine Society’s 94th Annual Meeting, ENDO 2012, in Houston, Texas, and they were published in Diabetes, Obesity and Metabolism (see Suggested reading).

Robust data from a large patient population

We conducted this retrospective analysis using the Cleveland Clinic Diabetes Registry, a repository comprising data on patients with diabetes treated with oral anti-diabetic agents. We identified 23,915 patients with type 2 diabetes who were seen at Cleveland Clinic between 1998 and 2006 who received monotherapy with metformin (n=12,774), glipizide (n=4,325), glyburide (n=4,279) or glimepiride (n=2,537). The patients were followed for mortality by documentation of death within the enterprisewide electronic health record (EHR) system and/or Social Security Death Index (SSDI) records.

There were a total of 2,546 deaths in 58,513 person years of follow-up in the entire cohort, and 419 deaths in 5,980 person-years of follow-up in the subgroup with a history of documented CAD (n=2,721). Multivariable Cox models with propensity analysis were used to compare cohorts.

Cleveland Clinic is ideally suited to this type of study, given our large patient population with type 2 diabetes and CAD and our multidisciplinary approach in treating a high volume of patients within the Endocrinology & Metabolism Institute and the Sydell and Arnold Miller Family Heart & Vascular Institute.

Practical clinical considerations

The precise reason why glimepiride may be safer than the other sulfonylureas in patients with underlying CAD remains unclear and requires further study.
Over the past few decades, research has suggested that the individual sulfonylureas differ considerably in terms of their pharmacologic properties, including:

- Hypoglycemic risk
- Sulfonylurea receptor selectivity
- Effects on myocardial ischemic preconditioning (a cardioprotective phenomenon in which short periods of nonlethal ischemia help protect the myocardium from subsequent damage in the setting of recurrent ischemia)

Some reports that have suggested that glimepiride, unlike other sulfonylureas, may be a mild insulin sensitizer. These differences in pharmacologic properties may translate into differences in clinical outcomes, including mortality risk.

Because glipizide, glyburide, glimepiride and metformin are all readily available as generic agents at a similar cost to the patient, it would seem inappropriate when no contraindications exist and adequate glucose control is not an issue to prescribe those medications that are associated with a higher risk of mortality.

The results of this retrospective study are clinically significant for endocrinologists and primary care physicians who manage this patient population, especially in light of the fact that prospective, randomized controlled clinical trials comparing the mortality risk of these agents may not be a high priority given that the drugs are all available at bargain-basement pricing at local pharmacies. However, the sulfonylurea drug class remains a mainstay of therapy for patients with type 2 diabetes and is recommended as a tier-1, well-validated core therapy in the American Diabetes Association/European Association for the Study of Diabetes Consensus Treatment Algorithm. Therefore, randomized controlled clinical trials examining the mortality risk of various sulfonylureas, especially in patients with CAD, would provide endocrinologists and other physicians with evidence-based data — beyond expert opinion — to guide us in this area.

About the authors

Dr. Pantalone is an endocrinologist who specializes in the evaluation and management of diabetes mellitus, with a particular focus on type 2 diabetes. Dr. Zimmerman is Vice Chairman of the Department of Endocrinology, Diabetes and Metabolism and Director of the Diabetes Center.

For more information, please contact Dr. Pantalone at 216.445.9060 or pantalk@ccf.org. Dr. Zimmerman can be reached at 216.444.9428 or zimmerr@ccf.org.

Suggested reading


Differentiating Normocalcemic Primary Hyperparathyroidism and Secondary Hyperparathyroidism

Cleveland Clinic endocrine surgeons create mathematical model to clarify diagnosis

With awareness increasing about primary hyperparathyroidism, clinicians are discovering that rather than one disease entity of high calcium and high parathyroid hormone (PTH), primary hyperparathyroidism presents across a wide spectrum. Just one year ago, endocrine surgeons at Cleveland Clinic described the new parathyroid disease entity normohormonal primary hyperparathyroidism (www.clevelandclinic.org/endonotes2011). This is a presentation in which the patient’s calcium level is elevated but his/her PTH level is within normal range.

In this article, I describe a new mathematical model developed by clinicians in Cleveland Clinic’s Department of Endocrine Surgery that can help clarify the diagnosis of another challenging disease presentation: normal calcium level with elevated PTH, or normocalcemic primary hyperparathyroidism (NCPHP).

Overlapping biochemical presentation

NCPHP can at times be confused with secondary hyperparathyroidism. Patients with 2° hyperparathyroidism (HPT) caused by vitamin D deficiency can present with a biochemical profile similar to patients with NCPHP: normal calcium level, elevated PTH level and low or low-normal vitamin D level. Because of the overlapping biochemical presentation, many patients with NCPHP may be diagnosed initially with 2° HPT; then, worsening osteoporosis despite treatment or recurrent kidney stones brings them back to the attention of endocrine surgeons.

To facilitate the initial diagnosis of NCPHP, Cleveland Clinic’s endocrine surgeons proposed a mathematical formula that allows the calculation of a maximally expected normal PTH (maxPTH) level when taking into account the patient’s age and serum calcium and vitamin D levels (Table 1). When the serum PTH is higher than the calculated maxPTH, a diagnosis of normocalcemic primary hyperparathyroidism is suspected.

We identified 477 patients diagnosed between 2007 and 2010 with primary hyperparathyroidism who underwent surgery and were found to have abnormal parathyroid glands. Of these 477 patients, 66 were diagnosed with NCPHP. We reviewed these 66 patients’ preoperative biochemical profiles and tested whether our formula would have predicted primary hyperparathyroidism rather than 2° HPT.

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**Table 1**

<table>
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<tr>
<th>Patient #</th>
<th>Age</th>
<th>Calcium</th>
<th>VitD25</th>
<th>PTH</th>
<th>maxPTH</th>
<th>PTH&gt;maxPTH</th>
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<tr>
<td>2</td>
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</tr>
</tbody>
</table>

This mathematical formula developed by Cleveland Clinic’s Department of Endocrine Surgery calculates the maximally expected normal PTH level when taking into account the patient’s age and serum calcium and vitamin D levels. When the serum PTH is higher than the calculated maxPTH, a diagnosis of normocalcemic primary hyperparathyroidism is suspected.
In order to use the decision tree, we asked that all patients undergo a comprehensive biochemical workup (Figure 2). The protocol then takes the clinician through a review of the patient’s ionized calcium and vitamin D levels and the calculated maxPTH level to identify the next management plan. This protocol clearly outlines when a referral to the endocrine surgeon should be made.

Our retrospective analysis found that if the formula developed by Cleveland Clinic’s endocrine surgeons had been used as another diagnostic tool prior to surgery, it would have correctly identified all 66 patients to have NCPHP. Even in patients with coexisting vitamin D deficiency, the formula was able to sort these patients into the NCPHP group and not the 2° HPT group. Furthermore, we found that even though patients with NCPHP had calcium levels in the normal range, they were often in the high-normal range, whereas patients with 2° HPT usually had mid- to low-normal-range calcium levels. The PTH levels in patients with NCPHP were significantly higher than those in patients with 2° HPT, despite similar vitamin D levels.

