Endocrinology News From Mayo Clinic

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Bariatric Surgery in Adolescents

Childhood obesity has emerged as one of the most important public health problems in the United States. Almost one-fifth of adolescents in the United States are obese and approximately 7 percent have severe obesity — defined as a body mass index (BMI) either ≥ 120 percent of the 95th percentile or ≥ 35 kg/m².

Seema Kumar, M.D., a pediatric endocrinology consultant at Mayo Clinic in Rochester, Minnesota, says: “Children and adolescents with severe obesity are at risk of important comorbidities, including obstructive sleep apnea, diabetes, hypertension, cardiac hypertrophy and nonalcoholic steatohepatitis, as well as depression and impaired quality of life. Children with severe obesity almost always remain in the obese range as adults, and 65 percent will have class III obesity as adults (BMI ≥ 40 kg/m²). Additionally, children with obesity during childhood have been shown to have more health complications and higher mortality as compared with those who developed obesity during adulthood. Therefore, treatment that is targeted at achieving weight loss during childhood and adolescence may treat or prevent these problems and improve long-term health outcomes.”

Medical options consisting of lifestyle
modifications to support changes in diet and physical activity, with goals of reducing caloric intake and increasing energy expenditure are the first line treatment for children and adolescents with obesity. Dr. Kumar comments: “Unfortunately, dietary and behavioral interventions alone have not been demonstrated to result in significant long-term success for children and adolescents with severe obesity. Pharmacotherapy options in adolescents with obesity are very limited, and currently orlistat is the only medication that is approved in the United States for the indication of weight loss in adolescents. This medication has been shown to have low efficacy in obese adolescents.”

Due to the mounting evidence of the adverse long-term consequences of severe adolescent obesity coupled with poor efficacy of nonsurgical options for weight loss, and a demonstrated safety and efficacy record of bariatric procedures in adults, there has been increasing interest in bariatric surgery for adolescents with severe obesity. Experts in pediatric obesity and bariatric surgery recommend that adolescents with BMI ≥ 35 kg/m² and a severe comorbidity that has significant short-term effects on health — such as moderate to severe obstructive sleep apnea, type 2 diabetes mellitus, pseudotumor cerebri, or severe and progressive steatohepatitis — or BMI ≥ 40 kg/m² with more minor comorbidities be considered as candidates for bariatric surgery.

Todd A. Kellogg, M.D., a bariatric surgeon at Mayo Clinic in Rochester, Minnesota, says: “Other important criteria for patient selection include physical maturity, lack of medically correctable causes of obesity, and adequate emotional maturity and stability to ensure competent decision-making and good adherence to medical follow-up. Most experts also agree that the patient should have failed organized and sustained attempts to lose weight through lifestyle intervention. Contraindications to bariatric surgery include an ongoing substance abuse problem (within the preceding year) and medical, psychiatric, psychosocial or cognitive conditions that prevent adherence to postoperative dietary and medication regimens or impair decisional capacity. Weight-loss surgery for adolescents should be performed in the context of a multidisciplinary program with specific expertise in pediatric obesity, bariatric surgery, nutrition and psychology. The evaluation for weight-loss procedures includes evaluation for the presence and severity of coexisting diseases as well as assessment of the patient’s and family’s understanding and readiness for a life-changing and often permanent procedure. The risks and benefits of weight-loss surgery for individuals with syndromic obesity (such as Prader-Willi syndrome) have not been adequately explored.”

Currently, the most widely performed procedures in adolescents and adults are the Roux-en-Y gastric bypass (RYGB), the sleeve gastrectomy (SG) and the adjustable gastric band (AGB). Dr. Kellogg explains: “The AGB is not approved by the Food and Drug Administration for patients less than 18 years of age. Accumulating adolescent data suggest that SG may prove to be a safe alternative to RYGB, probably with fewer nutritional risks. As compared with AGB, SG has the advantage of avoiding a foreign body and potential associated complications. Malabsorptive procedures such as biliopancreatic diversion are not recommended for adolescents due to lack of safety data in this age group and concerns about long-term nutritional complications.”

