Dear Colleagues,

We are pleased to share our latest edition of *Update in Endocrinology*. Even amid the global pandemic, we are closing out 2020 strong and are looking forward to many exciting endeavors in 2021. In this issue, we continue to highlight our contributions to the research, educational, clinical, and quality missions.

To highlight our research excellence, basic scientist Alison B. Kohan, PhD, discusses intestinal lipoproteins in normal metabolism and disease and the ongoing research the Kohan Lab is conducting on this topic. Dr. Kohan has been awarded a Kenneth Rainin Foundation Synergy Award in collaboration with Gwendolyn Randolph, PhD, to further the research on intestinal lipoproteins and their relation to Crohn’s disease.

On the clinical front, Jagdeesh Ullal, MD, MS, FACE, FACP, ECNU and Kara S. Hughan, MD, directors of the UPMC Adult and Pediatric Endocrinology Cystic Fibrosis Centers, respectively, discuss the multidisciplinary aspects of the Centers and how the care of patients with cystic fibrosis has evolved over the last 70 years. Drs. Ullal and Hughan were both awarded a grant through the Cystic Fibrosis Foundation EnVision CF: Emerging Leaders in CF Endocrinology II Program as mentee and mentor.

Complex cases continue to challenge our expertise and provide fellows with transformative lessons in clinical care. Clinical fellow Divya Sistla, MD, and her mentor, Hussain Mahmud, MD, present a clinical case discussing an unusual case of medullary thyroid cancer.

Lauren Willard, DO, and Archana Bandi, MD, discuss how the Endocrinology Divisions at UPMC and the VA Pittsburgh Healthcare System expanded their current telemedicine practices to create continuity of care for patients during the global COVID-19 pandemic.

Our division continues to grow as we welcome Stephanie Hakimian, MD, and Andrey Parkhiko, PhD, to our faculty. Dr. Hakimian’s clinical interests include diabetes care and complications prevention in underserved populations, as well as diabetes technology and artificial pancreases. Dr. Parkhiko’s research interests include the use of tumor models in *Drosophila* for the search of new modulators of tumorigenesis, as well as metabolic alterations and their potential targeting during aging.

In addition, we also celebrate many accomplishments of our faculty and trainees. Helena Levitt, MD, was chosen as one of the 2020 Best Doctors in America. Anjana Murali, a Physician Scientist Training Program student in the University of Pittsburgh School of Medicine, was awarded a NIDDK T32 supplement under the mentorship of Michael Jurczak, PhD.

Finally, we want to send a heartfelt message of gratitude and encouragement to all of our health care colleagues and essential workers for their dedication to our collective well-being during these challenging times. We are all in this together, and we will overcome. Please stay safe and well, and have a happy holiday season.

Best wishes,

Erin E. Kershaw, MD
Chief, Division of Endocrinology and Metabolism
Intestinal Lipoproteins in Normal Metabolism and Disease

Allison B. Kohan, PhD
Associate Professor of Medicine
Endocrinology and Metabolism

Critical Importance of Plasma Triglycerides in Disease
Cardiovascular disease (CVD) is the leading cause of mortality in the United States. In the past 40+ years, research and epidemiology has largely focused on the role of cholesterol, as low-density lipoprotein (LDL) as a major modifiable risk. As a result, we now have a variety of clinical approaches to lowering plasma cholesterol (most notably statin therapies). Despite the widespread and successful use of statins in patients to reduce blood cholesterol (by lowering non-cholesterol lipoproteins), LDL patients who present at the emergency room with myocardial infarction are almost all already prescribed statins3,4. Despite the widespread and successful use of statins, there are additional residual risk factors that we must find and treat in order to reduce CVD mortality.

In recent years, there has been significant progress in identifying and defining these residual risk factors. Most remarkably, triglycerides, especially after a meal, have been found to be strongly predictive of ischemic events in the U.S. population still have moderate-to-high cardiovascular disease risk, approximately 30% of the U.S. population still have moderate-to-high cardiovascular disease risk, approximately 30% of the U.S. population still have moderate-to-high cardiovascular disease risk. This highlights the fact that lowering blood cholesterol level, and successful statin therapy, does not fully reduce the risk of cardiovascular disease. There are additional residual risk factors that we must find and treat in order to reduce CVD mortality.

The small intestine as a metabolic organ.

Dietary Fat Absorption and Intestinal Lipoproteins
The crypt is found at the base of the villus, and the crypts house the entire intestinal stem cell population. The stem cells differentiate in culture with bile salts. These are relatively antagonistic to lipid absorption, which is a significant hurdle to studying the intestinal epithelium: the villus and crypt. The crypts are surrounded by the enteric nervous system, which secretes immune modulators. The crypts are also secreting VLDL to keep up with energy demands. Ultimately, patients can become a larger focus.

Conclusion and Future Directions
Lipid absorption by the small intestine is absolutely critical for whole-body metabolism and overall triglyceride concentration, but cannot be controlled by dietary risk factors for cardiovascular disease. Chylomicron metabolism also plays a critical role in determining plasma levels of triglycerides. The body's triglycerides to the rest of the body in easily metabolizable form (chylomicrons), the importance of the lymphatic route of lipid absorption (because otherwise all nutrients are shunted to the liver via portal circulation), and finally the inability to sustain energy homeostasis without dietary lipids. Diseases where these lipases are absent or reduced also cause a significant defect in dietary fat absorption.

