MAYO CLINIC

EndocrinologyUpdate

Endocrinology News From Mayo Clinic

Vol. 15, No. 1, 2020

INSIDE THIS ISSUE

Managing Skeletal Issues in Transgender and Gender Nonconforming Individuals

Importance of Pre-Pregnancy Care for Women with Diabetes: A Case From the Endocrine Teaching Clinics

Familial Partial Lipodystrophy — One Size Does Not Fit All: Cases From the Endocrine Teaching Clinic

Greet reported in Clinic in Rochester, Minnesota, where

Lapart scopic adrenal ectomy was first reported in 1992. Since the technique has evolved into applications for ready all patients with benign adrenal disease and the selected patients with malignant adrenal disease.

The standard of care s widely considered to be either a transabdonanal aparoscopic approach or a retroperitoneo correspondent for adrenal tumors amenable to minimuly invasive surgery. More recently, the robotic technique has been adopted as an alternative for mered patients. The robotic camera provides better depth perception for the surgeon, as it offers higher resolution and a 3D view. The arms of the robot also allow for a greater range of motion than that offered by conventional laparoscopy in confined spaces.

"Endocrine surgeons at Mayo Clinic have taken this a step further by offering single-site adrenalectomy in selected patients," explains Benzon M. Dy, M.D., Endocrine Surgery, at Mayo



Figure. Single-site adrenalectomy robotic technology at Mayo Clinic.

Clinic in Rochester, Minnesota, where over 150 single-site robotic adrenalectomies have been performed. "The single-site technology allows for adrenalectomy to be safely performed through a single 2.5-cm incision. The single-site robotic port accommodates the camera, an assist port and two working hands."

A meta-analysis of robotic — compared with laparoscopic — adrenalectomy published in *Oncotarget* in 2017 shows no differences in the rate of complications, the rate of conversion to an open procedure or intraoperative blood loss. The robotic approach is associated with a longer prating time that is known to improve with surgeon experience.

I is not a replacement for laparoscopy or standard multiport technology," reports Dr. Dy. Rathenit complements the variety of approachesement we offer to patients so that we can provide the best opproach without compromising outcomes."

Endocrine surgions a Mayo Clinic in Rochester, Minnesota, reported on their experience using single-site robotic adrenalectomy in *Surgical Endoscopy* in 2016. The authors noted that they found this approach sife even in obese patients. The surgeos teaming curve at Mayo Clinic was shown to result in significant reduction in operative time after 21 surgeries.

Dr. Dy notes: "These findings suggest that centers with high-volume adrenalectomy can adopt the single-site robotic technique and overcome the concerns about operative time as surgeon experience in single-site robotic surgery builds. The robotic approach has also been shown to be less expensive, as it can be associated with a shorter hospital stay and reduced narcotic use.



Benzon M. Dy, M.D., and Melanie L. Lyden, M.D.

"Single-site robotic adrenalectomy is not yet FDA approved, but that situation may change as surgeons such as those at Mayo Clinic report their success with this technique. Single-site robotic adrenalectomy is another example of how minimally invasive surgery is evolving to improve patient satisfaction and outcomes."

For more information

Agrusa A, et al. Innovation in endocrine surgery: Robotic versus laparoscopic adrenalectomy. Meta-analysis and systematic literature review. *Oncotarget*. 2017;8:102392.

Lee GS, et al. Robotic single-site adrenalectomy. *Surgical Endoscopy.* 2016;30:3351.

Managing Skeletal Issues in Transgender and Gender Nonconforming Individuals

Endocrinologists play an important role in prescribing and managing hormone therapy for gender dysphoria, and guidelines regarding the care of transgender patients are available. There is now a growing recognition that long-term hormone therapy may impact the risk of a number of chronic diseases, including osteoporosis.

Estrogen is the dominant sex steroid regulating bone resorption and formation in both cisgender (identify with sex assigned at birth)



Figure. Working model for sex steroid action on cancellous versus cortical bone in (A) cisgender females and (B) cisgender males. Panels (C) and (D) show the analogous models in transgender females and males, respectively, placing the models in the context of exogenous hormone therapies. Image reprinted with permission from *The Lancet Diabetes & Endocrinology*.

males and cisgender females."However, evolving evidence has highlighted a potential independent role for androgens in regulating cancellous bone remodeling (as in the vertebrae) in cisgender males, with estrogen likely mainly regulating cortical remodeling (as in the long bones)," clarifies Sundeep Khosla, M.D., Endocrinology, Diabetes, Metabolism and Nutrition, at Mayo Clinic in Rochester, Minnesota.

