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DIVISION OF ENDOCRINOLOGY AND METABOLISM

UPDATE IN

# ENDOCRINOLOGY

## Inside This Edition



### CME Credit

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Dear Colleagues,

We are pleased to share our latest edition of *Update in Endocrinology.* 2021 was another abnormal year, yet we continued to find ways to innovate and adapt. In this issue, we continue to highlight our contributions to the research, educational, clinical, and quality missions.

**J. Peter Rubin, MD, MBA**, professor and chair of the Department of Plastic Surgery, highlights our exciting collaboration with the UPMC Wound Healing Services. Dr. Rubin gives an overview of this multidisciplinary service line, as well as describing how this collaboration is improving clinical outcomes for diabetic foot ulcer within the UPMC health system.

On the clinical front, our medical director for the Pituitary Center of Excellence and director of the Neuroendocrinology Unit, **Pouneh K. Fazeli, MD, MPH**, gives an overview of the criteria proposed by the Pituitary Society to establish a Pituitary Center of Excellence, as well as how it came to be established at UPMC Presbyterian.

Complex cases continue to challenge our expertise and provide fellows with transformative lessons in clinical care. Second year clinical fellow, **Anamil Khiyami, MBBS**, and her mentor, **Pouneh K. Fazeli, MD, MPH**, present a clinical case outlining the physiology of the growth hormone/insulin-like-growth-factor 1 (GH/IGF-1) axis, silent somatotrophs adenomas, and potential causes of low IGF-1 levels.

Our Division continues to grow as we welcome **Sandhya Venkataraman, DO**, to our clinical faculty. Dr. Venkataraman joined us after completion of her endocrinology fellowship at Lehigh Valley Health Network. We also welcome **Sarah Snyder, MBA, PMP, LSSGB**, as our new director of operations for Endocrinology. Sarah came to our Division from UPMC Health Plan where she was the senior digital product manager.

In addition, we celebrate many accomplishments of our faculty and trainees. **Robert M. O'Doherty, PhD**, has accepted a new role as an Ombudsperson in the newly formed Ombuds Office within the School of Medicine. **Mara J. Horwitz, MD**, was promoted to assistant Vice-Chancellor within the Office of Research Protections. **Michael Jurczak, PhD**, was promoted to director for the Center for Metabolic and Mitochondrial Medicine (C3M). **Ruya Liu, MD, PhD**, and **Andrey Parkhitko, PhD**, were both awarded Catalytic Grant Awards.

Finally, we would like to extend our gratitude once again to all health care and essential workers for their dedication during these challenging times. Please continue to stay safe and well.

Best wishes,

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

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UPMC LIFE CHANGING MEDICINE

# It Takes a Village: Helping Diabetic Foot Ulcer Patients Through Collaborative Team Care

**J. Peter Rubin, MD, MBA**

*Professor and Chair, Department of Plastic Surgery*

**Lauren Kokai, PhD**

*Assistant Professor, Department of Plastic Surgery*

Patients with diabetes are at high risk for diabetic foot ulcer (DFU), with an annual incidence of 6% in the diabetic population. The annual cost of diabetes is estimated to be around 250 billion dollars, and, alarmingly, patients who develop a diabetic foot ulcer have a five-year mortality approaching 50%. Throughout the state of Pennsylvania, and in particular the southwestern region of the state, diabetes is endemic. Moreover, many of the patients are members of underserved populations. Amputation rates and major mortality are much more likely in DFU patients that are underserved.