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chylomicron synthesis and secretion, malabsorption, and inflammation with immune cells is a critical frontier for understanding inflammatory disease. The Kohan Lab has been using primary intestinal organoids to dissect these chylomycin-driven effects on human disease. Dr. Kohan’s team was the first to show that organoids recapitulate intestinal fat absorption by taking up triglycerides and secreting lipoprotein lipase (LPL) and low-density lipoprotein lipase (LDLr) in a chylomycin particle.31

Chylomicrons are difficult to isolate, and the intestine is notoriously finicky to study. Dr. Kohan’s team uses primary intestinal organoids to get around these issues and discover new metabolic processes that are chylomycin-driven. Researchers in the Kohan Lab have recently discovered a mechanism of regulatory T cell (Treg) regulation by intestinal chylomicrons. Specifically, they discovered that mice overexpressing apolipoprotein C-III are protected from dextran-sodium sulfate (DSS)-induced colitis and its associated symptoms. Conversely, apoC-III knockout mice are susceptible to severe colitis and have fewer colonic Tregs than their wild-type counterparts.

The canonical role of apoC-III is to inhibit lipoprotein Particle from triacylglycerol-rich lipoproteins like chylomicrons, by inhibiting lipoprotein lipase (LPL) and low-density lipoprotein receptor (LDLR). Building upon their team’s expertise in intestinal lipid metabolism and lipoprotein clearance, Dr. Kohan’s team found that intestinal Tregs and T cell express high levels of LPL and, in response to apoC-III, T cells take up less triacylglyceride. These data suggest that inhibiting lipoprotein uptake from chylomicrons into Tregs stimulates intestinal Tregs and protects against colitis. Dr. Kohan’s team is now dissecting the molecular mechanisms in the hopes that this pathway might be a therapeutic target for inflammatory bowel diseases.

References

Heralding a New Era in Cystic Fibrosis Care

Cystic Fibrosis Endocrinopathies

Cystic fibrosis (CF) is a multisystem disorder that results from pathogenic variants of the CF transmembrane conductance regulator (CFTR) gene on chromosome 7. The most common endocrinopathies that result from CF are manyfold, including diabetes, bone disease, hypogonadism, infertility, growth disorders, and malnutrition, in addition to multiple far-soluble vitamin deficiencies. While the most common pathophysiology is a progressive lung disease, which is often the cause of death, poor glycemic control and malnutrition greatly contribute to the worsening of lung disease. Individuals with CF have been known to develop a distinct form of diabetes referred to as type 3c diabetes mellitus (DM), which is distinct from type 1 and type 2 DM. Type 3c DM is characterized by exocrine pancreatic insufficiency and consequent a-t- cell dysfunction in the absence of autoimmune. This CF-related diabetes (CFRD) was previously referred to as pancreaticogenous diabetes; however, the American Diabetes Association and the World Health Organization have changed the terminology to type 3c diabetes. Individuals with CFRD are subject to the DM-related risks of microvascular disease such as nephropathy, nephropathy, and mortality.

The Cystic Fibrosis Center at the University of Pittsburgh

In 1955, a group of volunteers in the mid-1980s to lead what became the Cystic Fibrosis Center at the University of Pittsburgh. Dr. Joel Weinberg in 1983 to build the adult CF Program in Pittsburgh. The Lung Transplant Program at UPMC is a hallmark of the CFF, yet long before the concept of lung transplantation, the need to recruit an adult pulmonologist increased from 16 years in the 1970s, to 29 years, in the late 1980s. This generation needed to recruit an adult pulmonologist for adult CF care, leading to the hire of Dr. Joel Weinberg in 1983 to build the adult CF Center at the University of Pittsburgh and UPMC. Pediatric pulmonologist Dr. David Orenstein was recruited in the mid-1980s to lead what became the Antono J. and Janet Palumbo Cystic Fibrosis Center. Adult CF care are spearheaded by Dr. Kara Hughan at the Adult CF Center. The CF Center also supports basic and clinical research in CF. Via its role as a major participant in the National CF Clinical Research Network, the CF Center contributes to pre-clinical development and Phase 2 and 3 clinical trials of modulators of the CF transmembrane conductance regulator (CFTR). CFTR modulator treatments is a new class of small molecule therapeutics that represent a major development in the therapeutics of CF. With the approval and use of CFTR modulators and other pulmonary therapies over the last three decades, the median predicted survival for CF patients now approaches 50 years.

For more information, please visit the CFF’s website.
A Groundbreaking Change in Cystic Fibrosis Care

The CFTR gene regulates the chloride channel, and the lack of function of the chloride channels causes decreased transport of chloride and sodium. This leads to dehydration and ascension of epithelial cells and mucus membranes. CFTR is highly expressed in the pancreatic ducts and is essential for proper duct function. Its loss from ductal epithelium causes a profound improvement in lung function (FEV1), sweat chloride concentration, and quality of life. The combination medication ivacaftor-tezacaftor-lumacaftor (Trikafta®) with at least one F508del mutation. This represents a significant milestone in the development of therapeutics for CF.

