

# UPDATE IN ENDOCRINOLOGY



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## Faculty Positions Available

- *Outcomes and Health Services Physician Scientist*
- *Academic Clinical Endocrinologists*

Full descriptions and contact information on Page 14.

## CME Credit

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Dear Colleagues,

We are pleased to share our latest edition of *Update in Endocrinology*. We have had a very auspicious beginning to 2019 and plan to finish out the year strong! In this issue, we continue to highlight our contributions to the research, educational, clinical, and quality missions.

On the clinical front, endocrinology medical director **Esra Karslioglu French, MD**, discusses how she and her colleagues in the UPMC Multidisciplinary Thyroid Eye Disease Clinic are implementing a care model that allows patients with Graves' ophthalmopathy (GO) to obtain coordinated visits. This care model not only provides specialty care for patients with GO but improves outcomes for this challenging disease.

Our fellows continue to gain experience through complex cases that intrigue and challenge our expertise. Recently graduated clinical fellow **Samina Afreen, MD**, and her mentor, endocrine genetics expert **Helena Levitt, MD**, present a clinical case that discusses the challenges of evaluating and managing hypercalcemia and hyperparathyroidism in a young woman.

To highlight our research excellence, **Sadeesh Ramakrishnan, DVM, PhD**, discusses his research on the gut as an endocrine organ. Dr. Ramakrishnan recently was awarded a pilot grant from the Pittsburgh Liver Research Center (PLRC) to expand his research on hypoxia signaling in Nonalcoholic Fatty Liver Disease (NAFLD).

We continue to place a priority on the career development of trainees at all levels. The University of Pittsburgh offers a variety of opportunities for future physician-scientists and researchers to grow their expertise under the guidance of highly trained professionals. Andin Fosam, a recent University of Pittsburgh graduate, has progressed through different levels of the opportunities available at Pitt, from student athlete to metabolic researcher and burgeoning physician-scientist.

Our division recently welcomed four new faculty members: **Diana Pinkhasova, MD; Pouneh Fazeli, MD, MPH; Alison Kohan, PhD; and Charity Kwamanakweenda, MD, MBA**. Each of these new faculty members comes to us with specific expertise and interests that will continue to expand the academic mission of our division.

In addition, we also celebrate many accomplishments of our faculty, trainees, and staff. **Jagdeesh Ullal, MD**, was awarded an EnVision CF: Emerging Leaders in Cystic Fibrosis Endocrinology II Program grant. Postdoctoral Scholar **Lia Edmunds, PhD**, under the mentorship of **Michael Jurczak, PhD**, was awarded an American Diabetes Association Postdoctoral Fellowship Award.

Finally, we enjoyed celebrating with our colleagues, alumni, and friends at our 2019 American Diabetes Association (ADA) Annual Reception in San Francisco, California. We look forward to continuing to connect with colleagues across the nation!

Best wishes,



**Erin E. Kershaw, MD**

Chief, Division of Endocrinology and Metabolism  
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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

# Multidisciplinary Thyroid Eye Disease Clinic



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Graves' disease (GD) is the most common cause of hyperthyroidism, with an annual incidence of 20 to 50 cases per 100,000 persons.<sup>1</sup> Graves' ophthalmopathy (GO), which can present with proptosis, tearing, and periorbital edema, is detected in up to 50 percent of patients with Graves' disease. The majority of GO cases are mild, and patients recover after treatment of hyperthyroidism, whereas 5 percent of GD patients will develop moderate to severe GO.

Quality of life (QoL) surveys (i.e., SF-36) show that people with GO have substantially reduced QoL, equivalent to having diabetes or certain cancers.<sup>2</sup> Current therapeutic approaches for GO often fail to significantly improve QoL, as patients continue to have changes in their vision and appearance.

When patients are assessed and treated in multidisciplinary thyroid eye clinics, they have a more favorable outcome compared with patients who are not managed in such clinics.<sup>3</sup> A survey study of clinicians showed a lack of "best practice" in a significant number of responders for everyday clinical issues, such as urgent referral to an ophthalmologist in case of a possible dysthyroid optic neuropathy.<sup>3</sup> The American Thyroid Association (ATA) and European Group on Graves' Orbitopathy (EUGOGO) recommend the implementation of multidisciplinary thyroid eye clinics for assessment and treatment of GO.<sup>4,5</sup>

Medical professionals at UPMC have worked together to establish a Multidisciplinary Thyroid Eye Disease Clinic to improve patient care and satisfaction. This multidisciplinary clinic allows patients to be seen simultaneously by an ophthalmologist and endocrinologist. Endocrine surgery; ear, nose, and throat (ENT); and other specialists are consulted in appropriate cases.

Patients seen in the UPMC Multidisciplinary Thyroid Eye Disease Clinic are first evaluated by using clinical activity score (CAS) (Table 1) and severity (Table 2) assessments to establish the degree of GO while modifiable risk factors are

identified. All hyperthyroid patients are treated to achieve euthyroidism expeditiously. Smokers are referred to tobacco cessation centers, as smoking increases the risk for diplopia and proptosis by eight-fold. Selenium, which is shown to improve QoL and overall eye evaluation in patients with GO,<sup>6</sup> is recommended. Thyroid-stimulating immunoglobulin (TSI) levels are measured, as TSI predicts GO risk and GO therapeutic response.<sup>7</sup>

Hyperthyroidism and ophthalmopathy typically occur within one year of each other but can be separated by decades.<sup>8</sup> In 10 percent of patients with GO, either thyroid levels remain normal or autoimmune hypothyroidism develops. Radioiodine (RAI) is not recommended in patients with moderate-to-severe or sight-threatening GO, as it can worsen eye disease, possibly due to TSI elevation after treatment. Patients with moderate-to-severe or sight-threatening eye disease are treated by antithyroid drugs (ATD) or thyroid surgery. Thyroidectomy is preferred in patients who have adverse reactions to ATD, enlarged thyroid glands, or a pregnancy in the near future.<sup>4</sup>

The approach to patients with GO is summarized in Figure 1, which involves local measures, corticosteroids, orbital radiation, and surgery.

## GO Challenges Continue

GO continues to be a challenging disease despite the current management options. A recent Phase 3 OPTIC clinical trial showed promising results for the use of the experimental drug teprotumumab, which is a human monoclonal antibody that targets the insulin-like growth factor 1 receptor. When given during the active phase of disease, teprotumumab reversed eyelid swelling, reduced eye bulging and double vision, and improved quality of life.<sup>9,10</sup> Teprotumumab is expected to be submitted to the U.S. Food and Drug Administration (FDA) for approval this year.

The Multidisciplinary Thyroid Eye Disease Clinic at UPMC allows patients with GO the opportunity to coordinate multiple visits in a timely manner, which can be a challenging aspect of care for these patients. Comprehensive counseling is provided by experts to aid patients in making appropriate treatment decisions. Our team also aids in educating patients about common misperceptions related to GO.<sup>11</sup> The continuing goal of the UPMC Multidisciplinary Thyroid Eye Disease Clinic is to provide multispecialty care to patients with GO and improve outcomes for this challenging disease.

