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DIVISION OF ENDOCRINOLOGY AND METABOLISM

UPDATE IN

ENDOCRINOLOGY

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Dear Colleagues,

We are pleased to share our latest edition of *Update in Endocrinology*. Despite the pandemic, we had a successful 2020 full of innovation and adaptability. In this issue, we continue to highlight our contributions to the research, educational, clinical, and quality missions.

To highlight our research excellence, physician-scientist **Frederico G. S. Toledo, MD**, chief of Endocrinology **Erin E. Kershaw, MD**, and chair of Epidemiology **Anne Newman, MD, MPH**, discuss the national, multi-site, NIH-funded "Study of Muscle, Mobility, and Aging (SOMMA)." Dr. Kershaw was recently awarded an ancillary R01 grant to study the role of adipose tissue in muscle, mobility, and aging to further the research of the primary SOMMA grant.

On the clinical front, Endocrine Director of Quality Improvement **Mary Korytkowski, MD**, and second year clinical fellow **Divya Sistla, MD**, discuss the importance of achieving glycemic control in patients with diabetes who are admitted to the hospital with COVID-19.

Complex cases continue to challenge our expertise and provide fellows with transformative lessons in clinical care. Second year clinical fellow, **Emily Gammoh, MD**, and her mentor, **Maja Stefanovic-Racic, MD, PhD**, present a clinical case discussing the diagnosis of a rare congenital endocrine syndrome after decades of misdiagnosis.

Co-directors of the Adult Endocrinology Advanced Practice Provider (APP) Fellowship Program, **Emily Emsurak, MPAS, PA-C**, and **Deborah Hlasnik, MSN, CRNP**, along with Endocrine Medical Director, **Esra Karslioglu-French, MD, MBA**, discuss the Division's Adult Endocrinology APP Fellowship Program. This Fellowship Program is one of the few in the country and provides specialty training to APPs to ensure high quality and evidence-based patient care in adult endocrinology.

Our Division continues to grow as we welcome **Janet Leung, MD** and **Brett Guinto, DO**, to our clinical faculty. Dr. Leung will serve as the Clinical Lead and Associate Program Director for Quality and Value. She has clinical subspecialty interests in caring for transgender and gender-diverse people. Dr. Guinto's clinical interests include general endocrinology, metabolic diseases (i.e. obesity, diabetes), and lifestyle medicine.

In addition, we also celebrate many accomplishments of our faculty. **Vijay Yechoor, MD**, from Endocrinology, was awarded a NIDDK R01 in collaboration with the team headed by Lans Taylor, PhD, and their collaborative team at the University of Pittsburgh Drug Discovery Institute to understand the pathogenesis of SARS-CoV-2 in the context of diabetes using microphysiological "tissues-on-a-chip" technology. **Frederico G. S. Toledo, MD**, from Endocrinology, in collaboration with Dhiraj Yadav, MD, from Gastroentrology, were awarded an NIH U01 grant to serve as a clinical center for a multi-site study to understand the relationship between diabetes and acute pancreatitis.

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

Best wishes,

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

BEST HOSPITALS U.S.News & WORLD REPORT NATIONAL DIABETES & ENDOCRINOLOGY 2020-21

Affiliated with the University of Pittsburgh School of Medicine, UPMC Presbyterian Shadyside is proud to be nationally ranked by *U.S. News & World Report* for excellence in endocrinology.

UPMC LIFE CHANGING MEDICINE

A Multidisciplinary Collaboration to Understand Muscle, Mobility, and Other Health Outcomes During Aging

Frederico G.S. Toledo, MD

Associate Professor of Medicine, Division of Endocrinology

Director of Clinical Research, Center or Metabolism and Mitochondrial Medicine (C3M)

Erin E. Kershaw, MD

Associate Professor of Medicine

Endowed Chair for Obesity Research

Chief, Division of Endocrinology

Anne B. Newman, MD, MPH

Chair, Department of Epidemiology

Katherine M. Detre Endowed Chair of Population Health Sciences

Distinguished Professor of Epidemiology

The Divisions of Endocrinology and Geriatrics in the Department of Medicine and the Department of Epidemiology at the University of Pittsburgh have teamed up with investigators from the University of California San Francisco, Wake Forest University, and the Advent Health Research Institute to "Study Muscle, Mobility, and Aging (SOMMA)" - a large multi-center grant funded by the National Institutes of Health.

