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Endocrinology Update

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Treatment of Dyslipidemia in Patients With Chronic Kidney Diseases

In 2003, the National Kidney Foundation published the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines, which included recommendations for assessment and treatment of dyslipidemia in patients with chronic kidney diseases (CKDs). The KDOQI guidelines recommend evaluation of all patients with CKD for dyslipidemia through testing for fasting blood concentrations of total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides. For patients with stage 5 CKD (Table 1), the lipid panel should be performed at presentation, annually thereafter, and at 2 to 3 months after every change in treatment. In addition, patients with dyslipidemia should be evaluated for possible secondary causes of dyslipidemia (Box).

Pankaj Shah, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: "Cardiovascular events are the number 1 cause of death in patients with CKD. These patients have an increase in their blood concentrations of LDL-C, non–HDL-C, small dense LDL-C, modified LDL-C, lipoprotein(a), and C-reactive protein. The increase in blood triglycerides and decrease in HDL-C are more marked in CKD patients who also have nephrotic syndrome. The KDOQI guidelines [Figure and Table 2, see page 2] recommend treatment with a fibrate

Table 1. Stages of Chronic Kidney Disease

Stage No.	Stage Description	GFR, mL/min/1.73 m^2
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with decreased GFR	60-89
3	Kidney damage with moderately decreased GFR	30-59
4	Kidney damage with severely decreased GFR	15-29
5	Kidney failure	<15 or dialysis

Abbreviation: GFR, glomerular filtration rate.

Box. Secondary Causes of Dyslipidemia in Patients With Chronic Kidney Disease

Medical conditions

- Alcohol consumption
- Diabetes mellitus
- Hypothyroidism
- Liver disease
- Nephrotic syndrome

Medications

- Androgens and estrogens
- Anticonvulsants
- β-Adrenergic inhibitors
- Corticosteroids
- Cyclosporine
- Diuretics
- Highly active antiretroviral therapy (HAART)
- Sirolimus
- 13-*cis*-retinoic acid

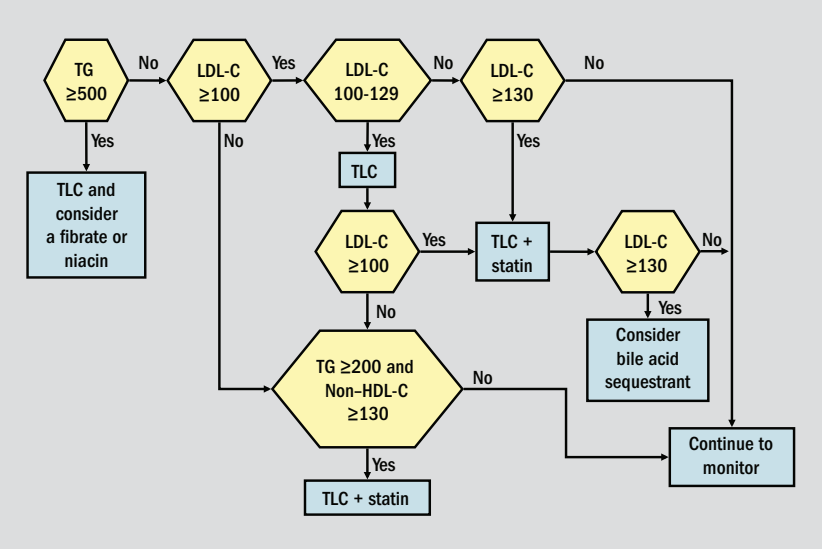


Figure. *Approach to the treatment of dyslipidemia in patients with chronic kidney disease. Units for cholesterols and triglycerides are mg/dL. HDL-C indicates high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TLC, therapeutic lifestyle changes. Adapted from Kidney Disease Outcomes Quality Initiative (K/DOQI) Group. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. Am J Kidney Dis. 2003 Apr;41(4 Suppl 3):I-IV, S1-91. Used with permission.*