**Table 1. GO Activity Assessment According to Clinical Activity Score (CAS)**

Spontaneous retrobulbar pain	1
Pain on attempted upward or downward gaze	1
Redness of eyelids	1
Redness of conjunctiva	1
Swelling of caruncle or plica	1
Swelling of eyelids	1
Swelling of conjunctiva (chemosis)	1
* Inactive GO = CAS < 3	
* Active GO = CAS ≥ 3	

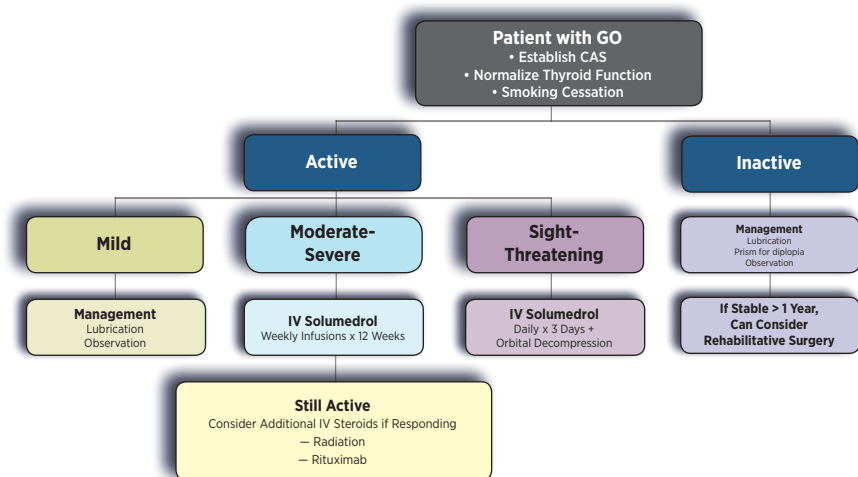
**Table 2. GO Severity Assessment According to EUGOGO**

<p><b>* Mild GO</b></p> <p>Patients whose features of GO have only a minor impact on daily life insufficient to justify immuno-suppressive or surgical treatment.</p> <p>They usually have one or more of the following:</p> <ul style="list-style-type: none"> <li>• Minor lid retraction (&lt; 2 mm), mild soft-tissue involvement</li> <li>• Exophthalmos &lt; 3 mm above normal for race and gender</li> </ul> <p>No or intermittent diplopia and corneal exposure responsive to lubricants</p>
<p><b>* Moderate-to-Severe GO</b></p> <p>Patients without sight-threatening GO whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive).</p> <p>They usually have two or more of the following:</p> <ul style="list-style-type: none"> <li>• Lid retraction ≥ 2 mm, moderate or severe soft-tissue involvement</li> <li>• Exophthalmos ≥ 3 mm above normal for race and gender</li> <li>• Inconstant or constant diplopia</li> </ul>
<p><b>* Sight-Threatening GO (Very Severe GO)</b></p> <ul style="list-style-type: none"> <li>• Patients with dysthyroid optic neuropathy (DON) and/or corneal breakdown</li> </ul>

**References**

- Smith TJ, Hegedüs L. Graves' Disease. *N Eng J Med.* 2016; 375(16): 1552-65.
- Kahaly GJ, Petrak F, Hardt J, Pitz S, Egle UT. Psychosocial Morbidity of Graves' Orbitopathy. *Clin Endocrinol (Oxf).* 2005; 63: 395-402.
- Perros P, Baldeschi L, Boboridis K, Dickinson AJ, Hullo A, Kahaly GJ, et al. A Questionnaire Survey on the Management of Graves' Orbitopathy in Europe. *Eur J Endocrinol.* 2006; 155(2): 207-11.
- Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. *Thyroid.* 2016; 26(10): 1343-421.
- Bartalena L, Baldeschi L, Boboridis K, Eckstein A, Kahaly GJ, Marcocci C, Perros P, Salvi M, Wiersinga WM: The 2016 European Thyroid Association/ European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy. *Eur Thyroid J.* 2016; 5: 9-26.
- Marcocci C, Kahaly GJ, Krassas GE, Bartalena L, Prummel M, Stahl M, et al. Selenium and the Course of Mild Graves' Orbitopathy. *N Eng J Med.* 2011; 364(20): 1920-31.
- Barbesino G, Tomer Y. Clinical Review: Clinical Utility of TSH Receptor Antibodies. *J Clin Endocrinol Metab.* 2013; 98(6): 2247-55.
- Bahn RS. Graves' Ophthalmopathy. *N Eng J Med.* 2010; 362(8): 726-38.
- Douglas R. Teprotumumab Treatment Effect on Proptosis in Patients With Active Thyroid Eye Disease: Results From a Phase 3, Randomized, Double-masked Placebo-controlled, Parallel-group, Multicenter Study. Presented at the American Association of Clinical Endocrinologists 28th Annual Scientific and Clinical Congress, April 25-28, 2019, in San Francisco, California.
- Smith TJ, Kahaly GJ, Ezra DG, Fleming JC, Dailey RA, Tang RA, et al. Teprotumumab for Thyroid-Associated Ophthalmopathy. *N Eng J Med.* 2017; 376(18): 1748-61.
- Edmunds MR, Boelaert K. Knowledge of Thyroid Eye Disease in Graves' Disease Patients With and Without Orbitopathy. *Thyroid.* 2019; 29(4): 557-62.

**Figure 1. GO Evaluation and Treatment Algorithm.**



# Hypercalcemia in a Young Woman



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*At UPMC, our dedicated Endocrine Genetics Clinic combines the expertise of endocrinologists, endocrine surgeons, and clinical geneticists in a team-based approach to treating endocrine disorders with potential underlying genetic contributions.*

## Case Presentation

A 37-year-old Caucasian female presented to the UPMC Endocrine Genetics Clinic in 2019 for evaluation and management of hypercalcemia and hyperparathyroidism. She had previously undergone parathyroid surgery at an outside institution in 2013 for presumed primary hyperparathyroidism (pHPT). Since then, her serum calcium remained elevated in the range of 10.4–11.1 mg/dL with concomitant nonsuppressed parathyroid hormone (PTH) levels ranging from 66–178 pg/mL.

The patient initially was noted to have hypercalcemia on routine laboratory evaluation in 2008 when she was 26 years old. She had no known prior history of hypercalcemia, hyperparathyroidism, nephrolithiasis, fracture, or other condition associated with abnormal serum calcium levels. Likewise, she had no known family history of hypercalcemia or hyperparathyroidism. Her initial serum calcium was 10.9 mg/dL, and a confirmatory repeat albumin-corrected serum calcium was 11.0 mg/dL. A concurrent serum PTH was 170 pg/mL. Serum 25-hydroxy vitamin D was within the normal range. Additional oral vitamin D supplementation did not suppress the serum PTH level. Bone mineral densitometry (BMD) by dual x-ray absorptiometry (DXA) was normal. The 24-hour urinary calcium to creatinine clearance ratio (UCCR) was 0.01 on two occasions. Based on the above information, it was felt that both pHPT and familial hypocalciuric hypercalcemia (FHH) remained possible diagnoses, so the patient was managed conservatively with annual clinical re-evaluation.

After five years, the patient ultimately decided to undergo parathyroid exploration in 2013. During this parathyroid exploration, a minimally enlarged left inferior parathyroid gland was identified and resected. However, her intraoperative serum PTH level did not decrease significantly (178 pg/mL to 122 pg/mL). Subsequent calcium and PTH levels at two weeks and three months postoperatively remained elevated, providing evidence supporting FHH as a potential diagnosis. She was again managed conservatively

with annual clinical re-evaluation until 2018 when she again presented for surgical consultation. Repeat-operation was deferred, and instead, her surgeon recommended genetic testing for calcium-sensing receptor (CASR) mutations. The results revealed a variant of undetermined significance (VUS) in her CASR gene. Her surgeon then referred her to the UPMC Endocrine Genetics Clinic for further evaluation and management in early 2019.

The UPMC Endocrine Genetics Clinic consists of a team of endocrinologists, endocrine surgeons, and clinical geneticists with specialized expertise in genetic endocrine disorders. Clinical history confirmed the key elements noted above. History and physical exam likewise confirmed that the patient was generally in excellent health other than the elevated serum calcium and PTH levels. She had no personal or family history of any conditions associated with abnormal serum calcium or PTH. She had no other significant medical history. Family history was notable for lung cancer in her paternal grandfather, leukemia in her maternal grandfather, and stomach cancer in her paternal grandmother. She had no allergies. She was not taking any medications or over-the-counter supplements. Laboratory data revealed elevated serum calcium of 10.7 mg/dL and PTH of 120 pg/mL. Other electrolytes, including magnesium and phosphorus, were normal. Serum 25-hydroxy vitamin D also was normal. The UCCR was 0.015.

