The social awareness and acceptance of transgender individuals has increased dramatically in the past several years. Todd B. Nippoldt, M.D., a consultant in Endocrinology, Diabetes, Metabolism and Nutrition, at Mayo Clinic in Rochester, Minnesota, says: “The transgender population continues to face major challenges in accessing and obtaining appropriate health care. A disproportionate number of transgender people are uninsured and 19 percent have been denied care by health care providers. Most health care providers have had little or no formal training in addressing the needs of these patients, which can contribute to the minority stress that members of the transgender community may develop through stigmatization, avoidance, discrimination and prejudice.

In addition, Lambda Legal reports that 70 percent of transgender individuals have suffered some form of maltreatment at the hands of medical providers, including harassment and violence. Suicide attempts among transgender individuals are also extraordinarily high at approximately 25 to 43 percent. The prevalence increases in those who have had a negative experience with a health care professional.”

Transgender and Intersex Specialty Care Clinic

The Mayo Clinic Transgender and Intersex Specialty Care Clinic (TISCC) was developed to provide for the mental health, hormonal and surgical needs of transgender patients and those with differences of sexual development (DSD), or intersex.

DSD may include discrepancies among sex chromosomes, genitalia, reproductive duct development and gonadal development. DSD may also be referred to as intersex. A variety of underlying conditions can cause DSD, including congenital adrenal hyperplasia, androgen resistance syndrome and many others.

Caroline J. Davidge-Pitts, M.B., Ch.B., Endocrinology, Diabetes, Metabolism and Nutrition at Mayo Clinic in Rochester, Minnesota, explains: “Gender identity can be defined as one’s internal sense of being male, female, neither or both (Figure). A transgender or gender-nonconforming person has a gender identity that does not conform to sex (chromosomal or anatomical) assigned at birth. Gender identity is quite different from sexual orientation, which includes the gender(s) a person is emotionally or physically attracted to, or both. Being transgender indicates diversity and not pathology.”

Figure. Relationships among chromosomal and anatomical sex, gender identity, gender expression and gender orientation.
“The clinical distress that may accompany being transgender (gender dysphoria) is what needs to be evaluated and treated by health professionals. Gender dysphoria may arise as a result of internal conflict associated with incongruence between gender identity and sex assigned at birth. Other contributors include work, school, home and social environments (including issues related to discrimination, relationship abuse and minority stress), and social support from family, peers and friends. The interventions to relieve gender dysphoria are unique for every person. For some, dressing in congruence with their gender identities is enough. For others, hormonal treatment and gender confirmation surgery is necessary.”

Patients seen in the Mayo Clinic TISCC are initially evaluated by an endocrinologist and a mental health provider.

**Mental health evaluation**

All patients with suspected gender dysphoria will require evaluation by a trained mental health professional to establish the diagnosis, assess comorbid psychiatric diagnoses and evaluate social support structures. The evaluation may include a psychologist, psychiatrist or licensed independent clinical social worker. Patients with gender dysphoria may have coexisting mental health conditions, such as autism spectrum disorder, body dysmorphic disorder or eating disorders, which should be treated with standard psychological therapy and other appropriate interventions.

Dr. Nippoldt outlines: “The individual’s needs and desires are identified during initial visits and a plan is formulated. Depending on the patient’s needs, referral to surgical or other specialties can occur, specifically including voice therapy; preventive gynecology care for transgender men; mental health counseling for patients, their families, or both; and assistance with school, social and legal issues. In addition to the care provided in the TISCC, we are striving to provide competent and sensitive care for transgender and intersex patients at all Mayo Clinic campuses. Efforts include sensitivity training for staff, finding an electronic record and intake form solution for gender declaration, and providing a safe and welcoming environment, such as unisex restroom options, in all areas at Mayo Clinic.

“To date, we are caring for over 100 unique patients. Fifty-seven percent are local to Olmsted County, 22 percent are regional, 20 percent are national, and 1 percent is international. Forty-nine percent of patients are under age 30, and 8 percent are over age 60.”

Dr. Davidge-Pitts notes: “Despite the multiple difficulties these patients face, each individual shows great determination, resilience and resourcefulness. At Mayo Clinic, we continue to promote advocacy for transgender patients and provide a safe, competent environment for their care.”

