SPRING 2019

DIVISION OF ENDOCRINOLOGY AND METABOLISM

UPDATE IN

ENDOCRINOLOGY

Inside This Edition

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- *Academic Clinical Endocrinologists*
- *Academic Research Faculty*

Full descriptions and contact information on Page 12.

CME Credit

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Dear Colleagues,

We are pleased to share our latest edition of *Update in Endocrinology*. We had a very successful 2018 and are looking forward to a productive and exciting 2019! In this issue, we continue to highlight our contributions to the research, educational, clinical, and quality missions of the Division.

To highlight our research excellence, researcher **Michael Jurczak, PhD**, physician-scientist **Maja Stefanovic-Racic, MD, PhD**, and clinical fellow **Ramya Undamatla, MD**, discuss how the Division is collaborating with others across the University of Pittsburgh and UPMC to better understand and treat metabolic liver disease. Dr. Jurczak has recently been awarded a multi-PI R01 grant from the NIH for his work related to nonalcoholic fatty liver disease (NAFLD).

On the clinical front, endocrinologist **Alexandra Clark, MD**, discusses how she and her colleagues at the VA Pittsburgh Healthcare System (VAPHS) are addressing the challenges of diagnosing and managing hypogonadism. Dr. Clark is currently leading a clinical study to understand and define "best practices" in prescribing supplemental androgen therapy.

Patients continue to intrigue and challenge our expertise with complex cases. Clinical fellow **Diana Pinkhasova, MD**, and her mentor, metabolic bone expert **Mara Horwitz, MD**, present a clinical case that uses a new approach to treating X-linked hypophosphatemia.

Finally, in the ever-challenging modern health care environment, it is becoming increasingly important to develop new collaborative models of care. **Linda Siminerio, RN, CDE, PhD**, and clinical fellow **Margaret Zupa, MD**, review an insurer-based diabetes program. Dr. Zupa also discusses how her work on this project has led her to pursue a T32 fellowship training position to continue research on this critical area in clinical care.

Our Division continues to grow as **Diana Lynn Pakstis, MBA, BSN, RN**, was recently promoted to associate division administrator for the Divisions of Endocrinology, Geriatric Medicine, and Infectious Diseases. We also welcomed **Milay Luis Lam, MD**, to our faculty. In addition to her expertise in endocrinology, diabetes, and metabolism, Dr. Luis Lam is board certified in obesity medicine and will be joining our rapidly growing UPMC Obesity Medicine Group.

In addition, we also celebrate many accomplishments of our faculty, trainees, and staff. **Mary Korytkowski, MD**, was honored as one of Castle Connolly's Exceptional Women in Medicine 2018. Postdoctoral associate **Dan Harmon, PhD**, under the mentorship of Robert O'Doherty, PhD, was awarded the Society for Redox Biology and Medicine Young Investigator Award.

Finally, please remember to join us at our annual UPMC Endocrinology Reception at the American Diabetes Association (ADA) Scientific Sessions in San Francisco this June (details on Page 15 and to follow). We always look forward to seeing you and hearing from you.

Best wishes,

Erin E. Kershaw, MD
Chief, Division of Endocrinology and Metabolism

BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL DIABETES & ENDOCRINOLOGY 2018-19

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UPMC LIFE CHANGING MEDICINE

A Multidisciplinary Approach to Metabolic Liver Disease

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Nonalcoholic Fatty Liver Disease — A Recent History

In the not too distant past, a diagnosis of fatty liver with inflammation, or steato-hepatitis, unrelated to alcohol consumption, generally did not exist. Then in 1980, nonalcoholic steatohepatitis (NASH) was described for the first time, noting that the majority of patients with NASH were moderately obese and presented with obesity-associated diseases, such as type 2 diabetes (T2DM).[1] Similarly, nonalcoholic fatty liver (NAFL), or the presence of liver fat greater than five percent without inflammation, has long been considered benign. However, over the last two decades NAFL gained recognition as a clinically relevant pathology that may portend the development of more serious liver disease, including NASH, cirrhosis, and hepatocellular carcinoma.

"...although age, ethnicity, sex, and a small number of genetic variations are associated with NAFLD, obesity and diabetes are the primary risk factors for developing the disease."

NAFL and NASH now represent the early and late histological characteristics of a liver disease spectrum referred to as nonalcoholic fatty liver disease (NAFLD), which also encompasses fibrosis and cirrhosis. In 2005, the Pathology Committee of the NASH Clinical Research Network, which was established in 2002 by the National Institute of Diabetes and Digestive and Kidney Diseases, published a validated histological scoring system for NAFLD. Referred to as the NAFLD activity score or NAS, the system is comprised of four semi-quantitative features, including steatosis (scored 0–3), lobular inflammation (scored 0–2), hepatocellular ballooning (scored 0–2), and fibrosis (scored 0–4), as well as nine features documented as present or absent.[2] The proposed NAS not only solidified key histological features that define NAFLD progression but, importantly, provided a standardized means of evaluating interventions to treat NAFLD and also paved the way for the more than 200 clinical trials for NAFLD treatments currently underway.