CFTR modulator drugs may help to treat and/or prevent CFRD by recovering function, by improving insulin secretion, and reducing the inflammation and insulin resistance of systemic illnesses. The therapeutic effects of this drug class on endocrine pancreatic function and other organs remain to be ascertainment. A two-year observational study, in which UPMC Children’s Hospital of Pittsburgh is participating, (PRIDE: ClinicalTrials.gov: NCT04084047) has been designed to address longer-term, multi-system outcomes.

Case Reports of Individuals with CF Treated with Triple Combination Therapy

Case 1: A 48-year-old female with homozygous delta F508 mutation deletion CF was first identified to have CFRD in 2011 and was started on insulin therapy in early 2013. His HbA1c was 6.2% with insulin therapy. His CFRD had progressed to uncontrolled CFRD by mid-2015 with worsening glycemic control, an HbA1c of 9.2%, and a 4.7 kg weight loss noted. The worsening control of his blood glucose levels accompanied increased insulin needs. This required use of insulin, which further worsened blood glucose control. Eventually, his Lispro insulin was added with a carbohydrate ratio of 110:30, and he is given 1 unit for every 25 mg/dl above 150 mg/dl. The patient had a fear of needles, which may have contributed to his poor adherence to the prescribed insulin regimen. A team-based approach helped to identify his fear of needles. The problem was ameliorated by introducing him to AutoSched Duo needles that keep the needle tip hidden from view at the time of the injection. The patient worked closely with his psychologist and the social worker from his CF team to help overcome his anxiety and improve his willingness to take his injections, which yielded in improved weight gain. Unfortunately, the patient was unable to maintain self-management tasks, self-monitoring, and insulin adherence, which resulted in a subsequent rise of HbA1c levels to the 10-11% range. Insulin Degludec was his total daily Lispro doses remained constant at 60 units in divided doses. A professional CGM revealed an average sensor glucose of 220± 108 mg/dl. In 2019, the patient’s HbA1c again increased to 11.8%. Following this the patient was placed on the triple combination CFTR modulator, which led to rapid improvement in his HbA1c to 7.9%. With an HbA1c of 7.9% and a weight of 81 kg, insulin doses were reduced by 20% in order to prevent low blood glucose. While both patients above demonstrated a change in their insulin requirements and improvements in glycemic control, these are not universal results with triple combination therapy. Many of our CF endocrine colleagues, both adult and pediatric, across the country have reported varying effects of triple combination therapy on glycemic control. Until data from long-term studies are available, we recommend close monitoring of patients’ glycemic control in the weeks and months following initiation of modulator therapy. The care of CF is entering a new age where drug therapy is dramatically improving the pathophysiologic defect caused by mutation of CFTR.

Conclusion

CF is a complex disease that requires a team of professionals to deliver specialized and comprehensive care. Over the years, the natural evolution of CF care and best practices have grown and developed into one that is best delivered through the combined effort of a multidisciplinary team. The figure below represents members of a typical interdisciplinary CF care team. A group of trained and experienced CF specialist health care professionals can offer care that improves morbidity and mortality and face the challenges of addressing complex issues such as treatment of CFRD, pregnancy, renal disease, metabolic bone disease, malnutrition, and transplantation. Indeed, at CF centers, we embody a slogan from the Cystic Fibrosis Foundation – “Together is the way forward.”

References


Leaders in CF Endocrinology II Program as members of the Cystic Fibrosis Foundation. This award program provides training in developing expertise in the endocrinologic care of patients with CF. by developing and maintaining a CF Endocrine Clinic, a series of monthly webinars, and lectures and participation in local and national meetings. The program encourages the development of a research track in CF and promotes scholarly activity in CF Endocrine care. Drs. Hughson and Uhl have CF-designed Endocrine clinics that are conducted in conjunction with CF Pulmonary clinics and are actively engaged in their own clinical research projects. Continuity of care is established through a smooth transition from the pediatric CF Endocrine clinic to the adult CF Endocrine clinic. This multidisciplinary care model, along with ongoing research projects and the continuously growing literature on clinical care for patients with CF, enables the team at the CF Center to provide the most up-to-date evidenced-based care for our patients.
An Unusual Case of Medullary Thyroid Cancer

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Case Presentation

An 18-year-old Caucasian male presented to the UPMC Ear, Nose, and Throat Center with recent onset of painful neck nodules. He denied any swallowing difficulty, hoarseness, or other neck symptoms. He also denied fever, chills, night sweats, or weight loss. There was no history of head and neck radiation exposure. His past medical history included von Willebrand disease and asthma. His father had passed away from cholangiocarcinoma. Willebrand disease and asthma. His father had passed away from cholangiocarcinoma.

There was no family history of thyroid disease, including thyroid cancer. Physical examination showed left sided level III/IV diffuse enlargement of lymph nodes that were nontender and firm to palpation. Ultrasound imaging of the neck revealed a 1.8 x 1.4 x 1.4 cm heterogeneous hypoechoic thyroid nodule and a 2.5 cm left level IV cervical lymph node (see Figure 1). This thyroid nodule met criteria for FNA biopsy according to the American Thyroid Association (ATA) guidelines. Cytology from FNA of the thyroid nodule and lymph node was consistent with medullary thyroid cancer (MTC). Molecular testing with ThyroSeq V3 was positive for calcitonin expression and BRAF K601E mutation. Serum calcitonin was significantly elevated at 8268 pg/ml (normal 0-8 pg/ml), supporting the diagnosis of MTC.