After clinical evaluation of the patient, the endocrine genetics team decided to pursue additional genetic testing, including testing for FHH1 (CASR), FHH2 (GNA11), and FHH3 (AP2S1), as well as additional genes associated with familial hyperparathyroidism. Subsequent results were negative for mutations in the CASR, GNA11, AP2S1, and CDC73 genes, as well as the CDKN1B, MEN-1, RET, and GCM2 genes. In addition, the prior 2013 CASR VUS results were revised to indicate that this VUS was predicted to be nonpathogenic.



With a UCCR of 0.01-0.02 and persistent hypercalcemia following parathyroid surgery, FHH remains a possible explanation for the patient's PTH-mediated hypercalcemia. However, genetic testing results for CASR, AP2S1, and GNA11 mutations failed to provide confirmatory evidence for this diagnosis. The patient was encouraged to have her first-degree family members tested for hypercalcemia, because identification of additional cases of familial hypercalcemia would support a diagnosis of FHH. Thus far, normal serum calcium levels have been confirmed in her three children.

## Discussion

This case demonstrates many of the diagnostic challenges in differentiating between primary hyperparathyroidism (pHPT) and familial hypocalciuric hypercalcemia (FHH). These diagnoses have different clinical courses and require different treatments. pHPT can be associated with significant morbidity, whereas FHH generally has a more benign clinical course. Since treatment of FHH can cause harm, it is essential to rule out this diagnosis before pursuing medical or surgical therapy for hypercalcemia. A diagnosis of FHH also has implications for affected family members. Surgery is the definitive treatment for pHPT but should be avoided with FHH. Clinical suspicion for FHH should be higher in asymptomatic patients with a low 24-hour UCCR who also are diagnosed with parathyroid-dependent hypercalcemia at a young age, in patients with a family history of hypercalcemia, or patients with multiglandular disease. Clinical and biochemical evidence may be insufficient to differentiate between pHPT and FHH definitively. Indeed, FHH, which represents ~2 percent of pHPT cases, is diagnosed in up to 23 percent of cases that failed to respond to parathyroid surgery. Recent advances in understanding the genetic causes of FHH have improved the diagnosis and treatment of FHH. This article reviews the diagnostic challenges and use of genetic testing in differentiating between pHPT and FHH.

## Serum Biochemical Abnormalities

Because of the significant overlap of serum parameters between FHH and pHPT, serum biochemical studies are often inadequate to differentiate between these diagnoses. In pHPT, calcium levels can be mildly to severely elevated and may progressively worsen over time. Serum phosphorus levels tend to be in the low-normal range but can be low in approximately one-third of cases. Serum 25-hydroxy vitamin D levels are typically normal or low-normal, in part due to PTH-driven conversion of 25-hydroxy vitamin D levels to 1,25-dihydroxy vitamin D. Correspondingly, 1,25-dihydroxy vitamin D levels tend to be high or high-normal. In FHH, calcium is mildly and stably elevated throughout life (generally below 12 mg/dL). PTH levels are normal in approximately 80 percent of patients and mildly elevated in the other 20 percent. Serum phosphorus levels are often reduced. Serum 1,25-dihydroxy vitamin D levels are normal or elevated. In addition, a history of hypercalcemia at a young age is helpful in differentiating between these diagnoses.

## Urine Calcium to Creatinine Ratio (UCCR)

The UCCR [calculated as a (24-hour urine calcium in mg x serum creatinine in mg/dL)/(serum calcium in mg/dL x 24-hour urine creatinine in mg)] can help to differentiate between FHH and pHPT. Different UCCR cutoff criteria have been proposed. Generally, a UCCR of less than 0.01 is most consistent with FHH, whereas a UCCR of greater than 0.02 is most consistent with pHPT. However, the utility of the UCCR is not without limitations. Between 63 to 68 percent of patients with confirmed pHPT have UCCRs of less than 0.02.<sup>1</sup> Likewise, up to 35 percent of patients with confirmed FHH have UCCRs of greater than 0.01.<sup>1</sup>

Several factors can influence urinary calcium excretion and, consequently, the UCCR. Vitamin D deficiency (25-hydroxy vitamin D < 10 ng/mL) is associated with 27 percent higher PTH hypersecretion, 26 percent lower impairment of urinary

calcium excretion, and reduced sensitivity of the UCCR in diagnosing pHPT.<sup>2</sup> Thiazide diuretics, estrogen, and potassium citrate can decrease urinary calcium excretion. Conversely, many pharmacological agents can increase urinary calcium excretion, including drugs that contain calcium (antacids and calcium supplements), diuretics (spironolactone and furosemide), androgens, growth hormone, systemic corticosteroids, and acetazolamide.<sup>3</sup> In addition, ethnic differences in urinary calcium excretion have been noted. For example, African Americans generally have lower urinary calcium excretion than Caucasians.<sup>4</sup> A study published in 2018, conducted with a subject size of 1,000 patients, suggested that UCCR was nondiscriminatory for all biochemical presentations, subtle and more severe.<sup>1</sup>

Thus, the Proceedings of the Fourth International Workshop for Diagnosis of Asymptomatic Primary Hyperparathyroidism recommends that if UCCR is 0.01-0.02 and 25-hydroxy vitamin D is greater than 20 ng/mL, with a normal eGFR of greater than 60 mL/min, then genetic testing for FHH should be considered (see Page 10).<sup>5</sup>

## Dual X-ray Absorptiometry (DXA)

A DXA scan of a patient presenting with pHPT generally shows reduced BMD of the distal third of the forearm, a site enriched in cortical bone, whereas the lumbar spine, a site enriched in cancellous bone, is relatively preserved. However, approximately 15 percent of patients with pHPT present with an atypical BMD profile, characterized by vertebral osteopenia or osteoporosis. Occasionally, patients with pHPT may show reduced BMD at all sites. In contrast, FHH usually is not associated with BMD abnormalities, though abnormalities may be noted. In addition, FHH3, in particular, is associated with reduced BMD along with cognitive deficits and/or behavioral disturbances in children.<sup>6</sup>

*Continued on Page 10*

# The Gut as an Endocrine Organ: Hypoxia Signaling, Gut Hormones, and Metabolic Homeostasis



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*Researchers at the University of Pittsburgh are working to understand the metabolic effects and therapeutic potential of hypoxia signaling in the gut. Understanding these pathways may improve the prevention and treatment of metabolic diseases, including, but not limited to, obesity.*

## Obesity and Diabetes Are Global Public Health Problems

Obesity is a key contributor to the growing epidemic of metabolic and cardiovascular diseases. According to the most recent health statistics from the World Health Organization (WHO), more than 13 percent of the global population and 40 percent of Americans are obese (defined as a body mass index of  $\geq 30$ ).<sup>1</sup> The prevalence and severity of obesity are not only rising in adults but also in children and adolescents. As of 2013, the American Medical Association (AMA) officially designated obesity as a chronic disease.<sup>2</sup> In addition, obesity often is associated with many other chronic and progressive diseases, including diabetes and fatty liver disease. Clearly, there is an urgent need to improve the understanding and treatment of obesity and related metabolic disorders.