An exciting collaboration between the UPMC Division of Endocrinology and Metabolism and the UPMC Wound Healing Services is working to improve clinical outcomes for diabetic foot ulcer patients within the UPMC health system. UPMC Wound Healing Services, led by **J. Peter Rubin, MD, MBA**, professor and chair of the Department of Plastic Surgery, is a multidisciplinary service line encompassing 19 outpatient centers throughout Pennsylvania and western Maryland. Fourteen of these sites offer hyperbaric oxygen therapy. UPMC wound healing centers, collectively, have more than 70,000 patient visits annually. The multidisciplinary nature of the service line is a key factor in optimizing care for patients with diabetic foot ulcers and other chronic wounds. Specialties involved with the wound centers include plastic surgeons, vascular surgeons, general surgeons, orthopaedic surgeons, dermatologists, podiatrists, infectious disease experts, internists, family practice physicians, nephrologists, rheumatologists, gerontologists, and, of course, diabetes experts within the UPMC Division of Endocrinology and Metabolism. A keystone project in the service line has been the development of a standardized and integrated clinical pathway for diabetic foot ulcer management. Because evaluation and management of medical comorbidities play such an important role in the care of the diabetic foot ulcer patient, the entry point of the pathway includes evaluation and optimization of glycemic control, renal function, nutritional status, blood pressure, coronary artery disease, obstructive sleep apnea, and other significant morbidities. Lifestyle optimization, including smoking cessation and management of obesity, are also included in the early phases of the pathway. This is an area where the collaboration between the Division of Endocrinology and Metabolism and the UPMC Wound Healing Services has been particularly important and impactful. A direct link with Diabetes Education Services has been established throughout all our wound care centers so that glycemic control can be optimized in these patients. Notably, the collaboration has been deepened to include the UPMC Health Plan, which ensures more than 3 million people. **Esra Karslioglu-French, MD, MBA, ECNU**, who works across the UPMC Health Plan and the UPMC health system, and is herself a diabetes expert, has coordinated a data analysis project with the Wound Healing Service. Through this collaboration, we are now able to identify a subset of patients with poor glycemic control (A1C >8%) who also have a diabetic foot ulcer. This leverages the database capacity across the UPMC system to the benefit of our patients. The Division of Endocrinology and Metabolism and the UPMC Wound Healing Services will be piloting specific health coaching strategies to ensure greater attention and access to care for these patients who are at high risk for limb loss.

## Basic Science Research to Support Innovation

Given the cost, complexity, and comorbidity associated with diabetic ulcers, it is imperative we generate reliable preclinical models which can accurately replicate key biochemical and architectural components of chronic wounds. **Lauren Kokai, PhD**, who is an assistant professor of Plastic Surgery, and **Shawn Loder, MD**, a Burroughs-Welcome Fellow, are spearheading pioneering work. Large animal porcine models, commonly referred to as gold-standard for their similarity to human skin, are costly, limited by logistical barriers to training and husbandry, and critically lack the genetic tractability needed to easily dissect out biochemical pathways involved in wound pathology. Murine models, which are more affordable, accessible, and biologically versatile, remain critical. However, murine skin healing is typically dissimilar to the clinical reality of human diabetic wounds. While humans heal through slow stages of granulation and reepithelization, mice primarily heal by rapid contracture, often achieving epithelialization in under seven days. Radiation, infection, and genetic knockout of the wound healing cascade can more readily induce chronicity; however, model-specific side effects limit their broader applicability to diabetic wounds. Manipulation of the model to better replicate clinical conditions, a process referred to as “humanization,” is thus critical to this effect. In their

laboratory, they have capitalized on prior efforts to develop "humanized" murine wounds, including "oxidative stress" models, which manipulate the wound environment to delay healing. In this vein, they have developed a surgical model of wounding which reliably extends wound closure in diabetic animals past the seven-week mark with predictable delays in closure and a quasi-nonhealing state achievable between four and six weeks. The team has focused on the optimization of surgical models, specifically because of their replicability, ease of training and dissemination of technique, and applicability to the wide range of genetic backgrounds and systemic insults available in the murine space which allows us to better address the range of pathologies present in the human chronic diabetic wound.

### Clinical Research to Define Future Care

UPMC Wound Healing Services is part of the NIH NIDDK Consortium for research in diabetic foot ulcer biomarkers. UPMC is one of six sites nationally on the steering committee. This research team, including the chief of the Division of Endocrinology and Metabolism, **Erin Kershaw, MD**, seeks to investigate and validate clinically useful biomarkers that can be employed for diagnosis, prognosis, risk stratification, and treatment decisions. Additionally, basic science research in diabetic wound healing has yielded innovative new rodent models that better simulate the chronic state and inflammatory microenvironment of human diabetic wounds.

UPMC has a rich tradition of clinical excellence and research in diabetic wound healing. **David Steed, MD**, professor emeritus of Vascular Surgery, laid the groundwork for many current clinical algorithms. The UPMC Orthopaedic Foot and Ankle Division, led by **MaCalus Hogan, MD, MBA**, brings extensive expertise in managing boney deformities associated with higher risk of ulceration. Podiatric experts such as **Jarrett Cain, DPM, MSc**, also within the UPMC Orthopaedic Foot and Ankle Division, brings additional multidisciplinary expertise. The UPMC Division of Endocrinology and Metabolism plays a central role in the multidisciplinary landscape, and this team care approach is rapidly evolving to meet changing patient needs. Meaningful datasets enable detailed analysis across large diabetic patient populations and fuels innovation in this program.