The patient underwent total thyroidectomy with extensive lymph node dissection. Surgical pathology revealed a 2.1 cm primary tumor and 39 out of 41 lymph nodes positive for metastatic MTC with extrathyroidal and extra nodal extension. The margins were uninvolved by carcinoma. C-cell hyperplasia was also noted in background thyroid parenchyma. Pathological stage was pT3N1.

Genetics

Due to the patient’s young age, presence of an aggressive tumor, C-cell hyperplasia, and unusual molecular findings on cytology, aspirate, further testing to evaluate driver mutations and rule out heritable causes was performed. ThyroSeq V3 testing was performed both on the tumor sample and surrounding tissue. BRAF K601E mutation was only noted in the tumor, thus proving that this was a somatic mutation. Interestingly, RET mutation, which is the most common genetic mutation associated with hereditary MTC, was tested negative. The patient did not meet criteria for Familial Medullary Thyroid Cancer (FMTC) or Multiple Endocrine Neoplasia Type 2 (MEN2A).

Post Op Surveillance

The patient is continuing his care in the Endocrine Clinic with calcitonin monitoring and serial imaging. Eight months post thyroidectomy he was noted to have an increasing calcitonin level (1,295 pg/mL), and malignant appearing lymphadenopathy on imaging. He underwent selective bilateral neck dissection. Pathology confirmed the presence of metastatic MTC in 13/66 resected lymph nodes. Twenty-two months from initial diagnosis, a doubling of calcitonin (3,622 pg/mL) was observed (see Figure 2). A neck ultrasound at this time showed metastatic appearing lymphadenopathy increasing in size. Due to significant elevation in calcitonin level, and in order to rule out distant metastases, a Ga68-dotatate PET/CT scan was performed. Results did not show distant spread.

At the patient’s latest follow up visit (27 months after initial diagnosis), the calcitonin spontaneously decreased to 1538 pg/mL. Neck ultrasound showed marginal increase in size of a heterogeneous isoechoic and vascular right supraclavicular level 4/7 nodule when compared to the previous study six months prior (see Figure 3). Bilateral nonenlarged and nonspecific cervical lymph nodes were also noted.

The impression is that he has persistent but stable locoregional disease. Following extensive discussion with the patient and family, a third surgery was deferred due to high risk of local complications, which possibly include recurrent laryngeal nerve damage, hypoparathyroidism, and low probability of attaining a surgical cure.

Discussion

Medullary thyroid cancer (MTC) is a neuroendocrine tumor that originates from neural crest derived parafollicular C-cells of thyroid gland, accounting for one to two percent of thyroid cancers in the USA1 (some studies report 3-5% prevalence). MTC can occur sporadically (75%) or can be hereditary (25%). RET proto oncogene (rearranged during transfection) located on chromosome 10q11.2 contains a transmembrane receptor of tyrosine kinase family which is the most common gene associated with MTC. 2 Most patients with MEN2A, 2B and Familial MTC have RET germline mutation and ~ 50% of sporadic MTCs have somatic RET mutation.3 Somatic RET codon M918T mutation in sporadic MTC often has an aggressive clinical course.

RET was the first MTC-causing gene to be defined, but several other genes associated with MTC have now also been identified. In one study4, 84 cases of MTC were evaluated with whole-exome sequencing and fluorescence in situ hybridization. The analysis confirmed that mutations in the RET gene are the most common (~50%), followed by mutations in the HRAS and KRAS genes (combined incidence of 20% of MTCs in this study). Furthermore, RAS mutations were only found in sporadic tumors. In addition, a BRAF mutation leading to Lys601Asn (K601N) substitution was identified in one tumor.

Figure 1: Ultrasound of neck. Left panel showing a 1.8 x 1.4 x 1.4 cm heterogeneous hypoechoic left thyroid nodule. Right panel showing a 2.5 cm left cervical level IV lymph node.

Figure 2: Latest ultrasound imaging of neck showed metastatic appearing lymphadenopathy.
BRAF V600E mutations are the most common mutational events in papillary thyroid cancer. BRAF V600E mutations have also been previously described in well-differentiated thyroid cancer but lead to different biological behavior compared to BRAF V600E mutations, causing follicular patterned lesions. The presented case is particularly unique and challenging due to the lack of literature regarding BRAF V600E mutation in MTC. A Greek study reported the presence of KRAS (18 of 44 MTC cases - 40.9%) and BRAF V600E (30 of 44 MTC cases - 68.2%), but the MTC related findings have not been replicated in other studies. In another study, ALK fusions, including EML4-ALK and GFPT1-ALK, were found in 2% of MTCs (2 out of 98 cases). EML4-ALK has previously been reported in a variety of cancers but GFPT1-ALK seems to be a novel type of ALK fusion. With the advent of targeted therapies, identification of genetic drivers of cancer has become very important. ALK fusions represent good therapeutic targets and a number of effective ALK inhibitors (such as Crizotinib and Ceritinib) are approved for use in lung cancers that are positive for ALK fusions. One of the patients in this earlier study presented with a metastatic MTC carrying EML4-ALK, which was treated with Crizotinib and showed a clinically significant response. Unfortunately, none of the approved targeted therapies for MTC show activity against BRAF. Furthermore, the BRAF V600E targeting drug vemurafenib was not effective in a melanoma patient with BRAF K601I mutation, which potentially limits the targeted therapeutic options for our patient.