Addressing the needs of the rapidly expanding aging population has become one of the most daunting challenges of our time. As individuals age, there is a gradual and progressive loss of physiological reserves that affects nearly every cell and organ system in the body. This ultimately contributes to frailty, a condition characterized by increased physical vulnerability during the aging process.[1] Body composition and fuel metabolism are also significantly impacted. With aging, there is an increase in whole-body adiposity and ectopic fat deposition, which contributes to the deterioration of glucose homeostasis and increases the prevalence of type 2 diabetes among the elderly. Other body composition changes include loss of bone mineral density, which can lead to osteoporosis and fractures, and a progressive and generalized decline in skeletal muscle mass and strength. This age-related decrease in skeletal muscle mass and function is known by the term sarcopenia and can result in significant clinical morbidity.[2] Sarcopenia has been associated with mobility disability, which substantially impacts quality of life.

Furthermore, loss of skeletal muscle strength can also indirectly contribute to the risk of falls and osteoporosis-related fractures, which are both common in the elderly population.

Because mobility disability is an important determinant of health and well-being among older adults, understanding its etiology is of paramount importance. To date, research has shown that no single factor uniquely explains the etiology of age-related sarcopenia and loss of mobility. Instead, there has been a realization that multiple factors contribute to its pathophysiology.[3] It has long been known in the field of endocrinology that androgens and the GH/IGF-1 axis exert anabolic effects on skeletal muscle and that both circulating sex hormone concentrations and GH/IGF-1 axis activity decline with aging. However, these changes only partially explain the multifactorial pathophysiology of age-related sarcopenia. In recent years, it has become apparent that advanced age is causally linked to intrinsic perturbations in several biological qualities of skeletal muscle. In addition to a decrease in muscle mass, there are changes in contractile capacity, mitochondrial bioenergetics, oxidative stress, and possibly even subtle degrees of denervation.[4] Cross-sectional studies and case-control studies of older vs. younger individuals have reported reduced mitochondrial content, function, and efficiency in connection with the aging process. Experiments in animals also suggest that subtle degrees of muscle cell denervation occur as a result of aging.[5]

However, what has not been elucidated yet is the relative importance and contribution of each one of these aspects of skeletal muscle biology to the pathogenesis of age-related declines in locomotor dysfunction and whether they explain the clinically-meaningful degrees of impairment in mobility among the elderly.

Furthermore, skeletal muscle itself functions as an endocrine organ that communicates multi-directionally with other important endocrine organs, such as adipose tissue, liver, pancreas, etc. Identifying mechanism-based biomarkers and/or therapeutic targets that can prevent, slow, or reverse aging-related mobility disability and other adverse effects of aging are urgently needed to develop therapeutic strategies that could preserve quality of life, prevent disability, and improve high-value care of the expanding aging population.

To answer these important questions, the National Institutes of Health (NIH) has awarded a research grant to conduct a large, multicenter, prospective observational study to understand the causes of mobility disability in elderly adults. The study, entitled "Study of Muscle Mobility and Aging (SOMMA)," targets the enrollment of 875 adults for a three-year observation period and examines how different properties of the skeletal muscle system affect the decline of locomotor function over time. SOMMA will be the first study to bring to light the specific biological changes in skeletal muscle that most strongly predict the development of major mobility disability and declines in fitness

