

UPDATE IN ENDOCRINOLOGY



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Dear Colleagues,

We are pleased to share our latest edition of *Update in Endocrinology*! We finished out 2019 strong and are looking forward to many exciting endeavors in 2020! In this issue, we continue to highlight our contributions to the research, educational, clinical, and quality missions.

To highlight our research excellence, physician-scientist **Pouneh Fazeli, MD, MPH**, discusses ongoing research in regards to neuroendocrine adaptations and bone loss due to starvation. Dr. Fazeli recently has been awarded an R01 grant from the NICHD to continue research in this critical field.

On the clinical front, **Sann Mon, MD, MPH, FACE**, and **Linda Siminerio, RN, PhD, CDE**, discuss how a coordinated-care model was created to provide evidence-based care to patients in disadvantaged communities. Dr. Mon and her team have received awards for patient care based on this model, and Dr. Siminerio was recently awarded an R34 grant by the NIDDK to expand the current research literature on how collaborated-care models can better reach disadvantaged patients.

Diana Pinkhasova, MD, and clinical fellow **Vrushali Shah, MD**, discuss the Division's commitment to wellness. Wellness initiatives aim to create a work environment that prioritizes values and behaviors that promote personal and professional growth. Dr. Shah describes one such initiative that has been supported by a UPMC Physician Thrive grant that was awarded to Clinical Medical Director **Esra Karslioglu-French, MD**.

Complex cases continue to challenge our expertise and provide fellows with transformative lessons in clinical care. Clinical fellow **Hammam Alquadan, MD**, and his mentor, physician-scientist **Maja Stefanovic-Racic, MD, PhD**, present a clinical case that discusses the difficulties of treating paraganglioma in pregnancy. Dr. Alquadan was recently awarded an Endocrine Society Early Career Forum and Travel Award based on his poster submission of this case to the Endocrine Society Annual Meeting.

In addition, we also celebrate many of the accomplishments of our faculty and trainees. **Mary Korytkowski, MD**, was honored as one of Castle Connolly's Exceptional Women in Medicine 2019.

Our Division continues to grow as we welcome **Yong Wan, PhD**, to our research faculty. Dr. Wan's research focuses on understanding the molecular and cellular causes of aging-related bone disease, as well as the mitochondrial function involved in bone metabolism.

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

Best wishes,



Erin E. Kershaw, MD

Chief, Division of Endocrinology and Metabolism
University of Pittsburgh School of Medicine



Affiliated with the University of Pittsburgh School of Medicine, UPMC Presbyterian Shadyside is ranked among America's Best Hospitals by *U.S. News & World Report*.

UPMC LIFE CHANGING MEDICINE

Starvation: Friend or Foe?

Introduction

Our evolutionary past was punctuated by periods of famine. As a result, human physiology has developed a coordinated set of responses to survive these prolonged periods of low or no caloric intake. Understanding the neuroendocrine adaptations, which allow us to survive periods of starvation, is critical for at least three reasons: 1) famine is still an important health threat for a significant portion of the world's population; 2) studying the adaptations that allow us to survive periods of low or no caloric intake provides insight into normal human physiology; and 3) understanding the hormonal adaptations to starvation may inform potential therapeutic strategies for obesity, which plagues a significant portion of the developed world.

What Are the Neuroendocrine Adaptations to Starvation?

During periods of low caloric intake, energy utilization is shifted *away* from processes that are not critical for survival. Two of these processes are reproduction — which is important for the survival of our species but not critical for the survival of an individual — and IGF-1 dependent processes, which include maintenance of bone mass in adults. Therefore, hypogonadotropic hypogonadism (or functional hypothalamic amenorrhea in women) and growth hormone resistance are two neuroendocrine adaptations that help preserve energy in states of low nutrient intake (See Figure 1).

Hypogonadotropic Hypogonadism

Hypogonadotropic hypogonadism is a common finding in individuals who are expending more energy than they are consuming.

In premenopausal women, this is a common cause of amenorrhea — termed functional hypothalamic amenorrhea. In states of chronic undernutrition, hypogonadotropic hypogonadism is characterized by disrupted gonadotropin-releasing hormone pulsatility,¹ and low leptin levels likely mediate this. Levels of leptin, a hormone secreted primarily by subcutaneous adipose tissue, drop by approximately 50% within 24 hours of an acute fast² and women in a state of negative energy balance with functional hypothalamic amenorrhea have low leptin levels and decreased luteinizing hormone pulsatility. Treatment with recombinant human leptin in women with functional hypothalamic amenorrhea increases luteinizing hormone pulse frequency after two weeks of treatment, and ovulation and recovery of menses occur in a substantial portion of these women after three months of treatment.³ Therefore, low levels of leptin appear to be an important intermediary between nutrient stores/intake and the hypothalamic-pituitary-gonadal axis.

Growth Hormone Resistance

Growth hormone resistance is another neuroendocrine adaptation to starvation. Growth hormone (GH) has both growth-promoting effects, mediated in part by IGF-1, but also lipolytic and insulin-resistant actions, which likely help us maintain euglycemia during periods of fasting.⁴ Therefore, it is advantageous for GH levels to be normal or elevated during periods of caloric deprivation. In contrast, utilizing energy on growth during periods of starvation is not advantageous. In individuals with appropriate nutrient intake, GH stimulates IGF-1 production by the liver, whereas in states of undernutrition, GH levels are normal or even elevated, but IGF-1 levels are low — a state of growth hormone resistance.

In animal models, FGF21, a starvation-induced hormone, has been shown to be a mediator of GH resistance,⁵ and we have demonstrated an association between GH resistance and FGF21 in a human model of chronic starvation,⁶ but additional mediators of GH resistance in human starvation also likely exist.

Although both hypogonadotropic hypogonadism and GH resistance are critical for our survival during periods of low caloric intake, these adaptive responses have long-term negative consequences. Anorexia nervosa is a psychiatric disorder primarily affecting women, which is characterized by self-induced starvation. This disorder is prevalent in premenopausal women and serves as a human model of chronic starvation. Nearly 90% of women with anorexia nervosa have low bone mass, defined as bone mineral density values more than one standard deviation below those of normal-weight women of comparable age, and there is an increased rate of fracture in this population.⁷ Both the duration of amenorrhea⁸ and low IGF-1 levels⁹ are associated with low bone mineral density in women with anorexia nervosa, suggesting that functional hypothalamic amenorrhea and GH resistance have long-term negative effects on bone metabolism.