Clinical management and referrals

One drawback of the formula was that while it was very sensitive, it also sorted some patients with 2° HPT into the NCPHP group. Therefore, we have proposed a management protocol to help clinicians effectively triage patients to their correct disease group (Figure 1). In order to use the decision tree, we asked that all patients undergo a comprehensive biochemical workup (Figure 2). The protocol then takes the clinician through a review of the patient’s ionized calcium and vitamin D levels and the calculated maxPTH level to identify the next management plan. This protocol clearly outlines when a referral to the endocrine surgeon should be made.

We are currently in the process of implementing this protocol in the offices of the primary care physicians and endocrinologists at Cleveland Clinic so that we may prospectively evaluate the efficacy of the management protocol when incorporating the maxPTH calculation.

Our retrospective study found that if the formula developed by Cleveland Clinic’s endocrine surgeons had been used as another diagnostic tool prior to surgery, it would have correctly identified all 66 patients to have normocalcemic primary hyperparathyroidism.

About the author

Dr. Jin serves as associate staff in the Department of Endocrine Surgery.

For more information, please contact Dr. Jin at 216.445.3411 or at jinj@ccf.org.
Although a pituitary adenoma is the most common cause of adrenocorticotropic hormone (ACTH)-dependent Cushing syndrome, the distinction from ectopic ACTH production can be difficult. This is because approximately 25 to 40 percent of pituitary microadenomas causing Cushing syndrome are too small to be detected by MRI, and also because about 10 percent of adults have (usually nonfunctional) microadenomas that are incidentally found on MRI screening.

Inferior petrosal sinus sampling (IPSS) is the gold standard test to determine the etiology of ACTH-dependent Cushing syndrome. An inferior petrosal sinus to peripheral (IPS:P) ACTH ratio >2 before or >3 after corticotropin-releasing hormone (CRH) administration confirms a pituitary source of ACTH.

False-negative results, or the presence of Cushing disease in the absence of a diagnostic IPS:P ACTH ratio, may occur in up to 10 percent of patients and can be a source of confusion. In contrast, the presence of a false-positive IPSS — that is, the test suggests a pituitary source of ACTH when in fact the source is ectopic or peripheral — is rare.

In the past two years, we have published two reports in Clinical Endocrinology and Endocrine Practice concerning the utility of IPSS and its interpretation in challenging cases of ACTH-dependent Cushing syndrome (see Suggested reading). Here we review the principles — referred to as the Five IPSS Pillars — that are key to the appropriate use and interpretation of IPSS. To illustrate how the pillars can be used, we also share a report on a challenging case (see sidebar article).
The Five IPSS Pillars
Based on our experience at Cleveland Clinic, we believe clinicians should adhere to the following principles for IPSS testing:

1. **Do not perform IPSS before confirming the presence of ACTH-dependent hypercortisolemia.** The result of IPSS in a healthy volunteer or a patient with pseudo-Cushing may mimic the result in a patient with Cushing disease.

2. **Confirm hypercortisolemia at the time of IPSS.** Patients with cyclic Cushing syndrome may have a false-positive or false-negative IPSS result, depending on where the tumor is located and the degree and duration of eucortisolemia or hypocortisolemia between the hypercortisolemia episodes. We obtain a stat cortisol level in the morning the day that IPSS is planned and do not proceed with the IPSS if serum cortisol is <10 µg/dL.

3. **Confirm catheter placement.** Radiological confirmation of catheter tip placement during IPSS using venous angiography to demonstrate retrograde flow into the cavernous sinuses before sampling and by intermittent fluoroscopy during sampling may not be reliable, especially in centers with less experience with this procedure. At the same time, since there are collateral vessels draining to the inferior petrosal sinus (IPS), the aspirated venous sample from a properly placed catheter may occasionally come from a collateral vessel and may not accurately represent true pituitary venous efflux. We recently confirmed that the prolactin measurement during IPSS can reduce false-negative results. Based on our data, if the IPS:P prolactin ratio is <1.3 and the corresponding IPS:P ACTH ratio is negative (i.e., <2 and <3 for pre- and post-CRH samples, respectively), the clinician cannot be sure that the negative result is valid. Others have recommended an IPS:P prolactin ratio >1.8 as an indication of appropriate IPS venous sampling. Currently, we have a dedicated interventional neuroradiologist perform all IPSS procedures.

4. **Note that proper unilateral IPS venous sampling does not rule out a corticotroph adenoma in the contralateral side.** As is illustrated in the accompanying case study, the patient had a tumor on the right side yet had appropriate IPS venous sampling only on the left side. Based on the presence or absence of collateral venous plexus to the contralateral side, the IPS on the contralateral side may not show a significant IPS:P ACTH ratio.

5. **Calculate prolactin-adjusted ACTH ratios.** Prolactin-adjusted ACTH ratios may help to lateralize a corticotroph adenoma and may have an impact on surgical outcome. While the utility of IPSS to diagnose pituitary-mediated ACTH-dependent Cushing syndrome is well-established, to date the technique does not appear reliable for predicting precisely where within the pituitary — right, left, center — a microadenoma will be localized. A proposed criterion for localization indicates that an intersinus ACTH gradient of ≥1.4 before or after CRH stimulation is accurate in approximately 50 to 70 percent of cases. Variable patterns of venous drainage and catheter misplacement or improper venous sampling during IPSS are important factors that can lead to inaccuracy in lateralization of the tumor.

We have demonstrated that the prolactin-adjusted ACTH ratio may be particularly useful when there is proper bilateral IPS venous sampling based on concurrent IPS:P prolactin ratios. In fact, no patient in our initial series of 14 patients — with the number now extending to about 20 patients — had a dominant prolactin-adjusted ACTH ratio (≥1.4) and a lesion on the opposite side of the pituitary gland. Such measurement could not be applied to the patient in the case study presented here because she had successful IPS sampling only on one side. We have encountered cases in which a pituitary adenoma has been found at neurosurgery contralateral to the side suggested by the prolactin-adjusted ACTH ratio; however, further meticulous pituitary exploration on the other side, prompted by the IPSS result, has uncovered a very small microadenoma on the side predicted by the ratio. If our data are confirmed by additional studies, the IPSS prolactin-adjusted ACTH ratio may conceivably be used to guide the neurosurgeon if hemi-hypophysectomy is to be performed.

Finally, desmopressin has been used successfully in place of CRH in centers around the world, with similar diagnostic accuracy. Desmopressin is given as a 10-µg IV push; an IPS:P ACTH ratio >2 before and >3 after desmopressin administration is usually used to confirm a pituitary source. Considering that CRH cannot be obtained in this country at the present time, the use of desmopressin seems a reasonable option until CRH again becomes clinically available.

In conclusion, IPSS is best performed by experienced hands, and adherence to the Five IPSS Pillars outlined here will increase the likelihood of successful localization and treatment of pituitary adenomas causing Cushing disease.
A 30-year-old woman with progressive weight gain, fatigue, muscle weakness and skin changes suggestive of hypercortisolism was found to have the following biochemical results: cortisol after 1-mg dexamethasone suppression test, 44.8 µg/dL; 24-hour UFC, 824 and 3,515 µg (0-50); ACTH, 80 and 102 pg/mL (8-24). The pituitary MRI failed to reveal a pituitary adenoma. She was referred for IPSS, during which the neuroradiologist believed that he had achieved successful bilateral IPS catheter placement.