# Pituitary Center of Excellence Established at UPMC Presbyterian

**Pouneh K. Fazeli, MD, MPH**

*Medical Director for the Pituitary Center of Excellence*

*Director of the Neuroendocrinology Unit*

*Associate Professor of Medicine*

The optimal management of pituitary tumors requires complex and seamless coordination between a multidisciplinary team of care providers. This multidisciplinary team consists of specialists in neuro-endocrinology and neurosurgery, as well as otorhinolaryngology, neuro-ophthalmology, neuroradiology, neuropathology, endovascular neurosurgery, neuro-oncology, and radiation oncology, among others. Recently, centers of excellence have been established in several specialties to designate institutions with the expertise, resources, and the ability to achieve optimal patient outcomes1 and in 2017, the International Pituitary Society proposed criteria for a Pituitary Center of Excellence.2

The characteristics proposed by the Pituitary Society for a Pituitary Center of Excellence include centers performing a high volume of pituitary surgeries, centers with a widely recognized group of multidisciplinary providers that are able to provide the best possible care for patients with pituitary pathology, centers that are leaders in training residents and fellows in the treatment of pituitary disease, and centers that provide community outreach and support to endocrinologists outside the Pituitary Center of Excellence.[2]

As a founding leader in endoscopic endonasal techniques, the team of pituitary surgery experts at UPMC, consisting of **Paul Gardner, MD**, and **Georgios Zenonos, MD**, both from the Department of Neurosurgery, and **Carl Snyderman, MD, MBA**, and **Eric Wang, MD**, both from the Department of Otolaryngology, far surpasses the criteria set by the Pituitary Society for yearly pituitary surgical volume. The surgical team is an unrivaled international leader in pioneering new techniques in endoscopic endonasal resection of

tumors and educating neurosurgeons and otorhinolaryngologists around the world on these techniques. In addition to surgical volume, the establishment of an innovative inpatient service aimed at optimizing the care of pituitary tumor patients sets us apart as a clear leader in pituitary tumor care. In November of 2019, an inpatient neuroendocrine service was established at UPMC Presbyterian. The service is staffed by a team of three neuroendocrine subspecialists who personally follow patients admitted to UPMC with pituitary pathology including all patients undergoing pituitary surgery. Since its inception, the team consisting of neuroendocrinologists **Hussain Mahmud, MD**, **Esra Karslioglu-French MD, MBA, ECNU**, and **Pouneh K. Fazeli, MD, MPH**, have performed nearly 400 inpatient consults. This specialized inpatient team has developed protocols to optimize the endocrine management of post-surgical pituitary patients, and the neuroendocrine service is continuously assessing the outcomes of these protocols through quality improvement analyses.

The team has also been a leader in educating the next generation of pituitary experts. In addition to the formally established surgical fellowships in neurosurgery and otorhinolaryngology for subspecialty training in endoscopic endonasal techniques, the Neuroendocrinology Unit has established weekly neuroendocrine rounds attended by all clinical endocrine fellows, medical residents, and advanced practice providers. At these formal weekly rounds, the management of all inpatients on the neuroendocrine service are discussed and reviewed in detail. In addition, University of Pittsburgh medical students, residents, and fellows actively participate in neuroendocrine research protocols and quality improvement projects.

A monthly Multidisciplinary Pituitary Conference is also held which further highlights the coordinated management of pituitary tumor patients by an interdisciplinary group of subspecialty experts. Discussion of each patient's case includes input from neuroendocrine, neurosurgery, neuroradiology, neuropathology, and often neuro-ophthalmology and radiation oncology. The conference is widely attended by members of the UPMC community and is a required conference for trainees, illustrating another important way in which the pituitary center is training future pituitary tumor subspecialists.

In 2021, UPMC Presbyterian was formally accredited as a Pituitary Center of Excellence with Dr. Pouneh Fazeli serving as medical director, and Dr. Paul Gardner serving as surgical director. This accreditation underscores the dedication of the Pituitary Center and its members to providing optimal, personalized care for patients with pituitary disease. Highlights of the Center's first year include the development of a virtual webinar on the "Multidisciplinary Management of Pituitary Tumors," which consisted of more than eight hours of lectures and was attended by more than 100 national and international participants; a subset of these lectures are now available for view on VuMedi. Members of the Pituitary Center of Excellence also participated in providing international guidance on the management of pituitary tumors during the early stages of the COVID-19 pandemic.[3-7] UPMC Presbyterian is also a newly established site for studies investigating medications for the treatment of functional pituitary tumors, such as Cushing's and acromegaly, providing patients access to new state of the art therapies.