**Top 10 tips to become a transgender-friendly and competent provider**

1. If you have a question about your patient’s gender nonconformity, do not be afraid to ask.
2. Ask patients their preferred names and pronouns and use them during the encounter. If you make a mistake, apologize and continue.
3. The preferred name and pronoun will often differ from what is in the medical record as many transgender people have not changed their names and genders legally. Ask the patient if you can use this preferred name and pronoun in the medical record. Remember that many patients may have access to their medical records,
More than one-third of American adults are obese, with a body mass index (BMI) of 30 kg/m\(^2\) or greater. Obesity is associated with functional impairments and comorbidities, including hypertension, cardiovascular disease, metabolic disorders, arthrosis and obstructive sleep apnea. In the U.S., obesity accounts for 18 percent of deaths among people ages 40 to 85.

Manpreet S. Mundi, M.D., a consultant in Endocrinology, Diabetes, Metabolism and Nutrition at Mayo Clinic’s campus in Rochester, Minnesota, says: “Despite advances, obesity management remains challenging. Diet and exercise often don’t produce significant and sustained weight loss. And although bariatric surgery produces durable weight loss and shows the most promise for diabetes resolution, only about 2 percent of people who qualify for surgery undergo it.”

“There is a big gap in the management of obesity, where diet and exercise aren’t enough, but patients either don’t qualify for a surgical option or don’t want it because of the cost and risks. People who fall into this gap represent the majority of those with mild to moderate obesity,” says Barham K. Abu Dayyeh, M.D., a gastroenterologist who specializes in bariatric and metabolic endoscopy at Mayo Clinic in Rochester, Minnesota. “For these patients — with a BMI of 30 to 40 kg/m\(^2\) — the newly approved intragastric balloon procedure represents an intermediate option between lifestyle change and bariatric surgery.”

**Intragastric Balloon: A Re-Emerging Approach for Obesity**

Garren-Edwards Gastric Bubble was an air-filled polyurethane device approved by the Food and Drug Administration (FDA) in 1985, but it was withdrawn from the market soon afterward due to lack of efficacy and serious complications such as bowel obstructions arising from balloon deflation. In August 2015, two next-generation intragastric balloons were approved by the FDA. These balloons — the Apollo Endosurgery Orbera Intragastric Balloon system (Figure) and the ReShape Integrated Dual Balloon System — are made of silicone and are more resistant to deflation. They are endoscopically placed and filled with saline solution up to 650 mL. The outpatient placement procedure takes 20 minutes, and the balloon remains in place for six months. Although the Orbera system was available outside of the U.S., approval by the FDA was largely based on efficacy and safety data from a multicenter clinical trial that

and therefore your sensitivity should be reflected in the notes.

4. If possible, intake forms should include an option to disclose transgender status.

5. Sensitivity training should be required for all staff members who interact with the patient. The Center of Excellence for Transgender Health at the University of California, San Francisco, has published a helpful online course called Acknowledging Gender and Sex. The course is available at [http://transhealth.ucsf.edu/video/story.html](http://transhealth.ucsf.edu/video/story.html).

6. Public restrooms should include a unisex option.

7. Have local transgender resources, such as local transgender support groups, available to help guide the patient if needed.

8. Include transgender health topics as part of your medical school and training programs to increase the competence of future leaders in transgender health care.

9. Provide faculty development in transgender health. Many national and international meetings now include transgender health topics, and more online resources are becoming more available.

10. Phone a friend: Be aware of qualified providers in your area that you can contact about transgender-related questions.
Dr. Abu Dayyeh presented at Digestive Disease Week 2015. “Study results were published in Gastrointestinal Endoscopy in 2015.

**Orbera Intragastric Balloon**

Dr. Abu Dayyeh highlights: “In this trial, 125 patients were randomly assigned to balloon treatment and a 12-month behavioral therapy program compared with 113 patients who received only behavioral therapy and served as controls. The majority of participants were female with a mean BMI of 35 kg/m² and mean excess weight of 36 kg. After 52 weeks of follow-up, the patients in the balloon group lost 29.29 percent of the excess weight compared with 14.2 percent in the control group. The patients in the balloon group also experienced an improvement in quality of life as measured by Beck Depression Inventory scores in addition to a reduction in comorbid conditions such as diabetes mellitus, hypertension and dyslipidemia. Serious adverse events were rare.”