The patient's IPS:P ACTH ratio was <2 and <3 in all pre- and post-CRH samples, respectively (Table 1). The IPS:P prolactin levels indicated that the right IPS was not successfully catheterized or that the venous drainage did not represent IPS venous flux, as all the IPS:P prolactin ratios on the right side were <1.3. This, taken along with the robust ACTH response to CRH, which is reported in similar cases, suggested that the IPSS results were falsely negative and that the source of the ACTH was more likely pituitary than ectopic. The patient subsequently was found to have a right-sided pituitary adenoma, developed adrenal insufficiency postoperatively, and the tumor was stained positive for ACTH.

The application of our Five IPSS Pillars for ordering and interpreting IPSS results, along with our clinical experience, guided us in diagnosing and treating the patient discussed in this case.
Table 1

<table>
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<tr>
<th>TIME (min)</th>
<th>ACTH (µg/mL)</th>
<th>ACTH ratio</th>
<th>PRL (ng/mL)</th>
<th>CORT (µg/dL)</th>
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</table>

ACTH, corticotropin; PRL, prolactin; CORT, cortisol; RPS, right petrosal sinus; LPS, left petrosal sinus; P, peripheral; R/P, right petrosal sinus to peripheral ratio; L/P, left petrosal sinus to peripheral ratio


About the authors

Dr. Hamrahian specializes in pituitary and adrenal disorders in the Department of Endocrinology, Diabetes and Metabolism. Dr. Hui is a neurointerventional surgeon and neuroradiologist in the Cerebrovascular Center. Dr. Weil is Section Head of Neuro-Endocrine Surgery. Dr. Kennedy is Chair of the Department of Endocrinology, Diabetes and Metabolism and has a special interest in pituitary conditions.

For more information, please contact Dr. Hamrahian at 216.445.8538 or hamraha@ccf.org. Dr. Kennedy can be reached at 216.445.8645 or kennedlj4@ccf.org.

Suggested reading


Our patient was a 60-year-old man with bilateral macronodular adrenal masses. These masses were incidentally identified on a CT scan ordered for abdominal pain in December 2011 in an outside hospital. He was referred to Cleveland Clinic’s Department of Endocrine Surgery within the Endocrinology & Metabolism Institute on February 15, 2012. At his office visit, the patient’s only complaint was a weight gain of 20 pounds over the past six months without any change in his dietary habits.

By Eren Berber, MD
We believe that avoiding the abdominal cavity helped with the patient’s quick recovery. Use of the robotic system facilitated the procedure by providing a three-dimensional view and wristed instrumentation in a small space. This case also takes its place in the literature as the first bilateral posterior adrenalectomy that was performed robotically.

About the author

Dr. Berber is an Associate Professor of Surgery and Director of Robotic Endocrine Surgery in the Department of Endocrine Surgery, Endocrinology & Metabolism Institute. His specialty interests include minimally invasive and robotic endocrine and liver surgery.

For more information, please contact Dr. Berber at 216.445.0555 or berbere@ccf.org.

Suggested reading


At Cleveland Clinic, where endocrinologists and endocrine surgeons from the Endocrinology & Metabolism Institute work collaboratively with geneticists, researchers and other clinicians, referrals for thyroid screening are frequent among those with inherited cancer syndromes. One such example is Cowden syndrome (CS), a rare, dominantly heritable disorder that typically falls beyond routine recognition.

Traditional aspects of care for CS patients have focused on the treatment of breast and thyroid cancer, both of which demonstrate increased incidence among CS patients. However, there has been evolution in the way that genetics professionals diagnose CS — and subsequently, a broader understanding of its associated disease spectrum, including CS-related cancers.

Housed under the umbrella diagnosis of PTEN hamartoma tumor syndrome (PHTS), CS is one of several genetic syndromes, including Bannayan-Riley-Ruvalcaba syndrome (BRRS) and Proteus-like syndrome, characterized by germline mutations of the tumor suppressor PTEN. These mutations predispose patients to benign hamartomatous changes (Figure 1) as well as malignant transformation of epithelial tissues, including breast, thyroid, kidney, intestine and endometrium. Although being PTEN mutation-positive imparts the ultimate diagnostic confirmation of CS, diagnosis can also be made on clinical grounds, as outlined by the International Cowden Consortium (ICC) Diagnostic Categories.

Recognizing patients with CS is especially important given the frequency of associated cancers and the inherent implications for screening. Until recently, the exact magnitude and proportion of lifetime cancer risks in these patients were not fully appreciated. New data indicate that the lifetime risks in PTEN mutation-positive patients for breast, thyroid, endometrial, colorectal and kidney cancer, as well as melanoma, are elevated beyond those expected in the general population. Moreover, the lifetime risk of differentiated thyroid cancer for this group of patients is 35 percent.

Given the importance of recognizing patients who potentially have CS and initiating appropriate cancer screening, a dedicated thyroid screening program was developed at Cleveland Clinic in 2007. Recently, we evaluated the outcomes of our thyroid screening program in PTEN mutation-positive CS patients and delineated the characteristics of both malignant and benign thyroid disease in this population.

Study results

The patient population for this study was derived from a large database of CS and CS-like patients that is part of a national multi-institutional study that is centrally coordinated at Cleveland Clinic by Charis Eng, MD, PhD, Chair and Founding Director of the Genomic Medicine Institute.

For the purpose of our investigation, we looked at only those patients with a known germline pathogenic PTEN mutation (n=225). From the cohort of 225 patients, we identified 32 individuals (14 percent) with differentiated thyroid cancer. The median age at cancer diagnosis for the overall group was 35 years. Tumors were multifocal in 54 percent of patients and generally small (mean size, 1.4 cm). Distant (n=1) and cervical (n=2) metastases were rare. At the time of surgery for thyroid cancer, 25/32 patients (78 percent) had clinical and histologic evidence of goiter, and 16/32 (50 percent) had a background of Hashimoto thyroiditis noted on the pathology report. In patients with benign disease only, goiter was present in more than 70 percent, and Hashimoto thyroiditis in nearly 30 percent.

Twenty-five of the 225 patients were seen and screened at Cleveland Clinic. Sixteen of these 25 patients underwent their first formal ultrasound screening or second opinion evaluation by endocrine surgeons at Cleveland Clinic. Nine (56 percent) of these 16 patients had ultrasound-evident thyroid abnor-
malities consisting of multinodular goiter (n=6), Hashimoto thyroiditis (n=2) or both (n=1). Seven patients (44 percent) required thyroid nodule fine-needle aspiration biopsy at the first office visit, which was abnormal in three patients (19 percent), leading to total thyroidectomy. Two of these (12.5 percent of the group of 16) were diagnosed with thyroid cancer, unsuspected prior to screening.