Nonalcoholic Fatty Liver Disease on the Rise

Over the past decade, NAFLD has emerged as the leading cause of chronic liver disease in the United States, with NASH now representing the second most common indication for liver transplant after chronic hepatitis C. The prevalence of NAFLD and NASH in the United States is currently estimated to be approximately 30 percent and five percent, respectively, and NASH is predicted to soon become the most common indication for liver transplant.[3] Paralleling the increase in NAFLD is a rise in the prevalence of obesity and T2DM, which now afflicts as many as 93.3 million and 30.3 million Americans, respectively.[4,5] There is a strong positive association among obesity, T2DM, and NAFLD, and greater than 70 percent of patients with T2DM have NAFLD.[6,7] In fact, although age, ethnicity, sex, and a small number of genetic variations are associated with NAFLD, obesity and diabetes are the primary risk factors for developing the disease. The association of NAFLD with obesity and T2DM holds true not only for adults but also for children and adolescents for whom NAFLD prevalence in the United States is estimated at 11 percent, representing a doubling over the last decade.[8]

The exact sequence of events leading to NAFLD remains unclear, in part because the natural history of NAFLD appears variable. Approximately 30 percent of patients with NAFL will develop NASH and about 20 percent of patients with NASH will develop fibrosis. Understanding which patients with steatosis will progress to the more advanced stages of NAFLD is a major unmet clinical challenge. Currently, the first line of defense for treating patients with NASH is to prescribe lifestyle modifications, including dietary changes and exercise. Several studies

have demonstrated that achieving weight loss of five to 10 percent is associated with improvement in histological features of NAFLD, and paired biopsy studies suggest that fibrosis regression can occur.[9,10] There is currently no FDA-approved pharmacological treatment specifically for NAFLD, but the surge in activity in the pharmaceutical industry related to NAFLD and the large number of ongoing clinical trials suggests the first drug-based therapies may be on the horizon.

Nonalcoholic Fatty Liver Disease Pathogenesis — A Mitochondrial Component?

The observations that obesity is strongly associated with NAFLD and that body weight loss can prevent or reverse NAFLD progression provide some clues as to the pathophysiology of the disease, where exposure of the liver to energy excess, particularly fatty acids, is a key feature. Increased hepatic fatty acid exposure may derive from multiple sources, including dietary excess, increased rates of adipose tissue lipolysis, and hepatic de novo lipogenesis. The liver possesses multiple mechanisms to cope with fatty acid oversupply, such as esterification to triglyceride for hepatocellular storage or export as triglyceride-rich lipoproteins, and increased rates of mitochondrial oxidation. While the liver may be able to compensate for overexposure to metabolic stress in the short term, observations in patients with established obesity, T2DM, or NAFLD suggest that this compensation fails over time. This decompensation eventually leads to dysfunction in many of these pathways, particularly mitochondrial respiration, thereby contributing to NASH pathogenesis. For example, a recent first-of-its-kind human study in which liver biopsies were collected from healthy patients, obese patients with and without NAFL, and obese patients with NAFL and NASH demonstrated distinct changes in mitochondrial function that occurred in response to obesity and were subsequently lost after the onset of NASH.[11] More specifically, mitochondrial respiration was increased despite no change in mitochondrial mass in obese subjects with and without NAFL compared with controls, whereas mitochondrial respiration was reduced despite increased mitochondrial mass in patients with NASH compared with the lean and obese groups. Another interesting observation within this study was that mitochondrial respiratory control, a measure of mitochondrial electron transport chain efficiency, was reduced in obese patients with and without fatty liver or NASH. These observations suggest that energy excess, which is common in obesity, increases the metabolic load placed on hepatic mitochondria, inducing adaptations to buffer this load, which eventually fail. Mitochondrial function and mass are in part maintained by balancing the production of new mitochondria through mitochondrial biogenesis and removal of damaged mitochondria through a recently described process called mitophagy. Mitophagy is an essential cellular mitochondrial quality control process that regulates selective removal of damaged mitochondria from the cell, preventing abnormal mitochondrial function. Rates of mitophagy in the liver recently were reported to be reduced in a preclinical animal model of obesity-associated NAFL,[12] raising the possibility that defective hepatic mitophagy contributes to obesity-associated NAFL and the subsequent pathogenesis of NAFLD.

Nonalcoholic Fatty Liver Disease and Mitophagy

At the University of Pittsburgh Division of Endocrinology, investigators in the laboratory of Michael Jurczak, PhD, are investigating the pathogenesis of NAFLD, and more specifically, the role of mitophagy in NAFLD, as well as other diseases.[13,14] Dr. Jurczak,

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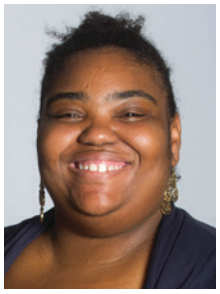
The Nuances, Controversies, and Challenges of Diagnosing and Managing Hypogonadism



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We currently live in a society that values very simple solutions to complex medical or aging-related problems, providing fertile ground for advertising initiatives[1] focused on the promise of a quick fix or immediate satisfaction. A prime example of this type of marketing platform is the promotion of "Low T" or hypogonadism. Consumers are led to believe that they are affected by this specific syndrome and that treatment with Testosterone Replacement Therapy (TRT) will be a magic key able to unlock their previous feelings of youth and vitality. Unbranded direct-to-consumer advertising for "Low T" represents a highly successful "disease-awareness" campaign[2] that is now considered a template for "how to sell a disease".[3] In 2014, the United States Food and Drug Administration (FDA) changed its testosterone labeling to emphasize the restriction of the indication to pathological causes, specifically excluding age-related testosterone decline as a reason for TRT. Nevertheless, the damage wrought by poorly regulated advertising continues to play a major role in driving the prescribing of TRT in the United States. As a result, patients present to their health care providers with preconceived notions of diagnosis and treatment, leading to a sometimes antagonistic refusal to accept reasoned advice to the contrary. This is particularly problematic because the diagnosis of potential androgen deficiency (AD) or hypogonadism is both nuanced and controversial, with considerable debate regarding the costs versus benefits of TRT.

The Nuances of Diagnosing Hypogonadism

The diagnosis of AD rests on both symptoms and laboratory data. Symptoms associated with hypogonadism such as low libido, erectile dysfunction, decreased energy, depressed mood, poor concentration, sleep disturbance, reduced muscle bulk and strength, increased body fat, and/or increased BMI are nonspecific. These symptoms can be associated with other medical comorbidities, including undiagnosed sleep apnea, obesity, or even just the natural aging process. Obtaining a testosterone level in order to assist with the diagnosis of hypogonadism has not been standardized, though the most recent Endocrine Society Clinical Practice Guidelines[4] go a long way to clarify this issue.