Role of Calcitonin

Secretory products of C-cells (Calcitonin and CEA) are valuable tumor markers in MTC. The serum concentrations of these markers are directly related to C-cell mass. New immunohistochemical assays (ICMAs) are highly sensitive and specific for monomeric calcitonin. With ICMAs, cross-reactivity with procalcitonin or other calcitonin-related peptides is largely eliminated, which reduces the need to perform standardized testing. Calcitonin doubling time of less than six months has been correlated with an adverse prognosis.

Role of Imaging in Follow Up

Several imaging modalities are available for ongoing surveillance. Ultrasound examination of the neck is recommended in all patients with MTC. Contrast-enhanced CT of the neck and chest, three-phase contrast-enhanced multi-detector liver CT or contrast-enhanced MRI of the liver and axial MRI and bone scintigraphy are recommended in patients with extensive neck disease and signs of regional or distant metastases, and in all patients with a serum Calcitonin > 500 pg/mL. F-DOPA PET/CT has been shown to have a higher sensitivity in detecting tumor load and extent of disease while FDG-PET/CT is more accurate in identifying disease progression. Ga68-dotatate PET/CT has been noted to be superior at detecting bone metastatic lesions. After a prior negative contrast enhanced CT scan of the chest, abdomen, and pelvis in the setting of rapidly rising calcitonin levels, the Ga68-dotatate PET/CT was performed to rule out bone metastases and distant metastatic disease as described above.

Conclusion

This challenging case and literature review are aimed to bring attention to the molecular landscape of MTC and new diagnostic and therapeutic approaches for this frequently aggressive type of thyroid cancer. This case adds information regarding a new genetic mutation associated with MTC.

References

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COVID-19, a disease caused by a novel coronavirus, SARS-CoV-2, has now become a worldwide pandemic. By October 2020, this disease has claimed more than 1 million lives worldwide, and more than 30,000 lives in the USA, with over 35.8 million cases worldwide. Originating as zoonotic transmission in wet markets in Wuhan, China, this disease quickly became highly transmissible in humans through aerosol droplets. The challenges of social distancing, containment, isolation, and providing capacity across hospitals, clinics, and emergency departments have led to an increase in demands for technologically-assisted care delivery strategies, such as telemedicine and web-based care. Recognizing the dire need for telemedicine, the U.S. Department of Health and Human Services modified federal privacy and billing regulations under the CARES Act Provider Relief Fund, allowing nationwide escalation of adoption telemedicine modalities. The Endocrinology Telemedicine Unit, under the leadership of Lauren Willard, DO, (Clinical Lead, Telemedicine, UPMC Endocrine Division) and Archana Bandi, MD, (Clinical Director, Telehealth Services, VA Pittsburgh Healthcare System Endocrine Division) have experienced the rapid growth of telemedicine services over the last two quarters. While the global COVID-19 pandemic encouraged this growth, our division had already recognized the importance of telehealth services and were on a trajectory to more broadly and rapidly incorporate virtual visits. These services were pivotal to the care of patients living in remote communities.

UPMC Telemedicine

A diabetes team-based telemedicine glycemic management model, known as Telemedicine for Reach, Education, Access, and Treatment (TREAT) was introduced in 2010. Patients identified by their local primary care provider are referred to TREAT, a model that integrates the specialty expertise of an endocrinologist and diabetes educator, whose services are often unavailable to people in these outlying communities. The local diabetes educator attends the visit with the patient at the remote site and is able to help with implementation and provide ongoing follow-up and support for the treatment plan prescribed by the endocrinologist. Although TREAT was shown to improve glycemic, behavioral, and psychosocial outcomes, the program was limited by requiring the patient to travel to a teleconsult center. Patients with impaired mobility or access to transportation still experienced unaddressed barriers to care despite local teleconsult centers. In 2019, to address these limitations as telehealth opportunities evolved and expanded, a video model of telehealth services was launched to provide direct patient video conferencing for access to specialist care. Patients are connected to the endocrinologist via their personal cell phone or computer, which eliminated the need to travel to a teleconsult center. With positive provider and patient feedback this program was expanded pre-COVID-19 to offer direct to patient video conferencing services care to patients with diabetes.

In addition to outpatient telehealth, our inpatient services, at all sites, are using HIPAA compliant video platforms to communicate with patients and provide effective inpatient consultations. As of 2019, under the leadership of Endocrine Medical Director Ezra Karlsig-lou-French, MD, provider-to-provider e-consults were launched to address clinical questions and provide expedited care for PCs with endocrine concerns for their patients. Provider-to-provider e-consults also help to improve patient access for when face-to-face or video encounters are required.