Clinical applications

Based on our findings, PTEN mutation-positive patients with CS have an increased prevalence of thyroid disease, both malignant and benign, and it occurs much sooner than is widely appreciated. Data from the Surveillance Epidemiology and End Results (SEER) cancer registry indicate that the median age at thyroid cancer diagnosis in the general population is 49 years. The onset of thyroid cancer by the middle of the third decade in this PTEN mutation-positive population is striking in comparison. Screening for thyroid disease is therefore advisable at the time of diagnosis, regardless of age, and preferably by dedicated thyroid specialists.

Thyroid surgery, if needed, should be a total thyroidectomy. This makes sense biologically, since the hereditary process places the entire thyroid tissue at risk. Furthermore, this approach avoids multiple partial resections and repeat surgeries, which are riskier procedures.

Although CS may be somewhat difficult to recognize, the implications are so valuable that it is a worthwhile investment of effort and vigilance. PTEN mutation-positive patients are at risk for multiple cancer diagnoses, and increased screening is recommended to decrease the resultant morbidity and mortality from disease. The challenge is to notice the subtleties and hints of something unusual — the recognition of kidney and endometrial cancers, for instance. Unfortunately, skin findings can be difficult to recognize, and biopsy is needed to properly identify a trichilemmoma (Figure 1). Oral papillomas may be more discernible and certainly can be incorporated into a head and neck exam, as could measurement of head circumference (Figure 2).

We recently developed a risk calculator at Cleveland Clinic to estimate the possibility of CS. You can access this clinical tool online at lerner.ccf.org/gmi/ccscore/ to facilitate identifying patients who will benefit from genetics consultation.

About the authors

Dr. Metzger is an endocrine surgeon in the Department of Endocrine Surgery who specializes in the thyroid and parathyroid. Dr. Eng is Chair and Founding Director of the Genomic Medicine Institute.

For more information, please contact Dr. Metzger at 216.445.3695 or metzger@ccf.org.

Suggested reading


Numerous observational studies have documented the positive metabolic effects of bariatric surgery in morbidly obese patients with type 2 diabetes. However, despite initial weight loss, 25 to 40 percent of bariatric surgery patients improve glycemic control but do not necessarily achieve “biochemical remission” of hyperglycemia. Some achieve normal glycemic control (HbA1c <6 percent or <42 mmol/mol) initially but relapse later while others never quite reach normal blood sugar levels.

Proposed Clinical Algorithm Targets the Management of Residual Diabetes Following Bariatric Surgery

By Sangeeta Rao Kashyap, MD, and Philip R. Schauer, MD

Based on our experience, we have proposed a clinical algorithm for the long-term management of residual diabetes following bariatric surgery in the absence and presence of weight regain. Our clinical approach, which is based on established pathophysiological effects of these procedures on diabetes remission, was published in Diabetes, Obesity and Metabolism in 2012 (14:773-779).

Cleveland Clinic’s Bariatric & Metabolic Institute is fully integrated within the broader Endocrinology & Metabolism Institute. As such, the patient’s endocrinologist, as part of a multidisciplinary obesity team, plays a key role in our bariatric surgery center of excellence and other settings in the long-term treatment, evaluation and monitoring of post-bariatric surgery patients with type 2 diabetes. Of specific importance is the need to monitor comorbidity status, weight regain and nutritional deficiencies.

Diabetes nonremission or re-emergence

Residual diabetes occurs more commonly following gastric restrictive (i.e., laparoscopic adjustable gastric banding [LAGB] and sleeve gastrectomy) procedures vs. intestinal bypass (i.e., Roux-en-Y gastric bypass [RYGB] and biliopancreatic diversion [BPD]) surgeries. Patients who undergo gastric bypass and BPD procedures improve sooner and maintain glucose control for longer periods than do patients treated by banding or sleeve gastrectomy procedures. Additionally, patients who do not achieve biochemical remission or who experience a re-emergence often have diabetes duration >10 years, are in advanced stages of the disease, and experience inadequate weight loss and regain weight. Other factors associated with suboptimal diabetes control following bariatric procedures are insulin use, male gender, lower preoperative BMI, severity of preoperative β-cell function (i.e., hyperglycemia) and potentially inadequate incretin stimulation following surgery.

Therapies for residual diabetes

Nonremission of hyperglycemia is indicated by an HbA1c level >7 percent or 53 mmol/mol that requires the use of anti-diabetic medications. Targeting weight regain and poor residual pancreatic β-cell function with insulin may be indicated by duration of diabetes >10 years, insulin use, poor glycemic control on oral agents and microvascular complications.

Gastric restrictive procedures

In patients who have had gastric restrictive procedures, nonremission is indicated when patients have inadequate weight loss or weight regain and progressive β-cell failure without weight regain. The management of residual type 2 diabetes due to insulin resistance and/or insulin secretion defects in these patients should focus on weight loss and glycemic control with anti-diabetic medications that have weight-negative or -neutral effects. Metformin remains the first-line agent in this context due to its mechanism of action that improves insulin sensitivity by suppressing hepatic gluconeogenesis and increasing muscle/liver glucose uptake through increased AMPK activity.
Caution should be exercised in these patients when considering sulphonylureas in the early postoperative period, because they may precipitate hypoglycemia and trigger dumping syndromes. In patients who experience suboptimal glycemic control several years after gastric restrictive surgery, the addition of a sulphonylurea to metformin could enhance insulin secretion and restore glycemic control by targeting β-cell failure. Patients who do not respond to this therapy should be prescribed basal insulin; if glycemic control is not adequate, then prandial insulin should be added.

Revisonal bariatric surgery is indicated primarily for patients with anatomical/mechanical issues or severe nutritional deficiencies and patients whose comorbid conditions worsen following LAGB or sleeve gastrectomy.

Intestinal bypass procedures
At our institution, we observed 12 months following RYGB that obese patients with type 2 diabetes experienced a greater than fourfold improvement in insulin sensitivity and a 10-fold increase in β-cell function with mixed meal testing (unpublished data). These improvements were not seen in patients who underwent gastric-restrictive procedures, even when they had significant weight loss.

In patients who have undergone gastric bypass surgery, the re-emergence of hyperglycemia without weight regain is likely related to β-cell exhaustion. Pharmacologic interventions in these patients should target β-cell failure with a trial of sulphonylureas and the subsequent addition of insulin. However, due to the insulin-sensitizing and incretin-related effects of gastric bypass in patients with diabetes, these agents should be used cautiously due to the potential for hypoglycemia. Revisonal bariatric surgery in these patients should be considered only for select surgical failure cases as it is associated with additional morbidity.

Looking forward
With an estimated 350,000 bariatric operations performed worldwide each year, additional research is needed regarding the adjunctive use of medications for long-term diabetes control. Safety and efficacy trials are warranted in this patient population to define the potential roles of alternative diabetes agents such as GLP-agonists, acarbose and bromocriptine in conjunction with lifestyle counseling.

Data regarding the use of alternative diabetes therapies including incretin analogues (i.e., DPP4 inhibitors and GLP-agonists) in bariatric patients is lacking. Studies have demonstrated that these agents enhance glucose-dependent insulin secretion and offer advantages for weight loss in obese type 2 diabetes patients. Because incretin stimulation of insulin secretion following gastric bypass helps improve glucose levels, the role of GLP-1 analogues in post-bariatric surgery patients must be further defined.