"Patients and health care providers need to understand that diagnosing hypogonadism is not the end of the story; rather, it may be an indication of an underlying causative disease such as a pituitary or genetic issue which has farther reaching implications."

The guidelines recommend total testosterone (TT) concentrations be obtained in the morning, fasting, and using an accurate and reliable method with confirmation of the results. Liquid chromatography–tandem mass spectrometry (LC/MS/MS) assays as opposed to immunoassays for TT offer higher specificity, sensitivity, and precision, so this assay is preferred if available.[4] Yet another nuance of diagnosing hypogonadism is deciding whether the TT concentration is an accurate assessment of the body's available testosterone concentration. The TT concentration includes sex hormone binding globulin (SHBG)-bound testosterone, albumin-bound testosterone, and free testosterone. The biologic activity of a hormone is dependent upon the concentrations of the free rather than protein-bound hormone in plasma.[5] Testosterone is tightly bound to SHBG, making it unavailable for use by the body, while testosterone is loosely bound to albumin, allowing it to dissociate and become biologically available for action in the tissues.[5] Free testosterone in combination with albumin-bound testosterone is termed bioavailable testosterone and is available for use by the body.

Conditions that lower SHBG, of which there are many, can lower TT concentrations to below the normal range, although bioavailable and free testosterone concentrations might remain within the normal range. This is particularly important given the increasing prevalence of obesity and type 2 diabetes, both of which can lower SHBG levels as well as have symptoms that mimic those associated with hypogonadism. To make matters worse, there is no universally accepted testosterone concentration cut-off below which a person is considered to definitively have hypogonadism.

Off-label Prescribing of TRT

The FDA released a safety announcement in 2015 against the habitual recommending and prescribing of TRT for "no reason other than age, even if symptoms seem related to low testosterone."[6] Despite this, testosterone products increasingly are being prescribed to treat a controversial condition termed late-onset hypogonadism (LOH), andropause, and/or partial androgen deficiency of the aging male.[7] This syndrome is diagnosed in men who, for no discernible reason other than older age, obesity, or ill health, have serum testosterone concentrations below the normal range for healthy young men and report one or more of the following symptoms: muscle weakness or wasting, mood, behavior and cognition-related symptoms, and sexual function or libido impairment.[1] In contemporary societies, individuals are required to be increasingly competitive in all areas of their personal and working life often with their much younger counterparts,[1] so the promised ability of TRT to delay or reverse aging is extremely appealing despite its modest symptomatic benefits in practice.[8]

Controversy Surrounding TRT and Cardiovascular Outcomes

Two studies[9,10] reporting a possible increased risk of heart attacks and strokes in patients using TRT prompted the FDA to issue an advisory in 2015 mandating that all product labeling include a warning of increased cardiovascular (CV) risk from TRT.[6] The impact of TRT on cardiovascular outcomes remains controversial with studies reporting widely discrepant results, from higher mortality and heightened CV risk[11-13] to improved survival and cardio-protection effect,[14,15] with a net neutral impact on meta-analysis.[16] However, most studies do not take CV risk profile into account, and they differ widely in how AD is defined. Therefore, it is uncertain whether TRT is beneficial or harmful when AD is established with the appropriate diagnostic criteria and when pre-existing vascular risk is taken into account. Our research at VA Pittsburgh Healthcare System (VAPHS) clarifies this area of uncertainty.

TRT and Vascular Outcomes at VAPHS

In a retrospective cohort study of more than 900 men at VAPHS who were prescribed TRT, the two most powerful predictors of vascular events (VEs) on TRT were a history of prior VEs and a lack of diagnostic rigor (DR) in diagnosing hypogonadism, defined as ≥ 1 unequivocally low early AM testosterone (T) by tandem mass spectrometry (Total T < 200 ng/dL, or Free T < 5 pg/mL, or calculated bioavailable T < 100 ng/dL). Kaplan-Meier analysis revealed that the probability of VEs on TRT was increased almost four-fold with a prior VE history (Hazard Ratio [HR] = 3·7) and decreased more than four-fold when TRT was initiated with DR (HR = 0·24). When both nonadherence to DR and prior VE history coexisted, the probability of VEs increased eight-fold compared to TRT initiated with DR in patients without prior VEs (HR = 8·2). The results suggest that TRT is harmful when prescribed to patients with a recent history of VEs or when initiated without DR. However, TRT initiated with DR may be safe in low-risk patients. This study was approved by the VAPHS Institutional Review Board and is currently being submitted for publication.

Studies of TRT's impact on outcomes have attempted to answer the relatively straightforward question: "Is TRT beneficial or harmful?" If the question is reframed to ask the more nuanced question: "When is TRT beneficial, and in whom is it harmful?", the answer can be found in patient selection and diagnostic rigor. Thus, TRT in low-risk patients with AD diagnosed with appropriate rigor is safe and potentially beneficial, whereas replacing testosterone in low-risk patients without proven AD is a recipe for futility. However, harm is inevitable in high-risk patients exposed to a therapy with potential risk of VEs, like TRT. Those three constructs provide a framework for reconciling the contradictory outcomes studies, from unequivocal benefit through no impact to unequivocal harm.

The fact that patient selection and diagnostic rigor influence outcomes during TRT has major implications for clinical practice. It provides a blueprint for restricting TRT to patients with a low CV risk profile and AD established with diagnostic rigor, while excluding those with a high CV risk, particularly if they have a history of prior VEs.

The Moral of the Story

Diagnosing and managing hypogonadism is not an easy task. Primary care providers (PCPs) are reported to prescribe the bulk of TRT in the United States, but with far less caution or selectivity than endocrinologists.[17] Almost 95 percent of TRT is prescribed in ways that are inconsistent with guideline recommendations.[17, 18] Endocrinologists have the responsibility to lead the way in the standardizing of diagnosis, ultimately making it easier to study hypogonadism.