Dr. Kumar highlights: “Existing data demonstrate that bariatric surgery in adolescents leads to clinically important decreases in weight and BMI in the majority of patients. Obesity-related diseases such as diabetes, obstructive sleep apnea, as well as depression and quality of life also have been demonstrated to improve or resolve after surgically induced weight loss in adolescents. Information about long-term outcomes (more than 2 years) is limited, but the weight loss appears to be sustained in most cases, as it is in adult cohorts. There is insufficient information at this time to directly compare the long-term weight-loss outcomes of RYGB with those for SG or AGB in adolescents. Lifelong supplementation with vitamins and minerals is recommended for all adolescents undergoing any bariatric procedure to avoid development of nutritional complications secondary to reduced intake, mild malabsorption or both. Adolescents that have undergone bariatric surgery should be followed on a regular basis by a multidisciplinary team consisting of a dietitian, an expert in obesity and a psychologist.”
Lipodystrophies are a heterogeneous group of rare acquired and inherited disorders characterized by selective loss of adipose tissue. Vinaya Simha, MBBS, M.D., an endocrinology consultant at Mayo Clinic’s campus in Rochester, Minnesota, says: “While the first reported case of lipodystrophy dates back to the late 19th century, much progress has occurred in the past decade in understanding both the molecular mechanisms of fat loss and its optimal treatment. These advances have not only offered a new ray of hope for patients with these rare syndromes but have also provided valuable insight into our understanding of adipose tissue biology, and the pathophysiology of other common obesity-related metabolic disorders such as diabetes, dyslipidemia, insulin resistance and steatohepatitis.”

**Classification and clinical features**
Dr. Simha explains: “Loss of adipose tissue can occur either due to genetic or acquired causes, and can involve either the entire body or be restricted to certain areas like the extremities, often with excess fat deposition in the unaffected areas. Accordingly, both acquired and genetic lipodystrophy may be associated with either a generalized or a partial lipodystrophy phenotype. The table provides a brief summary of the genotypic and phenotypic diversity of the different lipodystrophy syndromes.”

### Inherited Lipodystrophies

<table>
<thead>
<tr>
<th>Type</th>
<th>Salient features</th>
<th>Mode of inheritance</th>
<th>Genetic defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital generalized lipodystrophy</td>
<td>Generalized deficiency of subcutaneous fat from birth</td>
<td>Autosomal recessive</td>
<td>AGPAT2, BSCL2, CAV1, PTRF, FBN1, BANF1</td>
</tr>
<tr>
<td>Familial partial lipodystrophy</td>
<td>Loss of subcutaneous fat from extremities with variable loss/excess of fat from trunk and face</td>
<td>Autosomal dominant (usually)</td>
<td>LMNA, PPARG, AKT2, PLIN1, CIDEC*</td>
</tr>
<tr>
<td>Lipodystrophy in association with other rare syndromes</td>
<td>Variable degree of fat loss in association with features of other syndromes such as MAD, SHORT, progeria and autoinflammatory syndromes</td>
<td>Both autosomal recessive and autosomal dominant</td>
<td>LMNA, ZMPSTE24, PSMB8, PIK3R1</td>
</tr>
</tbody>
</table>

### Acquired Lipodystrophies

<table>
<thead>
<tr>
<th>Type</th>
<th>Salient features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acquired generalized lipodystrophy</td>
<td>Development of generalized loss of subcutaneous fat, with normal fat distribution at birth</td>
</tr>
<tr>
<td>Acquired partial lipodystrophy</td>
<td>Loss of subcutaneous fat from face, upper extremities and trunk, but not from lower extremities</td>
</tr>
<tr>
<td>HIV-associated lipodystrophy</td>
<td>Loss of fat from face and limbs with variable loss/excess from trunk and associated with antiretroviral therapy</td>
</tr>
<tr>
<td>Localized lipodystrophy</td>
<td>Patchy loss of subcutaneous fat usually following trauma or injections</td>
</tr>
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Abbreviations in the table: MAD, mandibuloacral dysplasia; SHORT, short stature, hyperextensibility, hernia, ocular depression, Rieger anomaly and teething delay.

*CIDEC reported in a single patient with autosomal recessive inheritance.

**Table.** Classification and overview of different lipodystrophy syndromes
over the face and neck. Metabolic abnormalities are similar to those seen in CGL patients but may not be as severe in some patients. Since the extent of fat loss is not uniform, circulating leptin levels may also vary from low to normal in these patients.

Acquired lipodystrophies may occur in association with other autoimmune disorders or panniculitis, or may be idiopathic. Patients with acquired generalized lipodystrophy (AGL) may show severe metabolic complications similar to patients with CGL, while patients with acquired partial lipodystrophy (APL), also known as Barraquer-Simons syndrome, who invariably have well-preserved lower body fat, have lesser incidences of metabolic complications compared with other lipodystrophy syndromes. Rare forms of acquired partial lipodystrophy associated with autoinflammatory syndromes may however be associated with significant metabolic abnormalities.