Dr. Fazeli's research program currently is investigating whether treatment with low-dose transdermal estrogen can improve bone mineral density in women with anorexia nervosa. Prior treatment studies investigating higher doses of oral estrogen, such as those found in oral contraceptive pills, have demonstrated no benefit with respect to bone mineral density in this population,¹⁰ but a study in adolescent girls with anorexia nervosa¹¹ and a pilot study conducted in adult women with anorexia nervosa¹² suggest that lower doses of transdermal estrogen may be beneficial.



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Are There Any Potential Benefits of Starvation?

With recent studies suggesting the metabolic benefits of intermittent fasting, the question arose whether a brief period of starvation would have metabolic benefits in normal and overweight individuals. In collaboration with **Matthew Steinhauser, MD**, of the Aging Institute and Division of Cardiology at the University of Pittsburgh School of Medicine, we conducted a 10-day zero-calorie fast in healthy, normal, and overweight individuals.^{2,13} Subjects were admitted to the Clinical Research Center for 10 days and were administered a multivitamin and 20 mEq of potassium chloride daily and were permitted to drink water ad-lib. Subjects, who lost between 7% and 11.7% of their initial body weight, tolerated the fast remarkably well with only two of the 12 subjects self-discontinuing the study protocol.² We performed plasma metabolite profiling in these subjects and, not surprisingly, we found a shift in circulating metabolites over the course of the fast. What was unexpected was that we found a preferential shift towards triglycerides with a higher carbon content and with a greater number of double-bonds during the fast, and this metabolite profile persisted even after one day of refeeding.²

This particular metabolite profile has been shown to be associated with a lower risk of diabetes mellitus using longitudinal data from the Framingham Heart Study,¹⁴ suggesting that there may be a potential metabolic benefit to an acute period of prolonged fasting.

Conclusions

Humans have evolved with a number of neuroendocrine adaptations that are critical for survival during periods of low or no caloric intake. Two of these adaptations, hypogonadotropic hypogonadism and growth hormone resistance, reduce energy expenditure during periods of starvation but are also associated with low bone mass and an increased risk of fracture long term. In contrast, in normal and overweight individuals, an acute 10-day fast is associated with a beneficial metabolic profile. Therefore, further study is necessary to better delineate both the beneficial and detrimental effects of starvation.

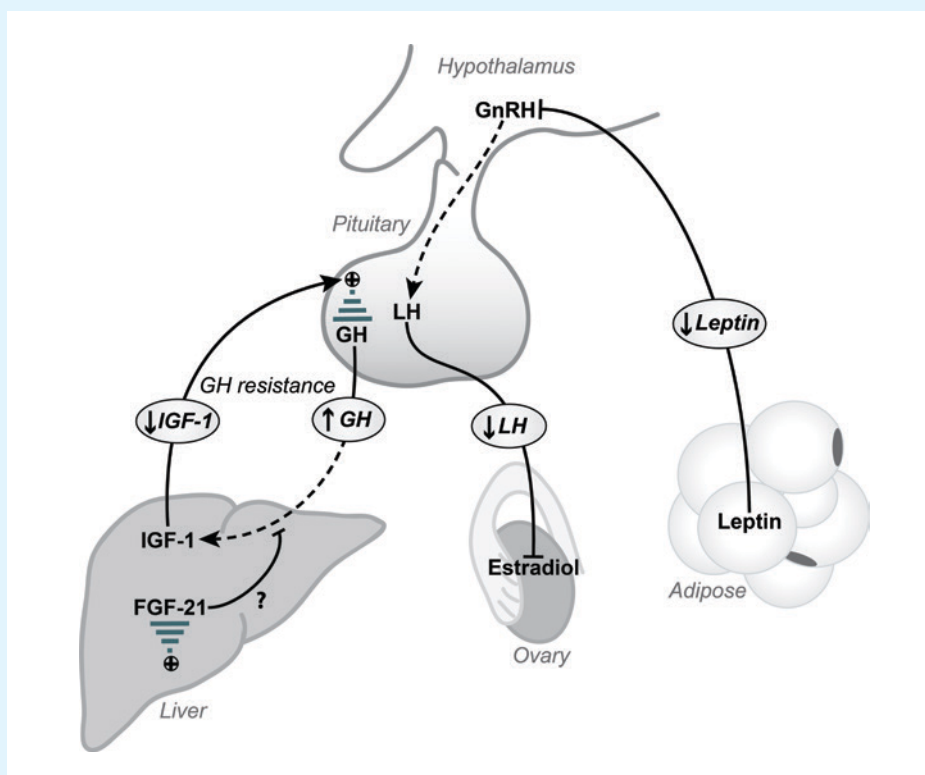


Figure 1. Hypogonadotropic hypogonadism and growth hormone (GH) resistance are two neuroendocrine adaptations to starvation. **Hypogonadotropic hypogonadism:** Low leptin levels are likely a mediator of disrupted gonadotropin-releasing hormone (GnRH) pulsatility resulting in low estrogen levels. **GH resistance:** GH levels are normal or even elevated in states of starvation, but IGF-1 levels are low; this disruption in GH signaling may, in part, be mediated by fibroblast growth factor (FGF)21. LH = luteinizing hormone.

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Meeting the Challenges of Diabetes Care in a Disadvantaged Community

The Impact of Income and Socioeconomic Status on Diabetes Care

Low income is associated with a higher prevalence of diabetes and diabetes-related complications.¹ Additionally, several studies have shown that mortality risk is higher among people with low socioeconomic status (SES) and diabetes as compared to those with higher SES and diabetes.^{2,3} Glycemic management can be very challenging for patients with low SES for several reasons, including the financial burden of increased health care costs and insufficient access to necessary resources to manage the condition (i.e., adequate housing, nutritious food, and health care services), as well as relatively limited educational attainment.⁴ Of these challenges, limited finances is often the most prevalent challenge for patients residing in disadvantaged communities. Health care costs for patients with diabetes can be 2.3 times higher than those without the disease,⁵ and these costs continue to escalate. For example, the cost of insulin has increased significantly over the years, from \$100 to \$200 per month to \$400 to \$500 per month, depending on the brand.⁶ Out-of-pocket costs for

medications, regimen complexity, and convenience in accessing medications represent some of the many barriers for patients in adhering to taking glucose-lowering agents.^{7,8}

Poor glycemic control can also be influenced by factors that are not directly limited to patients' circumstances. Patients with low SES living in disadvantaged communities are less likely to receive diabetes care that meets evidence-based standards⁹⁻¹¹ and have fewer opportunities to meet target treatment goals.¹² Reports also have shown that providers are less likely to perceive patients with low SES as being independent, knowledgeable, responsible, adherent to medical advice and follow-up visits, and willing to pursue healthier lifestyles and behaviors.¹³⁻¹⁵ These perceptions can influence provider-patient communication and jeopardize patients' ability to receive and adhere to appropriate medical advice, leading to poorer outcomes.¹⁶

Attention to these issues is critically important and, if neglected, can dramatically influence the ability to achieve and sustain glycemic control. Team care and diabetes self-management education and support

repeatedly have been shown to be effective in addressing these problems; however, implementing these services requires resources, time, and expertise.¹⁷ Although it may seem that these barriers are insurmountable, delivering quality health care to patients in a low SES community can be a unique and rewarding experience. To succeed, health care providers need to 1) be prepared to recognize and appreciate the socioeconomic challenges; 2) identify barriers to the specific patient population being treated; and 3) explore partnerships and community-based solutions for success.