**For more information regarding the Pituitary Center of Excellence at UPMC Presbyterian, please contact 412-586-9700.**


1. Elrod JK, Fortenberry JL. Centers of excellence in healthcare institutions: what they are and how to assemble them. BMC *Health Serv Res*. 2017;17(Suppl 1):425.
2. Casanueva FF, Barkan AL, Buchfelder M, Klibanski A, Laws ER, Loeffler JS, Melmed S, Mortini P, Wass J, Giustina A, Pituitary Society EpGoPT. Criteria for the definition of Pituitary Tumor Centers of Excellence (PTCOE): A Pituitary Society Statement. *Pituitary*. 2017;20(5):489-498.
3. Fleseriu M, Buchfelder M, Cetas JS, Fazeli PK, Mallea-Gil SM, Gurnell M, McCormack A, Pineyro MM, Syro LV, Tritos NA, Marcus HJ. Pituitary society guidance: pituitary disease management and patient care recommendations during the COVID-19 pandemic-an international perspective. *Pituitary*. 2020;23(4):327-337.
4. Taneja C, Fazeli PK, Gardner PA, Wang EW, Snyderman CH, Mahmud H. Rapidly Progressive Pituitary Apoplexy in a Patient with COVID-19 Disease Treated with Endoscopic Endonasal Surgery. *J Neurol Surg Rep*. 2022;83(1):e8-e12.
5. Champagne PO, McDowell MM, Wang EW, Snyderman CH, Zenonos GA, Gardner PA. Early practices in endonasal skull base surgery during the COVID-19 pandemic: a global survey. *Neurosurg Focus*. 2020;49(6):E12.
6. Dharmarajan H, Freiser ME, Sim E, Boorgu DSSK, Corcoran TE, Wang EW, Gardner PA, Snyderman CH. Droplet and Aerosol Generation With Endonasal Surgery: Methods to Mitigate Risk During the COVID-19 Pandemic. *Otolaryngol Head Neck Surg*. 2021;164(2):285-293.
7. Snyderman CH, Gardner PA. Endonasal drilling may be employed safely in the COVID-19 era. *Int Forum Allergy Rhinol*. 2020;10(9):1118-1119.


# NEW FACULTY

**Sandhya Venkataraman, DO**

Dr. Venkataraman obtained her DO at the Rowan University College of Osteopathic Medicine in 2016. She went on to complete an internal medicine residency at Lehigh Valley Health Network in 2019. Following completion of her residency, Dr. Venkataraman completed an endocrinology fellowship also at Lehigh Valley Health Network. Dr. Venkataraman will see patients at UPMC Passavant. Dr. Venkataraman joined our division as a clinical assistant professor in September 2021.

# A Challenging Case of a Silent Somatotroph Adenoma

**Pouneh K. Fazeli, MD, MPH**

*Medical Director for the Pituitary Center of Excellence*

*Director of the Neuroendocrinology Unit*

*Associate Professor of Medicine*

**Anamil Khiyami, MBBS**

*Second-Year Fellow, Division of Endocrinology and Metabolism, University of Pittsburgh School of Medicine*

## Case Presentation

A 23-year-old woman with no prior medical history presented to UPMC Presbyterian with a headache, nausea, and vomiting.

Three days prior to admission, the patient developed a sudden onset headache associated with nausea and vomiting. A brain MRI was performed in the emergency department and demonstrated a 2.8 cm sellar/suprasellar mass with evolving hemorrhage, suspicious for apoplexy. The neurosurgical and neuroendocrine teams were subsequently consulted. The patient reported regular monthly menstrual cycles and was not taking oral estrogen. She denied symptoms related to hyper or hypothyroidism. She also denied any changes in weight, and reported no history of nausea, vomiting, or orthostasis prior to this presentation. In addition, she was not experiencing any changes in shoe size or ring size, and denied galactorrhea, nocturia, polydipsia, or polyuria.

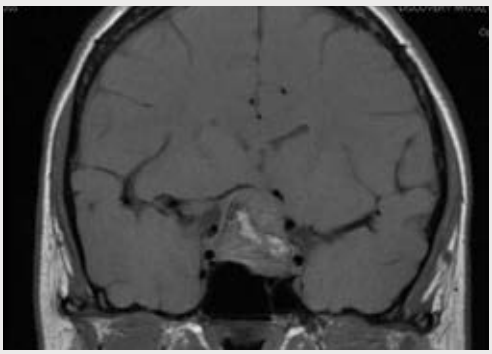
The patient was not taking any medications, vitamins, or supplements and denied using tobacco and EtOH. She reported working in a tire factory and following a vegan diet. The patient's family history was remarkable for a maternal grandfather and maternal uncle with nephrolithiasis. There was no reported history of pituitary tumors or neuroendocrine tumors.