included in the large randomized placebo-controlled trials that were designed to assess the effects of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). Dr Shah notes: "However, secondary analyses of the data from patients with mild to moderate CKD showed that treatment with statins caused statistically significant reductions in all-cause and cardiovascular mortality rates. These benefits seemed to be at least as remarkable as those found in the people without CKD. In addition, statins have been shown to be safe for patients with CKD, and they do not impact renal function. Yet, 2 large trials conducted of patients receiving hemodialysis revealed a lack of benefit from statin use in decreasing cardiovascular events or death, despite declines in blood lipid concentrations similar to those seen in patients with mild to moderate CKD. In addition, gemfibrozil use for patients with mild to moderate CKD has not been shown to have an impact on major cardiovascular events or overall mortality rate."

Dr Shah continues: "There is only 1 large study addressing the cardiovascular and survival benefits of statins in renal transplant recipients. A clinically significant reduction in

Pankaj Shah, MD

Table 2. Therapeutic Goals for Dyslipidemia in Adults With Chronic Kidney Disease

Lipid Concentration	Goal	Initial Treatment	If Not at Goal After Initial Treatment	Alternative Additional Treatment
TG ≥500 mg/dL	TG <500 mg/dL	TLC	Add fibrate or niacin	Add fibrate or niacin
LDL-C 100-129 mg/dL	LDL-C <100 mg/dL	TLC	Add low-dose statin	Add bile acid sequestrants or niacin
LDL-C ≥130 mg/dL	LDL-C <100 mg/dL	TLC + low-dose statin	↑ to maximum-dose statin	Add bile acid sequestrants or niacin
TG ≥200 mg/dL and non–HDL-C ≥130 mg/dL	Non–HDL-C <130 mg/dL	TLC + low-dose statin	↑ to maximum-dose statin	Add fibrate or niacin

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; TLC, therapeutic lifestyle changes. Adapted from Kidney Disease Outcomes Quality Initiative (K/DOQI) Group. K/DOQI clinical practice guidelines for management of dyslipidemias in patients with kidney disease. Am J Kidney Dis 2003 Apr;41(4 Suppl 3):I-IV, S1-91. Used with permission.

or niacin when the blood triglycerides concentration is 500 mg/dL or greater and the patient has no response to therapeutic lifestyle interventions. The targets and treatment strategies for blood LDL-C concentrations are not different from people without CKD."

Patients with severe CKD were not

hyperlipidemia, similar to that seen in patients with mild to moderate CKD, was observed in this study. Although there was a trend for reduced cardiovascular events, there was no impact on mortality outcomes. Potential effects of statin treatment on prevention of organ rejection, though, are under investiga-

tion. Screening for and treatment of dyslipidemia in patients with mild to moderate kidney disease appear to have fair evidence [Table 3]. However, statin use for patients receiving hemodialysis and for renal transplant recipients does not have a strong evidence base. More studies are required to establish the role of statins in patients with stage 5 CKD and renal transplant recipients."

Table 3. Summary of Effects of Statins (vs No Treatment) in Patients With CKD and Renal Transplant Recipients

	Patient Subgroups[a]		
Lipid Status or Risk Factor	**CKD Without Dialysis**	**CKD With Dialysis**	**Renal Transplant**
Decrease in total cholesterol, mg/dL	~42	~43	~42
Decrease in LDL-C, mg/dL	~42	~43	~46
Increase in HDL-C, mg/dL	~1.3	NS	NS
Decrease in triglycerides, mg/dL	~29	~24	~25
Risk reduction for all-cause death, %	~19	NS	NS
Risk reduction for CV death, %	~20	NS	NS
Risk reduction for nonfatal CV events, %	~25	NS	NS
Risk of increased creatine kinase, %	NS	NS	NS
Risk of increased liver function test results, %	NS	NS	NS
Risk of withdrawal due to adverse events, %	NS	NS	NS

Abbreviations: CKD, chronic kidney disease; CV, cardiovascular; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, not significant.