Developing a Model for Chronic Care of Diabetes in a Disadvantaged Community

The Division of Endocrinology and Metabolism has acknowledged this need for evidence-based care for patients residing in low SES communities. In order to expand our services to those in disadvantaged communities, a community-based diabetes clinic was formed within a disadvantaged urban area in the greater Pittsburgh area.



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The community was a former home to the steel industry but became a victim of industrial downsizing, with increased rates of unemployment and a subsequent out-migration of younger and more affluent members of the community. These factors encumbered the community with older, sicker, and more socioeconomically challenged individuals. Academic training at major medical centers does not always fully prepare physicians to provide the necessary care for patients with these complex needs.

The UPMC multidisciplinary diabetes care team has extensive experience in implementing innovative strategies to improve diabetes care in a variety of clinical and community-based settings. These strategies expand the scope and reach of the traditional 1:1 patient-provider interaction and instead emphasize practice redesign, coordinated team-based care, patient self-management, and patient/provider education and support. These approaches also engage the community and leverage local (as well as more distant) resources to optimize clinical outcomes, even in the most challenging settings. In addition, the UPMC diabetes care team has a strong record of aligning these “real-world” approaches with academic expertise to demonstrate the effectiveness of these approaches to diabetes care in community practices.¹⁸⁻²⁰ UPMC is dedicated to serving the needs of the entire community, with disadvantaged communities often posing the greatest challenges. Recognizing these needs, the UPMC diabetes team launched a specific initiative to understand and improve diabetes care in disadvantaged communities in the Pittsburgh area. The hope is that knowledge gained from projects like this will be more broadly transferrable to similar communities across the nation.

To lead this charge, UPMC recruited endocrinologist **Sann Mon, MD, MPH, FACE**, to design and implement a diabetes care model to improve diabetes outcomes in disadvantaged communities with a high prevalence of diabetes and its complications. Dr. Mon grew up in Myanmar and completed her initial medical training at the Institute of Medicine in Yangon Myanmar before emigrating to the United States for additional medical training.



She first completed her Master’s in Public Health (MPH) in Community Health Science at Harvard Medical School, followed by her residency in internal medicine at the Cleveland Clinic and then a fellowship in endocrinology at UPMC. Thus, she has knowledge and experience in meeting health care delivery challenges in different settings. In addition, Dr. Mon is certified in

endocrinology, diabetes, and metabolism by the American Board of Internal Medicine (ABIM), as well as obesity medicine by the American Board of Obesity Medicine (ABOM), making her particularly well suited to tackle these complex chronic diseases.

(Continued on Page 6)

Table 1. Baseline Characteristics and HbA1C at Baseline and at 3, 6, and 12 Month Intervals.

	Total	Diabetes Coordinated Care (DCC)	Usual Care (UC)	p-Value
N	80	49	31	
Age, years	57.1 ± 14.1	57.0 ± 13.9	57.1 ± 14.7	0.99
Female, %	52.5	57.1	45.2	0.42
BMI, kg/m ²	34.1 ± 10.4	33.5 ± 9.9	34.9 ± 11.3	0.56
Type 2 diabetes, %	80	71.4	93.5	0.05
HbA1C at baseline, %	9.2 ± 2.0	8.9 ± 1.6	9.6 ± 2.6	0.23
Change in HbA1C at 3 months from baseline		-1.5 ± 0.2 [▲]	-0.9 ± 0.4 [▲]	0.45
Change in HbA1C at 6 months from baseline		-1.1 ± 0.4 [▲]	-0.6 ± 0.6 [▲]	0.21
Change in HbA1C at 12 months from baseline		-1.6 ± 0.3 [▲]	-0.2 ± 0.4 [▲]	0.004*

Data is represented by mean ± Standard Deviation unless otherwise specified by ▲

▲Data is represented by mean ± Standard Error

Diabetes Care (Continued from Page 5)

Dr. Mon initially focused on the foundational elements of building a strong and committed multidisciplinary team and forging key partnerships with hospital and community leaders. A critical member of this diabetes chronic care team was a UPMC hospital-based certified diabetes educator (CDE), **Carla DeJesus, MS, RD, LDN, CDE**, who was already an experienced member of the hospital community and was, therefore, familiar with the many challenges that patients face in this underserved region. The next key element was forming strategic collaborations with local hospital administrators who understood the mission/goals and could facilitate important elements of success, including providing financial support and protected time for the CDE to partner with Dr. Mon, ensuring dedicated space and resources to conduct care and implement initiatives, and advocating for the program when appropriate. This partnership allowed Dr. Mon and the CDE to provide complementary, mutually reinforcing care and education to patients and increased the opportunity and time to address behavioral and psychosocial barriers to care.

The CDE was able to provide the support that the physician was unable to offer given other clinical and teaching responsibilities. Since ongoing support has been shown to be effective with sustained improvement

in glycemic outcomes,²⁰ patients were encouraged to schedule appointments with the CDE in between routine diabetes clinic visits. These follow-up visits opened opportunities for ongoing counseling, behavior modifications, and reinforcement that we believed helped to improve glycemic outcomes in this unique population. In addition, blood glucose readings were uploaded at each CDE visit for review and feedback. Treatment plans and medication adjustments were made in collaboration by the endocrinologist and the CDE. The immediate clinical goal was to reduce HbA1C levels to below 8%.