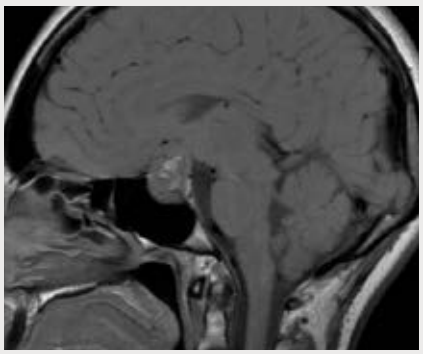
On examination, the patient was hemodynamically stable, and her BMI was low at 17.4 kg/m2. She did not appear Cushingoid or acromegalic. Her neurologic exam did not demonstrate any focal deficits, and ophthalmologic assessment was consistent with subjective blurring in her right peripheral visual field.

An evaluation was undertaken to assess for a functional adenoma as well as hypopituitarism, given the size of the sellar mass and the concern for apoplexy. Laboratory values were notable for a normal insulin-like-growth-factor 1 [IGF-1] level, normal TSH/Free T4, and a slightly elevated prolactin level (23.9 ng/mL), which was confirmed by serial dilution. A cortisol level of 4 mcg/dL was considered inappropriately low in the setting of acute illness, and stress-dose glucocorticoids were initiated. Given the clinical and radiologic findings suggestive of pituitary apoplexy, the patient under went emergent endoscopic endonasal resection of her tumor. Surgical pathology demonstrated a pituitary adenoma which was sparsely granulated and stained for growth hormone (GH). An IGF-1 level measured six weeks postoperatively was normal.

**Table I:** Preoperative Labs.

| Component | Latest Reference Range & Units | |
|---|---|---|
| Growth Hormone | 0.01 - 8.00 ng/mL | 2.90 |
| IGF-1 | 83 - 456 ng/mL | 163 |
| Z-score female | -2.0 - +2.0 | -0.5 |
| Prolactin | 0.6 - 20 ng/mL | 23.9 H |
| ACTH | 9 - 46 pg/mL | 12 |
| Cortisol | ug/dL | 18 |
| TSH | 0.300 - 5.000 uIU/mL | 0.332 |
| Free T4 | 0.89 - 1.78 ng/dL | 1.01 |
| FSH | 0.3 - 10.5 mIU/mL | 5.9 |
| LH | mIU/mL | 2.4 |





**Figures I and II:** A 2.8 x 1.9 x 2.5 cm heterogeneously enhancing sellar and suprasellar mass is seen. TheT1 bright area in the pituitary is consistent with hemorrhage or proteinaceous fluid. There is displacement of the optic chiasm.

## Discussion

As suggested by its name, the primary function of the GH/IGF-1 axis is to mediate growth. Importantly though, GH has another critical metabolic function. GH is a counter-regulatory hormone that allows us to survive prolonged periods of fasting; growth hormone has both lipolytic and insulin resistance effects.[1] Therefore, in patients with chronic caloric deprivation, such as those with anorexia nervosa, normal or high levels of GH are an adaptive response to the state of starvation; minimizing energy expenditure on growth is also an adaptive response, and IGF-1 levels are low in states of starvation.[2] This combination of adaptive responses is referred to as GH resistance.[2] GH resistance allows for the exploitation of the beneficial counter-regulatory effects of GH during periods of starvation, while minimizing energy expenditure on growth.

On the other end of the spectrum, in states of appropriate caloric intake, GH promotes anabolism by stimulating IGF-1 secretion from the liver. Normal functioning of this axis is essential during childhood and puberty for skeletal maturation. Among other anabolic effects, IGF-1 promotes bone acquisition via promotion of osteoblast differentiation.[3]