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X-Linked Hypophosphatemia: A New Therapeutic Approach

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Case Presentation

The patient is a 60-year-old female with X-linked hypophosphatemia (XLH) who was referred to our outpatient bone clinic for management of progressive bone and metabolic complications, including bowing deformities of the lower extremities, hypophosphatemia, hyperphosphaturia with nephrolithiasis, and tertiary hyperparathyroidism.

The patient initially was diagnosed incorrectly with vitamin D-resistant rickets at age 4 when she was noted to have bowing of her legs. Therapy with ergocalciferol was initiated at age 10, and the dose was escalated to 200,000 IU daily by age 18. On review of the patient's records, she continued to be hypophosphatemic on this regimen.

Once the correct diagnosis was made, she was started on phosphorus and calcitriol, which increased her serum phosphorus to just below the lower limit of the normal range. However, over time she developed tertiary hyperparathyroidism (See Table 1 on Page 7) and nephrolithiasis requiring lithotripsy for bilateral renal calculi. Despite discontinuation of calcitriol and initiation of cinacalcet, she eventually required a subtotal parathyroidectomy (PTX). Her parathyroid hormone (PTH) normalized intraoperatively but began to rise again over time (Table 1).

The patient began experiencing progressive and debilitating knee pain secondary to degenerative joint disease related to her bowing deformities. She eventually underwent bilateral knee replacements in her late 40s (Figure 1). She also experienced declining bone mineral density with loss of height but without fragility fractures. In addition, she developed progressive hearing loss, as well as recurrent dental abscesses since age 10, necessitating extensive dental work.

Notably, the patient had been evaluated and followed at many medical centers over her adult life. In 2010, genetic testing was done at another institution and no mutation of the PHEX gene was identified, but the patient's FGF23 was high at 659 pg/mL (reference range: 10-50 pg/mL). Her family history was negative for any relatives with documented XLH. However, one of her brothers had mild bowing deformities of the legs, and two of his children had recurrent dental caries.

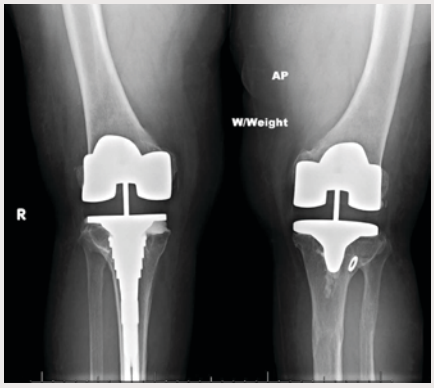

Figure 1. Partial x-ray image of the patient's lower extremities. The image shows bilateral total knee arthroplasties with diffuse generalized osteopenia and bowing of both femurs.

On physical exam, she had short stature (143 cm) with a disproportionally short lower segment compared to the upper segment with visible bowing deformities of her femurs. Her face was asymmetric and she had multiple fillings and healed implants on oral exam. Her spine was notable for moderate to severe scoliosis with loss of lumbar lordosis.

In September 2018, her phosphorus and calcitriol supplements were discontinued, as well as her cinacalcet in preparation for beginning burosumab/KRN23 (Crysvita), the first FDA-approved treatment for X-linked hypophosphatemia. Her serum phosphorus level in the absence of the above supplements and prior to burosumab therapy was 1.7. On September 24, 2018, she received her first monthly burosumab injection of 50 mg (1 mg/kg). Her serum phosphorus increased and has remained in the 2.2-2.7 range without supplements since starting the drug (Table 1). Overall, the patient states her quality of life has dramatically improved since starting burosumab.

Case Discussion

X-linked hypophosphatemia (XLH) (also known as X-linked hypophosphatemic rickets) accounts for ~80 percent of familial cases of hypophosphatemia.[1] The disease was first described in 1937 by Albright, Butler, and Bloomberg as a rare case of vitamin D-resistant rickets requiring more vitamin D than the amount ordinarily effective for prevention and cure of rickets.[2] Subsequently, many studies have shown that XLH is characterized by impaired renal phosphate transport. Insufficient reabsorption of phosphate from the proximal renal tubule into the bloodstream leads to increased phosphate excretion in the urine.[3] The prevalence of XLH is approximately one in 20,000 with no reported gender difference in disease severity.[6]

In 1995, the causative gene for XLH was identified on chromosome Xp22.1 and named PHEX (Phosphate regulating endopeptidase on the X chromosome).[4] This gene encodes a cell surface-bound protein-cleaving enzyme. Its expression is enriched in bone and teeth.[4] Loss of function mutations in PHEX lead to an increase in fibroblast growth factor-23 (FGF23), a hormone produced predominantly in bone.[4] High free FGF23 in plasma causes hypophosphatemia and hyperphosphaturia by decreasing renal phosphate reabsorption through downregulation of the phosphorus transporters NaPi-IIa and NaPi-IIc at the apical membrane of proximal renal tubular cells. High FGF23 also leads to inhibition of 1alpha-hydroxylase, resulting in decreased 1,25 vitamin D levels.[5]

Low serum phosphorus levels are usually present at birth but often remain undetected. For this reason, affected individuals may not present until weight-bearing age, when abnormal mineralization (rickets) leads to bowing deformities of the legs and progressive departure from normal growth rates.[8] Progressive enthesopathy, craniosynostosis, bone pain, insufficiency fractures, and dental abscesses also are common findings, particularly in adults.[8]

Younger siblings of affected patients should be screened to diagnose the disorder before complications develop. Screening can be accomplished by measuring fasting serum phosphorus, as well as renal phosphorus excretion. Laboratory abnormalities at the

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Table 1. Summary of the patient's laboratory values over time with corresponding treatment.