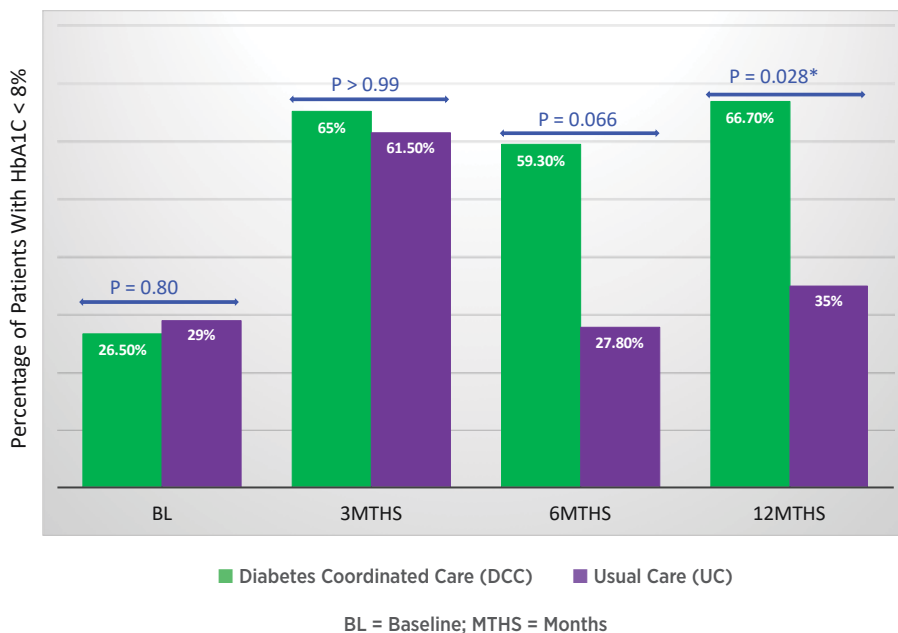
Already familiar with the area and community resources, the CDE helped to develop strong relationships among local primary care physicians, specialists, hospital staff, pharmacists, and social workers. While informed of therapy costs, the CDE was able to maintain up-to-date information on assistance programs that are supported through local foundations, industry, and government agencies. In addition, a nurse coordinator assigned to the clinic helped patients prepare their applications for medication assistance programs. The CDE and nurse coordinator, with their longstanding experience and relationship with the community, assumed responsibilities otherwise performed by a social worker.

The Diabetes Coordinated Care Program

The specialized, team-based clinic that includes an endocrinologist, CDE, and nurse coordinator is now referred to as the Diabetes Coordinated Care program (DCC). Among a total of 80 patients who have attended the general diabetes clinic, 49 agreed to participate in the DCC program while 31 patients received usual care (UC) (traditional 1:1 visit with the endocrinologist). Comparison of the CC and UC patient characteristics and changes in A1C levels from baseline to 3, 6, and 12 months are presented in Table 1 on Page 5. The mean age of the 80 patients seen at the diabetes clinic from July 1, 2017 to June 30, 2018 was 57.1 years, with 52.5% being female. The majority of the patients presented with type 2 diabetes (80%), had a mean BMI of 34.1 kg/m², and an HbA1C of 9.2%. No statistical differences were found in sex, age, BMI, diabetes type, or mean HbA1C between the DCC and UC groups at baseline. The percentage of patients with HbA1Cs < 8% were compared between the groups and presented in Figure 1. The majority of patients in the DCC group maintained lower HbA1C levels, meeting our immediate target of < 8%, while the UC group experienced a consistent rise in HbA1C over the course of the intervention. At 12 months, the DCC group experienced a significant improvement in HbA1C ($p = 0.028$) as compared to the UC group. Due to the coordinated care model that relied on a team-based approach, the relative influence of the team members' efforts is hard to discern. It appears though that both the endocrinologist and the CDE continued to drive and support the sustained improvement in glycemia.

The ability to demonstrate sustained glycemic improvements through our coordinated care model in this challenging community has contributed to ongoing community and organizational support for this important program. UPMC recognized these efforts and presented our team with the *UPMC 2018 Excellence in Patient Experience Award*.

Figure 1. Percent of Patients With HbA1C < 8% Diabetes Coordinated Care (DCC) as Compared to Usual Care (UC).



The Division of Endocrinology and Metabolism and the associated Diabetes Coordinated Care team at UPMC recognizes the tremendous need for more multidisciplinary, coordinated care of complex diseases such as diabetes. Such models of care have become increasingly important as the prevalence of diabetes continues to rise simultaneously with the need to move towards more effective value-based models of care. The above model is particularly important for targeting care specifically to patients and communities that have the greatest need and most daunting challenges.

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Our Commitment to Physician Well-Being: The Wellness Initiative

"In the midst of winter, I found there was, within me, an invincible summer. And that makes me happy. For it says that no matter how hard the world pushes against me, within me, there is something stronger — something better, pushing right back."

Albert Camus

Introduction

Resilience is a quality that is innate to physicians; however, in this era of "time poverty", "multiple hat" syndrome, and increasing expectations, this innate resilience is being challenged. In 1974, Herbert Freudenberger, a German-born American psychologist, described burnout as a state of fatigue or frustration that results from the failure of professional relationships to produce expected rewards. His writing goes on to state that burnout occurs more often in professionals who can be described as having stronger commitments and dedication to the work they do! These observations suggest that many physicians are at high risk for burnout.

Various definitions of burnout have been proposed since the introduction of the construct in the 1970s. Until recently, burnout had been called "stress syndrome." The World Health Organization includes burnout as an

occupational phenomenon in the International Classification of Diseases-11 (ICD 11).² According to the most widely endorsed of these definitions, burnout combines emotional exhaustion, depersonalization, and a sense of reduced personal accomplishment, evolving from prolonged exposure to chronic interpersonal stressors in the workplace. The significance of this three-dimensional model is that it clearly places the individual's experience with stress within a social context and involves a person's conception of both self and others.³

There is increasing attention being paid to the experience of burnout among physicians. An estimated 300 to 400 physicians commit suicide each year with a rate of 28 to 40 per 100,000, which is more than double that of the general population.⁴ On a national scale, the conservative base-case model describes significant negative economic consequences associated with physician burnout. The majority of these costs, estimated at \$7,600 per employed physician per year, are attributed to physician turnover and reductions in clinical hours.⁵

Although the practice of endocrinology is often perceived as offering a good work-life balance to those physicians choosing this subspecialty, endocrinologists are highly susceptible to the experience of burnout. The 2020 Medscape National Physician Burnout and Suicide Report provides evidence that endocrinology is among the top five medical specialties affected by burnout.⁶ Almost half (46%) of all diabetologists and endocrinologists report symptoms consistent with burnout.

Major contributors to physician burnout that have been described include excessive bureaucratic tasks (charting, paperwork, etc.), insufficient compensation or reimbursement for time spent with patients, and the increasing presence of computers with mandatory fields in electronic medical records.⁷

An internal survey conducted among endocrinologists providing care in one of the UPMC outpatient clinical centers found a higher rate of career satisfaction and lower level of burnout than the national average. The focus of this survey was on how diabetes technology and clinic workflow affected provider well-being. Despite the favorable survey findings, a considerable number of providers reported fatigue with technology and workflow processes, describing that this interfered with the time spent with patients.