Acromegaly, a disorder characterized by GH excess, is a rare and underdiagnosed disorder of the GH/IGF-1 axis. In well over 90% of cases, acromegaly results from GH hypersecretion from a pituitary adenoma. Much more rarely, it can be due to hypothalamic or ectopic GHRH hypersecretion or due to ectopic GH production. The GH hypersecretion leads to overproduction of IGF-1, which typically results in multiple clinical signs/symptoms, including soft-tissue growth, hypertension, insulin resistance, and arthropathy.[4] Patients suspected of having acromegaly are screened with an IGF-1 level. If this level is definitively elevated in the setting of signs/symptoms of acromegaly, no further testing is needed to make the clinical diagnosis of acromegaly. In patients whose diagnosis cannot be confirmed with an IGF-1 level alone, further dynamic testing with an oral glucose tolerance test should be performed. Individuals who fail to suppress GH to less than 1 ng/ml [or < 0.4 ng/mL depending on the sensitivity of the assay] after a glucose load are diagnosed with acromegaly.[5]

Silent somatotroph adenomas, defined as pituitary adenomas that stain for GH, but are not associated with biochemical evidence of GH excess, account for approximately 2-4.2% of pituitary adenomas.[6–8] In contrast, some individuals will have biochemical evidence of acromegaly without clinical features, and this has been termed "clinically silent acromegaly."[9]

In 2017, Langlois et al. compared silent somatotroph adenomas to silent gonadotroph adenomas, which is the most frequent type of nonfunctional adenoma, and found that silent somatotroph adenomas occurred more frequently in women, presented at an earlier age, and were more likely to recur. There was a 29% recurrence rate after a mean follow-up of approximately four years.[7]

As diagnosis of clinically evident acromegaly is often delayed many years, one hypothesis as to why silent somatotroph adenomas are biochemically and clinically silent is that acromegaly is a spectrum with silent somatotroph adenomas representing the first phase of the disease, and "clinically silent acromegaly" representing another phase early in the disease course before physical changes have occurred. The transition from silent somatotroph adenomas to more clinically apparent disease has been reported by Langlois et al.[7] Two patients with silent somatotroph adenomas in their series developed an elevated IGF-1 level on a follow-up, including a 38-year-old woman whose IGF-1 level increased to 1.5 times the upper limit of normal, and who developed symptoms of arthralgias in the setting of the IGF-1 elevation.[7] Other proposed theories for the lack of biochemically evident GH excess include the production of a biologically inactive hormone.[10]

There are several other factors that can affect IGF-1 levels, one of which is estrogen. Oral estrogen has been shown to suppresses IGF-1.11 Estrogen lower IGF-1 levels, in part by increasing GH binding protein concentrations, and also through disruption of GH signaling.[12] Therefore, estrogen may decrease IGF-1 levels into the normal range, especially in early acromegaly.

Another factor that can affect IGF-1 levels is nutritional status. GH resistance is an adaptive response to chronic undernutrition. In a state of GH resistance, levels of GH (a lipolytic hormone with insulin-resistant effects) are normal or elevated, but IGF-1 levels (which mediate most of the growth-related actions of GH) are low. These levels minimize energy expenditure on growth. By observing the effects of a 10 day fast on the GH/IGF-1 axis, Clemmons et al. demonstrated the development of GH resistance during acute starvation. A sharp drop in IGF-1 levels to below normal range within five days of fasting, concomitant with an eventual increase in GH levels, was observed during the 10 day fast.[13]

Anorexia nervosa, a psychiatric disorder characterized by self-imposed chronic starvation and an inability to maintain a normal BMI, is a human model of chronic starvation. Anorexia nervosa is a state of GH resistance, and adolescent girls with anorexia nervosa have significantly higher nadir GH levels in response to an oral glucose load compared to normal-weight controls.[14] Fazeli et al. performed a randomized study of rhGH in individuals with anorexia nervosa.[15] Despite supraphysiologic doses of rhGH, levels of IGF-1 were similar in both the rhGH and placebo groups, suggesting that GH resistance cannot be easily overcome in states of undernutrition. Similarly, isolated protein deficiency also results in GH resistance,[16] as do some isolated vitamin deficiencies.[2]

## Conclusion

This patient had numerous possible reasons to account for a normal IGF-1 level preoperatively. Her BMI was low (in the anorexia nervosa range), and she followed a vegan (low protein) diet, both of which could lead to a state of GH resistance. A silent somatotroph adenoma also cannot be excluded in this case. Given her low BMI and poor protein intake, an oral glucose tolerance test was not performed due to the possibility that GH may not suppress in response to a glucose load in this setting.[14] Therefore, the patient's clinical, biochemical, and radiologic parameters will continue to be carefully and closely monitored.

Please refer to the Update in Endocrinology Spring 2022 CME course on UPMCPhysicianResources.com for a full list of references featured in this article.