The pathophysiology underlying diabetes relapse following various bariatric surgery procedures is complex. Enhancing our understanding in this area will inform further research and treatment options.

Continued monitoring of long-term diabetes complications is essential following bariatric surgery, regardless of initial remission status.

About the authors
Dr. Kashyap is an endocrinologist in the Endocrinology & Metabolism Institute and Assistant Professor of Medicine at Cleveland Clinic Lerner College of Medicine. Dr. Schauer is Professor of Surgery and Director of Cleveland Clinic’s Bariatric & Metabolic Institute.

For more information, please contact Dr. Kashyap at 216.445.2679 or kashyas@ccf.org. Dr. Schauer can be reached at 216.444.4794 or schauep@ccf.org.

Suggested reading


Studies have demonstrated that the benefits of bariatric surgery extend beyond durable weight loss and include significant improvements in glycemic control and a sustainable improvement in diabetes. The results of a study that we conducted recently at the Bariatric & Metabolic Institute take that concept one step further: Bariatric surgery also can improve or even prevent microvascular complications such as diabetic nephropathy.

Our study included obese diabetic patients who had undergone bariatric surgery at our institution and who had completed a five-year follow-up (n=52; 75 percent female). The patients’ average preoperative BMI was 49, and the primary bariatric surgery performed was gastric bypass. The mean length of time patients had been diagnosed with diabetes was 8.5 years, HbA1c was 7.9±1.3 percent and 35 percent had diabetic nephropathy.

We hypothesized that improving diabetes control may have positive effects on end-organ complications of the disease, including diabetic nephropathy. Remarkably, we found that 55 percent of patients with diabetic nephropathy prior to their bariatric surgery had a resolution of the disease at a mean follow-up of 66 months.

Among those patients with no evidence of diabetic nephropathy prior to bariatric surgery, only 25 percent proceeded to develop albuminuria five years later. Additionally, the five-year remission and improvement rates for diabetes were 22 percent and 55 percent, respectively.
The presence of diabetic nephropathy, pre- and postoperatively, was determined by urinary albumin-creatinine ratio (uACR). Patients' current diabetes status (remission, improvement or no change) was determined by biochemical analyses and review of medications.

We presented our findings at the 29th Annual Meeting of the American Society of Metabolic and Bariatric Surgery in June 2012. The findings follow a study that I published with colleagues earlier in 2012 in the New England Journal of Medicine that showed bariatric surgery can cause remission of type 2 diabetes even before substantial weight loss occurs.

Sustainable clinical benefits

Studies have shown that patients may lose as much as 60 percent of their excess weight six months after bariatric/metabolic surgery and 77 percent of excess weight as early as 12 months after surgery.

In addition to remission or improvement in type 2 diabetes and its complications, the patients in our study were able to maintain 50 percent of their excess weight loss after five years and also achieved significant improvements in blood pressure and cholesterol levels.

When my colleagues and I initiated this study, we hypothesized that bariatric surgery may halt the progression of diabetic nephropathy. Instead we found that over half of the patients who had diabetic nephropathy prior to undergoing bariatric surgery experienced remission.

No medical therapy has been as effective as bariatric surgery in achieving an effect of this magnitude on diabetic nephropathy. This is an important finding that warrants further research and greater consideration of bariatric surgery in this patient population.

About the author

Dr. Schauer, Professor of Surgery and Director of Cleveland Clinic’s Bariatric & Metabolic Institute, can be reached at 216.444.4794 or schauer@ccf.org.

Suggested reading


“No medical therapy has been as effective as bariatric surgery in achieving an effect of this magnitude on diabetic nephropathy.”
Gastric Bypass

Improves Glucose Homeostasis by Attenuating the Effect of Ghrelin on β-cell Function

By Sangeeta Rao Kashyap, MD; Steven K. Malin, PhD; and Aashish Samat, MD

STAMPEDE (Surgical Therapy and Medications Potentially Eradicate Diabetes Efficiently) was a single-center prospective, randomized, controlled trial conducted at Cleveland Clinic’s Endocrinology & Metabolism Institute. We designed this metabolic substudy to determine the impact of intensive medical therapy combined with either Roux-en-Y gastric bypass or sleeve gastrectomy on glycemic control in obese adults with type 2 diabetes mellitus.

As a continuation of the STAMPEDE trial, we are now looking at the effects of two bariatric surgery procedures on ghrelin as a mediator of glucose regulation and will be presenting related substudy results at the American Diabetes Association’s 73rd Scientific Sessions (2013), June 21-25, 2013, Chicago, Ill.

Despite the known effects of surgery-induced diabetes remission, the mechanism responsible for this improved glycemic control remains unclear. Ghrelin is a fundus-derived hormone that has glucoregulatory effects on β-cell function and insulin sensitivity.

In addition, ghrelin is an appetite-stimulating hormone that plays a key role in body weight regulation. For example, obese, insulin-resistant adults with type 2 diabetes mellitus have decreased abilities to suppress ghrelin following food intake. This impaired response subsequently leads to overeating and the development of poor insulin secretion. Improving ghrelin suppression therefore represents an important endocrine-related mechanism for diabetes remission.

In our recent substudy, 53 moderately obese adults with poorly controlled diabetes were randomized to intensive medical therapy alone vs. gastric bypass and sleeve gastrectomy. At baseline and 24 months, we measured β-cell function, insulin sensitivity (determined by mixed-meal tolerance testing), body fat and postprandial ghrelin levels.

Gastric bypass and sleeve gastrectomy decreased body fat by approximately 12 percent at 24 months, while intensive medical therapy had little effect (Table 1). Although fasting glycemia improved in all three groups at 24 months (P<0.05), insulin sensitivity and β-cell function increased most following gastric bypass compared with sleeve gastrectomy or intensive medical therapy.
After 24 months, only gastric bypass improved ghrelin suppression ($P<0.05$ vs. sleeve gastrectomy; $P=0.09$ vs. intensive medical therapy). Lower ghrelin levels correlated with enhanced β-cell function ($r=-0.29$, $P=0.03$) and decreased abdominal fat ($r=0.37$, $P=0.006$). Improved insulin secretion correlated with reduced fasting glucose levels ($r=-0.39$, $P<0.01$).

Together, these findings suggest that gastric bypass restores normal glucose homeostasis by attenuating the negative effect of ghrelin on β-cell function. Although follow-up studies are required to understand how ghrelin affects insulin secretion, our data suggest a role for decreased abdominal body fat.

Although follow-up studies are required to understand how ghrelin affects insulin secretion, our data suggest a role for ghrelin as a regulator of glucose metabolism after gastric bypass surgery.

**Table 1**

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<th>IMT</th>
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<tr>
<td>Ghrelin Suppression (pg/mL)</td>
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<td>Baseline</td>
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<td>24 months</td>
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*IMT vs. SG vs. RYGB at 24 months ($P<0.001$)
^Change from 0-24 months RYGB vs. SG ($P=0.03$) and IMT ($P=0.09$)

**About the authors**

*Dr. Kashyap is an endocrinologist in the Department of Endocrinology, Diabetes and Metabolism and is a co-lead investigator in the STAMPEDE trial. Dr. Malin is a postdoctoral fellow in Pathobiology at Cleveland Clinic Lerner Research Institute. Dr. Samat is an endocrinology fellow in the Department of Endocrinology, Diabetes and Metabolism.*

For more information, please contact Dr. Kashyap at 216.445.2679 or kashyas@ccf.org.
Below are peer-reviewed journal articles and book chapters published within the past year by Endocrinology & Metabolism Institute staff.