**ReShape Integrated Dual Balloon System**

As opposed to the Orbera system, the ReShape Duo is an endoscopically placed system that features dual intragastric balloons that are attached to each other with a flexible tube. Dr. Abu Dayyeh explains: “Each balloon can be filled with 450 mL of saline, allowing one balloon to maintain the system in the stomach in case the other balloon ruptures. One of the main trials with this system randomized 326 participants with BMIs of 30 to 40 kg/m² to either the dual balloon system along with diet and exercise (n = 187) or sham endoscopy plus diet and exercise (n = 139). The trial showed that patients with the dual balloon lost 27.9 percent of excess weight compared with excess weight loss of 12.3 percent in the diet group. Most patients experienced nausea, vomiting, abdominal pain or a combination of all three, which resolved in three to seven days and was severe in 1 to 2 percent of patients.”

**Comprehensive obesity program**

Dr. Abu Dayyeh says: “The balloon procedure is safe and fully reversible. Severe side effects such as small bowel obstruction, perforation or tears in the stomach, and bleeding are rare. Many patients experience nausea and epigastric pain in the first week after implantation, but these are usually easily managed with medication and typically resolve in a few days after the stomach adjusts to the balloon.”

Dr. Mundi concludes: “The intragastric balloon aids weight loss by slowing the rate at which food enters the stomach and by stimulating gastric stretch receptors. But lifestyle changes, including behavior modification, exercise and a healthy diet are crucial for maintaining weight loss once the device is removed. We have designed a comprehensive 12-month program that uses a multidisciplinary team consisting of dietitians, psychologists, endocrinologists and gastroenterologists to support patients in their weight-loss journey. This program, unique to Mayo Clinic, uses innovative, proven tools to help people who aren’t ready or don’t qualify for surgery.

**For more information**

Incidentally Discovered Adrenal Masses and Subclinical Cushing Syndrome

The frequency of incidental discovery of adrenal masses (adrenal incidentaloma) is increasing due to widespread use of computerized abdominal imaging — adrenal incidentalomas are encountered in approximately 5 percent of imaging studies (Figure). Irina Bancos, M.D., a consultant with Endocrinology, Diabetes, Metabolism and Nutrition at Mayo Clinic’s campus in Rochester, Minnesota, explains: “Tumors of the adrenal cortex or medulla can result in hormonal excess, which includes catecholamine excess, mineralocorticoid excess and glucocorticoid excess (Cushing syndrome). Cushing syndrome (CS) is associated with clinically significant morbidity and mortality. Such patients may present with weight gain, altered fat redistribution, skin fragility, easy bruisability and purple striae, muscle loss and proximal myopathy, osteoporosis and fractures, diabetes mellitus, dyslipidemia, and hypertension.”

While CS is quite rare, much more commonly, patients with adrenal tumors present with biochemical evidence of mild autonomous cortisol production without development of overt cushingoid features. Dr. Bancos highlights: “This condition is frequently labeled as subclinical CS (SCS). The definition of SCS varies, but mainly relies on demonstration of nonsuppressible morning cortisol with the overnight 1-mg dexamethasone suppression test, or DST (Table, page 6). The 1-mg DST is considered the most valuable test in SCS despite the ongoing debate on the optimal dose of dexamethasone (for example, 1, 2 or 8 mg), the most accurate cortisol cutoff (for example, 1.8, 2.2 or 5 mcg/dL), and a wide range of reported sensitivity (44 to 100 percent) and specificity (24 to 100 percent).