Caroline J. Davidge-Pitts, M.B., B.Ch., Endocrinology, Diabetes, Metabolism and Nutrition, at Mayo Clinic in Rochester, Minnesota, explains: "In cisgender females (Figure A) prior to menopause, the high endogenous ovarian estrogen levels inhibit excessive bone resorption and help maintain bone formation in both cancellous and cortical bone. The role of the low androgen levels in regulating bone remodeling in cisgender females remains unclear, although evidence from androgen receptor knockout mice indicates that androgens may have some effects on cancellous, but not cortical, bone remodeling.

"By contrast, in cisgender males (Figure B), the relatively low estradiol levels coming both from the testes and via peripheral aromatization of testosterone are likely insufficient to fully prevent excessive bone remodeling and bone loss in cancellous bone, perhaps because cancellous bone also contains considerable amounts of estrogen receptor (ER) β , which serves to antagonize ER α action and thus make cancellous bone relatively resistant to estrogen. Cortical bone, which expresses little or no ER β , may be much more sensitive to estrogen, which appears to mainly target cortical bone in males. However, the existing mouse and human data are consistent with a significant effect of testosterone at the levels found in cisgender males, in the absence of aromatization to estrogen, in preventing loss of cancellous bone. In addition to having this effect, testosterone likely plays an important role in driving periosteal bone formation and the larger bone size in cisgender males achieved during puberty.

"In this context, one can then make some predictions regarding the skeletal effects of hormone therapy and compare these to the existing clinical data, with the caveat that most studies to date have utilized dual energy X-ray absorptiometry (DXA), which cannot distinguish cancellous bone from cortical bone.

"Thus, in transgender women (sex assigned male at birth, identify as female, Figure C), the high exogenous estradiol levels should be sufficient to protect both cancellous and cortical bone, although it is possible that there may be some deficits in cancellous bone if testosterone levels are very low due to gonadal suppression or orchiectomy. In transgender men (sex assigned female at birth, identify as male, Figure D), there should be sufficient exogenous testosterone to protect cancellous bone as well as aromatization of testosterone to estradiol to prevent cortical bone loss. These effects of sex steroids are likely amplified during puberty, as sex steroids clearly regulate bone mass acquisition during this period. Importantly, fusion of the growth plate is dependent on estrogen in both females and males."

Dr. Khosla highlights:"This working model would predict that, assuming compliance with hormone therapy, the skeleton should be relatively well protected in both transgender women and transgender men."

Compared with cisgender men, transgender women have lower bone mass and cortical size even prior to initiation of hormone therapy, suggesting sex steroid-independent effects in these individuals."These individuals are more likely to have vitamin D deficiency and less likely to be involved in sport than cisgender men," says Dr. Davidge-Pitts.

Although bone mineral density (BMD) is generally preserved in both transgender women and transgender men, there are sparse data on fracture risk. In the largest fracture study to date, which included 2,023 transgender women and 1,036 transgender men, fracture risk was not increased in transgender men when compared with either reference cisgender men or cis-



Sundeep Khosla, M.D., and Caroline J. Davidge-Pitts, M.B., B.Ch.

gender women, but it tended to be increased in transgender women younger than 50 years when compared with age-matched reference cisgender women but not when compared with age-matched reference cisgender men.

In transgender women older than 50 years, fracture risk was similar to that of age-matched reference cisgender women, but was increased almost twofold compared with that of agematched reference cisgender men."Whether this risk differential is related to the underlying skeletal deficits in transgender women even prior to starting hormone treatment noted earlier remains to be determined," says Dr. Khosla."It should be noted, however, that the observation period for this fracture cohort was only three years, so longer term fracture incidence data in transgender individuals are clearly needed. The bone-specific long-term effects of puberty blockers and hormone therapy initiated in adolescence are yet to be fully determined."