## The Gut Is an Endocrine Organ That Contributes to Normal Metabolism and Disease

The intestine (gut) was previously recognized solely for its role in nutrient absorption, but it is now recognized as playing a much more complex role in systemic metabolic and immune function. The intestine is the largest endocrine organ of the body, secreting more than 30 gut hormones.<sup>3-5</sup> These gut hormones have peripheral as well as central nervous system (CNS) effects in regulating energy and metabolic homeostasis. For example, glucagon-like peptides, such as glucagon-like peptide 1 (GLP1), are secreted by the intestinal endocrine (enteroendocrine) cells. In peripheral tissues, GLP1 augments pancreatic insulin secretion, improves insulin sensitivity, and promotes energy expenditure. In the CNS, GLP1 activates

the satiety center, thereby reducing food intake. These effects are the foundation for the well-known clinical therapies such as GLP1 agonists (which mimic the effects of GLP1) and dipeptidyl peptidase-4 (DPP-4) inhibitors (which delay the breakdown of GLP1). Likewise, the beneficial effects of bariatric surgery are believed to be, at least in part, due to alterations in gut hormones. Despite their critical importance, the mechanisms that regulate the intestinal secretion of gut hormones remain poorly understood.

## Hypoxia Signaling Is Essential for Metabolic Homeostasis and Represents a Novel Therapeutic Target for Metabolic Disease

Just as oxygen is required for whole-body survival, so is oxygen required for cell survival. Oxygen is required for cells to efficiently generate energy for essential cellular functions. Not surprisingly then, cells have developed very sensitive mechanisms to detect and respond to even minor fluctuations in oxygen tension at the cellular or tissue level, even when whole-body oxygen in the lungs and blood are normal. This oxygen sensing is mediated by hypoxia signaling via hypoxia-inducible factors (HIFs) (i.e., HIF-1, HIF-2). When oxygen levels are low or decreasing, these highly conserved proteins help cells survive by switching their metabolism to conserve available oxygen for vital cellular functions. HIFs conserve available oxygen by regulating the expression of numerous genes involved in cell stress, survival, proliferation, death, and metabolism. HIFs also influence the immune response. Thus, “hypoxia signaling” is critically important for metabolic homeostasis.<sup>6-8</sup>

Hypoxia signaling has been implicated in the pathogenesis of obesity and its metabolic complication. Obesity is well known to promote the accumulation of “toxic” fats in multiple tissues, including the liver and intestines. Regarding the former, the laboratory of Sadeesh Ramakrishnan, DVM, PhD, from the Division of Endocrinology and Metabolism at the University of Pittsburgh School of Medicine, has demonstrated an important role for HIFs, specifically HIF-2 $\alpha$ , in hepatic glucose homeostasis and insulin action.<sup>9,10</sup> Regarding the latter, Dr. Ramakrishnan’s collaborative group has demonstrated that HIF-2 $\alpha$  signaling in the intestines drives the obesity-associated increase in “toxic” fats and leads to fatty liver (hepatic steatosis). Conversely, inhibition of intestinal HIF-2 $\alpha$  signaling abolishes this obesity-associated increase in “toxic” fats and protects against fatty liver. This data suggests that inhibition of intestinal hypoxia signaling may have therapeutic potential in preventing or treating obesity-associated metabolic diseases.<sup>11</sup> Preclinical testing in mice indicates that a HIF-2-specific pharmacological inhibitor protects against diet-induced weight gain, hepatic steatosis, and inflammation. These data suggest that inhibition of HIF-2 can be an effective therapeutic target for metabolic disease and supports the need for future studies in humans.

### Intestinal “Hypoxia Signaling” and Gut Hormones

In the intestine, HIFs, and in particularly HIF-2, are expressed in the epithelial and endocrine cells. In the epithelial cells, HIF-2 regulates iron absorption and homeostasis.<sup>12</sup> Pharmacological stabilizers of HIF-2 (i.e., Roxadustat or FG-4592) are currently in phase III clinical trials for the treatment of anemia of chronic disease.<sup>13</sup>

Despite this ongoing research, the role of HIFs in enteroendocrine cells remains unknown. The Ramakrishnan lab has unveiled novel evidence linking hypoxia signaling to gut hormones and vice versa, specifically implicating HIF-2 $\alpha$  in gut hormone secretion from enteroendocrine cells. Ongoing studies are using cell type-specific preclinical models to manipulate HIF-2 $\alpha$  expression in enteroendocrine cells in order to systematically dissect their cellular and physiological role in regulating gut hormone secretion. Another area of intense investigation is whether HIF-2 $\alpha$  may mediate some of the metabolic effects of gut microbiota via its effects on GLP1 and other gut hormones. These studies may not only reveal novel therapeutic potential of targeting HIFs but may impact our understanding of existing therapies that target GLP1 or other gut hormones.

### Targeting HIFs in Metabolic Disease

In summary, the gut is an important endocrine organ that plays a critical role in normal metabolism and disease. Cellular hypoxia signaling and hypoxia-inducible factors are becoming increasingly recognized as important metabolic sensors and mediators in the gut. Researchers at the University of Pittsburgh are working to understand the metabolic effects and therapeutic potential of hypoxia signaling in the gut. Understanding these pathways may improve the prevention and treatment of metabolic diseases, including, but not limited to, obesity.

### References

- World Health Organization: *Obesity*. <https://www.who.int/topics/obesity/en/>.
- Pollack A. AMA Recognizes Obesity as a Disease. [Internet]. 2013 [cited 2014 Nov 20]. Available from: <http://www.nytimes.com/2013/06/19/business/ama-recognizes-obesity-as-a-disease.html>.
- Sun EWL, Martin AM, Young RL, Keating DJ. The Regulation of Peripheral Metabolism by Gut-derived Hormones. *Front Endocrinol (Lausanne)*. 2019 Jan 4; 9: 754.
- Melvin A, le Roux CW, Docherty NG. The Gut as an Endocrine Organ: Role in Regulation of Food Intake and Body Weight. *Curr Atheroscler Rep*. 2016 Aug; 18(8): 49.
- Reinehr T, Roth CL. The Gut Sensor as Regulator of Body Weight. *Endocrine*. 2015 May; 49(1): 35-50.
- Lee JW, Ko J, Ju C, Eltzschig HK. Hypoxia Signaling in Human Diseases and Therapeutic Targets. *Exp Mol Med*. 2019 Jun 20; 51(6): 68.
- Gonzalez FJ, Xie C, Jiang C. The Role of Hypoxia-inducible Factors in Metabolic Diseases. *Nat Rev Endocrinol*. 2018 Dec; 15(1): 21-32.
- Ramakrishnan SK, Shah YM. Role of Intestinal HIF-2 $\alpha$  in Health and Disease. *Annu Rev Physiol*. 2016; 78: 301-325.
- Ramakrishnan SK, Zhang H, Takahashi S, Centofanti B, Periyasamy S, Weisz K, Chen Z, Uhler MD, Rui L, Gonzalez FJ, Shah YM. HIF2 $\alpha$  Is an Essential Molecular Brake for Postprandial Hepatic Glucagon Response Independent of Insulin Signaling. *Cell Metab*. 2016 Mar 8; 23(3): 505-516.
- Ramakrishnan SK, Shah YM. A Central Role for Hypoxia-inducible Factor (HIF)-2 $\alpha$  in Hepatic Glucose Homeostasis. *Nutr Healthy Aging*. 2017 Dec 7; 4(3): 207-216.
- Xie C, Yagai T, Luo Y, Liang X, Chen T, Wang Q, Sun D, Zhao J, Ramakrishnan SK, Sun L, Jiang C, Xue X, Tian Y, Krausz KW, Patterson AD, Shah YM, Wu Y, Jiang C, Gonzalez FJ. Activation of Intestinal Hypoxia-inducible Factor 2 $\alpha$  During Obesity Contributes to Hepatic Steatosis. *Nat Med*. 2017 Nov; 23(11): 1298-1308.
- Sanghani NS, Haase VH. Hypoxia-Inducible Factor Activators in Renal Anemia: Current Clinical Experience. *Adv Chronic Kidney Dis*. 2019 Jul; 26(4): 253-266.
- Mastrogiannaki M, Matak P, Peyssonnaud C. The Gut in Iron Homeostasis: Role of HIF-2 Under Normal and Pathological Conditions. *Blood*. 2013 Aug 8; 122(6): 885-92.