The most prevalent form of lipodystrophy is seen in association with HIV infection (LD-HIV), with 40 to 50 percent of patients on long-term antiretroviral therapy being affected by either generalized lipoatrophy or partial fat loss involving the face and extremities. Even though the newer protease inhibitors cause less impact on body fat distribution and lipid homeostasis, LD-HIV is emerging as one of the most important challenges for long-term care of patients with HIV infection.

Novel treatment options for the metabolic complications of lipodystrophy

Dr. Simha notes: “Despite the marked heterogeneity in etiology and clinical features of the different lipodystrophy syndromes, they share common metabolic abnormalities such as diabetes with marked insulin resistance, severe hypertriglyceridemia, steatohepatitis and features of polycystic ovary syndrome. Often, the severity of these metabolic disturbances is related to the extent of fat loss, thus indicating the critical role of adipose tissue in maintenance of normal glucose and lipid homeostasis, and not surprisingly, adipose tissue transplantation in lipodystrophic mice has been shown to ameliorate hyperglycemia, hyperlipidemia and hepatic steatosis. However, if the donor fat was obtained from leptin knockout mice whose adipocytes could not secrete leptin, no metabolic benefits were observed, thus highlighting the endocrine functions of adipose tissue in preventing metabolic complications. These observations have led to the development of leptin-replacement therapy in patients with generalized lipodystrophy.”

In the initial open-label, prospective, phase II study, nine female patients with severe hypoleptinemia and metabolic abnormalities were treated with recombinant human leptin for four months. Results of the study by Elif A. Oral, M.D., and others were published in the New England Journal of Medicine in 2002. Dr. Simha, one of the co-authors of the study, explains: “Marked improvements in multiple metabolic variables were noted including a nearly 2 point reduction in hemoglobin A1C, a 60 percent reduction in serum triglycerides and hepatic transaminases, and 28 percent reduction in liver volume, besides improvements in glucose tolerance and insulin sensitivity. Further, leptin therapy facilitated a significant reduction in the burden of pharmacotherapy, and it was possible to reduce or completely stop glucose- and lipid-lowering medications in most of the subjects. Longitudinal follow-up of these patients for up to five years has demonstrated the durability of leptin’s beneficial effects, and other recent studies, including a study published in Diabetes in 2005 that discusses beneficial effects in children, have also shown similar results. A significant finding across many of these studies is a marked reduction in hepatic fat and histologic improvement in steatohepatitis. Based on these studies, as reviewed in Expert Review of Endocrinology & Metabolism in 2014, the Food and Drug Administration has approved recombinant human leptin (available as metreleptin) for treatment of adult and pediatric patients with generalized lipodystrophy. It is administered as a daily subcutaneous injection after reconstitution, and is likely to improve metabolic variables, which are usually very resistant to traditional therapies.”

Leptin therapy for lipodystrophy: Unresolved questions

Dr. Simha summarizes: “Leptin-replacement therapy is doubtless a promising option for patients with lipodystrophy, but many questions remain unanswered. One of them is the role of leptin therapy in patients with partial lipodystrophy who have variable fat loss and leptin levels. Despite a recent study in 24 female subjects with FPLD, published the Journal of Clinical Endocrinology & Metabolism in 2012, which showed a similar reduction in serum and hepatic triglycerides in those with severe and moderate hypoleptinemia, the overall response to leptin therapy in patients with partial lipodystrophy is not as robust as in those with generalized lipodystrophy. Indeed, leptin therapy is not approved for patients with partial lipodystrophy, including those with LD-HIV. The ‘anti-steatotic’ effect of leptin in patients with partial lipodystrophy without hypoleptinemia needs to be studied. The long-term efficacy and safety of leptin therapy also need to be closely
examined, as neutralizing antibodies may influence the biological activity of both endogenous and exogenous leptin. Jacques Beltrand, M.D., and others discussed immunological origin of resistance to leptin-replacement therapy in Berardinelli-Seip congenital lipodystrophy in European Journal of Endocrinology in 2010. Rare cases of hematologic malignancies also have been noted during leptin-replacement therapy in patients with AGL. Further, the molecular mechanisms underlying insulin resistance in lipodystrophy and its amelioration by leptin therapy need to be elucidated. We are specifically trying to study protein turnover and insulin action in the hypertrophied skeletal muscles of patients with lipodystrophy to get a better understanding of the interplay between adipose tissue and skeletal muscle in maintaining glucose and lipid homeostasis. These are indeed exciting times for both patients with lipodystrophy, and physicians and investigators involved in their care.”