Journals

**Academic Medicine**
Young JB, Cosgrove DM. Change we must: Putting patients first with the institute model of academic health center organization [Commentary]. *Acad Med.* 2012;87(5):552-554.

**American Journal of Cardiology**

**American Journal of Otolaryngology**

**American Journal of Physiology – Endocrinology and Metabolism**

**Annals of Surgical Oncology**


**Archives of Surgery**


**Bariatric Nursing and Surgical Patient Care**

**Best Practice & Research Clinical Endocrinology & Metabolism**


**Body Image**

**Canadian Journal of Anaesthesia**

**Circulation: Heart Failure**
Cleveland Clinic Journal of Medicine


Clinical Journal of the American Society of Nephrology


Diabetes Care


Diabetes, Obesity and Metabolism


Diabetes Research and Clinical Practice


Endocrine Practice


Expert Opinion on Pharmacotherapy


Expert Review of Endocrinology and Metabolism


Heart Failure Clinics


continued on next page
Baliga RR, Young JB. Reducing the burden of stage B heart failure and the global pandemic of cardiovascular disease: time to go to war with the “barefoot” troops! Heart Fail Clin. 2012;8(2):ix-xiii.

Baliga RR, Young JB. Reducing the burden of stage B heart failure will require connecting the dots between “knowns” and “known unknowns.” Heart Fail Clin. 2012;8(1):xi-xv.

Hepatology

International Journal of Cancer

International Journal of Obesity (London)

Issues in Science and Technology

The Journal of Clinical Endocrinology & Metabolism

Journal of Gastrointestinal Surgery

The Journal of Heart and Lung Transplantation

Journal of Medical Economics

Journal of Nutrition and Metabolism

Journal of Obesity

Medical Clinics of North America

Medicine and Science in Sports and Exercise

Metabolic Syndrome and Related Disorders

Minerva Endocrinologica

Neurology
The New England Journal of Medicine


Obesity (Silver Spring)


Obesity Surgery


Pediatric Emergency Care


Pituitary


Psychiatric Annals


Rheumatology (Oxford)


Surgeon


Surgery


Surgery for Obesity and Related Diseases


continued on next page


**Surgical Clinics of North America**


**Surgical Endoscopy**


**Surgical Laparoscopy Endoscopy & Percutaneous Techniques**


**Thyroid**


**Book Chapters**


Live and Online CME Opportunities

Cleveland Clinic’s Center for Continuing Education offers convenient, complimentary learning opportunities, from webcasts and podcasts to a host of medical publications, in addition to live CME symposia.

Thyroid Expo 2013

Jan. 26, 2013

Lerner College of Medicine | NA5-08 Auditorium and Conference Wing

This one-day course will highlight recent advances in the management of thyroid diseases. In 2012, these included molecular pathogenesis and prognostication in thyroid cancer. More so than ever before, innovations of new surgical technologies, thyroid cancer diagnostic tests, and new therapies for thyroid cancer are influencing patient care options. The format of the course is designed to address the key concepts of these advancements during lectures and panel discussions.

Diabetes Day 2013

May 31, 2013

Intercontinental Hotel and Bank of America Conference Center, Cleveland

Get up to date on the mechanisms of complications for patients with diabetes. This event is designed to increase your competency and performance when caring for this patient population, ultimately improving patient outcomes.

For more information on these events, visit our website:
clevelandclinic.org/endonotes

Online CME

Online webcasts and journal articles of interest to endocrinologists and approved for AMA PRA Category 1 Credits™ include:

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<tr>
<th>Online Webcast</th>
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<tr>
<td>ACROSS STUDY – 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>216.444.9612</td>
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<td>Somatuline® Depot (Lanreotide) Injection for Acromegaly (SODA): A Post-Marketing Observational Study</td>
<td>Betul Hatipoglu, MD</td>
<td>216.444.9612</td>
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<td>DiaPep277® – A Phase III, Multinational, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Investigate the Clinical Efficacy and Safety of DiaPep277 in Newly Diagnosed Type 1 Diabetes Subjects</td>
<td>Leann Olansky, MD</td>
<td>Bob McCoy 216.445.4029</td>
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<td>A Randomized, Double Masked, Placebo-Controlled, Multicenter, Phase 2 Study to Evaluate the Safety and Renal Efficacy of LY2382770 in Patients with Diabetic Kidney Disease Due to Type 1 or Type 2 Diabetes</td>
<td>Leann Olansky, MD</td>
<td>216.444.9612</td>
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<td>A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate Cardiovascular Outcomes During Treatment with Lixisenatide in Type 2 Diabetic Patients After an Acute Coronary Syndrome</td>
<td>Robert Zimmerman, MD</td>
<td>Bob McCoy 216.445.4029</td>
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<td>EXenatide Study of Cardiovascular Event Lowering Trial (EXSCEL)</td>
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<td>The Diagnostic Accuracy of the Glucagon Stimulation Test for Evaluation of Adult Growth Hormone Deficiency and the Hypothalamic-Pituitary-Adrenal Axis</td>
<td>Amir Hamrahian, MD</td>
<td>Bob McCoy 216.445.4029</td>
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<td>The CAROLINA Trial – A Multicentre, International, Randomized, Parallel Group, Double-Blind Study to Evaluate Cardiovascular Safety of Linagliptin vs. Glimepiride in Patients with Type 2 Diabetes Mellitus at High Cardiovascular Risk</td>
<td>Leann Olansky, MD</td>
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<td>Effect of a Portion-Controlled, Commercially Available Diet on Presurgical Weight Loss and Metabolic Outcomes in Patients Undergoing Laparoscopic Bariatric Surgery</td>
<td>Leslie Heinberg, PhD, MA</td>
<td>Chytaine Hall 216.445.3983</td>
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<td>Effect of Bariatric Surgery on Mechanisms of Type 2 Diabetes: The B2D Trial</td>
<td>John Kirwan, PhD</td>
<td>Chytaine Hall 216.445.3983</td>
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<td>Gastric Plication for the Treatment of Obesity and Related Conditions</td>
<td>Philip Schauer, MD</td>
<td>Janice Kakish 216.444.7551</td>
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<td>Parathyroidectomy – Effect of Parathyroidectomy in Reducing Coronary Artery Calcification and Improving Vascular Compliance in Patients with Primary and Secondary Hyperparathyroidism</td>
<td>Eren Berber, MD</td>
<td>Linda Heil 216.444.2262</td>
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<td>Randomized, Double-Blind, Phase II Trial of Radiofrequency Ablation +/- Lyso-Thermosensitive Liposomal Doxorubicin (ThermoDox®) for Colorectal Liver Metastases ≥2 cm Maximum Diameter</td>
<td>Allan Siperstein, MD</td>
<td>Linda Heil 216.444.2262</td>
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<td>Prospective Randomized Comparison of Bilateral vs. Focal Neck Exploration for Sporadic Hyperparathyroidism</td>
<td>Allan Siperstein, MD</td>
<td>Linda Heil 216.444.2262</td>
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Department of Endocrinology, Diabetes and Metabolism