that occur with advanced aging.
A unique characteristic of this study is the extremely comprehensive set of measurements. SOMMA employs highly-detailed cardiopulmonary and other specialized exercise tests to measure multiple aspects of physical activity performance. To understand the changes in mitochondrial bioenergetics and cellular and subcellular architecture, the investigational team has been performing muscle biopsies in all volunteers and is expected to generate one of the largest biorepositories of muscle biopsy samples from elderly volunteers at risk for mobility disability ever accumulated. The investigational team has also been employing state-of-the-art methodologies to study skeletal muscle and mitochondrial bioenergetics including high-resolution mitochondrial respirometry, histological assessments with immunofluorescence assays, electron microscopy, RNA-Seq for gene expression, 31-phosphorus magnetic resonance spectrometry to measure mitochondrial ATP production *in vivo*, and near-infrared spectrometry (NIRS). In addition, the NIH has also funded several SOMMA ancillary studies to examine important relationships between muscle/mobility and bone architecture/strength, brain function, and adipose tissue function, as well as inter-tissue endocrine communication during aging.

To accomplish these goals, the SOMMA study is led by a team of clinical and translational physician-scientists with complementary expertise and extensive clinical research experience across several academic sites. The University of Pittsburgh site includes investigators from the Department of Epidemiology (Graduate School of Public Health) and the Department of Medicine (School of Medicine). **Anne B. Newman, MD, MPH**, is the chair of the Department of Epidemiology and the Principal Investigator of the SOMMA study at the University of Pittsburgh site. She is an expert on the determinants of physical and cognitive function in aging and longevity. Multiple members of the Division of Endocrinology contribute to this study. **Frederico G.S. Toledo, MD**, is an associate professor of Medicine in the Division of Endocrinology and the director of Clinical Research for the Center for Metabolism and Mitochondrial Medicine. Dr. Toledo is an expert in insulin resistance and diabetes mellitus. He has published extensively on the topics of skeletal muscle metabolism and the effects of exercise on mitochondria. His laboratory of human metabolism conducts the detailed cardiometabolic exercise performance tests required by this study, as well as biopsies of skeletal muscle and adipose tissue for a range of assays. **Erin E. Kershaw, MD**, chief of the Division of Endocrinology, is an expert in adipose tissue biology and adipose-muscle endocrine communication and is investigating the role of adipose tissue in muscle, mobility, and aging through an NIH-funded SOMMA ancillary study on this topic. **Michael J. Jurczak, PhD**, is an assistant professor of Medicine in the Division of Endocrinology, the director of the Oroboros Respirometry Core in the Division of Endocrinology, and an expert in mitochondrial biology. He is responsible for determining muscle bioenergetics and mitochondrial function at the Pittsburgh site. **Daniel Forman, MD**, professor of Geriatrics, provides expertise in geriatric cardiology and aging. This broad multidisciplinary expertise and research infrastructure at the University of Pittsburgh, in combination with the complementary expertise at its partner institutions, will enable scientific inquiring to investigate some of the most elusive questions in the field of aging.

SOMMA is the first large longitudinal study in older adults to employ "gold standard" methods to solve persistent controversies about the relative contributions of age-related changes in muscle mass and function as a cause of impaired mobility in the elderly. As such, it is expected to generate results that will enhance our understanding of which key aspects of aging lead to mobility disability.

If you are interested in learning more about the Study of Muscle Mobility and Aging (SOMMA), please visit https://www.sommastudy.com or contact sommastudy@pitt.edu.

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Better Late Than Never: Diagnosis of a Rare Congenital Endocrine Syndrome

Emily Gammoh, MD

Co-Chief Clinical Fellow

Endocrinology and Metabolism

Maja Stefanovic-Racic, MD, PhD

Director, EDM Fellowship Training Program

Assistant Professor of Medicine
Endocrinology and Metabolism

Case Presentation

A 43-year-old Caucasian male presented to the outpatient Endocrinology Clinic for management of his long-standing pan-hypopituitarism and newly diagnosed osteoporosis. He had been previously managed by his primary care provider (PCP); however, after establishing care with a new PCP, he was then referred to the Endocrinology Clinic for management.