For more information

What’s for Dinner? 2015 Dietary Guidelines Advisory Committee Report

Studies continue to report that patients look to their physicians for advice about nutrition. M. Molly McMahon, M.D., an endocrinology consultant at Mayo Clinic’s campus in Rochester, Minnesota, says: “You may be familiar with the initial Dietary Guidelines Advisory Committee (DGAC) report released in February 2015. Dietary guidelines for Americans were first published in 1980. Beginning in 1990, Congress mandated that the Department of Health and Human Services (HHS) and the U.S. Department of Agriculture (USDA) release a new edition every five years. The report is written for nutrition and health professionals, policymakers, and educators, and is the framework for federal nutrition initiatives, including education initiatives and food assistance programs. Reports are sent to the HHS and USDA for review, and input from federal agencies and the public is requested in the process. The change will not be official until it is approved by the HHS and USDA, but these groups usually closely follow the committee’s recommendations.”

The DGAC was charged with developing food-based recommendations that are of public health importance for Americans ages 2 years and older and that were published since the 2010 guidelines. Dr. McMahon explains: “The DGAC stressed two key points: First, half of all American adults have one or more preventable, chronic disease, and approximately two-thirds of U.S. adults
are overweight or obese. Poor dietary patterns, excess calories and physical inactivity contribute to these results. Second, individual lifestyle behaviors are strongly influenced by organizational and environmental systems. The DGAC stated that the nation must accelerate progress toward reducing the incidence and prevalence of overweight and obesity and chronic disease risk and reduce disparities for certain ethnic and racial groups and for those with lower incomes.

The report assessed current status and trends in food and nutrient intakes, dietary patterns and health outcomes, individual diet and activity behavior change, food environment and settings, food sustainability and safety, topics of public health importance, and physical activity. Underconsumed nutrients of public health concern include calcium, vitamin D, fiber and potassium. Underconsumption has been linked in the scientific literature to adverse health outcomes. Iron is included for adolescent females and postmenopausal females. Two nutrients, sodium and saturated fat, are overconsumed by the U.S. population. The DGAC found that although food quality varies by setting, the diet quality of the U.S. population does not meet its recommendations for vegetables, fruits, dairy or whole grains, and exceeds recommendations, leading to overconsumption of the nutrients sodium and saturated fat and the food components of refined grains, solid fats and sugars.

Dr. McMahon notes: “The DGAC had enough information from research and data to model three dietary patterns and examine their nutrition adequacy. These patterns of eating include the Healthy U.S.-style Pattern, Healthy Mediterranean-style Pattern and the Healthy Vegetarian Pattern. In general, the healthier diet patterns are higher in vegetables, fruits, whole grains, low-or nonfat dairy, seafood, legumes, and nuts; moderate in alcohol (among adults); lower in red and processed meat; and low in sugar-sweetened foods and drinks and refined grains. The DGAC encourages the consumption of healthy dietary patterns that are low in saturated fat, sodium and added sugars — with a challenge to differentiate added sugars from natural sugars, as the current Nutrition Facts Label on packaged food does not differentiate the two. The goals for the general population are: less than 2,300 milligrams (mg) dietary sodium a day (or age-appropriate dietary reference intake amount), less than 10 percent of total calories from saturated fat a day and a maximum of 10 percent of total calories from added sugars a day. Newer recommendations include focusing on healthy patterns of eating, limiting sugar and red and processed meat, and not placing emphasis on the 1,500 mg daily intake of sodium. The committee also recommended a repeal of the guideline that Americans limit their cholesterol intake to 300 mg a day.”

Dr. McMahon concludes: “The report suggests a paradigm shift in health care toward a greater focus on prevention and integration with food systems. The recommendations suggest offering incentives to businesses that establish employee health benefit plans and support health care facilities, such as clinics and hospitals, to achieve ‘cultures of health’ by offering healthy food choices for patients, visitors and staff, and referring staff and patients to federal and local food assistance programs as needed.

“Mayo Clinic has introduced worksite wellness champions to help different medical areas become healthier while having fun. Nutrition physicians led the creation of evidence-based nutrition criteria to guide food that is served on campus to patients and employees, while focusing on great taste. Many nutrition-culinary, activity and stress management programs are offered in the Dan Abraham Healthy Living Center, the patient and employee wellness facility, in an effort to improve the health of Mayo Clinic staff and patients.”