“As shown in a study published by Melvin M. Grumbach, M.D., and others in Annals of Internal Medicine in 2003, around 30 percent of patients with adrenal incidentaloma fulfill the criteria of SCS. Though patients with SCS lack symptoms and signs of overt CS, several reports, including studies published by Maurizio Iacobone, M.D., and others in Surgery in 2012 and Valentina Morelli, M.D., Ph.D., and others, published in The Journal of Clinical Endocrinology & Metabolism in 2014, have shown that SCS is associated with a high prevalence of hypertension, obesity, diabetes mellitus, dyslipidemia and osteoporosis. As a group, patients with SCS have higher rates of cardiovascular risk factors and events. However, management of an individual patient with SCS is controversial as the contribution of mild hypercortisolism toward the development of otherwise prevalent hypertension, weight gain, dyslipidemia, diabetes mellitus and cardiovascular events is unknown. Indeed, while some studies reported partial improvement of cardiometabolic risk factors in certain patients, the degree of improvement was unpredictable.

**Figure.** Biochemical and clinical progression related to the degree of autonomous glucocorticoid production from an incidentally discovered adrenocortical tumor.
“The current classification of patients with adrenal tumors and glucocorticoid excess fails to accurately predict the individual harmful metabolic effect of hypercortisolism. Although it is well-known that glucocorticoids have a wide range of metabolic actions, it remains to be determined how exactly mild hypercortisolism affects metabolic parameters and whether any metabolic markers could identify individuals with SCS who would be more likely to benefit from the surgery. Currently, such patients usually undergo follow-up with targeted testing to identify any (possibly cortisol induced) metabolic abnormalities. And referral for adrenalectomy is largely dependent on the endocrinologist’s comfort level with SCS and the patient’s preference.”

A team of investigators at Mayo Clinic is currently attempting to better understand differences in steroid production in patients with SCS as well as tie in measured abnormalities with cortisol-induced metabolic changes. Dr. Bancos says: “Our team has recently developed a novel assay that measures 26 urinary steroid metabolites by high-resolution liquid chromatography–mass spectrometry (LC-MS). We are in the process of developing a serum steroid assay aimed to discern false-positives from true clinically significant abnormalities in steroid production of patients with SCS. Such in-depth adrenal steroid profiling allows us to better characterize adrenal tumor glucocorticoid production other than cortisol.

“In addition, we have an active trial for patients with adrenal tumors referred for adrenalectomy in whom we are able to combine in-depth steroid profiling with testing of beta cell function and insulin sensitivity before and after adrenalectomy (Sidebar). We are hopeful that identifying biomarkers of hypercortisolism’s influence on metabolism in the future will allow us to intervene in a timely manner and prevent irreversible complications that occur in select patients with SCS.”

For more information


### Table. Biochemical diagnosis of cortisol excess of adrenal origin.

<table>
<thead>
<tr>
<th>Test</th>
<th>No cortisol excess</th>
<th>Subclinical Cushing syndrome</th>
<th>Overt Cushing syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-mg DST cortisol*</td>
<td>&lt; 1.8 mcg/dL</td>
<td>&gt; 1.8 mcg/dL</td>
<td>&gt; 1.8 mcg/dL</td>
</tr>
<tr>
<td>24 hrs. urine cortisol</td>
<td>Within reference range</td>
<td>Usually within reference range</td>
<td>Higher than reference range</td>
</tr>
<tr>
<td>Late night salivary cortisol</td>
<td>Within reference range</td>
<td>Usually within reference range</td>
<td>Higher than reference range</td>
</tr>
<tr>
<td>Corticotropin (ACTH)</td>
<td>Within reference range</td>
<td>Normal/low normal/undetectable</td>
<td>Undetectable</td>
</tr>
</tbody>
</table>

*1-mg DST cortisol: The row shows 8 a.m. serum cortisol concentrations after the administration of 1 mg of dexamethasone at 11 p.m. the evening before.

Clinical Trial: Combined nontargeted and targeted metabolomics in adrenal tumors — implications for novel diagnostic strategies of hormonal excess

**Aim:** To correlate adrenalectomy-induced changes in beta cell function and insulin sensitivity with preoperative steroid profile in patients with adrenal tumors.

**Patients:** The study will enroll 45 patients presenting with a spectrum of cortisol production, including nonfunctioning adrenal tumors, SCS and overt CS.