Since diabetes visits for glycemic management are data driven encounters, the ability to download data from insulin pumps, meters, and continuous glucose monitors became apparent and imperative to assure quality care. The Endocrine Division implemented the Tidepool system, a nonprofit organization committed to providing free software for the diabetes community. Tidepool software provides support to more than 50 diabetes personal devices and applications so that patients can use a single platform for data sharing in their providers. The UPMC Thrive Grants for Change allowed for the installation of Tidepool at our clinical sites, as well as hiring a liaison to help support staff and patients with creating accounts. Although the Division was already engaging in telemedicine visits, the COVID-19 pandemic led to an increase from approximately eight outpati
...showed care was driven to be comparable to care to patients in achieving glycemic control and allowed for better long-term control without burdening resources. Furthering this approach of the telemedicine model and creating collaborative pathways through Diabetes Care Network, her team further elucidated the importance of breaking the silo among care using the telehealth technologies to expand the access to care for patients located in remote locations.

Prior to the pandemic, VAPHS had one of the most expansive telehealth programs in the nation, namely:

a) robust utilization of home telehealth monitoring services for various biotechs using diagnostic services during the COVID-19 environment,

b) store and forward program for tele-dermatology, tele-wound, and tele-renal tests,

c) Clinical Video Telehealth (CVT) that connected veterans from their remote, scalable primary care (PC) clinics to specialty care clinics located in Pittsburgh,

d) electronic consultation allowing specialists to provide consultations to patients and PC providers in an expedited manner,

e) MyHealthVet platform that allows veterans and assigned caregivers to schedule appointments, request refills on prescriptions, access their test results, and communicate with providers via secure messaging,

f) VA Video Connect allowing video-to-home visits.

While the VAPHS was prepared to rapidly expand the telemedicine services to telemedicine, there were some challenges to overcome. In March 2020, based on CDC guidance and the state mandated lockdown, VAPHS initiated care delivery transition strategies to implement virtual modes to prevent the spread of COVID-19 amongst veterans and healthcare providers. Under the leadership of Executive in Charge Richard Stone, MD, VA central leadership created a COVID-19 response plan.

Encompassing four phases, this plan laid out the procedures for transitioning care in phase-1 to sustain operations and recovery in phase-4. For each of these phases, telehealth is set to play a pivotal role in the provision of continuity of care for scheduled and incidental outpatient care for non-infected veterans, as well as limit the spread of COVID-19 infection to veterans with the onset of social distancing constraints.

To enhance service during the pandemic, clinical staff working remotely served as liaisons to patients, connecting them to the necessary technology. This additional support allowed for approximately 75% of our visits to be completed via video. Our division was able to successfully complete 5,075 video visits from March through early June. In review of this data, the average age of patients utilizing telemedicine did not differ from those requiring face-to-face visits. Our reach was extensive, with 86% of our patient telemedicine visit volume coming from seven adjacent counties. Our data suggests that this platform is not just for younger, more tech savvy patients, but can be widely utilized by many of our patients despite their age and/or technological ability.

UPMC diabetics and diabetes educators have also been engaging patients via telemedicine and health systems, a resource invaluable with gaining insight into home conditions, resources for cooking and preparing meals, and some understanding of the surrounding situations could be affecting glycemic control. As patients become more acclimated to this technology and access and app-driven care, we expect it will create broader opportunities for education and ongoing self-management support.

The expansion of the Division’s telemedicine services is due to consistent support from UPMC leadership with telehealth initiatives. UPMC is one of the nation’s leading integrated health systems, aiming to provide high quality and efficient health care to residents across the tri-state area. We have reasoned in-office care when feasible and preferred by the patient, i.e. for procedures such as thyroid imaging or biopsy. For patient safety, telemedicine (VAPHS) has expanded face-to-face to all patients and visitors, mandated mask use in all clinical areas, provided entrance screening, and implemented visitor restrictions.

The pandemic required an immediate response and accelerated the ability of our providers, staff, and patients to adopt to telehealth approaches to care. We anticipate more than half of visits moving forward will remain virtual. Patients feel this platform has provided a beneficial alternative to face-to-face visits with use of data-sharing applications such as Tidelapse. These telehealth strategies will remain a vital means of delivering high-value ongoing care to our patients.

VA Pittsburgh Healthcare System Telemedicine

The VA Pittsburgh Healthcare System (VAPHS), an academic affiliate of the University of Pittsburgh, serves the western market of the Veterans Integrated Service Network 4 (VISN 4). Operating in a hub and spoke manner, with its two medical centers and five community-based outpatient clinics (CBOCs), VAPHS serves as the specialty care hub for remotely located spoke hospitals and CBOCs from Altoona, Erie, Butler, and Clarksburg. A majority of veterans seeking care at VAPHS reside in the mostly rural area of Pennsylvania, New York, Ohio, and parts of West Virginia, and carry a higher burden of chronic medical conditions such as diabetes (25%), obesity (13%), COPD, and congestive heart failure, which instantly puts veterans at a higher risk of poorer outcomes should they contract COVID-19.