In 2003, at the age of 26, the patient was diagnosed with dermatomyositis and started on prednisone. In 2005, after two years of taking continuous steroids, the patient was diagnosed with adrenal suppression, likely secondary to exogenous steroid use. While taking the high dose prednisone, further work up at that time showed a normal growth hormone, IGF-1 and free T4, with a low thyroid-stimulating hormone (TSH), total testosterone, and free testosterone (Table 1). He was diagnosed with secondary hypogonadism and hypothyroidism and given the blanket diagnosis of pan-hypopituitarism. MRI of the pituitary was unremarkable. Along with continuing steroid therapy, testosterone replacement therapy and levothyroxine was initiated. Subsequent labs performed in 2011, after testosterone replacement therapy was withdrawn from the treatment regimen, revealed an elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which had not been previously checked (Table 1).

In 2019, one year prior to the patient's presentation to the Endocrinology Clinic, he was diagnosed with osteopenia and started on Fosamax once weekly by his PCP. The patient had gastric bypass surgery in 1997 and developed severe nausea and heartburn while taking Fosamax. That same year he had been complaining of increasing fatigue. He was prescribed increasing doses of prednisone under the presumption that his fatigue was due to inadequate steroid replacement for adrenal insufficiency. By the end of 2019, he was taking 120 mg of prednisone in daily divided doses. It is worth mentioning that the patient had not had a dermatomyositis flare in several years.

Unfortunately, the patient was admitted to the hospital in December of 2019 with a deep vein thrombosis (DVT) and pulmonary embolism (PE). He had experienced multiple DVTs and PEs in the past and had been diagnosed with antiphospholipid syndrome for which he was prescribed lifelong anti-coagulation treatment. Shortly afterwards, he was also found to have a vertebral compression fracture. The patient's prednisone dose was then tapered from 120 mg daily to 20-30 mg daily, which he had been taking at the time of his appointment in the Endocrinology Clinic in August 2020.

Other notable history included ongoing smoking of ½ a pack per day and no history of alcohol or drug use. He lives with his mother who helps manage all of his medications and appointments. He has never been married or fathered any children. He has a strong family history of rheumatoid arthritis and hypothyroidism, including Hashimoto's thyroiditis in one sister.

His extensive list of medications included prednisone 20-30 mg daily, testosterone cypionate 200 mg weekly IM, levothyroxine 125 mcg daily, Fosamax 70 mg weekly, and ergocalciferol 50,000 IU twice weekly.

At the time of presentation, the patient had multiple physical complaints including weight gain (50-60 pounds in one year), fatigue, leg swelling, muscle weakness, back pain, heartburn, and nausea.

The patient's physical examination was remarkable for marked central obesity, narrow shoulders, and broad hips, as well as an increased arm span (190 cm) compared to his height of 188 cm.

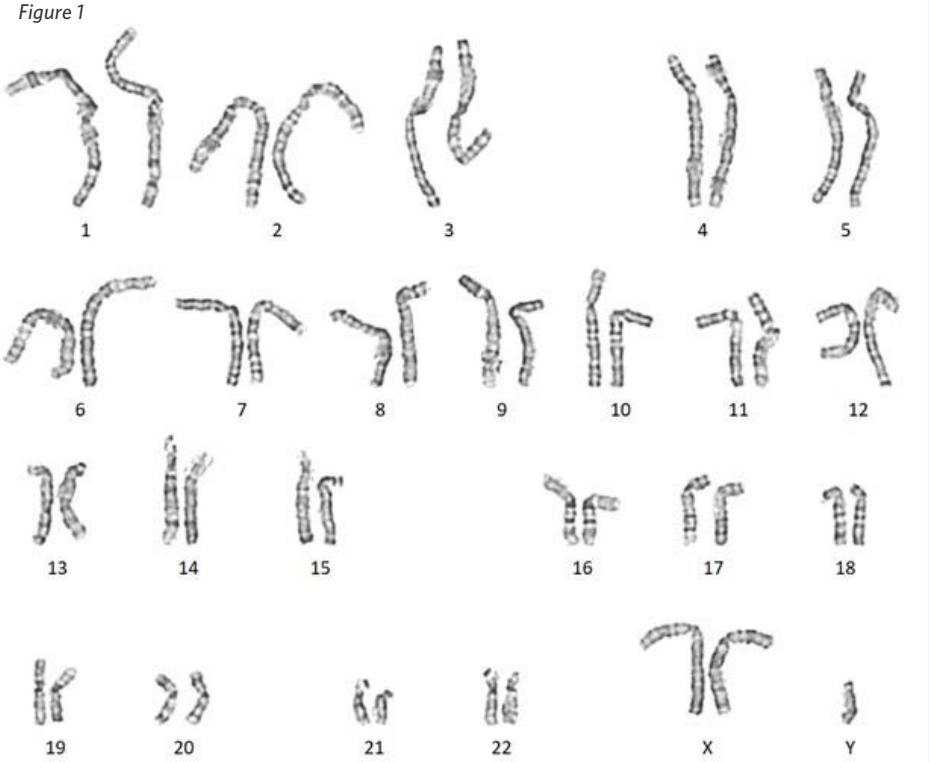
A recent ultrasound of the scrotum showed bilateral small testicles (~2 mL volume) with decreased vascularity.