# Notable Publications

**Morariu EM**, McCoy KL, Chiosea SI, Nikitski AV, Manroa P, Nikiforova MN, Nikiforov YE. Clinicopathologic Characteristics of Thyroid Nodules Positive for the THADA-IGF2BP3 Fusion on Preoperative Molecular Analysis. *Thyroid*. 2021 Aug;31(8):1212-1218. PMID: 33487086.

**Background:** Thyroid adenoma-associated *(THADA)-IGF2BP3* fusions have been identified as an oncogenic event in thyroid neoplasms. However, the prevalence of this gene fusion and associated phenotypical and clinical features are not well defined. The aim of this study was to characterize thyroid nodules positive for *THADA-IGF2BP3* fusions on preoperative molecular analysis, review surgical outcomes, and explore potential impact of the fusion detection on patient management.

**Methods:** Thyroid nodules positive for *THADA-IGF2BP3* fusion on ThyroSeq v3 genomic classifier (GC) testing of fine needle aspiration (FNA) (*n* = 30) samples from November 2017 to August 2019 were identified. Demographic and clinical data were obtained by retrospective chart review; pathology slides were re-examined.

**Results:** 30 nodules positive for *THADA-IGF2BP3* fusion on FNA were identified, representing 2% of 1280 nodules that underwent molecular analysis. Of the 27 nodules with available cytology diagnosis data, 22 (81%) were diagnosed as atypia of undetermined significance, 3 (11%) as follicular neoplasm, and 1 (4%) each were benign, and suspicious for malignancy. No additional mutations or gene fusions were identified in any of the nodules. Of the 24 cases with available clinical data, 22 (92%) *THADA-IGF2BP3*-positive nodules were managed surgically, 14 (64%) by thyroid lobectomy, and 8 (36%) by total thyroidectomy. Of the patients who had initial lobectomy, 3 (21%) had completion surgery. On surgical pathology, 7 (32%) *THADA-IGF2BP3*-positive nodules were malignant (six encapsulated follicular variant papillary thyroid carcinomas (EFVPTC), one minimally infiltrative FVPTC), 10 (45%) noninvasive follicular thyroid neoplasms with papillary-like nuclear features (NIFTP), and 5 (23%) follicular adenomas (FA). *THADA-IGF2BP3*-positive malignancies were intrathyroidal, without aggressive histology. Nodule size was similar between malignant nodules, NIFTP, and FA (2.6, 2.7, and 2.3 cm, respectively; p = 0.77). On limited follow-up (mean, 18 months) available for six patients with malignant fusion-positive nodule and four patients with NIFTP, no tumor recurrences were found.

**Conclusions:** In this series of patients, 77% of THADA-IGF2BP3 fusion-positive thyroid nodules were thyroid tumors requiring surgery, either papillary carcinoma or NIFTP. However, all cancers were low risk, predominantly encapsulated FVPTCs and can likely be adequately treated with lobectomy.

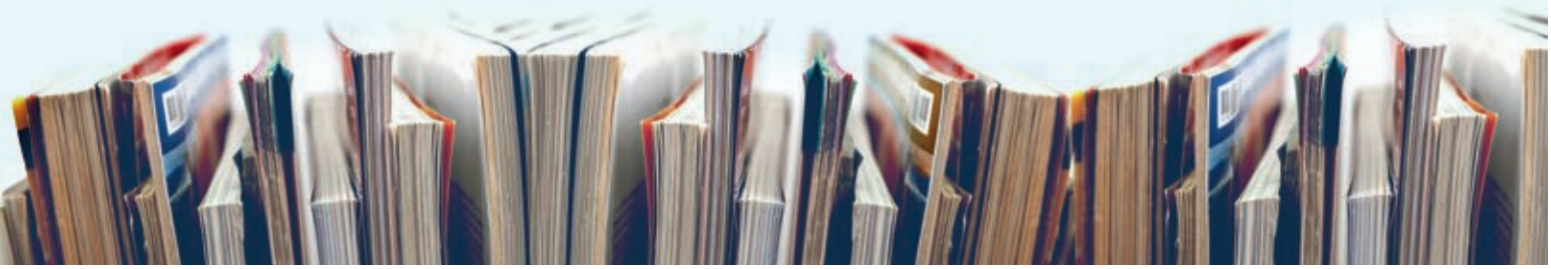
**Reddy Mooli RG**, Mukhi D, Pasupulati AK, Evers SS, **Sipula IJ**, **Jurczak M**, Seeley RJ, Shah YM, **Ramakrishnan SK**. Intestinal HIF-2α Regulates GLP-1 Secretion via Lipid Sensing in L-Cells. *Cell Mol Gastroenterol Hepatol*. 2021 Dec 11:S2352-345X(21)00254-X. Online ahead of print. PMID: 34902628.