Starting in 2010, Dr. Archana Bandi led a system wide endocrine core delivery transformation at VAPHS, initially with electronic consult services, and shortly thereafter with Clinical Video Telehealth services for veterans across geographic distanced areas served by VAPHS. In a large study comprising of more than 400 veterans in each cohort, her team showed that e-consults provide expedient care for veterans with type 2 diabetes mellitus (T2DM) located in remote locations. This...
Available Faculty Positions

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

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

Academic Clinical Neuroendocrinologist
The Division of Endocrinology at the University of Pittsburgh (Pitt) and its affiliated Medical Center (UPMC) seeks MD or MD/PhD candidates who are board-certified/eligible in Endocrinology for a position with a strong focus in neuroendocrinology. Pitt/UPMC has a well-established Multidisciplinary Neuroendocrinology Program, which includes multidisciplinary neuroendocrinology clinics, an active inpatient neuroendocrine service, a neuroendocrinology conference series, a quality improvement program, and ongoing research/scholarly work. Candidates should have a strong interest in neuroendocrinology and should be willing to contribute to all aspects of the academic mission (clinical care, education, and scholarly work). Candidates with research interests/qualifications are highly desirable. The primary appointment will be in the Division of Endocrinology within the Department of Medicine. An academic appointment at the University of Pittsburgh would be commensurate with experience, training, and achievement. Interested candidates should send a cover letter, curriculum vitae, and contact information for three references to Erin E. Kershaw, MD, Chief of Endocrinology, care of Chelsea Dempsey (email: endoadm@pitt.edu). EEO/AA/M/F/Vets/Disabled.

2020 ADA Tour de Cure Pittsburgh

The 2020 American Diabetes Association Tour de Cure Pittsburgh was held on Oct. 3, 2020. We again teamed up with the Pediatric Division of Endocrinology at UPMC Children’s Hospital of Pittsburgh and were able to donate over $6,000 to diabetes education, advocacy, and research. We look forward to this fantastic event again next year!

Multidisciplinary Thyroid Cancer Symposium

This year’s Multidisciplinary Thyroid Cancer Symposium was held on Nov. 14, 2020. Keynote speakers for this year’s Symposium were R. Michael Tuttle, MD, Acting Chief of the Endocrine Service at Memorial Sloan Kettering Cancer Center, and Kepal N. Patel, MD, Director of Endocrine Surgery at NYU Langone Health. Additional speakers discussed the most recent advances in thyroid cancer therapy, including but not limited to, methods of detection, treatment, and research.
Notable Publications


Interleukin-3 (IL-3) receptor α (IL3Rα) is a subunit of the ligand-specific IL-3R and initiates intracellular signaling in response to IL-3. IL-3 amplifies proinflammatory signaling and cytokine storm in murine sepsis models. Here we found that RNFT2 (RING finger transmembrane-domain containing protein 2, also TMEM118), a previously uncharacterized RING finger ubiquitin ligase, negatively regulated IL-3-dependent cellular responses through IL-3Rα ubiquitination and degradation in the proteasome. In vitro, IL-3 stimulation promoted IL-3Rα proteasomal degradation dependent on RNFT2, and we identified IL-3Rα lysine 357 as a ubiquitin acceptor site. We determined that LPS priming reduces RNFT2 and IL-3Rα abundance, extends IL-3Rα half-life, and sensitizes cells to IL-3Rα ubiquitination and degradation in the proteasome. Finally, we examined RNFT2 and IL-3Rα in human lung explants from patients with cystic fibrosis and also showed that IL-3 is elevated in mechanically ventilated critically ill humans at risk for acute respiratory distress syndrome. These results identify RNFT2 as a negative regulator of IL-3Rα and show a potential role for the RNFT2/IL-3Rα/IL-3 axis in regulating innate immune responses in the lung.


Prenatal alcohol exposure (PAE) affects at least 10% of newborns globally and leads to the development of fetal alcohol spectrum disorders (FASDs). Despite its high incidence, there is no consensus on the implications of PAE on metabolic disease risk in adults. Here, we describe a cohort of adults with FASDs that had an increased incidence of metabolic abnormalities, including type 2 diabetes, low HDL, high triglycerides, and female-specific overweight and obesity. Using a zebrafish model for PAE, we identified RNFT2 knockdown exacerbated inflammatory responses in LPS-induced murine lung injury. Finally, we examined RNFT2 and IL-3Rα in human lung explants from patients with cystic fibrosis and also showed that IL-3 is elevated in mechanically ventilated critically ill humans at risk for acute respiratory distress syndrome. These results identify RNFT2 as a negative regulator of IL-3Rα and show a potential role for the RNFT2/IL-3Rα/IL-3 axis in regulating innate immune responses in the lung.


Early onset insulin resistance, impaired glucose tolerance, and obesity were significantly elevated in PAE children. Although no differences in BMI were observed, PAE children showed an increased incidence of metabolic abnormalities compared to controls. These findings define metabolic vulnerabilities due to PAE and provide evidence that behavioral changes and primary organ dysfunction contribute to resultant metabolic abnormalities.