Creating a Culture of Physician Well-Being at UPMC

At UPMC, there is recognition of the fact that physicians are at risk for burnout, which has led to the development of structured training programs that support wellness initiatives and promote well-being. The UPMC Office of Graduate Medical Education has formed the Wellness, Environment, Learning, and Living (WELL) Committee that focuses on burnout among the community of residents and fellows. UPMC also collaborates with a national Physician Wellness Academic Consortium (PWAC) to monitor progress in this area with an annual wellness survey. Grant funding also is available for innovative



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approaches in this area. The UPMC Division of Endocrinology and Metabolism recently received funding from one such grant opportunity, the "UPMC Thrive Grants for Change."

UPMC hosted a Physician Thrive and Well-being Symposium in January 2020. This symposium was planned by physicians from throughout UPMC. The Physician Thrive and Well-being Symposium provided the opportunity for physicians to attend lectures on a range of topics, including diversity of all kinds, and its relationship to wellness. Tips and techniques for creating systemwide change also were presented. Workshops were conducted on guided meditations, healthy cooking, and personal financial planning to provide physicians with information related to well-being outside of their careers. Together, these workshops and presentations educated and encouraged physicians to create a culture of well-being both at work and at home.

UPMC is one of 22 U.S. health care organizations honored by the American Medical Association (AMA) in 2019 for their commitment to physician well-being. The UPMC Physician Thrive Committee, formed in 2018, develops strategies to address workplace factors that promote well-being or contribute to burnout. Additional support resources for physicians dealing with stress management include The Physician Assistance Program; Physicians for Physicians; health coaches; and the UPMC Critical Incident Stress Management (CISM) ASAP (as soon as possible) Program.

Building Upon a Culture of Wellness

Although the rates of burnout and career satisfaction were better at UPMC than the national average, faculty leaders in the UPMC Division of Endocrinology and Metabolism recognize the adverse impact burnout can have on physicians when it is not recognized or addressed. To expand on the current UPMC wellness initiative, the UPMC Division of Endocrinology and Metabolism has proposed a Wellness Initiative with an aim to create an organizational work environment that promotes values and behaviors to encourage self-care, personal and professional growth, and compassion for our colleagues, patients, and ourselves.

This Wellness Initiative is inspired by the Steps-Forward program sponsored by the AMA, and the Collaborative for Healing and Renewal in Medicine (CHARM), sponsored by the Alliance for Academic Internal Medicine (AAIM). With the support of divisional and departmental leadership, **Diana Pinkhasova, MD**, clinical assistant professor of medicine, is serving as the Endocrine Division Wellness Representative. **Vrushali Shah, MD**, one of the current chief clinical fellows, is serving as the Endocrine Fellowship Wellness Representative. These Endocrine Division Wellness leaders have joined other wellness leaders across all of the divisions and departments at UPMC to promote change that works toward the goal of a culture of wellness throughout the UPMC health system and beyond.

"Wellness is an active process through which people become aware of, and make choices toward, a more successful existence."

*National Wellness Institute —
Dr. Bill Hettler (co-founder of the
National Wellness Institute)*

The "UPMC Thrive Grants for Change" awarded to the Division of Endocrinology is being used to support system changes that will improve efficiency and workflow in the clinical centers. One example has been the successful installation of Tidepool®, a software that allows clinic staff to download more than 40 different devices (e.g., insulin pumps, glucometers, sensors) used for the patient population with diabetes. Tidepool encourages patients to take a proactive role in their health care by uploading diabetes-related data before their scheduled appointment in the UPMC Center for Diabetes and Endocrinology. Having the data available for review affords additional time for physicians and patients to discuss their clinical care and concerns.

The Wellness Initiative also is designed to meet the needs of fellows and faculty, embracing them in the culture of facilitating well-being within their place of work. The clinical fellowship program in the UPMC Division of Endocrinology and Metabolism is one of the largest programs in the country,

with five clinical fellows per year. In 2019, the Division decided to assign chief fellows to serve not only as a liaison between the fellows and the faculty but to serve as an initial point of contact and buffer to enhance efficiency and sensitivity in addressing fellow concerns. Each incoming fellow is paired with a senior fellow and faculty advisor to help adjust to new work and home environments in the scope of professional wellness.

The engagement of certified registered nurse practitioners (CRNP) on the inpatient endocrine weekend rounding schedule has led to a reduction in the number of weekend hours for fellows during their inpatient rotations. This has led to improved occupational and social well-being among the fellows in training. The introduction of flexibility in the timing of conference presentations for fellows also has contributed to an improved sense of well-being as they now can plan their preparation time when it fits best within their overall academic and clinical responsibilities.

To monitor the progress of the Wellness Initiative, we plan to conduct annual internal surveys regarding the implemented changes. The annual UPMC Physician Well-being Survey will aid in monitoring the progress of the initiative. While several changes have been put in place, the goal of the Wellness Initiative is to continuously improve upon these interventions as we identify additional opportunities for improvement.

With continued commitment and dedication, the mission of the Wellness Initiative is to deliberately and thoughtfully prevent and reduce the level of burnout, achieve a well-integrated work-life model, and enhance the overall wellness and satisfaction of all employees.

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A Case of Paraganglioma in Pregnancy

Case Presentation

A 28-year-old Asian female presented during pregnancy with elevated, difficult to control blood pressure (BP), leading to an induced delivery of a preterm 32-week-old infant. The infant was admitted to the neonatal intensive care unit (NICU), where she was hospitalized for three weeks with eventual discharge to home in good health.

A few weeks following the delivery, the patient (the mother) was evaluated in the endocrine clinic. She reported a history of episodic pulsatile headaches, palpitations, and excessive sweating for the past year. Each episode lasted approximately 10 minutes and resolved spontaneously. Her systolic blood pressure (SBP) was elevated during these episodes (200 mm/Hg) and would subsequently return to normal following the episode. Antihypertensive treatment was not started during or following the pregnancy.

There was no history of prior hospitalizations or surgeries. She never used cigarettes. The patient reported that her mother had died suddenly in her 30s from an unknown cause. The patient's physical exam was unremarkable at the time of her endocrine evaluation. Her BP was 105/76 at the time of her visit.

An evaluation for secondary causes of hypertension was initiated. Thyroid function studies, aldosterone, plasma renin activity, adrenocorticotropic hormone, and cortisol levels all were within normal limits. Plasma and urine metanephrines and normetanephrines were elevated (Table 1). Chromogranin A also was elevated.