Revital Gorodeski Baskin, MD
Specialty Interest(s): Endocrinology, thyroid disorders, thyroid cancer
Location(s): Independence Family Health Center
Office: 216.986.4000 | Fax: 216.986.4995
Appointments: 216.986.4000

Kevin Borst, DO
Specialty Interest(s): Endocrine disorders in pregnancy, general endocrinology, diabetes
Location(s): Lakewood Hospital Professional Building
Office: 216.529.5300 | Fax: 216.529.5301
Appointments: 216.444.6568

Krupa Doshi, MD
Specialty Interest(s): General endocrinology, diabetes, parathyroid and calcium disorders, hirsutism, thyroid disorders, adrenal disorders
Location(s): Main campus
Office: 216.445.0741 | Fax: 216.445.1656
Appointments: 216.444.6568

Marwan Hamaty, MD
Specialty Interest(s): General endocrinology, diabetes
Location(s): Main campus; Strongsville Family Health and Surgery Center
Office: 216.445.7568 | Fax: 216.445.1656
Appointments: Main campus, 216.444.6568; Strongsville, 440.878.2500

Amir Hamrahian, MD
Specialty Interest(s): Pituitary and adrenal disorders
Location(s): Main campus
Office: 216.445.8538 | Fax: 216.445.1656
Appointments: 216.444.6568

Betul Hatipoglu, MD
Specialty Interest(s): Diabetes, thyroid disorders, pituitary disorders, adrenal disorders, alternative medicine
Location(s): Main campus
Office: 216.445.2679 | Fax: 216.445.1656
Appointments: 216.444.6568

Suman Jana, MD
Specialty Interest(s): General endocrinology, diabetes, thyroid disease, thyroid cancer
Location(s): Main campus, Medina
Office: 216.445.0567 | Fax: 216.445.1656
Appointments: Main campus, 216.444.6568; Medina, 330.725.3713

Sangeeta Kashyap, MD
Specialty Interest(s): Endocrinology, diabetes, insulin resistance and cardiovascular risk prevention, obesity, metabolic syndrome and diseases, hyperlipidemia
Location(s): Main campus
Office: 216.445.2679 | Fax: 216.445.1656
Appointments: 216.444.6568

Laurence (Ned) Kennedy, MD
Department Chair
Specialty Interest(s): General endocrinology, diabetes, pituitary disorders, hyperthyroidism, hypothyroidism, thyroiditis
Location(s): Main campus; Ashtabula County Medical Center; Cleveland Clinic Florida, Weston
Office: 216.445.8645 | Fax: 216.445.1656
Appointments: Main campus, 216.444.6568; Ashtabula, 440.997.6910; Florida, 954.659.6038

Leila Khan, MD
Specialty Interest(s): General endocrinology, diabetes, calcium/bone disorders
Location(s): Main campus, Willoughby Hills Family Health Center
Office: 216.445.1598 | Fax: 216.445.1656
Appointments: Main campus, 216.444.6568; Willoughby Hills, 440.943.2500

Visit clevelandclinic.org/EndoStaff for the most current staff listings and locations.
Endocrinology & Metabolism Institute | Staff Directory

M. Cecilia Lansang, MD, MPH
Specialty Interest(s): General endocrinology, diabetes
Location(s): Main campus
Office: 216.444.5246 | Fax: 216.445.1656
Appointments: 216.444.6568

Melissa Li-Ng, MD
Specialty Interest(s): General endocrinology, diabetes
Location(s): Main campus
Office: 216.444.1949 | Fax: 216.445.1656
Appointments: 216.444.6568

Vinni Makin, MD
Specialty Interest(s): General endocrinology, diabetes, hirsutism, acne, thyroid disorders
Location(s): Main campus, Solon Family Health Center
Office: 216.444.0539 | Fax: 216.445.7261
Appointments: Main campus, 216.444.6568; Solon, 440.519.6800

Adi Mehta, MD
Specialty Interest(s): Diabetes, thyroid disorders, endocrine complications of pregnancy, menopause, lipid disorders, general and adolescent endocrinology
Location(s): Main campus, Beachwood Family Health Center (reproductive endocrinology only)
Office: 216.445.5312 | Fax: 216.445.7261
Appointments: Main campus, 216.444.6568; Beachwood, 216.839.3000

Guy Mulligan, MD
Specialty Interest(s): General endocrinology, diabetes
Location(s): Main campus, Independence Family Health Center; Twinsburg Family Health and Surgery Center
Office: 330.888.4000 | Fax: 330.963.4561
Appointments: Independence, 216.986.4000; Main campus, 216.444.6568; Twinsburg, 330.888.4000

Christian Nasr, MD
Specialty Interest(s): Thyroid nodules, thyroid cancers, flushing syndromes
Location(s): Main campus, Lorain Family Health and Surgery Center (thyroid cancer only)
Office: 216.445.1788 | Fax: 216.445.1656
Appointments: Main campus, 216.444.6568; Lorain, 440.204.7400

Leann Olansky, MD
Specialty Interest(s): Diabetes and diabetes complications, gestational diabetes, general endocrinology
Location(s): Main campus, Stephanie Tubbs Jones Health Center
Office: 216.444.2642 | Fax: 216.445.1656
Appointments: Main campus, 216.444.6568; Stephanie Tubbs Jones Health Center, 216.767.4242

Kevin Pantalone, DO
Specialty Interest(s): Type 2 diabetes mellitus; male hypogonadism (low testosterone); thyroid, pituitary and adrenal disorders
Location(s): Main campus, Twinsburg Family Health and Surgery Center
Office: 330.888.4000 | Fax: 216.445.1656
Appointments: Main campus, 216.444.6568; Twinsburg, 330.888.4000

Seenia Peechakara, MD
Specialty Interest(s): Endocrine disorders in pregnancy, thyroid disorders, thyroid cancer, diabetes, calcium and parathyroid disorders, lipid disorders, pituitary and adrenal disorders, general endocrinology
Location(s): Lakewood Hospital Professional Building
Office: 216.529.5300 | Fax: 216.529.5301
Appointments: 216.444.6568

Richard Shewbridge, MD
Specialty Interest(s): Endocrinology, diabetes, thyroid disorders, hyperlipidemia, osteoporosis
Location(s): Medina Medical Office Building
Office: 330.725.3713 | Fax: 330.725.2141
Appointments: 330.725.3713

David Shewmon, MD
Specialty Interest(s): General endocrinology, diabetes, high cholesterol, osteomalacia, osteoporosis, pituitary tumors, thyroid conditions, thyroid cancer
Location(s): Lakewood Hospital Professional Building
Office: 216.529.5300 | Fax: 216.529.5301
Appointments: 216.444.6568