Knowledge of the genetic landscape of aggressive well differentiated thyroid cancers (WDTC) is lacking. Retrospective review of institutional database was performed to identify locally-invasive thyroid carcinomas and a comparison cohort of low-risk WDTC. ThryoSeq v2 next-generation sequencing was performed on available tissue. Survival time was analyzed by Kaplan-Meier methods and compared between groups via the log-rank test. Time to recurrence, treating death as a competing risk, was analyzed by cumulative incidence and compared between groups. Of 80 T4 tumors, 29 (36%) met inclusion criteria, of which 25 had genetic and clinicopathologic data. Most (24/25, 96%) harbored at least one genetic alteration, most commonly BRAF V600E (19, 76%), followed by mutations in the promoter region of TERT (14, 56%). Co-occurrence of BRAF and TERT was identified in 12 (48%) and associated with significantly higher risk of recurrence (p < 0.05). Conversely, co-occurrence of BRAF and TERT was present in only 5 of 102 (5%) patients presenting with early-stage WDTC. Compared to early-stage WDTC, co-occurrence of BRAF and TERT mutations are common in locally advanced (T4) thyroid cancer and are associated with an increased risk of recurrence. This knowledge may help predict aggressive behavior pretreatment and inform perioperative decision-making.
Anjana Murali, Physician Scientist Training Program student in the University of Pittsburgh School of Medicine, was awarded a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) T32 Medical Student Research Training Supplement grant under the mentorship of Michael Jurczak, PhD.

Previous T32 fellow Brittany Durgin, PhD, was awarded a F32 grant from the National Institutes of Health (NIH) under the mentorship of Adam Straub, PhD.

Margaret Zupa, MD; Lia Edmunds, PhD; Vrashali Shah, MD; Anju Paul, MD; and Hammam Alquadan, MD, were accepted into the American Diabetes Association Focus on Fellows program.

Charity Kwamanakweenda, MD, MBA, was promoted to medical director of UPP Endocrinology at UPMC Passavant. In her new role, Dr. Kwamanakweenda will oversee a group of UPP endocrinologists and APPs who will provide inpatient and outpatient endocrine care to UPMC Passavant patients.

Elena Moreau, MD, was named director of the Endocrine Thyroid Unit. In her new role, Dr. Moreau will lead the clinical and academic mission in thyroidology.

Mary Korytkowski, MD, was recognized as one of America’s Top Doctors for 2020 and one of the 2020 Best Women in Medicine. Dr. Korytkowski also received a National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) R01 in collaboration with Daniel Rubin, MD, MSc, FACE from Temple University.

Mary Korytkowski, MD; Susan Greenspan, MD; and Helena Levitt, MD, were chosen as 2020 Best Doctors in America.

Alison Kohan, PhD, received a Kenneth Rainin Foundation Synergy Award in collaboration with Gwendolyn Randolph, PhD from Washington University in St. Louis. This grant will be used to expand current research on Crohn’s disease.

Yusuke Sekine, PhD, received a Samuel and Emma Winters Foundation grant.

Lauren Willard, DO, was honored as one of the people throughout UPMC chosen to receive the 2019 Excellence in Patient Experience Award.

Esra Karalioglu-French, MD, was honored as an Award for Commitment and Excellence in Service (ACES) awardee. Less than 1% of UPMC employees are awarded this recognition.

Bokai Zhu, PhD, has been awarded a National Institutes of Health Director’s New Innovator Award from the NIH Common Fund’s High Risk, High Reward Research Program. This grant supports exceptionally creative scientists pursuing highly innovative research with the potential for broad impact in biomedical, behavioral, or social sciences within the NIH mission.

Erin Kershaw, MD, was awarded a Medical Student Research Mentoring Merit Award. This is a prestigious award initiated by medical student recommendations and is presented to a Longitudinal Research Project mentor of a graduating University of Pittsburgh School of Medicine student.

Pouneh Fazeli, MD, MPH, was chosen by our fellows to receive the 2020 Dr. Frederick DeRubertis Golden Apple Teaching Award.

Sann Mon, MD, was named the UPMC McKeesport Family Medicine Teaching Attending of the Year for the sixth year in a row.
NEW FACULTY

Stephanie Hakimian, MD, received her medical degree from the American University of Beirut in 2013. In 2018, she completed an internal medicine residency at the University of Miami/JFK Medical Palm Beach Regional GME. Dr. Hakimian completed her fellowship in endocrinology, metabolism, and molecular medicine at Northwestern University Feinberg School of Medicine in June 2020. Dr. Hakimian’s clinical interests include diabetes care and complications prevention in underserved populations, diabetes technology and artificial pancreas, as well as the management of other endocrine disorders involving the thyroid, pituitary, and adrenal glands. Dr. Hakimian joined our Division as a clinical assistant professor in July 2020.

Andrey Parkhitko, PhD, received his PhD from Russian State Medical University in 2013. As part of an exchange program, he completed his graduate studies at Fox Chase Cancer Center and Brigham and Women’s Hospital/Harvard Medical School. Dr. Parkhitko comes to the University of Pittsburgh following a postdoctoral fellowship in the Department of Genetics at Harvard Medical School. His research interests include the use of tumor models in Drosophila for the search of new modulators of tumorigenesis, as well as metabolic alterations and their potential targeting during aging. Dr. Parkhitko joined the Division of Endocrinology and the Aging Institute as an assistant professor of medicine in September 2020.

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