Dr. Khosla stresses that the 2019 International Society for Clinical Densitometry guidelines have addressed the use of BMD determined with DXA in transgender and gender-nonconforming individuals. Baseline BMD measurement recommendations are similar to those in cisgender individuals. Followup BMD measurement can be considered in individuals with baseline low bone density, suboptimal dosing of or non-compliance with hormone therapy, or plans to discontinue hormone therapy; in those who are at increased risk of fracture; and in the setting of agents that suppress puberty.

It is also recommended that T-scores be calculated using the uniform Caucasian female normative database. Z-scores should be calculated using the affirmed gender normative database; however, providers could also request the normative database for sex assigned at birth. Additionally, nonbinary individuals should have Z-scores calculated using the normative database for sex assigned at birth.

Dr. Davidge-Pitts concludes:"Regarding bone health in transgender and gender-diverse individuals, there remain several important research and clinical issues that are unresolved. Further studies are needed to address these gaps."

The most current evidence was reviewed by Dr. Davidge-Pitts, Dr. Khosla and a research team at Mayo Clinic in *The Lancet Diabetes & Endocrinology* and *Maturitas* in 2019.

For more information

Khosla S, et al. Skeletal considerations in the medical treatment of transgender people. *The Lancet Diabetes & Endocrinology*. 2019;7:893.

Davidge-Pitts C, et al. Transgender bone health. *Maturitas*. 2019;127:35.

The International Society for Clinical Densitometry. *www.iscd.org*.

Importance of Pre-Pregnancy Care for Women with Diabetes: A Case From the Endocrine Teaching Clinics

A 24-year-old woman with type 1 diabetes mellitus presented at Mayo Clinic to establish care. She was diagnosed with diabetes at age 7 years after developing diabetic ketoacidosis. The patient was using a hybrid closed-loop insulin delivery system including an insulin pump and a continuous glucose monitor. The pump was in automatic mode, using a target of 120 mg/dL to adjust basal insulin delivery. HbA1c was 7.3% with minimal hypoglycemia, and while there were no known microvascular or macrovascular complications, the last screening was completed 12 months prior to this visit.

An intrauterine contraceptive device was in place, but the patient expressed a desire to have it removed and become pregnant in the near future. She had no prior pregnancies.

Discussion

While the vast majority of women with diabetes have positive pregnancy outcomes, extra care



Figure. The hyperglycemia-hyperinsulinemia (Pedersen) hypothesis.

and attention is required to achieve that outcome. Maternal glucose can diffuse to the fetal circulation and result in fetal hyperglycemia, which in turn promotes fetal hyperinsulinemia and contributes to abnormal growth and development (Figure).

Diabetes during pregnancy may be classified as pre-gestational (including type 1 and type 2) or gestational diabetes mellitus. This patient fell into the former category, as diabetes was established prior to conception. Women with pre-gestational diabetes are at increased risk of gestational hypertension and cesarean delivery. Their infants are at increased risk of:

- Congenital anomalies
- Birth injuries (associated with shoulder dystocia)
- Being large for gestational age
- Developing neonatal hypoglycemia

Structured programs providing coordinated, evidence-based care to women with diabetes before and during pregnancy, such as the program outcomes reported in *The Journal of Clinical Endocrinology and Metabolism* in 2016, have demonstrated improved clinical outcomes. In particular, the value of targeted pre-pregnancy care is well established. Pre-pregnancy care, including glycemic control right through conception and the critical early stages of pregnancy when organogenesis is taking place, ensures optimal maternal health. Typically, patients are reviewed every one to three months in the outpatient setting and contraception is advised until treatment goals are achieved.

Components of pre-pregnancy care

Among the key components of pre-pregnancy care (Table), a full medication review should occur and medications with teratogenic potential such as angiotensin-converting enzyme inhibitors or statins should be discontinued. Women should take at least 400 mcg or 0.4 mg of folic acid per day for a minimum of three months prior to conception. Baseline labs including thyroid function tests should be performed. Retinal screening and assessment for nephropathy and neuropathy should occur within a year of pregnancy. In certain clinical situations, screening for macrovascular complications may be required. Pregnancy should be deferred until complications are treated.

With the exception of metformin and insulin, all glucose-lowering agents should be discontinued. Previously, NPH insulin and regular insulin were typically used in this setting. Currently, rapid-acting insulins including insulin aspart and insulin lispro are considered safe and are commonly used before and during pregnancy. The long-acting insulin analogues insulin detemir and insulin glargine also appear safe and are frequently used in clinical practice. There are no significant data to support use of other insulins during pregnancy.