# Predoctoral Training Opportunities in Endocrinology, Diabetes, and Metabolism at the University of Pittsburgh



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The Division of Endocrinology and Metabolism at the University of Pittsburgh School of Medicine has a strong commitment to mentoring future generations of clinicians and researchers. Predoctoral students at all stages of their training (ranging from high school to medical school) have multiple outstanding opportunities to conduct biomedical research and develop fundamental research skills. These opportunities provide structured and supportive “hands-on” experiences in real-world, ongoing research at the University of Pittsburgh. Students also have the opportunity to conduct research as student workers or research interns. These opportunities allow the next generation of clinicians and scientists to gain valuable experience in basic, translational, and clinical research related to endocrinology, diabetes, and metabolism.

## How Science Works

The *How Science Works* program provides opportunities for high school and undergraduate college students to participate in state-of-the-art biomedical research at the University of Pittsburgh. The *How Science Works* program pairs trainees with experienced research mentors in their field of interest for a dedicated immersive summer research experience. This program is a great way for students to prepare for a career in science or medicine. Find more information at <https://www.howscienceworks.pitt.edu>.

## First Experiences in Research

The *First Experiences in Research (FE-R)* program is available to undergraduate college students in the Dietrich School of Arts and Sciences at the University of Pittsburgh. Students select a research mentor in the first semester of the academic year and conduct five to 10 hours of research per week in the second semester of the academic year. The program is supplemented by a structured

group program to learn essential research skills, including how to give an “elevator pitch,” write a scientific abstract, and present a scientific poster. This program is an outstanding introduction to the fundamentals of research. Find more information at <https://www.asundergrad.pitt.edu/research/fer>.

## Undergraduate Research Fellowships

The University of Pittsburgh Honors College hosts a wide variety of research fellowships from both internal and external sources. Internal fellowships that support biomedical research, such as the *Chancellor’s Undergraduate Research Fellowships*, *Health Science Fellowships*, and *Brackenridge Fellowships*, support research during the academic year or in the summer (<https://www.honorscollege.pitt.edu/fellowships>). The University of Pittsburgh Honors College also provides “scholarship mentors” to assist with applications to external scholarships such as Goldwater Scholarships, Fulbright Scholarships, DAAD RISE Scholarships, and Amgen Scholarships (<https://www.honorscollege.pitt.edu/research-scholarships>).

## Summer Undergraduate Research Program (SURP)

The *Summer Undergraduate Research Program (SURP)* is sponsored by six biomedical graduate programs in the University of Pittsburgh School of Medicine. The program provides undergraduate college students with a summer research experience in the field of their choice under the guidance of an experienced mentor. The program also includes structured group activities to promote development of broadly transferable research skills. Find more information at <http://somgrad.pitt.edu/programs/summer-research/summer-undergraduate-research-program>.



### **Pitt-Med Research Experience for Pre-Matriculants (PREP) Program**

*PREP* is a recently established program that provides University of Pittsburgh medical students with the opportunity to gain experience during the summer prior to starting medical school. The intention of *PREP* is to encourage future clinicians to bring research experience into their medical training and, ultimately, future medical practice. This is a unique program that integrates biomedical research into medical training and nicely complements other programs at the University of Pittsburgh School of Medicine, such as the *Dean's Summer Research Program (DSRP)* and *Longitudinal Research Project (LRP)*. Applicants identify a research mentor and submit an application the spring prior to starting medical school. Find more information at <https://scholarlyproject.medschool.pitt.edu/programs/prep>.

### **Physician-Scientist Training Program (PSTP) and Clinical Scientist Training Program (CSTP)**

In addition to a traditional *Medical Scientist Training Program (MSTP)* (i.e., MD/PhD), the University of Pittsburgh offers several unique training programs for medical students. These include the *Physician Scientist Training Program (PSTP)* and *Clinical Scientist Training Program (CSTP)*, which focus on basic and clinical research, respectively. Students apply in conjunction with their application for medical school. The program provides students with structured supplemental curriculum that nicely integrates their medical studies with related biomedical research and training in transferable research skills. They then commit one year to a dedicated research experience between their second and third years of medical school. Information related to the *PSTP* can be found at <https://www.pstp.pitt.edu/> and information related to the *CSTP* can be found at [https://www.icre.pitt.edu/cstp/cstp\\_programDetails.html](https://www.icre.pitt.edu/cstp/cstp_programDetails.html).

### **The Dean's Summer Research Program (DSRP) and NIH-funded Training Opportunities**

The University of Pittsburgh supports a dedicated summer research experience for all interested medical students during the summer between their first and second years of medical school. This well-established *Dean's Summer Research Program (DSRP)* is supported by numerous sources and culminates in the Fall *DSRP* Research Symposium. This very successful program segues into the University of Pittsburgh's *Longitudinal Research Project (LRP)*, also known as the *Scholarly Project* in which students continue their research throughout the remainder of medical school (<https://scholarlyproject.medschool.pitt.edu/>). One mechanism supporting medical student participation in dedicated summer research in endocrinology and metabolism is the NIH-funded T35 research training program in Renal, GI, Endocrine, and Epithelial Biology. This long-standing NIH-funded training program promotes the development of future physicians in these important fields. For those students interested in a longer (i.e.,  $\geq 1$  year) research training experience, it is also possible to apply for a predoctoral supplement to our NIH-funded T32 Research Training Fellowship in Endocrinology and Metabolism, which has been in place for more than 40 years.

### **Research Training Fellowships From the American Heart Association, Endocrine Society, and American Diabetes Association**

Numerous foundations play an essential role in fostering the training and career development of students in the fields of endocrinology, diabetes, metabolism, and cardiometabolic diseases. The University of Pittsburgh's Vascular Medicine Institute, in cooperation with the American Heart

Association, offers a dedicated summer undergraduate research program (AHA-SURP) designed to expose students to cutting-edge basic and translational cardiovascular research (<http://www.vmi.pitt.edu/AHA-SURP/index.html>). The Endocrine Society offers support for a Summer Research Program to encourage undergraduate students, medical students, and graduate students to pursue careers in endocrinology. The Endocrine Society provides a stipend to each award recipient to participate in research projects under the guidance of an Endocrine Society member, as well as support to attend the Annual Meeting of the Endocrine Society (<https://www.endocrine.org/awards/research-fellowship-awards/summer-research-fellowships>). The American Diabetes Association (ADA) also supports undergraduate research training with an emphasis on promoting diversity and inclusion through its Minority Undergraduate Internship (MUI) program (<https://professional.diabetes.org/meetings/core-program>). The ADA-MUI provides support to an ADA Research Grant Principle Investigator to sponsor an undergraduate trainee from an underrepresented group for one year. The trainee is encouraged to present their work at the ADA's Annual Scientific Sessions. The above programs also include a structured didactic component that imparts disease-specific knowledge as well as transferable research skills offered through the University of Pittsburgh's Division of Endocrinology and/or the Vascular Medicine Institute.

*Continued on Page 11*

## Hypercalcemia in a Young Woman *(Continued from Page 5)*

### Genetic Testing

FHH is a well-established heritable disorder of serum calcium homeostasis. However, only recently has a vast array of genetic contributions to FHH been delineated. FHH was initially identified to be caused by an inactivating mutation in the calcium-sensing receptor (CASR) gene, a G-protein-coupled calcium-sensing receptor localized on chromosome 3q13.3-21.3. CASR mutations define FHH type 1 (FHH1). However, up to 30 percent of cases with a typical FHH phenotype do not harbor CASR mutations. In these cases, analysis for loci linked to hypercalcemia on chromosome 19p or 19q.13 revealed additional causative mutations in G Protein Subunit alpha 11 (GNA11, FHH-2)<sup>7</sup> and Adaptor Related Protein Complex 2 Subunit Sigma 1 (AP2S1, FHH-3),<sup>8</sup> respectively.