For more information
The final report, Dietary Guidelines for Americans, 2015, is due out at the end of 2015. For more-specific information and scientific rationale regarding recommendations about nutrition; activity; worksite, school and community efforts; or sustainable practices, refer to the Scientific Report of the 2015 Dietary Guidelines Advisory Committee at http://www.health.gov/dietaryguidelines/2015-scientific-report.
Correspondence: The 100-Year Anniversary of the Isolation of Thyroid Hormone in Rochester, Minnesota

To the editor:

I really enjoyed reading the article on the crystallization of levothyroxine in the December 2014 issue of the Mayo Clinic Endocrinology Update (Volume 9, No. 4, 2014). It brought back nice memories of my first American Thyroid Association meeting at Mayo Clinic in Rochester, Minnesota, in 1964 or 1965 that celebrated the 50th anniversary of the isolation of thyroid hormone. A symposium was held, and there were a number of excellent presentations by outstanding scientists, including Alvin Taurog, Sam Barker, Sidney Ingbar, Kenneth Sterling and Lester VanMiddlesworth.

The major address was by Kendall himself, and was inspiring. I do remember that after isolating the crystals, he could not repeat the isolation, I think, twice. He then realized that the initial isolation used distilled water from a copper still, and the ones that didn’t work used water from an iron still. When he did it a final time with the copper still water, he confirmed the initial findings. I attached a photograph of the equipment used [in Kendall’s laboratory] at that time (Figures 1 and 2).

His rigor and discipline in confirming his great findings before publishing impressed me greatly, and I have always tried to do so. Importantly, attending the symposium was inspirational and contributed to my subsequent decision to continue in academic medicine rather than be a general internist in the Bronx, which had been my early goal.

Marty Surks, M.D., MACP
Montefiore Medical Center
Bronx, New York

Figure 1. The three tanks in which 6,550 pounds of hog thyroid glands were treated for the isolation of thyroid hormone, circa 1915.

Figure 2. Equipment used in isolation of thyroid hormone, circa 1915.
Education Opportunities

Mayo Clinic Nutrition and Wellness in Health and Disease 2015
Sept. 25-26, 2015, in Washington, D.C.

Nutrition, physical activity and other healthy lifestyle behaviors are vital components in the promotion of health and the treatment of disease. This course — designed for physicians, advanced practice clinicians, dietitians, nurses, and health and wellness staff — will provide a full-spectrum, in-depth overview of situations and topics that clinicians encounter in the ambulatory setting, including obesity in adults and children, weight management strategies, obesity-associated medical conditions, the role of healthy diets, bariatric surgery and pre- and post-surgery medical management, prevention of common medical conditions through healthy lifestyles, effective ways to provide coaching, nutrition for selected groups, nutrition topics in the news, behavior modification, and resilience, in addition to physical activity and wellness. A culinary demonstration will highlight cooking techniques to prepare healthy, great-tasting food. Current clinical topics will be highlighted through presentations that offer practical clinical management pearls, interactive case studies and panel discussions. The course will be held at The Mayflower Renaissance Washington, D.C., Hotel.

For more information, visit www.Mayo.edu/cme/endocrinology or call 800-323-2688 (toll-free). Course hashtag: #MayoNutrCME

19th Annual Mayo Clinic Endocrine Update 2016
Feb. 28-March 4, 2016, at Hyatt Regency Maui Resort and Spa in Lahaina, Hawaii

Designed for endocrinologists and interested internists and surgeons, the 19th Annual Mayo Clinic Endocrine Update will address gaps in medical knowledge and barriers in clinical practice in order to improve the outcomes of patients with endocrine and metabolic disorders. This course will span the full range of endocrinology, through lectures, debates, panel discussions, clinicopathologic sessions, clinical pearls sessions, informal breakfast roundtable discussions and small-group discussions with experts. Attendees will have plenty of opportunity for interaction with the course faculty, who are selected from Mayo Clinic for their expertise and clinical acumen. The course will be held at Hyatt Regency Maui Resort and Spa, Lahaina, Hawaii. To ensure accommodations at the discounted rate, please make your reservations directly with the hotel by calling 888-421-1442 (toll-free). Identify yourself as a participant of the Mayo Clinic Endocrine Update Course.

For more information, visit www.Mayo.edu/cme/endocrinology or call 800-323-2688 (toll-free).