Table 1. Laboratory Results

Test	Lab Value	Normal Range
Plasma Metanephrine	327 pg/mL	< 57 pg/mL
Plasma Normetanephrine	7135 pg/mL	< 148 pg/mL
24-hour Urine Fractionated Metanephrine	81 mcg/24h	94-604 mcg/24h
24-hour Urine Fractionated Normetanephrine	10,092 mcg/24h	25-222 mcg/24h
24-hour Urine Total Fractionated Metanephrines	10,173 mcg/24h	40-412 mcg/24h
Chromogranin A	768 ng/mL	< 93 ng/mL

A computed tomography (CT) scan of the chest, abdomen, and pelvis demonstrated a large right retroperitoneal, heterogeneously enhancing mass, measuring 5.8 x 3.7 x 8.3 cm, which encircled the aorta approximately 180 degrees. There was no evidence of vascular invasion (Figure 1).

In preparation for surgical excision of this mass, treatment with diltiazem 60/30/60 mg three times a day was initiated for preoperative BP control. Two weeks after diltiazem initiation, the patient underwent laparoscopic resection of the tumor. Surgical pathology showed a 6.8 cm mass with lesional cells that were positive for synaptophysin and chromogranin. Staining was negative for AE1/3 and sustentacular cells that were highlighted by S100. These results were consistent with a diagnosis of paraganglioma.

Postoperatively, the patient was weaned from antihypertensive medications for two weeks. She did not experience postoperative pain. Two weeks after surgery, repeat plasma metanephrines were 26 pg/mL and normetanephrines 164 pg/mL.

The patient agreed to proceed with genetic testing in the UPMC Endocrine Genetics Clinic to determine a potential hereditary cause for the development of paragangliomas and pheochromocytomas. This panel included testing for mutations in the *SDHx* genes, Von Hippel-Lindau syndrome (VHL), Multiple Endocrine Neoplasia type 1 (MEN1), Multiple Endocrine Neoplasia type 2 (MEN2), and neurofibromatosis type 1 (NF1).

The genetic testing was positive for a pathogenic heterozygous mutation (deletion



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of Exon 1) of the SDHB gene, which is associated with autosomal dominant pheochromocytoma-paranglioma syndrome. Due to these results, genetic testing is planned for family members, including the patient's daughter and sister.

Discussion

The finding of a paraganglioma or pheochromocytoma (PGL/PHEO) during pregnancy is a rare diagnosis. The prevalence is reported to be less than one case in 50,000 full-term pregnancies.¹ In approximately 20% of the cases, the diagnosis is made during the postpartum period, increasing the risk of potentially unfavorable pregnancy outcomes. Timely diagnosis decreases the maternal mortality rate from 40% to 5% and fetal mortality rate from 50% to 15%.²

The diagnosis of PGL/PHEO during pregnancy is challenging due in part to its rare occurrence, as well as the similarity of presentation to other, more frequent pregnancy-related hypertensive disorders. Gestational hypertension and preeclampsia/eclampsia are more commonly observed causes of hypertension during pregnancy. Paroxysmal episodes of elevated BP, occurring before 20 weeks of gestation, without edema or proteinuria, can serve to alert clinicians caring for women during pregnancy to consider a diagnosis of PGL/PHEO. A personal or family history of NF1, MEN2, or VHL makes a diagnosis of PGL/PHEO in pregnancy more likely. Patients may become increasingly symptomatic as the pregnancy progresses, and 50% of patients also can experience hypotensive episodes.²

When PGL/PHEO is suspected, the diagnosis must be confirmed by the demonstration of increased plasma or urinary metanephrines and normetanephrines. These tests have a sensitivity of 98% with a high negative predictive value, allowing exclusion of the diagnosis if results are in the normal range.¹

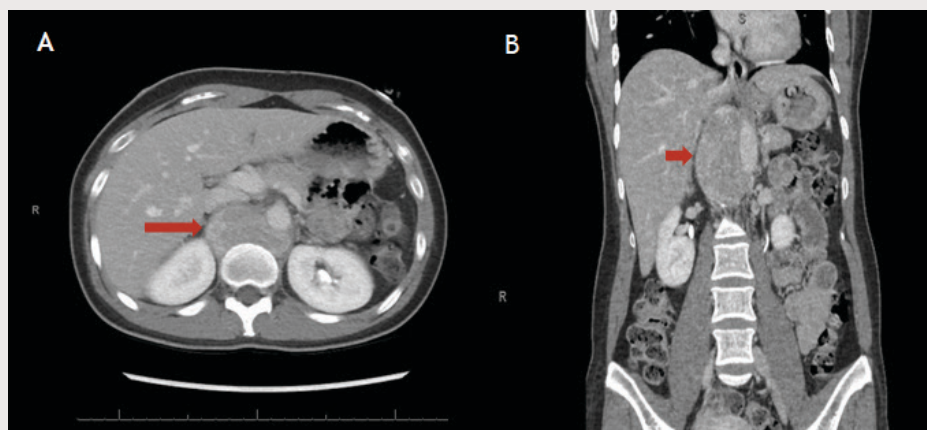


Figure 1. A large retroperitoneal para-aortic heterogeneously enhancing mass measuring 5.8 x 3.7 x 8.3 cm was noted on abdominal CT. The mass abuts and displaces the aorta anteriorly and laterally. No evidence of vascular invasion is identified; however, the mass encircles the aorta approximately 180 degrees.

A healthy pregnancy does not significantly affect plasma catecholamine levels, which are only slightly elevated in the setting of preeclampsia.³ False-positive results can occur with improper blood sampling (e.g., failure to rest a patient for 30 minutes in quiet surroundings) and with the use of β -adrenergic receptor blockers or tricyclic antidepressants.¹

Once the diagnosis of PGL/PHEO is established with appropriate hormonal studies, tumor localization is the next step in the evaluation. Magnetic resonance imaging (MRI) without contrast is the modality of choice to diagnose PGL/PHEO in pregnancy, with sensitivity similar to that of CT scanning (90% to 100%).⁴ CT and MIBG scans are contraindicated during pregnancy.^{1,3} The patient in this case was diagnosed following delivery, which allowed for CT scanning to be performed. Although abdominal ultrasound is safe and affordable, its diagnostic sensitivity for small tumors is limited; thus, a normal test result does not always exclude the diagnosis.⁴

Once imaging studies confirm the presence of a mass suggestive of PGL/PHEO, surgery will be required as part of the treatment regime. The timing of surgery depends on many factors, including gestational age (if the patient is pregnant), location of the tumor, and adequate preoperative α -blockade. In women diagnosed during pregnancy, if an adequate α -blockade can be established before 24 weeks of gestation, laparoscopic

surgical resection is recommended in the second trimester.³ Otherwise, medical treatment is preferred, and laparoscopic resection is postponed until after delivery of the child.