**Intervention:**
1. Steroid profiling
2. Minimal oral method (three-hour oral glucose tolerance test, along with measurement for C-peptide, insulin and glucose) before adrenalectomy and at least six weeks after adrenalectomy

**Outcomes:**
Adrenalectomy-induced changes in insulin sensitivity, glucose effectiveness and beta cell responsivity in three groups will be compared with changes in steroid metabolites.

**For more information:**
Email Dr. Bancos at bancos.irina@mayo.edu.
A 41-year-old man with multiple endocrine neoplasia, type 1 (MEN1) presented for management of recurrent primary hyperparathyroidism (PHPT). He had undergone a 3.5 parathyroid gland resection at age 22. At age 33, 11 years after his initial subtotal parathyroidectomy, his serum calcium concentration was noted to be mildly elevated at 10.2 mg/dL (normal, 8.9 to 10.1 mg/dL) and was associated with an elevated parathyroid hormone (PTH) level and normal serum creatinine. No further interventions were recommended because he was asymptomatic.

At age 39, he continued to be in good health, but his serum calcium level was 10.9 mg/dL on two separate occasions, in the setting of elevated serum PTH levels and normal serum creatinine — findings consistent with recurrent PHPT. A parathyroid sestamibi scan showed uptake consistent with a right inferior parathyroid adenoma. Treatment options were discussed with the patient by a multidisciplinary team involving his endocrinologist, endocrine surgeon and interventional radiologist. The team made a final recommendation to pursue percutaneous ethanol ablation (PEA).

A neck ultrasound was performed to identify a potential target for PEA and showed a 9 mm right inferior parathyroid adenoma (Figure panels A and B). The ultrasound was consistent with the finding on the parathyroid sestamibi scan. The patient was treated with a percutaneous 0.3 mL ethanol injection. The calcium level the day after the procedure was 9.6 mg/dL, and the vascularity of the parathyroid tissue resolved (Figure panel C).

However, recurrent hypercalcemia two years later prompted a second injection of ethanol — the patient required two sessions of PEA (total volume of 0.6 mL) into a 7 mm adenoma seen on neck ultrasound. He tolerated both procedures without complications such as hypocalcemia, hoarseness, bleeding or infection. Follow-up three years later shows that he continues to have normal serum calcium levels and is in overall good health.

MEN1 is a rare endocrine disorder characterized by loss of function of the tumor suppression protein MENIN, leading to the development of tumors in endocrine glands. Most commonly the parathyroid glands are affected, leading to PHPT. The clinical presentation of patients with PHPT

Figure. Panels A and B. Right inferior parathyroid adenoma on axial ultrasound image (A) and sagittal ultrasound image (B) measuring 9 mm and with detectable blood flow before ethanol injection. Panel C. Right inferior parathyroid adenoma on sagittal ultrasound image is approximately the same size with but with undetectable blood flow after ethanol injection.
and MEN1 differs from those with sporadic PHPT; patients with MEN1 have an earlier onset and commonly more-severe disease. Most importantly, the rate of recurrence after initial surgery in these patients is higher (up to 67 percent).

At this time, there is no clear consensus about which of the available treatment options provides the most benefit to these patients while limiting risk. Treatment options include re-operation, PEA and medical treatment with cinacalcet. Surgical intervention is able to resolve hypercalcemia in the majority of patients but carries a significant risk of hypoparathyroidism (approximately 10 percent), which can affect the quality of life of these patients. PEA, although not available in many centers, is considered an effective and overall safe treatment option.

The main difference between these two treatment approaches is the need for repeated injection in patients who receive PEA (mean duration of eucalcemia is approximately 24 months), since this treatment appears to control the disease but does not provide a definitive cure. On the other hand, re-operation might be considered a more definitive approach but has a higher risk of hypoparathyroidism.

Moreover, when to re-intervene in these patients is also a matter of debate, given the limitations of the available treatment options. Observation in cases of recurrence associated with mild hypercalcemia in patients who are asymptomatic might be a reasonable option.

**Key message**

PHPT is the most common clinical manifestation of patients with MEN1 and is associated with high recurrence rates after initial surgical intervention. A discussion of the risks and benefits of each of the available treatment options should be carried out by an experienced multidisciplinary team in the setting of the patient’s values and preferences to provide the patient with the treatment recommendation that best fits his or her needs.