Month/Year	4/2010 (Pre-PTX)	8/2010 (Post-PTX)	4/2018	9/2018 Before burosumab	12/2018 After burosumab
Treatment (Daily Dose)	D3 1000 IU Cinacalcet 120 mg	D3 1000 IU Phos 500 mg Calcitriol 0.75 mcg Cinacalcet 30 mg	D3 1000 Phos 500 mg Calcitriol 0.5 mcg Cinacalcet 30 mg	Off supplements for 1 week	Burosumab 50 mg SC Q28 days
Serum Total Calcium (8.4-10.2 mg/dL)	11	9.1	9.2		10.7
Serum Albumin (3.4-5.0 g/dL)	4.1	4.1	4.0		4.0
Serum Phosphorus (2.5-4.5 mg/dL)	1.4	1.5	2.2	1.7	2.4
Intact PTH (14-64 pg/mL)	368	59.4	169		186
Phosphorus/Creat 24 hr Urine (270-1,030 mg/g creat)	1678		1369		1263
Vitamin D 25-OH total (30-100 ng/mL)	44	39	48		48

Adding Value in Primary Care: An Insurer-Based Diabetes Program

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Models that address the needs of patients with diabetes mellitus (DM) in primary care (PC) are being explored as health systems move to value-based care. A paradigm change is underway that focuses on patient-centered, team-care that aims for high-value, high-quality health care delivery at the PC level. While the number of patients with DM in the United States continues to rise, with 1.5 million new cases diagnosed per year,[1] there is an inverse number of providers to deliver comprehensive, quality care.

While serving as the front line of care for patients with DM, PC requires additional assistance to optimize quality and value in the care of these patients. Studies have shown that primary care physicians (PCPs) consider DM more difficult to treat than other chronic diseases, as more monitoring and medication adjustment is required to achieve treatment goals.[2,3] Meanwhile, physicians also report that they feel ill-equipped to counsel patients regarding behavior change.[4,5] In a survey of physicians and nurses regarding DM care responsibilities, nurses reported that they felt capable and ready to assume these responsibilities. They were reported to have more time to spend with patients, were better listeners, knew patients better, and provided better education than physicians.[6] Although specialty endocrinology clinics traditionally have been a referral resource for comprehensive team care, the current national shortage of endocrinologists often limits access to this service. Endocrinologists will need to serve as a critical resource for their DM expertise while PC will continue to be the mainstay of care for patients with increasingly complex DM needs.

Insurers, who ultimately are responsible for services and costs, are keenly aware of the current PC challenges and limitations. For payers, suboptimal DM care translates into higher expenditures. UPMC is an integrated health system that includes more than 40 academic, community, and specialty hospitals and 600 outpatient sites serving diverse populations throughout western Pennsylvania and beyond. The reach and impact of UPMC are extended through its Insurances Services Division (ISD) and UPMC Health Plan, which partners with UPMC and additional community network providers to provide high-quality care. For these reasons, UPMC provides an ideal "community laboratory" to examine methods that promote access and best practice to the patients it serves.

Diabetes education is recognized as an essential component of DM care. It has been shown to reduce health care costs, increase adherence, and improve glycemia among patients with DM.[7] It is not always feasible, however, for the individual PC practice to employ a diabetes educator (DE) to provide this service. To address health care gaps and improve DM outcomes in remote community practices, the UPMC Health Plan partnered with members of the Division of Endocrinology and Metabolism to implement and evaluate a DE-driven high-risk initiative. DEs were employed by the UPMC Health Plan under the direction of the Division of Endocrinology and Metabolism and took an active role in supporting PCPs to meet the complex demands of diabetes management.

DEs worked with care managers within PC practices to identify and target DM patients at high risk, specifically those with HbA1c > 9 percent, DM-related ER visits and hospitalizations, and self-reported barriers to care. A practice-based visit included an individualized assessment and self-management education with treatment recommendations shared with the PCP. Patients referred for the DE intervention during the first year of the program had a mean reduction in HbA1c from 9.6 to 8.4 over six months (108 patients, $p < 0.001$) and 9.2 to 8.1 percent over 12 months (80 patients, $p < 0.001$). While the decrease in HbA1c seen at six months was encouraging, the persistent improvement in glycemic control at 12 months indicated that this change was durable. The sustainability likely is due to both the DE intervention and the implementation of a process in which the PC team also gained skills in

providing ongoing support. In addition, the program has influenced PCP's ability to meet quality measures and has been well received. The demonstrated success of the intervention has prompted continued support of the program.

Furthermore, this project has spurred continued interest in models of care delivery for patients with DM for Margaret Zupa, MD, a first-year endocrine fellow. Motivated by the success of this program and the desire to find additional ways to improve the care of patients with diabetes at a system level, Dr. Zupa plans to pursue the T32 research fellowship track with a focus on health systems research. Working in collaboration with a mentor in the UPMC Department of General Internal Medicine, Anne-Marie Rosland, MD, Dr. Zupa will examine the impact of a patient activation and family supporter engagement intervention in the PC setting on medication adherence and health care utilization patterns among patients with DM. Linda Siminerio, RN, CDE, PhD, and the Diabetes Medical Home team also are collaborating in designing a DE-driven patient-centered model. This interdepartmental collaboration will contribute to the Division's ability to develop and evaluate novel models of care for patients with DM, and advance the quality and value goals of the Division in collaboration with partners at the UPMC Health Plan and in primary care.

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Presented by Mary Korytkowski, MD

Management of Thyroid Nodules and Thyroid Cancer in Pediatric Populations
Presented by Pushpa Viswanathan, MD

2015 ATA Guidelines for Management of Thyroid Nodules
Presented by Elena Morariu, MD

Management of Concomitant Thyroid and Parathyroid Disease
Presented by Sally E. Carty, MD, FACS

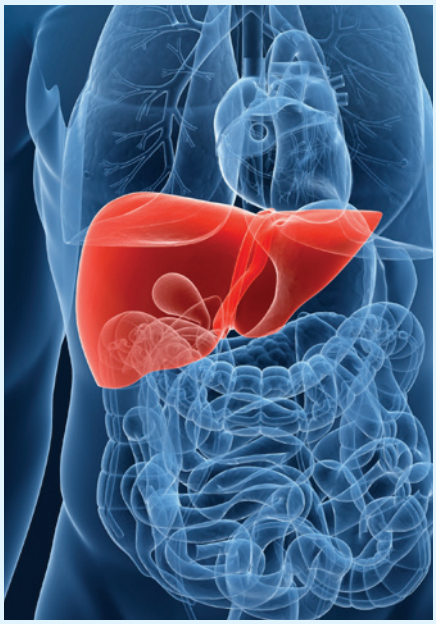
Comprehensive Care of Transgender and Gender Nonconforming Patients
Presented by Ronald Codario, MD