[a] Data summarized from Navaneethan SD, Pansini F, Perkovic V, et al. HMG CoA reductase inhibitors (statins) for people with chronic kidney disease not requiring dialysis. Cochrane Database Syst Rev 2009 Apr 15;(2):CD007784; Navaneethan SD, Nigwekar SU, Perkovic V, et al. HMG CoA reductase inhibitors (statins) for dialysis patients. Cochrane Database Syst Rev 2009 Jul 8;(3):CD004289; Navaneethan SD, Perkovic V, Johnson DW, et al. HMG CoA reductase inhibitors (statins) for kidney transplant recipients. Cochrane Database Syst Rev 2009 Apr 15;(2):CD005019.

Prader-Willi Syndrome

Prader-Willi syndrome (PWS) is a rare genetic disorder with an incidence of 1 in 30,000 live births. PWS is caused by a lack of expression of imprinted genes of the paternally derived chromosome 15q11-q13. It is characterized by severe hypotonia in the newborn period; children and adolescents have hyperphagia and weight gain and most have morbid obesity.

Siobhan T. Pittock, MD, of the Division of Pediatric Endocrinology, Department of Pediatric and Adolescent Medicine, at Mayo Clinic in Rochester, Minnesota, says: "Patients with PWS require care from multiple subspecialists from infancy through adulthood. The endocrinologist is frequently involved in management of several specific areas, such as growth, obesity, and hypogonadism. We also need to be aware of other complications of PWS, which include osteoporosis, sleep-disordered breathing, and sudden death."

Growth

Short stature in patients with PWS is caused by growth hormone (GH) deficiency and an inadequate pubertal growth spurt. Dr Pittock explains: "The mean spontaneous adult height in individuals with PWS is 5 feet 4 inches in men and 4 feet 11 inches in women. The treatment of short stature in PWS patients with GH was approved by the US Food and Drug Administration in 2000. GH treatment for these children not only increases final height, but also improves lean body mass, strength and agility, motor development, and bone mineral


Siobhan T. Pittock, MD

density. The diagnosis of GH deficiency in adults with PWS is difficult because of a lack of reference ranges for the severely obese population. Several short-term studies in adult patients with PWS suggest that GH treatment improves lean body mass, bone density, and sense of well-being."

Obesity

PWS is associated with hypotonia in infancy, leading to poor feeding and poor weight gain. The poor feeding usually resolves by 1 to 2 years of age. When children reach 3 to 4 years of age, they have marked hyperphagia and decreased satiety. Dr Pittock adds: "When unrestricted, children with PWS consume 3 times the calories of age-matched controls. The cause of this hyperphagia is unknown but is likely due to a combination of factors that include abnormalities in satiety response in corticolimbic regions (seen on functional imaging studies), neuroanatomical abnormalities in the hypothalamus (seen at postmortem examinations), elevated levels of ghrelin (which is orexigenic), and low levels of the anorexigenic pancreatic polypeptide. Marked obesity results from the poor satiety, reduced resting energy expenditure, and reduced physical activity. Despite their obesity, patients with PWS have relatively low rates of hyperlipidemia, diabetes mellitus, and hypertension."

Dr Pittock continues: "Treatment of obesity in PWS is particularly challenging in the face of aggressive food-seeking behaviors, developmental delay, and behavioral problems. Pharmacologic treatment of obesity in PWS has not been effective. Restrictive bariatric surgery procedures in small numbers of patients have not resulted in sustained weight reduction. Bariatric surgery in these patients is also associated with unacceptably high morbidity and mortality rates and a high rate of gastric dilatation and perforation related to ongoing poor satiety. Environmental control still offers the best chance for weight management."