Mario Skugor, MD
Associate Director, Endocrinology Fellowship Program
Specialty Interest(s): Osteoporosis and calcium metabolism, obesity and diabetes, multiple endocrine neoplasia syndromes, thyroid disorders, thyroid cancer
Location(s): Main campus
Office: 216.445.0739 | Fax: 216.445.1656
Appointments: 216.444.6568

Mariam Stevens, MD
Specialty Interest(s): Diabetes, gestational diabetes, goiter, Graves disease, Hashimoto disease, hirsutism, hyperthyroidism, hypoglycemia, hypothyroidism, polycystic ovary syndrome, thyroid disease, Location(s): Independence Family Health Center
Office: 216.986.4000 | Fax: 216.986.4995
Appointments: 216.986.4000

Mary Vouyiouklis, MD
Specialty Interest(s): Thyroid disorders, thyroid cancer, parathyroid and calcium disorders, adrenal disorders, diabetes
Location(s): Main campus; Solon Family Health Center; Willoughby Hills Family Health Center
Office: 216.444.6568 | Fax: 216.445.1656
Appointments: Main campus, 216.444.6568; Solon, 440.519.6908; Willoughby Hills, 440.943.2500

Susan Williams, MD
Specialty Interest(s): Bone and mineral metabolism, metabolic bone disease, calcium disorders, malabsorption and malnutrition in adults, medical bariatrics
Location(s): Main campus
Office: 216.444.5665 | Fax: 216.445.1656
Appointments: 216.444.6568

Robert Zimmerman, MD
Director, Cleveland Clinic Diabetes Center
Department Vice Chair
Program Director, Endocrinology Training Program
Specialty Interest(s): Diabetes, thyroid disorders, growth hormone in adults
Location(s): Main campus
Office: 216.444.9428 | Fax: 216.445.1656
Appointments: 216.444.6568
Department of Endocrine Surgery

Eren Berber, MD
Director, Robotic Endocrine Surgery
Specialty Interest(s): Endocrine surgery (thyroid and parathyroid), laparoscopic radiofrequency ablation of liver tumors, pancreatic neuroendocrine tumors, robotic thyroid and parathyroid surgery, laparoscopic and robotic adrenalectomy and liver surgery
Location(s): Main campus
Office: 216.445.0555 | Fax: 216.636.0662
Appointments: 216.444.6568

Judy Jin, MD
Specialty Interest(s): Endocrine surgery (thyroid and parathyroid), advanced laparoscopic surgery, laparoscopic adrenalectomy, laparoscopic radiofrequency ablation of liver tumors
Location(s): Main campus
Office: 216.445.3411 | Fax: 216.636.0662
Appointments: 216.444.6568

Rosemarie Metzger, MD
Specialty Interest(s): Endocrine surgery (thyroid, parathyroid and adrenal)
Location(s): Main campus
Office: 216.445.3695 | Fax: 216.636.0662
Appointments: 216.444.6568

Jamie Mitchell, MD
Specialty Interest(s): Endocrine surgery (thyroid, parathyroid and adrenal), laparoscopic solid organ surgery, advanced laparoscopic surgery, laparoscopic radiofrequency ablation of liver tumors
Location(s): Main campus; Independence Family Health Center; Solon Family Health Center
Office: 216.445.9713 | Fax: 216.636.0662
Appointments: Main campus, 216.444.6568; Independence, 216.986.4000; Solon, 440.519.6800

Joyce J. Shin, MD
Specialty Interest(s): Endocrine surgery (thyroid and parathyroid), advanced laparoscopic surgery, laparoscopic adrenalectomy, neuroendocrine tumors, thyroid/parathyroid ultrasound, intra-abdominal ultrasound, laparoscopic radiofrequency thermal ablation of liver tumors
Location(s): Main campus; Willoughby Hills Family Health Center
Office: 216.636.9365 | Fax: 216.636.0662
Appointments: Main campus, 216.444.6568; Willoughby Hills, 440.943.2500

Allan Siperstein, MD
Department Chair
Specialty Interest(s): Endocrine surgery (thyroid and parathyroid), advanced laparoscopic surgery, laparoscopic thermal ablation of liver tumors, pancreatic endocrine tumors
Location(s): Main campus
Office: 216.444.5664 | Fax: 216.636.0662
Appointments: 216.444.6568

Bariatric & Metabolic Institute

Stacy Brethauer, MD
Department Vice Chair
Specialty Interest(s): Bariatric surgery, laparoscopic surgery, gastrointestinal surgery, hernia repair, endoscopy, surgery for GERD, hiatal hernia, solid-organ endoluminal surgery, single-incision laparoscopic surgery
Location(s): Main campus; Richard E. Jacobs Health Center
Office: 216.444.9244 | Fax: 216.445.1586
Appointments: Main campus, 216.445.2224; Richard E. Jacobs, 440.695.4000

Derrick Cetin, DO
Specialty Interest(s): Bariatric medicine, medical weight management, nutrition sciences, obesity management, preoperative evaluation, diabetes care
Location(s): Main campus
Office: 216.445.4255 | Fax: 216.636.1588
Appointments: 216.445.2224

Karen Cooper, DO
Specialty Interest(s): Bariatric medicine, family medicine, kinesiology and nutrition sciences, exercise instruction
Location(s): Main campus
Office: 216.445.1114 | Fax: 216.445.2153
Appointments: 216.445.2224

Matthew Kroh, MD
Specialty Interest(s): Advanced laparoscopic surgery, bariatric surgery, gastrointestinal surgery, endoscopy, single-incision laparoscopic surgery
Location(s): Main campus
Office: 216.445.9966 | Fax: 216.444.2153
Appointments: 216.445.2224

Tomasz Rogula, MD, PhD
Specialty Interest(s): Advanced laparoscopic surgery, bariatric surgery, gastrointestinal surgery, endoscopy, single-incision laparoscopic surgery
Location(s): Main campus; Strongsville Family Health and Surgery Center
Office: 216.445.0255 | Fax: 216.445.1586
Appointments: Main campus, 216.445.2224; Strongsville, 440.878.2500

Philip Schauer, MD
Department Chair
Specialty Interest(s): Bariatric surgery, laparoscopic surgery, gastrointestinal surgery, colon surgery, weight management, hernia surgery, biliary surgery, surgery for GERD
Location(s): Main campus
Office: 216.444.4794 | Fax: 216.445.1586
Appointments: 216.445.2224

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In 2012, Cleveland Clinic was ranked one of America’s top 4 hospitals in U.S. News & World Report’s annual “America’s Best Hospitals” survey. The survey ranks Cleveland Clinic among the nation’s top 10 hospitals in 14 specialty areas, and the top hospital in three of those areas.

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Resources for Physicians

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Outcomes Data

View clinical Outcomes books from all Cleveland Clinic institutes at clevelandclinic.org/outcomes.

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Cleveland Clinic offers same-day appointments to help your patients get the care they need, right away. Have your patients call our same-day appointment line, **216.444.CARE** (2273) or **800.223.CARE** (2273).

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For complimentary assistance for out-of-state patients and families, call 800.223.2273, ext. 55580, or email medicalconcierge@ccf.org.

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Cleveland Clinic’s Diabetes and Endocrinology Program is ranked No. 2 in the nation in the annual *U.S. News & World Report* “America’s Best Hospitals” survey.

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