GNA11 is a gene that regulates CASR activity. A loss-of-function mutation in GNA11 reduces signaling through CASR and causes hypercalcemia. In contrast, a gain-of-function mutation in GNA11 increases signaling through CASR and causes hypocalcemia. The latter is designated as autosomal dominant hypocalcemia type 2 to distinguish it from type 1, which is due to gain-of-function of the CASR.

AP2S1 is a gene that regulates CASR cellular trafficking. Loss-of-function mutations in GNA11 reduce signaling through CASR and cause hypercalcemia. A hotspot missense mutation in codon 15 is one of the causes of FHH3.<sup>9</sup> AP2S1 may be involved in psychiatric diseases and depression. Due to this possibility, patients with isolated familial hyperparathyroidism and a phenotype compatible with FHH who have learning disabilities and/or psychiatric disorders should be genetically tested for AP2S1 exon 2 mutations before proceeding to other genetic tests. This set of testing will gather results more quickly than whole CASR sequencing while also being more cost-efficient. Patients who do not present with these comorbid diagnoses should have an evaluation of CASR as an initial genetic test.<sup>8</sup>

Sporadically occurring new mutations causing FHH are seen in 15 to 30 percent of new index cases of FHH.<sup>10</sup> Thirty percent of typical FHH cases are negative for a CASR mutation. In these cases, further analyses may identify mutations in GNA11 (FHH2) or AP2S1 (FHH3). FHH2 mutations, found in ~20 percent of FHH patients with negative CASR testing, are more common than FHH3, which is found in less than 5 percent of patients with FHH and normal CASR gene sequencing. Acquired auto-antibodies that block the interaction of extracellular calcium with CASR have been found in patients presenting with the FHH phenotype without CASR mutations.<sup>10</sup>

Genetic testing for Multiple Endocrine Neoplasia type 1 (MEN-1) should be considered in patients with pHPT who are below the age of 30 or at any age in patients presenting with multiglandular parathyroid disease.<sup>11</sup> Patients who meet the criteria for a clinical diagnosis of MEN-1 also should receive genetic testing for MEN-1. In addition to testing for MEN-1 and FHH, if there is clinical suspicion for hereditary hyperparathyroidism, additional genetic testing can be considered, including the following: RET (MEN-2), CDKN1B (MEN-4), GCM2 (familial isolated hyperparathyroidism type 4), and CDC73 (hyperparathyroidism-jaw tumor syndrome).<sup>12</sup> Some laboratories offer gene panel testing, which allows for simultaneous testing for multiple genes responsible for hereditary hyperparathyroidism.

### Conclusions

In summary, clinical and biochemical parameters are not always sufficient for discriminating between pHPT and FHH. In addition, factors that influence biochemical testing (e.g., ethnicity, drugs) should be considered when interpreting test results. If a family history of hypercalcemia is known, Marx et al. proposed the diagnosis of FHH based on characteristic features within a family.<sup>13</sup> Clinical red flags for FHH include asymptomatic hypercalcemia beginning in early life, relative hypocalciuria, and multiple affected family members in an autosomal dominant inheritance pattern.<sup>1</sup>

In cases where the diagnosis remains uncertain or would be important for clinical decision-making, genetic testing is becoming a more frequent option. Genetic testing for FHH recently has expanded to cover not only FHH1 (CASR mutations) but also FHH2 (GNA11) and FHH3 (AP2S1) mutations. When clinical findings are suggestive of FHH, the diagnosis occurs in the context of familial hyperparathyroidism, and when FHH testing is negative, consideration should be given to testing additional genes associated with familial hyperparathyroidism (MEN-1, RET, CDKN1B, GCM2, and CDC73). Sporadically occurring new mutations causing FHH are not uncommon. For such patients, when genetic test results are negative, it is important to obtain additional family history and calcium testing in family members. It also may be helpful to follow these patients over several years with lab tests (i.e., for calcium and PTH) and monitor them for complications like low BMD.

At UPMC, our dedicated Endocrine Genetics Clinic combines the expertise of endocrinologists, endocrine surgeons, and clinical geneticists in a team-based approach to treating endocrine disorders with potential underlying genetic contributions. Patients and their family members can schedule multidisciplinary group appointments to address the specific complexities of genetic disorders. Our team members provide advice to patients as well as to family members. We assist with decision-making related to genetic testing, and the psychological and financial implications of such testing. In the era of genetics and personalized medicine, in which genetic contributions to disease are increasingly identified, it is more important than ever to have an integrated approach that brings genetics to the patient in the clinic. The UPMC Endocrine Genetics Clinic, which has been operating for more than a decade, is at the forefront of providing this integrated care to our patients with genetic endocrine disorders.

*(References on Page 11)*

## Predoctoral Training Opportunities *(Continued from Page 9)*



### A Case Story: From Student Athlete to Metabolic Researcher and Burgeoning Physician-Scientist

**Andin Fosam** (above, left), a 2018 graduate of the University of Pittsburgh, is a prime example of a student who really leveraged the above support mechanisms to achieve her dreams, in collaboration with Erin E. Kershaw, MD, as her Endocrine Division Mentor. Andin was a student athlete on the University of Pittsburgh's Track and Field team. Her interest in health, nutrition,

and physical fitness led her to seek opportunities in basic research related to metabolism. After an initial year of part-time work in the Kershaw lab to get her feet wet, she successfully applied for the University of Pittsburgh and American Heart Association Summer Undergraduate Research Programs, Pitt-SURP and AHA-SURP, respectively. She accepted the latter (2016). Her research related to the impact of a metabolic risk variant on cardiac metabolism and function won her the program's Best Summer Research Project Award. The following year, she successfully applied for a University of Pittsburgh Chancellor's Undergraduate Research Award to continue her research during the academic year (2017). Then, in 2018, in collaboration with her ADA-funded research mentor, Dr. Kershaw, she successfully applied for a Minority Undergraduate Internship from the American Diabetes Association (2018). In her final year of college, she applied for a Fulbright Scholarship to study human metabolism, as well as for a Postbaccalaureate Intramural Research

Training Award (IRTA) at the National Institutes of Health (NIH). She chose to pursue the latter, and is now conducting human translational metabolic research in the Diabetes, Endocrinology, and Obesity Branch of the NIH. She also is applying for MD/PhD programs for 2020. To learn more about Andin's success as an Endocrine Division predoctoral trainee, see <https://www.pittwire.pitt.edu/news/star-athlete-sets-sights-medical-career>.

### Summary

In summary, the University of Pittsburgh and the Division of Endocrinology and Metabolism have multiple faculty with diverse research interests who are eager to promote the research, training, and career development of students and trainees at all levels. There are a wealth of opportunities to support dedicated research training experiences during the summer and throughout the school year. We encourage you to take advantage of these opportunities. Please feel free to contact our Division for more information.