Hypogonadism

Central hypogonadism is found in both males and females with PWS. The hypogonadism in males is complicated by primary testicular dysfunction. Dr Pittock explains: "Most PWS patients need hormonal treatment for induction, promotion, or maintenance of puberty. With this treatment, we try to mimic the normal timing and tempo of puberty. Oral or transdermal estrogen preparations are used for girls; transdermal or intramuscularly administered testosterone preparations are used for boys. Hypogonadism is common in adulthood. Aromatization of androgens in excess adipose tissue results in estrogen levels in women that are not as low as expected. Low blood sex hormone–binding levels in men result in a higher proportion of total testosterone as bioavailable testosterone. There are no controlled studies on appropriate sex hormone replacement for adults with PWS. Pregnancies have been described in several women with PWS. No paternity has been reported in males."

Osteoporosis

The factors that contribute to osteoporosis in patients with PWS include hypogonadism, GH deficiency, and poor muscle tone with decreased muscle activity. Dr Pittock highlights: "Adolescence represents a crucial time in bone mass accrual, and we try to optimize bone health by ensuring appropriate calcium and vitamin D intake, encouraging weight-bearing exercise, and correcting deficient levels of GH and sex steroids. Low or decreasing bone mineral density in adults may also warrant GH and sex steroid replacement."

Sleep-Disordered Breathing

There have been multiple reports of sudden death in children with PWS. Most of these deaths occurred during sleep and in the context of an apparently mild respiratory illness. Patients with PWS are obese and therefore are at risk for obstructive sleep apnea. Dr Pittock points out: "One study of 53 prepubertal children with PWS showed an average apnea hypopnea index (AHI) of more than 4 (reference, <1). When studied during respiratory illness, the AHI was even higher, at 36.5. Studies were performed before and after the initiation of GH therapy and no differences in AHI were seen. Therefore, although sleep-disordered breathing may predispose to sudden death in PWS patients, it does not appear to be exacerbated by GH therapy. We recommend maintaining insulinlike growth factor-1 levels within the reference range to decrease the risk of adenotonsillar hypertrophy, which could potentially worsen obstructive sleep apnea. We also recommend that all of our patients with PWS have sleep evaluations performed and follow up with a sleep specialist both before and after initiation of GH therapy. Many benefit from the use of a continuous or bilevel positive airway pressure device."

Adrenal Dysfunction

Not every PWS-related death can be attributed to sleep-disordered breathing. Because several

deaths have occurred during minor illnesses, the question of adrenal insufficiency has been raised. Dr Pittock explains: "Several studies have shown normal results on baseline tests of adrenal function but a lack of normal response to dynamic testing (eg, metyrapone stimulation test). Those patients who had a subnormal response to metyrapone also had a higher AHI, suggesting a possible additive effect. Large studies have yet to be performed to validate this finding. However, since these children are at high risk for sudden death and the risk of stress dosing of corticosteroids is low, we frequently suggest stress doses of hydrocortisone during times of intercurrent illnesses."

Clinical Endocrinology Training at Mayo Clinic

The first clinical endocrinology fellow at Mayo Clinic graduated in 1955. Full accreditation was granted to the Mayo Clinic clinical endocrinology training program by the Accreditation Council for Graduate Medical Education (ACGME) in 1987. Neena Natt, MD, of the Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota, says: "Each year, 4 new fellows join the program, spending 2 years in clinical training and 1 year pursuing an in-depth research project [Box]. During the clinical years, considerable time is spent in specific teaching clinic settings geared toward diseases related to diabetes and metabolism, bone and calcium, and the thyroid gland. Patients in these clinics have a wide range of both common and rare endocrine disorders. Fellows also work one-on-one with faculty during their rotation devoted to patients with pituitary, gonad, and adrenal disorders. In addition, the program has a strong nutrition component that focuses on the management of obesity and inpatient nutrition support. Further inpatient experience is achieved through participation in a diabetes and endocrine consulting service. Throughout these clinical experiences, fellows have an important role in the education of their peers, medical students, and residents."

Important training also occurs outside of the endocrinology division, with rotations in pediatric endocrinology, reproductive endocrinology, nuclear medicine, and endocrine surgery. Dr Natt notes: "The endocrine surgery rotation is a particular fellows' favorite because it provides the opportunity to follow patients from the preoperative counseling stage through the actual surgical procedure (yes, they scrub in!) and the subsequent postoperative care and management."