Metabolic Liver Disease *(Continued from Page 3)*

in collaboration with clinical endocrinology fellow Ramya Undamatla, MD, are currently testing the hypothesis that reduced hepatic mitophagy is a specific feature of NAFLD that marks the transition from benign steatosis to NASH. While previous work in this area demonstrated that reduced mitophagy is associated with NAFL, these will be some of the first studies to determine the cause and effect relationship of liver fat content and changes in mitophagy flux. These studies are made possible in part by the recent development of genetic tools for monitoring rates of mitophagy in preclinical animal models[12] and directly modulating rates of mitophagy in the liver. If this hypothesis is confirmed, enhancing mitochondrial quality control by augmenting mitophagy in the liver could represent a novel target for NAFLD treatment. This new mode of therapy could conceivably complement current strategies undergoing testing in clinical trials that include targeting metabolic stress, inflammation and cell death, and fibrosis,[9] each of which touch upon distinct aspects of mitochondrial function and signaling. This research is but one of many research projects addressing metabolic/fatty liver disease being conducted in the Division of Endocrinology and Metabolism at the University of Pittsburgh.[15-19]

Nonalcoholic Fatty Liver Disease at UPMC

With the expanding epidemic of NAFLD and other complications of obesity, it is more necessary than ever to promote multidisciplinary collaborative approaches to understanding and treating metabolic liver disease. To achieve this goal, the Division of Endocrinology at the University of Pittsburgh contributes to both clinical and basic research efforts in this area. The Divisions of Endocrinology and Gastroenterology, Hepatology and



Nutrition have a multidisciplinary NAFLD clinic, led by Maja Stefanovic-Racic, MD, and Jaideep Behari, MD, respectively. This clinic provides comprehensive expertise in hepatology, as well as endocrinology, diabetes, metabolism, nutrition, lipidology, and obesity. In addition to the above clinical collaboration, the Pittsburgh Liver Research Center (PLRC) (**http://www.livercenter.pitt.edu/**) promotes collaboration between clinicians and researchers to improve the clinical care of patients with liver disease through innovative research into the fundamental mechanisms underlying these disorders. Led by Paul Monga, MD, from the Department of Pathology, and Ramon Bataller, MD, PhD, from the Division of Gastroenterology, Hepatology and Nutrition, the PLRC provides pilot grant funding to support innovative new projects related to liver disease, including the above-described project being conducted in Dr. Jurczak's laboratory. Together, these activities provide a rich environment for research, education, and clinical care to address NAFLD and other metabolic disorders.

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X-Linked Hypophosphatemia *(Continued from Page 7)*

time of diagnosis often include the following: low serum phosphorus with high urinary phosphorus excretion; elevated FGF23; normal serum calcium, 25-hydroxy vitamin D and PTH levels; elevated alkaline phosphatase; and absence of the normally expected rise in the concentration of 1,25-dihydroxy vitamin D in response to the low serum phosphate.[7] In addition, the diagnosis can often be confirmed with genetic testing for PHEX gene mutations, which account for up to 87 percent of cases.[13] It is important to note, however, that a PHEX gene mutation cannot be identified in all patients. Novel mutations in the PHEX gene are still being identified, including 14 new mutations that were reported in a cohort of 59 adults with XLH in 2017.[14] This could explain the negative genetic testing in this patient in 2010 and can be confirmed with whole genome sequencing.

Most children with XLH are treated with oral phosphorus supplements and 1,25 vitamin D from initial diagnosis until growth is complete.[7] Initiation of treatment in early infancy results in improved patient outcomes but does not completely normalize skeletal development or fully correct the metabolic abnormalities.[9] The response to treatment is often variable.

Osteomalacia and spontaneous insufficiency fractures should trigger treatment in adults. Treatment with calcitriol and phosphate supplements decreases bone pain, increases serum phosphorus, and reduces osteomalacia as quantified by bone biopsies.[10] Long-term complications with standard therapy in both children and adults include hyperphosphaturia with nephrocalcinosis and secondary hyperparathyroidism.[7] Treatment with calcitriol and phosphorus requires frequent monitoring and dose adjustments to minimize complications.

As exemplified in this case, a transformative therapy for patients suffering from XLH was approved by the FDA in April 2018. Burosumab/KRN23 (Crysvita), a human monoclonal antibody to FGF23, is the first therapy for X-linked hypophosphatemia that specifically targets the underlying causative mechanism. Studies in adults have demonstrated that subcutaneous administration of KRN23 every four weeks for 16 months increases serum phosphorus levels to the low normal range in 94 percent of subjects and increases 1,25(OH)2D from baseline in all subjects, consistent with inhibition of FGF23 activity.[11] In children, treatment with burosumab administered once every two weeks provides a sustained increase in serum phosphorus levels to normal or near-normal levels.[12] In addition, studies in both adults and children have revealed improved healing of fractures and pseudo-fractures, as well as improvement in osteomalacia on bone biopsy. Adults also report substantially improved quality of life. Current recommendations for dosing are 0.8 mg/kg every 14 days for children and adolescents and 1 mg/kg every 28 days for adults. The maximum dose is 90 mg for children and adults. All phosphorus and 1,25 vitamin D supplements must be discontinued one week before beginning burosumab with close monitoring for hyperphosphatemia during treatment.