If possible, an HbA1c of less than 6.5% should be targeted pre-pregnancy, as rates of congenital anomalies drop to close to those of the background population in this setting. In order to achieve this goal, patients should target a fasting glucose of less than 95 mg/dL and a two-hour postprandial glucose of less than 120 mg/dL.

A randomized controlled trial (CONCEPTT) recently demonstrated that the use of continuous

Baseline investigations:

Including HbA1c, creatinine, thyroid-stimulating hormone, urine albumin-creatinine ratio.

Medications and supplements: Discontinue medications with teratogenic potential. Commence at least 400 mcg or 0.4 mg folic acid a day. Ensure 1,000 mg elemental calcium and 600 IU vitamin D a day.

Glycemic targets: HbA1c target is less than 6.5%. Review hypoglycemia management and testing for ketones.

Nutritionist referral and weight optimization

Screening for diabetes-related complications

Table. Key components of pre-pregnancy care.



Adrian Vella, M.D., and Aoife M. Egan, M.B., B.Ch., Ph.D.

glucose monitoring during pregnancy in patients with type 1 diabetes is associated with improved neonatal outcomes, and this technology may be initiated in the pre-pregnancy setting if clinically appropriate. Study results were published in *The Lancet* in 2017.

At Mayo Clinic, the patient was followed in clinic regularly. She worked with members of the multidisciplinary team, including a dietitian and a nurse educator. The insulin pump was switched to manual mode to tighten glycemic control, and screening for complications was completed.

The patient's thyroid-stimulating hormone level was 4.0 mIU/L. Levothyroxine was introduced to target a thyroid-stimulating hormone level of 0.1 to 2.5 mIU/L, which is considered optimal for the first trimester of pregnancy. At six months, the patient's HbA1c had improved to 6.2% and her intrauterine device was removed.

Three months later the woman became pregnant. She was followed closely during pregnancy by providers in Obstetrics and Endocrinology. She developed preeclampsia at 35 weeks of gestation. After induction of labor at 37 weeks, she delivered a healthy baby girl weighing 3.3 kg. The vaginal delivery was normal and there were no neonatal complications.

For more information

Egan AM, et al. A prepregnancy care program for women with diabetes: Effective and cost saving. *The Journal of Clinical Endocrinology and Metabolism.* 2016;101:1807.

Feig DS, et al. Continuous glucose monitoring in pregnant women with type 1 diabetes (CONCEPTT): A multicentre international randomised controlled trial. *The Lancet*. 2017;390:2347.

Familial Partial Lipodystrophy — One Size Does Not Fit All: Cases From the Endocrine Teaching Clinic

Familial partial lipodystrophy (FPLD) is a heterogeneous group of rare inherited disorders characterized by varying degrees of fat loss and metabolic abnormalities. The severity of metabolic derangements correlates with the extent of fat loss, thus highlighting the critical role of adipose tissue in glucose and lipid metabolism. The following vignettes highlight the genotypic and phenotypic diversity of FPLD and associated metabolic abnormalities and comorbidities, and discuss standard management approaches for patients with these disorders (Table).

Case 1: Type 2 FPLD (Dunnigan variety)

A 40-year-old Asian Indian woman belonging to a large pedigree harboring the *LMNA* R482W mutation presented to the metabolism

Features	Case 1	Case 2	Case 3
Familial lipodystrophy variety	Type 2 FPLD (Dunnigan)	Type 1 FPLD (Köbberling)	Generalized lipodystrophy
Genetic mutation	<i>LMNA</i> (R482W)	NA	<i>LMNA</i> (R349W)
Sex (M/F)	F	F	F
Age of onset of fat loss (years)	10	11	Late 20s
Areas of fat loss	Arms, legs, hips, buttocks	Arms, legs, hips, buttocks	Face, neck, arms, legs, palms, soles
Areas of fat excess	Face, neck, upper back	Face, neck, abdomen	None
BMI (kg/m²)	19.42	38.5	16
Metabolic abnormalities			
Triglycerides, on therapy (mg/dL)	140	1,349	801
HDL, most recent (mg/dL)	45	24	38
Total daily insulin requirements (units)	70	460	120
Polycystic ovary syndrome	Yes	Yes	No
Atherosclerotic cardiovascular events	No	No	No
Non-alcoholic steatohepatitis	Yes	Yes	Yes
Other clinical features	NA	NA	Dilated cardiomyopathy, mitral valve regurgitation, progeria, focal segmental glomerulosclerosis, glottis carcinoma

Genotypic and phenotypic diversity of familial partial lipodystrophy (FPLD), associated metabolic abnormalities and comorbidities.