The program has seen many changes over the past decade. To keep pace with advances in technology and endocrine clinical practice, senior fellows evaluate and treat patients who

Box. Educational Components of the 3-Year Clinical Endocrinology Training Program at Mayo Clinic

Year 1

Continuity care clinic (1/2 day every week)

Electives

- Endocrine clinics (diabetes and metabolism, thyroid, bone and calcium)
- Endocrine testing center
- Hospital-based diabetes consulting service
- Hospital-based endocrine consulting service
- Nuclear medicine
- Inpatient nutrition consulting service
- Outpatient nutrition clinic
- Pediatric endocrinology
- Pituitary, gonad, and adrenal clinic
- Reproductive gynecology
- Wound care clinic

Year 2

Continuity care clinic (1/2 day every week)

Research project

Year 3

Advanced diabetes clinic

Continuity care clinic (1/2 day every week)

Electives

- Endocrine clinics (diabetes and metabolism, thyroid, bone and calcium)
- Endocrine surgery rotation
- Hospital-based diabetes consulting service
- Hospital-based endocrine consulting service
- Outpatient nutrition clinic
- Pituitary, gonad, and adrenal clinic
- Transplant endocrinology clinic

have complex conditions in both transplant endocrinology and an advanced diabetes clinic focused on insulin pump therapy. In addition, dedicated time is devoted to acquisition of competency in ultrasound-guided fine-needle aspiration of thyroid nodules.

Changes to the fellowship have also been necessitated by new accreditation requirements, with a shift from emphasis on structure and process components to an emphasis on outcomes. Dr Natt explains: "The ACGME has identified 6 'core competencies' required of graduating fellows that include not only medical knowledge and patient care skills, but also professional behavior, communication skills with patients and colleagues, self-assessment skills and resultant ability to improve one's own clinical practice, and navigation through the complex system of health care. Multiple assessment tools are used to measure competency in each of these areas, with observation of clinical performance having an increasingly important role. Sandwiched between the clinical years is a full year dedicated to either basic or clinical research with close mentorship from a faculty member. All fellows present their work at national meetings and, in many cases, go on to publish their findings."

Neena Natt, MD, Clinical Endocrinology Training Program Director, and Denise A. Bargsten, Education Coordinator, Division of Endocrinology, Diabetes, Metabolism, and Nutrition at Mayo Clinic in Rochester, Minnesota

In 2009, the endocrinology fellowship program graduated its 100th fellow (164th if data from before ACGME accreditation are used). Dr Natt concludes: "We look forward to graduating many more fellows in the future and are honored to have a role in the first stage of their careers in endocrinology."

Research

Rituximab in the Treatment of Graves' Ophthalmopathy

Graves' ophthalmopathy (GO), the inflammatory eye disease associated with Graves' hyperthyroidism, is characterized by proptosis, eye pain, periorbital edema, and extraocular muscle dysfunction. The signs and symptoms of GO are detectable in most patients with Graves' disease, with severe and potentially sight-threatening disease present in 5% of patients. The natural history of GO is deterioration during the active phase, followed by gradual improvement over months to years. Some patients have severe, active disease for several years with considerable negative impact on their quality of life. Current therapeutic options—including systemically administered corticosteroids, orbital radiation, and surgery—are of limited efficacy or are associated with potentially serious adverse effects.

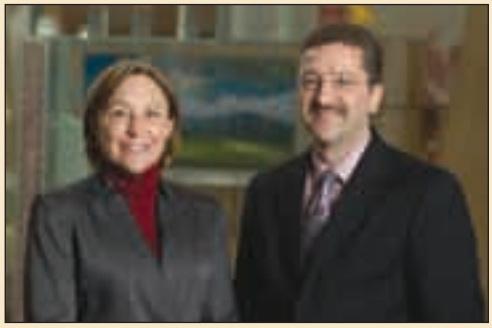
Recent experimental evidence suggests that B-cell–produced thyrotropin receptor autoantibodies are central to the pathophysiologic factors of GO. On the basis of this work, endocrinologists and ophthalmologists at Mayo Clinic in Rochester, Minnesota, are studying the efficacy of rituximab, an anti-CD20 monoclonal antibody that induces transient B-cell depletion and impacts antigen presentation, in the treatment of moderate to severe active GO.