Conclusion

In summary, we describe a patient with XLH with multiple bone and metabolic complications who recently commenced treatment with burosumab/KRN23 (Crysvita), a new FDA-approved human monoclonal antibody to FGF23. This treatment allowed her to maintain desired serum phosphorus and 1,25 dihydroxy vitamin D levels without calcitriol and phosphorus supplementation, and has resulted in improved quality of life. This therapy is still relatively new, and while it corrects hypophosphatemia it does not treat secondary complications of this disease that are present prior to beginning treatment. This patient's serum calcium has increased slightly, which is not unexpected, with the decrease in FGF23 inhibition of 1,25 D activation. In her case, this also likely reflects her tertiary hyperparathyroidism and discontinuation of her cinacalcet. Nevertheless, burosumab/KRN23 (Crysvita) represents an exciting new drug in the armamentarium to treat this rare and devastating disorder. The hope is that early treatment of XLH with this targeted, mechanism-based therapy will reduce long-term complications while improving the quality of life in patients with XLH.

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Open Faculty Positions

Director, Multidisciplinary Thyroid Center (MTC). The Division of Endocrinology and Metabolism at the University of Pittsburgh (Pitt) and its affiliated medical center (UPMC) seeks an MD or MD/PhD board-certified endocrinologist for a full-time academic faculty position as the Director of its Multidisciplinary Thyroid Center (MTC). The successful candidates should have leadership experience, strong academic expertise in thyroidology/thyroid cancer, and a desire to participate in all aspects of the academic mission (clinical care, education, and scholarly work). *Candidates with research experience/interests/qualifications and potential for external funding are highly desirable. Interested candidates should send a cover letter, curriculum vitae, and contact information for three references to Erin E. Kershaw, MD, Chief of Endocrinology, care of Chelsea Dempsey (email: cad183@pitt.edu). EEO/AA/M/F/Vets/Disabled*

Academic Clinical Endocrinologists. The Division of Endocrinology at the University of Pittsburgh Medical Center (UPMC) seeks full-time BC/BE Endocrinologists to join our premier, academic, high-volume outpatient and inpatient practices. Our nationally ranked Endocrinology program provides a diverse patient mix and substantial opportunity for academic and career growth. Successful candidates will have a strong foundation in endocrinology and diabetes and a desire to participate in all aspects of the academic mission (clinical care, education, and scholarly work). *Candidates with an interest in telehealth are particularly desirable to help grow our expanding telehealth program. Interested candidates should send a cover letter, curriculum vitae, and contact information for three references to Erin E. Kershaw, MD, Chief of Endocrinology, care of Chelsea Dempsey (email: cad183@pitt.edu). EEO/AA/M/F/Vets/Disabled*

Academic Research Faculty. The Division of Endocrinology and Metabolism at the University of Pittsburgh seeks MD, MD/PhD, or PhD scientists for full-time, tenure stream, academic faculty positions (Assistant to Full Professor) in the fields of obesity, diabetes, metabolism, nutrition, and/or metabolic disease prevention. All types of research in these areas will be considered (basic, translational, clinical, epidemiological, health outcomes). *Physician-scientists and candidates with cross/multidisciplinary research programs are particularly desirable. Successful candidates will have a history of academic research scholarship, a strong publication record, and a demonstrated capacity to secure external research funding. Interested candidates should send a cover letter, curriculum vitae, and contact information for three references to Erin E. Kershaw, MD, Chief of Endocrinology, care of Chelsea Dempsey (email: cad183@pitt.edu). EEO/AA/M/F/Vets/Disabled*

Hypogonadism

(Continued from Page 5)

Given the myriad reports on this topic with variable results, it is also the duty of the endocrine specialist to critically evaluate the data to the best of our ability in order to be able to honestly communicate to our patients the controversies and uncertainties that exist. Attending to our patients' expectations in relationship to TRT is critically important given the commercial initiatives bombarding them with the promise of a potential "fountain of youth." Patients and health care providers need to understand that diagnosing hypogonadism is not the end of the story; rather, it may be an indication of an underlying causative disease such as a pituitary or genetic issue which has farther reaching implications. Those with advanced training in endocrinology need to help others appreciate that TRT is not a benign treatment. Even putting aside controversies when it comes to the association of TRT and vascular outcomes, DEA licensing is required for prescribing TRT, and there is potential for requirement of long-term and possibly even lifetime therapy. Given this, we as health care providers need to model prescription appropriateness as this is currently the simplest and most efficacious method[1] to challenge the complex environment enveloping TRT.

Our clinic is proud to foster an environment of health care providers who are unafraid to tackle a controversial and rapidly shifting area of medicine such as hypogonadism. We pride ourselves on being an advocate for our patients as well as a resource and example to the medical community by our adherence to available clinical practice guidelines, and contributing to ongoing investigations to improve the understanding and treatment of hypogonadism.

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Department News

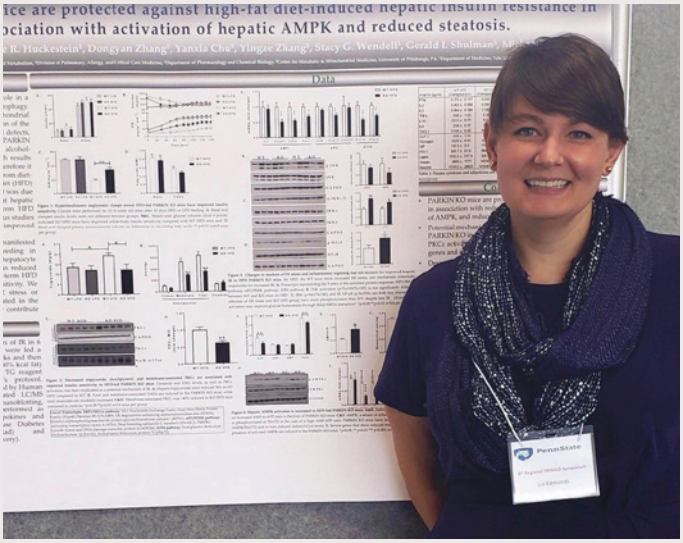
Awards and Accomplishments

Mary Korytkowski, MD, was selected as one of the Exceptional Women in Medicine 2018 by Castle Connolly Medical LTD.