## References *(Continued from Page 10)*

- Moore EC, Berber E, Jin J, Krishnamurthy V, Shin J, Siperstein A. Calcium Creatinine Clearance Ratio Is Not Helpful in Differentiating Primary Hyperparathyroidism From Familial Hypercalcemic Hypocalciuria. *Endocr Pract*. 2018; Oct 5. Epub ahead of print.
- Jayasena CN, Mahmud M, Palazzo F, Donaldson M, Meeran K, Dhillon WS. Utility of the Urine Calcium-to-Creatinine Ratio to Diagnose Primary Hyperparathyroidism in Asymptomatic Hypercalcemic Patients With Vitamin D Deficiency. *Ann Clin Biochem*. 2011 Mar; 48(Pt 2): 126-129.
- Foley KF, Boccuzzi L. Urine Calcium: Laboratory Measurement and Clinical Utility. *Lab Med*. 2010 Nov; 41(11): 683-686.
- Redmond J, Jarjou LM, Zhou B, Prentice A, Schoenmakers I. Ethnic Differences in Calcium, Phosphate and Bone Metabolism. *Proc Nutr Soc*. 2014 May; 73(2): 340-351.
- Bilezikian JP, Brandi ML, Eastell R, Silverberg SJ, Udelsman R, Marcocci C, Potts JT Jr. Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement From the Fourth International Workshop. *J Clin Endocrinol Metab*. 2014 Oct; 99(10): 3561-3569.
- Hannan FM, Howles SA, Rogers A, Cranston T, Gorvin CM, Babinsky VN, Reed AA, Thakker CE, Bockenhauer D, Brown RS, Connell JM, Cook J, Darzy K, Ehtisham S, Graham U, Hulse T, Hunter SJ, Izatt L, Kumar D, McKenna MJ, McKnight JA, Morrison PJ, Mughal MZ, O'Halloran D, Pearce SH, Porteous ME, Rahman M, Richardson T, Robinson R, Scheers I, Siddique H, Van't Hoff WG, Wang T, Whyte MP, Nesbit MA, Thakker RV. Adaptor Protein-2 Sigma Subunit Mutations Causing Familial Hypocalciuric Hypercalcaemia Type 3 (FHH3) Demonstrate Genotype-Phenotype Correlations, Codon Bias and Dominant-Negative Effects. *Hum Mol Genet*. 2015 Sep 15; 24(18): 5079-5092.
- Nesbit MA, Hannan FM, Howles SA, Babinsky VN, Head RA, Cranston T, Rust N, Hobbs MR, Heath H 3rd, Thakker RV. Mutations Affecting G-protein Subunit  $\alpha 1$  in Hypercalcemia and Hypocalcemia. *N Engl J Med*. 2013 Jun 27; 368(26): 2476-2486.
- Szalat A, Shpitzen S, Tsur A, Zalmon Koren I, Shilo S, Tripto-Shkolnik L, Durst R, Leitersdorf E, Meiner V. Stepwise CASR, AP2S1, and GNA11 Sequencing in Patients With Suspected Familial Hypocalciuric Hypercalcemia. *Endocrine*. 2017 Mar; 55(3): 741-747.
- Vargas-Poussou R, Mansour-Hendili L, Baron S, Bertocchio JP, Travers C, Simian C, Treard C, Baudouin V, Beltran S, Broux F, Camard O, Cloarec S, Cormier C, Debussche X, Dubosclard E, Eid C, Haymann JP, Kiando SR, Kuhn JM, Lefort G, Linglart A, Lucas-Pouliquen B, Macher MA, Maruani G, Ouzounian S, Polak M, Requeda E, Robier D, Silve C, Souberbielle JC, Tack I, Vezzosi D, Jeunemaitre X, Houillier P. Familial Hypocalciuric Hypercalcemia Types 1 and 3 and Primary Hyperparathyroidism: Similarities and Differences. *J Clin Endocrinol Metab*. 2016 May; 101(5): 2185-2195.
- Lee JY, Shoback DM. Familial Hypocalciuric Hypercalcemia and Related Disorders. *Best Pract Res Clin Endocrinol Metab*. 2018 Oct; 32(5): 609-619.
- Lassen T, Friis-Hansen L, Rasmussen AK, Knigge U, Feldt-Rasmussen U. Primary Hyperparathyroidism in Young People. When Should We Perform Genetic Testing for Multiple Endocrine Neoplasia 1 (MEN-1)? *J Clin Endocrinol Metab*. 2014 Nov; 99(11): 3983-3987.
- DeLellis RA, Mazzaglia P, Mangray S. Primary Hyperparathyroidism: A Current Perspective. *Arch Pathol Lab Med*. 2008 Aug; 132(8): 1251-1262.
- Marx SJ, Attie MF, Levine MA, Spiegel AM, Downs RW Jr, Lasker RD. The Hypocalciuric or Benign Variant of Familial Hypercalcemia: Clinical and Biochemical Features in Fifteen Kindreds. *Medicine (Baltimore)*. 1981 Nov; 60(6): 397-412.

# Division News

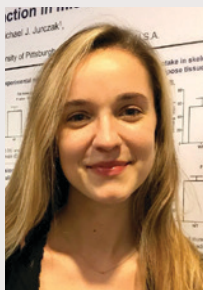
## Awards and Accomplishments



**Moira Anderson**, a John Carroll University undergraduate, received an American Heart Association Summer Undergraduate Research Program award under the mentorship of Michael Jurczak, PhD.



**Gillian Ahrendt** (left, above) and **Mackenzie Moon** (left, below), University of Pittsburgh medical students, were awarded T35 research fellowships through the Dean's Summer Research Program to conduct research, both of which received Certificates of Merit, with mentor Michael Jurczak, PhD.



**Aneta Kowalski**, University of Pittsburgh medical student and Howard Hughes Medical Institute (HHMI) Fellow, received a second year of support from the HHMI to continue her research under the mentorship of Erin Kershaw, MD. She was also awarded the Bench/Basic Research Science Award during the annual University of Pittsburgh Department of Medicine Research Day.



**Lia Edmunds, PhD** (Postdoctoral Scholar), under the mentorship of Michael Jurczak, PhD, was awarded an American Diabetes Association Postdoctoral Fellowship Award and was also accepted into the American Diabetes Association's Focus on Fellows Program.



**Ruya Liu, MD, PhD** (Instructor), under the mentorship of Vijay Yechoor, MD, was awarded an American Heart Association Career Development Award.



**Krystle Frahm, PhD** (Instructor), under the mentorship of Erin Kershaw, MD, was awarded a Samuel and Emma Winters Foundation Grant, as well as an R21 from the NIH.

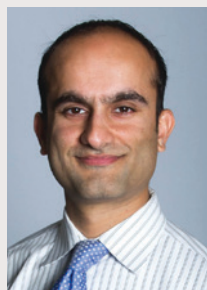


**Helena Levitt, MD** (left, above), **Mary Korytkowski, MD** (left, below), **Susan Greenspan, MD**, and **Sue Challinor, MD**, were awarded the honor of being named to the 2019 *Pittsburgh Magazine* Best Doctors.



**Sann Mon, MD** (Clinical Assistant Professor) was elected as a fellow of the American Association of Clinical Endocrinologists.





**Hussain Mahmud, MD** (Clinical Assistant Professor), became certified in Obesity Medicine by the American Board of Obesity Medicine.



**Jason Ng, MD** (left, above), and **Esra Karslioglu French, MD** (left, below), were promoted to Clinical Associate Professors.



**Sadeesh Ramakrishnan, DVM, PhD** (Assistant Professor), was awarded a pilot grant from the Pittsburgh Liver Research Center.



**Jagdeesh Uljal, MD** (Clinical Associate Professor), was awarded an EnVision CF: Emerging Leaders in Cystic Fibrosis Endocrinology II Program grant.

## At the ADA



The UPMC Division of Endocrinology and Metabolism continued to maintain a large presence at the 2019 American Diabetes Association Scientific Sessions in San Francisco, California. Faculty and fellows served as invited speakers and presented research and clinical findings. UPMC and the Division of Endocrinology hosted the Third Annual UPMC Alumni and Friends Reception, continuing the tradition of creating a warm and exciting atmosphere for colleagues and invited guests to enjoy drinks and hors d'oeuvres while they network. **Erin Kershaw, MD** (above, left), and **Ingrid Libman DeGordon, MD, PhD** (above, right), hosted the reception.



**Alexandra Clark, MD** (above, fifth from left), was nominated by our endocrine fellows to receive the 2019 Frederick DeRubertis Golden Apple Teaching Award.

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## Division News (Continued from Page 13)

### New Faculty



**Diana Pinkhasova, MD**, completed her residency in internal medicine (2017) and fellowship in endocrinology (2019) at UPMC before joining our Division as a Clinical Assistant Professor of Medicine in August. Her clinical interests include general endocrinology and diabetes. Her scholarly interests include improving the inpatient discharge process for patients with diabetes with the goal of reducing hospital readmissions. Dr. Pinkhasova also is serving as the Division's Wellness Champion.