**Background:** Compelling evidence shows that glucagon-like peptide-1 (GLP-1) has a profound effect in restoring normoglycemia in type 2 diabetic patients by increasing pancreatic insulin secretion. Although L cells are the primary source of circulating GLP-1, the current therapies do not target L cells to increase GLP-1 levels. Our study aimed to determine the molecular underpinnings of GLP-1 secretion as an impetus to identify new interventions to target endogenous L cells.

**Methods:** We used genetic mouse models of intestine-specific overexpression of hypoxia-inducible factor (HIF)-1α and HIF-2α ($Vhl^{\Delta IE}$), conditional overexpression of intestinal HIF-2α (Hif-2αLSL;Vilin-Cre/ERT2), and intestine-specific HIF-2α knockout mice (Hif-2αΔIE) to show that HIF signaling, especially HIF-2α, regulates GLP-1 secretion.

**Results:** Our data show that intestinal HIF signaling improved glucose homeostasis in a GLP-1-dependent manner. Intestinal HIF potentiated GLP-1 secretion via the lipid sensor G-protein-coupled receptor (GPR)40 enriched in L cells. We show that HIF-2α regulates GPR40 in L cells and potentiates fatty acid-induced GLP-1 secretion via ERK. Using a genetic model of intestine-specific overexpression of HIF-2α, we show that HIF-2α is sufficient to increase GLP-1 levels and attenuate diet-induced metabolic perturbations such as visceral adiposity, glucose intolerance, and hepatic steatosis. Lastly, we show that intestinal HIF-2α signaling acts as a priming mechanism crucial for postprandial lipid-mediated GLP-1 secretion. Thus, disruption of intestinal HIF-2α decreases GLP-1 secretion, leading to glucose intolerance.

**Conclusions:** In summary, we show that intestinal HIF signaling, particularly HIF-2α, regulates the lipid sensor GPR40, which is crucial for the lipid-mediated GLP-1 secretion, and suggest that HIF-2α is a potential target to induce endogenous GLP-1 secretion.



# Awards and Accomplishments

**Robert M. O'Doherty, PhD**, has accepted a new role as an Ombudsperson in the newly formed Ombuds Office within the School of Medicine. The Ombuds team of early career to retired faculty will help identify new opportunities for systemic change and also serve as a conduit in a confidential, safe, and unbiased way for students to bring meaningful suggestions for improving the school.

**Mara J. Horwitz, MD**, was promoted to assistant Vice-Chancellor within the Office of Research Protections.

**Michael Jurczak, PhD**, was promoted to director for the Center for Metabolic and Mitochondrial Medicine (C3M).

**Ruya Liu, MD, PhD**, has been awarded a Catalytic Grant Award through the K Awardee to R Advancement Training (KARAT) Program. The project supported by this funding is titled "Mechanistic Investigation of C5x Regulation of Cardiomyocyte Renewal."

**Andrey Parkhitko, PhD**, has been awarded a Catalytic Grant Award through the K Awardee to R Advancement Training (KARAT) Program. The project supported by this funding is titled "Targeting PRMT5 or E9z methyltransferases to delay frailty, improve motor function, and modulate epigenetic clock."

**Robert M O'Doherty, PhD**, was awarded an NIH R01 in collaboration with Zachery Freyberg, PhD, appointed in the Department of Psychiatry at the University of Pittsburgh. The title of this project is "Novel dopaminergic mechanisms of islet hormone secretion and antipsychotic drug-induced metabolic disturbances."

**Alison B. Kohan, PhD**, was awarded an NIH R01 in collaboration with Cristian Apetrei, MD, PhD, from the University of Pittsburgh Division of Infectious Diseases. The title of this project is "Impact of metabolic programing of T cells from the GI tract and related tissues on HIV reservoir seeding, maintenance and reactivation."

**Vijay Yechoor, MD**, was awarded an NIH R01 grant. The title of this project is "Circadian disruption-induced mitochondrial dysfunction in diabetes."

**Sarah Snyder, MBA, PMP, LSSGB**, has joined the Division as our new director of operations for Endocrinology. Sarah came to our Division from UPMC Health Plan where she was the senior digital product manager.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