To best serve this patient, priority was placed on weaning steroids to physiological doses (total daily dose of 30mg

Table 1

	July 2005	April 2011	November 2019
TSH	0.21 microIU/mL	1.92 microIU/mL	0.204 microIU/mL
Free T4	1.1 ng/mL		0.9 ng/dL
Total Testosterone	144.21 ng/dL	112 ng/dL	490 ng/dL
Free Testosterone		10.2 pg/mL	114.2 pg/mL
FSH		51.4 mIU/mL	0.4 mIU/mL
LH		25.7 mIU/mL	<0.2 mIU/mL
Prolactin	19 ng/mL		7.4 ng/mL
IGF-1	292 ng/mL		147 ng/mL
HbA1c			5.7%
Comments	On high dose steroids	Off testosterone	On high dose steroids and testosterone

Figure 1



hydrocortisone), changing Fosamax® therapy to Reclast®, and checking adequacy of testosterone and thyroid hormone replacement doses. Beyond this, the previously noted elevations in FSH and LH levels confirmed that this patient did not have secondary hypogonadism, but primary hypogonadism. This, in addition to his phenotypic appearance, prompted a karyotype analysis for Klinefelter Syndrome (KS). Three weeks later, the karyotype analysis resulted in a positive diagnosis for KS (Figure 1).

Discussion

Klinefelter Syndrome was first described in 1959 in males with tall stature, small testes, gynecomastia, and azoospermia in association with a supernumerary X chromosome.[1] The most common karyotype is 47, XXY, but mosaic karyotypes exist along with other aneuploidies such as 48, XXXY and 49, XXXXY. As with other trisomies, a risk of KS increases with maternal age.[2,3] In contrast to other trisomies, in which <10% are paternally derived, the supernumerary X in half of KS patients originates from paternal non-disjunction.[4] One European registry has shown that increasing paternal age also increases the risk of KS.[4] Other studies have failed to support the same association.

Klinefelter Syndrome is the most common cause of primary hypogonadism with a prevalence between 1:500 to 1:1000 males, but only 25-50% of patients with KS are diagnosed during their lifetime.[1] If not diagnosed prenatally, patients usually go undiagnosed until the ages of 25-40 and are diagnosed primarily in the setting of seeking infertility treatment.[2,3] Late diagnosis places patients at increased risk of developmental abnormalities,specifically in bone, muscle, and secondary sexual characteristics, leading to classic eunuchoid body proportions. Early testosterone replacement can help ensure normal pubertal development and increase peak bone mass to prevent future osteoporosis. It may also improve attention, self-esteem, and cognitive function.[3]

The most common clinical features presenting in >95% of patients with KS are infertility, small testes, and increased gonadotrophin levels.[5] Patients with KS have also been shown to have increased mortality, with one study presenting a hazard ratio of 1.4; this was equivalent to KS patients losing 2.1 years compared to controls.[6] The increase in mortality is likely secondary to the direct and indirect association with multiple systemic problems such as metabolic syndrome, increased cardiovascular risk, increased breast cancer risk, and decreased bone mineral density.[5]