Mara Horwitz, MD, Mary Korytkowski, MD, and Susan Greenspan, MD, were selected as 2018 Top Doctors by Castle Connolly Medical LTD.

Sue Challinor, MD, Mary Korytkowski, MD, and Susan Greenspan, MD, were selected as *Pittsburgh Magazine's* "Best Doctors."

Dan Harmon, PhD, postdoctoral associate, under the mentorship of Robert O'Doherty, PhD, received the 2018 Society for Redox Biology and Medicine Young Investigator Award for his work titled "Hepatocyte-Specific Ablation or Whole-Body Inhibition of Xanthine Oxidoreductase in Mice Corrects Obesity-Induced Hyperuricemia Without Improving Metabolic Abnormalities."

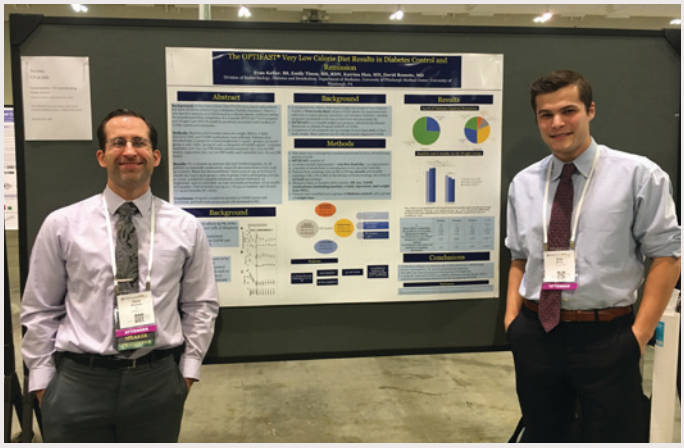


Lia Edmunds, PhD, F32-funded postdoctoral associate, under the mentorship of Michael Jurczak, PhD, presented a collaborative poster titled "PARKIN KO mice are protected against high-fat diet-induced hepatic insulin resistance in association with activation of hepatic AMPK and reduced steatosis" at the Translational Research on Mitochondria, Metabolism, Aging, and Disease Symposium (TRiMAD) at Penn State, State College, Pennsylvania, in September 2018. Dr. Edmunds has recently received a Postdoctoral Fellowship Award from the American Diabetes Association to further pursue her research.

Ruya Liu, MD, PhD, instructor of medicine, received the 2018 Basic Cardiovascular Sciences Abstract Travel Grant offered by the American Heart Association's Council on Basic Cardiovascular Sciences for the American Heart Association Annual Sessions in Chicago, IL in November 2018.

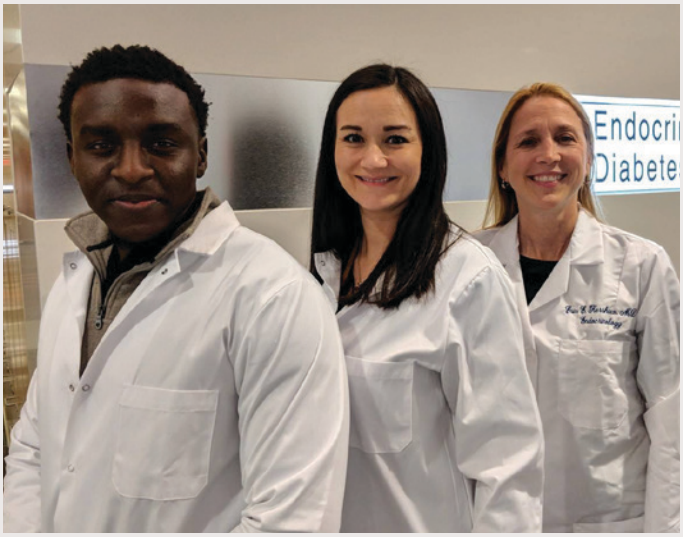
Samina Afreen, MD, clinical fellow, was awarded a travel grant to attend Obesity Week in Nashville, TN in November 2018.

Sann Mon, MD, and the UPMC McKeesport Endocrine Division was awarded the 2018 UPMC Excellence in Patient Experience Award.



David Rometo, MD, (above left) presented multiple posters with his research team at Obesity Week in Nashville, TN, in November 2018. His team included **Evan Keller**, T32-funded medical student (above right), Emily Timm, MS, clinical metabolic programs coordinator, and Katrina Han, MD, medical student.

Anna Meyer, undergraduate at Allegheny College, received an Endocrine Society Summer Undergraduate Research Program (SURP) Award under the guidance of her mentor Erin Kershaw, MD.



University of Pittsburgh undergraduate **Akeem Williams** (left), received a 2019 American Diabetes Association Minority Undergraduate Internship for his work with mentors **Krystle Frahm, PhD**, (middle), and **Erin Kershaw, MD** (right).

ADA Save the Date: June 7–11, 2019

The UPMC Division of Endocrinology and Metabolism will be hosting their annual Alumni and Friends Reception at the 79th American Diabetes Association Scientific Sessions in San Francisco, California (June 7-11, 2019). The reception will be held on the evening of June 9. Stay tuned for more details or contact Chelsea Dempsey for further details (cad183@pitt.edu).

New Faculty

Milay Luis Lam, MD, received her medical degree at the Universidad Peruana Cayetano Heredia Facultad de Medicina Alberto Hurtado in Peru. She then completed her postgraduate training at Woodhull Medical Center at New York University School of Medicine and SUNY Downstate Medical Center. She currently holds the position of Chair Elect for 2018-2019 for the Clinical Management of Obesity Section for the Obesity Society. She also was selected recently to join the Endocrine Society's Trainee and Career Development Core Committee. She joined the Division of Endocrinology and Metabolism as a clinical assistant professor in March 2019.

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- Lipid Disorders
- Muscle Metabolism and Function
- Osteoporosis and Metabolic Bone Disorders
- Thyroid Cancer Molecular Diagnosis

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