Thirty patients will be enrolled in a double-blind, randomized, placebo-controlled study. Of these patients, 15 will receive rituximab (1,000 mg administered intravenously twice at a 2-week interval) and 15 will receive 2 saline infusions. All patients will return to Mayo Clinic in Rochester an additional 4 times during the subsequent year for clinical evaluations along with blood and ocular testing.

Inclusion Criteria: men and women, age 18 to 75 years, affected by active ophthalmopathy (clinical activity score, ≥4) of moderate to severe degree

Exclusion Criteria: contraindications to therapy with rituximab, including human immunodeficiency viral (HIV) infection, hepatitis B, and hepatitis C; denied consent to HIV or hepatitis testing; inactive or mild GO; absolute neutrophil count of less than 1.5×10^9/L; allergy to diphenhydramine hydrochloride.

To refer a patient with GO to be considered for this research study, please contact Rebecca S. Bahn, MD, at 507-284-2462, or Marius N. Stan, MD, at 507-284-2463.



Rebecca S. Bahn, MD, received the 2009 Department of Medicine Outstanding Mentor Award. Robert A. Wermers, MD, received the 2009 Department of Internal Medicine Laureate Award.

Hossein Gharib, MD, MACP, MACE, will be given the 2010 Distinguished Physician Award from The Endocrine Society. B. Lawrence Riggs Jr, MD, (not pictured) received The Legends in Osteoporosis Award from the National Osteoporosis Foundation, and in August 2009, he was inducted into the Hall of Fame by the University of Arkansas for Medical Sciences Alumni Association and College of Medicine. Sundeep Khosla, MD, received the 2009 Distinguished Investigator Award from the Mayo Clinic Rochester Executive Board and Rochester Research Committee, and in June 2010, he will receive the 2010 Clinical Investigator Award Lectureship from The Endocrine Society.

Robert A. Rizza, MD, (seen on right) was awarded the Banting Medal for Scientific Achievement from the American Diabetes Association (ADA) for 2010. The Banting Medal for Scientific Achievement Award is the ADA's highest scientific award and honors an individual who has made significant, long-term contributions to the understanding of diabetes, its treatment, and/or its prevention. The award is named after Nobel Prize winner Sir Frederick Banting, who codiscovered insulin treatment for diabetes. Dr Rizza was also inducted into the Royal College of Physicians of Ireland in 2009. James A. Levine, MD, PhD, (seen on left) won the 2009 Wakley Prize Essay, as judged by Lancet editors for the best essay on a clinical topic of public health importance (Lancet 2009; 374: 2126–27).

Diana S. Dean, MD, received the 2009 Outstanding Faculty Member of the Year Award from the Mayo School of Continuous Professional Development. In 2009, Geoffrey B. Thompson, MD, was appointed secretary-treasurer of the International Association of Endocrine Surgeons.

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CME Opportunities

13th Mayo Clinic Endocrine Course

July 14-17, 2010, Rochester, Minnesota

This course, created for endocrinologists and interested internists and surgeons, will present the latest material on the diagnosis and treatment of endocrine disorders. For more information about this course, please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.html.

Mayo Clinic Nutrition and Wellness in Health and Disease

November 4-5, 2010, San Francisco, California

This course—designed for physicians, nurse practitioners, physician assistants, dietitians, and health and wellness staff—will provide a full-spectrum, in-depth overview of challenging nutritional issues that clinicians encounter in the ambulatory setting. An additional objective is to discuss wellness programs that include nutrition, activity, and other lifestyle behaviors. For more information about this course, please call 800-323-2688 or visit www.mayo.edu/cme/endocrinology.html.

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