**Charity Kwamanakweenda, MD, MBA**, completed her residency in internal medicine at Medstar Health Baltimore (2017) and her fellowship in endocrinology at the University of Virginia (2019) before joining our Division as a Clinical Assistant Professor of Medicine in September. She has also completed a Masters of Business Administration (MBA) with a concentration in Health Care (2017). Her clinical and scholarly interests are related to telehealth and the use of telehealth platforms for patient and provider education.



**Pouneh Fazeli, MD, MPH**, received her MD from the University of Pennsylvania (2002) and her Master's in Public Health (MPH) from the Harvard School of Public Health (2012). She completed her residency in internal medicine at Columbia University Medical Center (2005) and her fellowship in endocrinology at Massachusetts General Hospital in Boston (2010). Her scholarly interests focus on neuroendocrine and hormonal adaptations to undernutrition and starvation. Her clinical interests focus on neuroendocrinology. She is serving as our new Director of Neuroendocrinology. Dr. Fazeli joined our Division as an Associate Professor of Medicine in September.



**Alison Kohan, PhD**, received her PhD in Biochemistry and Pharmacology from West Virginia University (2009). She went on to complete a fellowship in lipid and lipoprotein metabolism at the University of Cincinnati (2014). Her research interests include the role of systemic and intestinal lipoproteins biology and how they impact normal metabolism and disease. Dr. Kohan joined our Division as an Associate Professor of Medicine in September.

## Faculty Positions Available

**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](mailto: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](mailto:endoadm@pitt.edu)). *EEO/AA/M/F/Vets/Disabled*

## Notable Publications

**Karajgikar ND, Manroa P, Acharya R, Codario RA, Reider JA, Donihi AC, Salata RA, Korytkowski MT. Addressing Pitfalls in Management of Diabetic Ketoacidosis (DKA) With a Standardized Protocol. *Endocr Pract.* 2019 May; 25(5): 407-412. doi: 10.4158/EP-2018-0398. Epub 2019 Jan 18.**

The objective of this study was to determine the efficacy and safety of a diabetic ketoacidosis (DKA)-Power Plan (PP) for guiding intravenous (IV) insulin infusions prior to anion gap (AG) closure and administering subcutaneous (SC) insulin  $\geq 1$  hour before discontinuing IV insulin. To achieve this goal the authors performed a retrospective chart review of patients with DKA before (pre-PP) ( $n = 60$ ) and following (post-PP) ( $n = 60$ ) implementation of a DKA-PP. Groups were compared for percentage of patients for whom IV insulin therapy was continued until AG closure, the percentage of patients receiving SC insulin  $\geq 1$  hour before discontinuation of IV insulin, and percentage of patients with rebound DKA during the index hospitalization. Results revealed that admission plasma glucose (514 mg/dL vs. 500 mg/dL;  $P = .36$ ) and venous pH (7.2 vs. 7.2;  $P = .57$ ) were similar in pre- and post-PP groups. Inappropriate discontinuation of IV insulin occurred less frequently in post-PP patients (28% vs. 7%;  $P = .007$ ), with a lower frequency of rebound DKA (40% vs. 8%;  $P = .001$ ) following acute management. More post-PP patients received SC insulin  $\geq 1$  hour before discontinuation of IV insulin (65% vs. 78%;  $P = .05$ ). In conclusion, implementation of a DKA-PP was associated with appropriate discontinuation of IV insulin in more patients, more frequent administration of SC insulin  $\geq 1$  hour prior to discontinuation of IV insulin, and fewer episodes of rebound DKA.

**Karslioglu French E, Donihi AC, Korytkowski MT. Diabetic Ketoacidosis and Hyperosmolar Hyperglycemic Syndrome: Review of Acute Decompensated Diabetes in Adult Patients. *BMJ.* 2019 May 29; 365: l1114. doi: 10.1136/bmj.l1114. Review.**

Diabetic ketoacidosis and hyperosmolar hyperglycemic syndrome (HHS) are life threatening complications that occur in patients with diabetes. In addition to timely identification of the precipitating cause, the first step in acute management of these disorders includes aggressive administration of intravenous fluids with appropriate replacement of electrolytes (primarily potassium). In patients with diabetic ketoacidosis, this is always followed by administration of insulin, usually via an intravenous insulin infusion that is continued until resolution of ketonemia, but potentially via the subcutaneous route in mild cases. Careful monitoring by experienced physicians is needed during treatment for diabetic ketoacidosis and HHS. Common pitfalls in management include premature termination of intravenous insulin therapy and insufficient timing or dosing of subcutaneous insulin before discontinuation of intravenous insulin. This review covers recommendations for acute management of diabetic ketoacidosis and HHS, the complications associated with these disorders, and methods for preventing recurrence. It also discusses why many patients who present with these disorders are at high risk for hospital readmissions, early morbidity, and mortality well beyond the acute presentation.

**Ramakrishnan SK, Zhang H, Ma X, Jung I, Schwartz AJ, Triner D, Devenport SN, Das NK, Xue X, Zeng MY, Hu Y, Mortensen RM, Greenson JK, Cascalho M, Wobus CE, Colacino JA, Nunez G, Rui L, Shah YM. Intestinal Non-canonical NF $\kappa$ B Signaling Shapes the Local and Systemic Immune Response. *Nat Commun.* 2019 Feb 8; 10(1): 660. doi: 10.1038/s41467-019-08581-8.**

Microfold cells (M-cells) are specialized cells of the intestine that sample luminal microbiota and dietary antigens to educate the immune cells of the intestinal

lymphoid follicles. The function of M-cells in systemic inflammatory responses is still unclear. Here we show that epithelial non-canonical NF $\kappa$ B signaling mediated by NF $\kappa$ B-inducing kinase (NIK) is highly active in intestinal lymphoid follicles and is required for M-cell maintenance. Intestinal NIK signaling modulates M-cell differentiation and elicits both local and systemic IL-17A and IgA production. Importantly, intestinal NIK signaling is active in mouse models of colitis and patients with inflammatory bowel diseases; meanwhile, constitutive NIK signaling increases the susceptibility to inflammatory injury by inducing ectopic M-cell differentiation and a chronic increase of IL-17A. Our work thus defines an important function of non-canonical NF $\kappa$ B and M-cells in immune homeostasis, inflammation, and polymicrobial sepsis.

**Shah FA, Mahmud H, Gallego-Martin T, Jurczak MJ, O'Donnell CP, McVerry BJ. Therapeutic Effects of Endogenous Incretin Hormones and Exogenous Incretin-Based Medications in Sepsis. *J Clin Endocrinol Metab.* 2019 Jun 19. pii: jc.2019-00296. doi: 10.1210/jc.2019-00296. [Epub ahead of print]**

Sepsis, a complex disorder characterized by a dysregulated immune response to an inciting infection, affects over 1 million Americans annually. Dysglycemia during sepsis hospitalization confers increased risk of organ dysfunction and death, and novel targets for the treatment of sepsis and maintenance of glucose homeostasis are needed. Incretin hormones are secreted by enteroendocrine cells in response to enteral nutrients and potentiate insulin release from pancreatic beta cells in a glucose-dependent manner, thereby reducing the risk of insulin-induced hypoglycemia. Incretin hormones also reduce systemic inflammation in preclinical studies, but studies of incretins in the setting of sepsis are limited. This study found that targeting the incretin hormone axis in sepsis may provide a means of not only promoting euglycemia in sepsis, but also attenuating the pro-inflammatory response and improving clinical outcomes.



## DIVISION OF ENDOCRINOLOGY AND METABOLISM

### Clinical Treatment Areas

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

### Research Areas of Focus

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

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