Management of elevated HTN in pregnant patients with PGL/PHEO is challenging. Although the placenta shields the fetus from high circulating levels of catecholamines, the utero-placental circulation can still be compromised due to severe arterial vasoconstriction.⁴ Treatment with α -adrenergic receptor blockers can counteract these effects but also can increase the risk of hypotension, which can further compromise utero-placental circulation. Phenoxybenzamine and doxazosin are the usual first therapeutic options for patients presenting with elevated BP during pregnancy who are suspected of having PGL/PHEO.⁵ Both medications can cross the placenta and are considered fetal risk category C, which categorizes these medications as generally safe to use during pregnancy with careful monitoring. Neonatal hypotension and respiratory depression have been reported with phenoxybenzamine, but not with doxazosin.⁵ Therefore, close neonatal monitoring during the first days of life is advised if a mother has been treated with phenoxybenzamine.

(Continued on Page 12)

A Case of Paraganglioma in Pregnancy (Continued from Page 11)

Catecholamine induced tachycardia and α -blockade can induce a reflex tachycardia that can be treated with β -blockers if this becomes necessary.¹ Beta blockers have been associated with intrauterine growth restriction. Therefore, short-term use with the lowest possible dose is advised.² Initiation of a β -blocker should occur only after an appropriate α -adrenergic blockade is achieved. This time lag is necessary to prevent precipitation of a hypertensive crisis.¹ If β -blockers are contraindicated or fail to control blood pressure, and there is an absence of tachycardia, calcium channel blockers can be added to the treatment regimen. These medications also are categorized as fetal risk category C.

For pregnant patients with PGL/PHEO, there is no clear consensus regarding the preferred route for delivery. The elective Caesarean section was long favored based on prior case reports that suggested higher maternal mortality rates with vaginal delivery.³ More recent studies⁶ describe vaginal delivery as both acceptable and safe provided that there is adequate epidural analgesia to minimize pain and stress and by reducing the second stage of labor using instrumental delivery to reduce the need for excessive pushing.

If oxytocin is used to induce labor, it should be used with caution, as it may cause tachycardia and hypotension.

In this case, the patient had induced vaginal delivery. Because of a presumed diagnosis of preeclampsia, intravenous (IV) magnesium sulfate was used during labor to control her elevated BP and reduce the risk of seizure. IV magnesium was discontinued shortly after initiation due to a severe hypotensive reaction.

Once the diagnosis of PGL/PHEO is confirmed, either with hormonal testing or surgical pathology, genetic counseling should be offered even if the family history is negative or unknown. Approximately 30% to 40% of individuals with an isolated PGL/PHEO have an underlying genetic cause for this diagnosis.⁷ There is an even stronger indication for genetic testing when PGL/PHEO is diagnosed during pregnancy, given the relatively young age of patients. The susceptibility genes that have been associated with PGL/PHEO include NF1, RET, VHL, succinate dehydrogenase subunits (SDHA, SDHB, SDHC, and SDHD), co-factor for succinate dehydrogenase complex (SDHAF2), and MEN1.

Conclusion

This case illustrates the importance of a timely diagnosis of paraganglioma/pheochromocytoma during pregnancy, as it can dramatically affect maternal and fetal mortality rates. High clinical suspicion for these tumors as a cause of elevated BP during pregnancy is critical for timely diagnosis, particularly in patients who lack other characteristics typical of pregnancy-related hypertensive disorders (proteinuria, edema, etc.) or who present with an elevated blood pressure early in pregnancy.

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Notable Publications

Zupa MF, Arena VC, Johnson PA, Thearle MB, Siminerio LM. A Coordinated Population Health Approach to Diabetes Education in Primary Care. *Diabetes Educ.* 2019 Dec; 45(6): 580-585.

The purpose of this feasibility study was to determine the effectiveness of an insurer-based diabetes educator (DE)-driven intervention that relies on systematic restructuring of primary care (PC) linking DE services through population health, practice redesign, and coordinated care for patients with diabetes mellitus (DM) identified as high risk. Findings support the feasibility of a DE-driven intervention for patients with DM at high risk through a coordinated PC approach that improves glycemic control. The feasibility and clinical outcome of this model warrant consideration of a fresh role for DEs in the complex environment of value-based care.

Dube JJ, Collyer ML, Trant S, Toledo FGS, Goodpaster BH, Kershaw EE, DeLany JP. Decreased Mitochondrial Dynamics Is Associated With Insulin Resistance, Metabolic Rate, and Fitness in African Americans. *J Clin Endocrinol Metab.* 2019 Dec 13. pii: dgz272. Epub ahead of print.

The goal of this study was to assess mitochondrial pathways and dynamics to examine the potential mechanisms of lower insulin sensitivity, RMR, VO₂max, and mitochondrial capacity in AAW. To achieve this goal, we assessed several mitochondrial pathways in skeletal muscle using gene array technology and semi-quantitative protein analysis. Together these data suggest that the metabolic racial disparity of insulin resistance, RMR, VO₂max, and mitochondrial capacity may be mediated by perturbations in mitochondrial pathways associated with membrane transport, fission-fusion, and autophagy. The mechanisms contributing to these differences remain unknown.

Pan Y, Balance H, Meng H, Gonzalez N, Kim S, Abdurehman L, York B, Chen X, Schnytzer Y, Levy O, Dacso CC, McClung CA, O'Malley BW, Liu S, **Zhu B.** 12-h Clock Regulation of Genetic Information Flow by XBPIs. *PLoS Biol.* 2020 Jan 14; 18(1): e3000580.

Our group recently characterized a cell-autonomous mammalian 12-h clock independent from the circadian clock, but its function and mechanism of regulation remain poorly understood. Here, we show that in mouse liver, transcriptional regulation significantly contributes to the establishment of 12-h rhythms of mRNA expression in a manner dependent on Spliced Form of X-box Binding Protein 1 (XBPIs). We further identified GA-binding proteins (GABPs) as putative novel transcriptional regulators driving 12-h rhythms of gene expression with more diverse phases. These 12-h rhythms of gene expression are cell autonomous and evolutionarily conserved in marine animals possessing a circatidal clock. Our results demonstrate an evolutionarily conserved, intricate network of transcriptional control of the mammalian 12-h clock that mediates diverse biological pathways. We speculate that the 12-h clock is co-opted to accommodate elevated gene expression and processing in mammals at the two rush hours, with the particular genes processed at each rush hour regulated by the circadian and/or tissue-specific pathways.