Regarding the patient presented here, KS patients are at a particularly increased risk of venous thromboembolism (VTE). The risk seems to be highest between the ages of 20-30.[7] Multiple theories have been proposed as an explanation for this increased risk, some postulating that increased factor VIII levels may be contributing (gene is localized on the X chromosome), while others propose a more multifactorial etiology from metabolic syndrome, abdominal adiposity, and diabetes.[7] One ongoing concern is that testosterone replacement therapy in these patients may increase the risk of VTE. Interestingly, a recent study published in January 2020 reviewed 1,155 men with KS over a 22-year period and found that those treated appropriately with testosterone had a non-significant reduction in VTE events when compared to men with KS not on therapy.[8] Further studies are needed to define whether testosterone therapy puts these patients at risk.

Patients with KS are also at increased risk of osteopenia/osteoporosis, consistent with this patient's presentation. However, initiation of testosterone replacement therapy after puberty does not reverse a loss of bone mass, unlike in patients with hypogonadism from other causes. In contrast, studies have shown that when testosterone replacement is started early (<20-years), a normal bone mineral density (BMD) can be achieved in men with KS.[9] Patients with KS have been found to have significantly lower vitamin D levels when compared to age matched controls, leading to the consideration that vitamin D plays a significant role in bone health in these patients.[10] One study compared vitamin D replacement to testosterone replacement effects on BMD and found that BMD significantly increased over a two year period with vitamin D replacement, but the same was not found with testosterone replacement.[10] Testosterone replacement alone is not sufficient for treating KS patients with

reduced BMD, further consideration for treatment is needed.

Although KS is largely considered to primarily be the cause of primary hypogonadism, it is, in fact, a systemic disease that can affect many aspects of a patient's health. A multidisciplinary approach is preferred when caring for these patients to ensure the best outcomes.

Conclusion

This case illustrates the importance of a comprehensive approach in treating a male with hypogonadism. Although common, KS is frequently undiagnosed, leaving patients at risk of multiple complications without timely treatment or screening for associated diseases.

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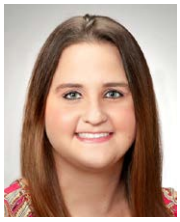
UPMC Adult Endocrinology Initiates Advanced Practice Provider (APP) Fellowship Program



Emily Emsurak, MPAS, PA-C

Co-Director, Adult Endocrinology APP Fellowship Program

Division of Endocrinology

Deborah Hlasnik, MSN, CRNP

Co-Director, Adult Endocrinology APP Fellowship Program

Division of Endocrinology

Esra Karslioglu-French, MD, MBA, ECNU

Clinical Associate Professor of Medicine

Medical Director of the Center for Diabetes and Endocrinology

While the rates of chronic diseases such as diabetes are escalating, the number of providers available to provide comprehensive care is shrinking. To address this growing need for providers, the UPMC Adult Endocrinology Advanced Practice Provider (APP) Fellowship Program was created to train APP clinicians new to endocrinology. This comprehensive post-graduate fellowship program was designed to provide education specific to endocrinology diagnoses and management to enhance the APP's skill set with the fundamental knowledge necessary in making sound clinical judgements. The Program's goal is to prepare APPs to be able to provide safe, evidence-based, high-quality, independent care, within the scope of their license, to patients with endocrine disorders. UPMC is now home to one of the few APP fellowship programs in the country.

The Program has a two-fold mission: to provide advanced training while creating enthusiasm and interest in endocrine practice for potential recruitment. The Fellowship Program is a six-month course based on a comprehensive curriculum that spans endocrine topics such as diabetes and thyroid disease. The Program includes clinical rotations, didactic lectures, and case presentations that offer education and experiences relevant to working in the field of endocrinology. Objective and subjective evaluation techniques are used to measure the fellow's progress throughout the Program.