Table. Characteristics of three patients with familial partial lipodystrophy (FPLD).

clinic at Mayo Clinic in Rochester, Minnesota. She had normal fat distribution as a child but noted onset of fat loss from the limbs at age 10. Menarche occurred at 13, but cycles were irregular. At age 26, the patient was diagnosed with type 2 diabetes mellitus (T2DM) and had developed excess fat in her face, neck and back. Other metabolic complications included hypertriglyceridemia, fatty liver disease and polycystic ovary syndrome (PCOS). Her physical exam revealed a BMI of 19.42 kg/m², absent fat in the extremities with muscular prominence, and excess fat over the face and posterior neck, as well as acanthosis.

The patient's mother, maternal aunt and several other maternal blood relatives had similar histories and phenotypes, including premature coronary artery disease in two family members. Notably, the patient's 12-year-old daughter also had clinical features of type 2 FPLD.

Case 2: Type 1 FPLD (Köbberling variety)

A 31-year-old white woman was evaluated for hypertriglyceridemia and T2DM. She had normal fat distribution until puberty, at which point she experienced fat loss in her extremities and fat excess in her abdomen, neck and face. Metabolic complications included PCOS, obesity (BMI 38.5 kg/m²), fatty liver disease, hypertriglyceridemia complicated by pancreatitis and T2DM requiring high doses of insulin. Her examination revealed excess adiposity in the face, neck and trunk; acanthosis; and fat loss with muscular prominence of the extremities and gluteal area.

Her mother, sister, maternal grandmother, and several maternal aunts and uncles had similar physical features. One maternal uncle had a myocardial infarction at age 40.

Case 3: *LMNA*-associated generalized lipodystrophy

A 44-year-old woman, also belonging to a large pedigree with lipodystrophy, began losing fat from the face and limbs in her late 20s, with relative sparing of the abdomen. At that time, she also developed gray hair, skin wrinkling and hearing impairment. In subsequent years she was diagnosed with T2DM, hypertriglyceridemia, fatty liver disease, nonischemic cardiomyopathy, focal segmental glomerulonephritis and glottis squamous cell carcinoma. The patient's BMI was 16 kg/m². Her physical exam revealed generalized fat loss involving all extremities, palms, soles and face. She also had progeroid features, a promi-

6

nent systolic murmur and hepatomegaly.

Genetic testing revealed a mutation involving the *LMNA* gene (c.1045C>T, p.R349W).

Her mother, maternal uncle and two siblings had similar physical features with onset in their 20s, and all had developed cardiomyopathy.

Discussion

As noted in research published in *The Journal of* Clinical Endocrinology and Metabolism in 2011, FPLD is a rare autosomal dominant disorder characterized by loss of subcutaneous fat from the extremities with sparing of the face, neck and variably the trunk. Onset occurs during childhood, puberty or later. To date, seven subtypes have been described, six of which are related to mutations in genes involved in adipose metabolism and development — LMNA, PPARG, AKT2, CIDEC, PLIN1 and LIPE though the exact mechanism by which these mutations lead to fat loss remains unclear. In these disorders both fat loss and subsequent caloric excess result in severe insulin resistance, hepatic steatosis, hypertriglyceridemia, low HDL, PCOS and cardiovascular disease.

Type 2 FPLD (Dunnigan variety) is the bestdescribed subtype. It is caused by a mutation in the *LMNA* gene. As demonstrated by case 1, the typical phenotype involves fat loss from the extremities with sparing of the face and neck.

Case 2 represents type 1 FPLD (Köbberling variety), the genetic basis of which has not been identified. This phenotype involves fat loss from the extremities and gluteal regions, often with excess fat over the trunk, face and neck.