Available Faculty Positions

Outcomes and Health Services Physician Scientist. The Division of Endocrinology at the University of Pittsburgh (Pitt) and its affiliated Medical Center (UPMC) and Veterans Administration Pittsburgh Health System (VAPHS) seek an MD or MD/PhD board-certified endocrinologist for a full-time academic faculty position, primarily to conduct outcomes, health services, and/or health equity research in the field of endocrinology, diabetes, and metabolism. In addition to clinical expertise, candidates should have a strong history of externally funded research (and associated publications) in outcomes and health services research. Leadership experience is highly desired, as this position has strong potential to develop into a substantial leadership role. 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: endoadm@pitt.edu). *EEO/AA/M/F/Vets/Disabled*

Director, Multidisciplinary Thyroid Center (MTC). The Division of Endocrinology 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: endoadm@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: endoadm@pitt.edu). *EEO/AA/M/F/Vets/Disabled*

Division News

ADA Save the Date: June 12-16, 2020

The UPMC Division of Endocrinology and Metabolism will be hosting their annual alumni and friends reception at the **80th American Diabetes Association Scientific Sessions** in Chicago **June 12-16, 2020**. The reception will be held on the evening of June 14 at the Marriott Marquis Chicago. Please contact Chelsea Dempsey for further details at cad183@pitt.edu.

ADA Tour de Cure Pittsburgh

The Divisions of Adult and Pediatric Endocrinology joined together to participate in the **2019 American Diabetes Association (ADA) Tour de Cure Pittsburgh**. The Tour de Cure allows participants to walk, run, bike, or virtually participate to help raise funds to further the ADA's mission of growing diabetes research, advocacy, and education. Our team was able to fundraise enough money to land in the top 10 corporate teams! The 2020 ADA Tour de Cure Pittsburgh will take place on **October 3, 2020**.



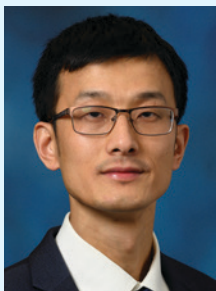
ADA Tour de Cure Pittsburgh

American Thyroid Association Conference

Members of the Division of Endocrinology and Metabolism and the Division of Endocrine Surgery collaborated on posters presented at the **89th Annual Meeting of the American Thyroid Association**.



American Thyroid Association Conference



New Faculty

Yong Wan, PhD, received his doctorate from Shanghai Jiao Tong University in 2013. He obtained the position of postdoctoral associate at the University of Pittsburgh in 2015. He remained in this position until he joined our Division as a research assistant professor in January 2020. Dr. Wan also has attained a faculty appointment within the Pittsburgh Aging Institute. Dr. Wan's research interests include understanding the molecular and cellular causes of aging-related bone disease and mitochondrial function involved in bone metabolism.

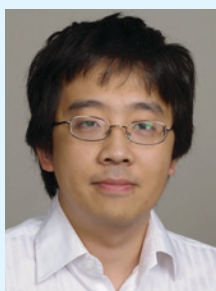
Awards and Accomplishments



Hammam Alquadan, MD, (clinical fellow), under the mentorship of Maja Stefanovic-Racic, MD, PhD, was awarded the Endocrine Society Early Career Forum and Travel Award.



Linda Siminerio, RN, PhD, CDE, was awarded an R34 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) for a research project involving telemedicine.



Bokai Zhu, PhD, was awarded a Pittsburgh Liver Research Center Pilot & Feasibility grant.



Esra Karslioglu-French, MD, received a Physicians Thrive Grants for Change award to expand an ongoing wellness initiative within the Division of Endocrinology and Metabolism.



Pouneh Fazeli, MD, MPH, was awarded an R01 grant by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) to expand her research on the use of transdermal estrogen as a form of treatment for bone loss in women with anorexia nervosa.



Mary Korytkowski, MD, was chosen as one of the 2019 Castle Connolly Exceptional Women in Medicine, and as one of the 2019 America's Top Doctors.

DIVISION OF ENDOCRINOLOGY AND METABOLISM

Clinical Treatment Areas

- Diabetes
- Endocrine Neoplasias
- Hypothalamic, Pituitary, and Adrenal Disorders
- Lipid Disorders
- Obesity
- Osteoporosis and Metabolic Bone Disorders
- Reproductive Hormonal Disorders
- Thyroid Disorders

Research Areas of Focus

- Diabetes Education and Management
- Healthy Lifestyles and Behaviors
- Lipid Disorders
- Metabolic Syndrome
- Muscle Metabolism and Function
- Obesity, Lipodystrophies, and Adipose Tissue Disorders
- Osteoporosis and Metabolic Bone Disorders
- Thyroid Cancer Molecular Diagnosis
- Type 1 Diabetes and Pancreatic Islet/Beta Cell Biology
- Type 2 Diabetes and Insulin Resistance

A Resource for You: UPMC Physician Resources brings world-class physicians and free educational opportunities to your computer. Learn new information while watching CME-accredited videos in the convenience of your home or office. Find out more at UPMCPhysicianResources.com/Endocrinology.

To learn more about the UPMC Division of Endocrinology and Metabolism, please visit UPMCPhysicianResources.com/Endocrinology.

UPMC
PHYSICIAN RESOURCES

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and Metabolism**
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Pittsburgh, PA 15213
Phone: 412-648-9770

A \$21 billion health care provider and insurer, Pittsburgh-based UPMC is inventing new models of patient-centered, cost-effective, accountable care. The largest nongovernmental employer in Pennsylvania, UPMC integrates 89,000 employees, 40 hospitals, 700 doctors' offices and outpatient sites, and a more than 3.7 million-member Insurance Services Division, the largest medical insurer in western Pennsylvania. In the most recent fiscal year, UPMC contributed \$1.2 billion in benefits to its communities, including more care to the region's most vulnerable citizens than any other health care institution, and paid \$587 million in federal, state, and local taxes. Working in close collaboration with the University of Pittsburgh Schools of the Health Sciences, UPMC shares its clinical, managerial, and technological skills worldwide through its innovation and commercialization arm, UPMC Enterprises, and through UPMC International. *U.S. News & World Report* consistently ranks UPMC Presbyterian Shadyside on its annual Honor Roll of America's Best Hospitals and ranks UPMC Children's Hospital of Pittsburgh on its Honor Roll of America's Best Children's Hospitals. For more information, go to UPMC.com.