Case 3 represents a rare phenotype of FPLD. It also involves a mutation of the *LMNA* gene (c.1045C>T, p.R349W), but instead of causing fat loss from the extremities with sparing of the



Vinaya Simha, M.B.B.S., M.D., and Kristen M. Gonzales, M.D.

face and neck, it causes generalized lipodystrophy. In addition to being characterized by the common metabolic abnormalities of FPLD, this variety is associated with progeroid features, focal segmental glomerulonephritis, cardiomyopathy and cardiac conduction defects.

It is important to recognize FPLD and its different subtypes in patients being evaluated for insulin resistance, hyperlipidemia, PCOS, nonalcoholic steatohepatitis and Cushing syndrome. Skinfold measurement of the anterior thigh and other appendicular and truncal sites can be helpful, although distinct cutoffs have not been standardized (Figure 1 on page 7 and Figure 2 on page 8).

Management for the metabolic complications of FPLD centers on dietary restriction of saturated fats and refined carbohydrates, as well as traditional glucose and lipid-lowering therapies. Recognition of the different FPLD subtypes



Figure 1. Coronal CT images of the patient in case 2 with type 1 FPLD (above) and the patient in case 3 with *LMNA* mutation-associated generalized lipo-dystrophy (right). Note the excess adiposity in the trunk and fat loss in the hips and legs of the patient in case 2 compared with the generalized loss of fat from trunk, hips and legs of the patient in case 3.



Mayo Clinic Endocrinology Update

Medical Editor: Meera Shah, M.B., Ch.B.

Editorial Board:

M. Regina Castro, M.D. Benzon M. Dy, M.D. Jad Sfeir, M.D. Peter J. Tebben, M.D.

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

Contact Us

Mayo Clinic welcomes inquiries and referrals, and a request to a specific physician is not required to refer a patient.

Phoenix/Scottsdale, Arizona 866-629-6362

Jacksonville, Florida 800-634-1417

Rochester, Minnesota 800-533-1564

Resources

MayoClinic.org/ medical-professionals

Clinical trials, CME, Grand Rounds, scientific videos and online referrals





Figure 2. Sagittal CT images of the patient in case 2 with type 1 FPLD (left) and the patient in case 3 with *LMNA* mutation-associated generalized lipodystrophy (right). Note the fat loss in the gluteal region of the patient in case 2. Note the generalized loss of truncal fat and hepatomegaly with steatosis (arrow) in the patient in case 3.

will aid in screening for appropriate metabolic complications and comorbidities.

For more information

Garg A. Lipodystrophies: Genetic and acquired body fat disorders. *The Journal* of Clinical Endocrinology and Metabolism. 2011;96:3313.

PGA Core Group Visiting Professor



Teresa K. Woodruff, Ph.D., Thomas J. Watkins Professor of Obstetrics & Gynecology and chief, Division of Reproductive Science in Medicine, Feinberg School of Medicine, Northwestern University, Chicago, with members of the Mayo Clinic Pituitary-Gonads-Adrenals (PGA) Core Group.

Standing: Justine S. Herndon, P.A.-C., Ravinder J. Singh, Ph.D., Neena Natt, M.D., Dana Erickson, M.D., Alice Y. Chang, M.D., and William F. Young Jr., M.D.

Seated: Irina Bancos, M.D., Teresa K. Woodruff, Ph.D., and Caroline J. Davidge-Pitts, M.B., B.Ch.

Education Opportunities

For more information or to register, visit *https://ce.mayo.edu/endocrinology*, call 800-323-2688 (toll-free) or email *cme@mayo.edu*.

Diabetes Intensive Training 2020 — Online

This graduate-level professional enhancement course is recommended for physicians, nurse practitioners, physician assistants and registered nurses seeking a higher level intense study course.

Principles in the Care of Transgender and Intersex Patients 2020

Oct. 8-10, 2020, in Phoenix

Experts from Mayo Clinic's Transgender and Intersex Multidisciplinary Clinic instruct attendees in medical, surgical, psychosocial, legal and ethical issues in transgender and intersex care.

MAYO CLINIC | mayoclinic.org

4500 San Pablo Road Jacksonville, FL 32224 200 First Street SW Rochester, MN 55905

13400 East Shea Boulevard Scottsdale, AZ 85259

©2020 Mayo Foundation for Medical Education and Research. All rights reserved. MAYO, MAYO CLINIC and the triple-shield Mayo logo are trademarks and service marks of MFMER.