The Program has been well-received. The APP Fellowship Program is dedicated to advancing UPMC as a premier educational setting in promoting excellence in patient care delivery through an innovative and world-class clinical program specifically tailored to prepare the APP to practice in an evolving and increasingly complex health care market.

Diabetes, COVID-19, and the Importance of Glycemic Control

Divya Sistla, MD

Co-Chief Clinical Fellow

Division of Endocrinology

Mary Korytkowski, MD

Endocrine Director of Quality Improvement

Professor of Medicine,
Division of Endocrinology

On March 11, 2020, life changed for millions of people around the world as Dr. Ghebreyesus from the United Nations World Health Organization announced that COVID-19 was now a worldwide pandemic for which there was no known cure. Early reports from areas hard hit early in the course of this pandemic indicated an over-representation of people with diabetes among the hospitalized population with moderate to severe COVID-19. This raised concern among people living with diabetes that they were particularly vulnerable for becoming infected. Fortunately, there is no evidence that people with diabetes are at higher risk for contracting the SARS-CoV-2 virus that causes COVID-19, but there is evidence that those who do become infected are at high risk for adverse outcomes.[1]

There are several reports investigating factors contributing to adverse outcomes in the hospitalized patient population with diabetes and COVID-19.[2,3] While not all studies are consistent in their findings, poor glycemic control determined by HbA1c or admission blood glucose (BG) has been described as a predictor of mortality.[4] Other factors that often present in people with diabetes include obesity, hypertension, and pre-existing cardiovascular disease are identified as predictors of adverse outcomes in the setting of COVID-19 infection. Some studies suggest that people with type 1 diabetes may be at even higher risk than those with type 2 diabetes. This means that recommendations from the Centers for Disease Control (CDC) emphasizing preventive measures that include wearing a mask, social distancing, and frequent hand washing hold particular importance for people living with diabetes. These recommendations from the CDC, together with an emphasis on maintaining good glycemic control, can potentially reduce the risk for severe COVID-19 infection in people who do contract this virus.

The number of people testing positive for COVID-19 continues to rise at alarming rates with an associated increase in the number of hospitalizations for moderate to severe COVID-19 infection. Patients hospitalized with COVID-19 require dedicated teams who are able to respond to the multiple and complex medical needs of these patients. For hospitalized patients with diabetes, glycemic management becomes yet another essential component of this complex medical care.

Several reports from China, the UK, Italy, and the U.S., demonstrated that hospitalized patients with COVID-19 who have diabetes or newly recognized hyperglycemia experience better outcomes when glycemic control is achieved and maintained.[2,4] Favorable outcomes are observed in patients with BG levels below 140 to 180 mg/dl when compared to those with BG levels above 180 mg/dl.[3,5] These reports provide evidence for pursuing a strategy of targeted glycemic management in this population already at high risk for adverse outcomes.

The community of endocrinologists at local and national levels responded to requests for guidance from providers at the front lines of managing COVID-19 patients with diabetes early in the course of this pandemic. Prior to the current pandemic, intravenous (IV) insulin infusions with hourly BG measurements were recommended as the optimal method for achieving desired glycemic targets in the majority of critically ill patients with diabetes or hyperglycemia. This monitoring requires frequent BG testing and adjustments to IV insulin infusions to avoid both hypo- and hyperglycemia. This need for frequent patient contact becomes an issue during a pandemic where major shortages in personal protective equipment (PPE) are still occurring in areas experiencing a large influx of patients with COVID-19.

At UPMC, a group of endocrinologists modified existing recommendations for inpatient management of hyperglycemia with the goal of achieving and maintaining glycemic control while protecting health care providers from prolonged exposure to COVID-19 patients. A focus of these modifications was to reserve the use of IV insulin infusions for patients experiencing wide fluctuations in BG levels or who are unable to achieve and maintain desired glycemic targets with scheduled subcutaneous (SC) insulin therapy. Scheduled SC insulin incorporates the use of a long or intermediate acting (basal) insulin preparation in combination with a short or rapid acting insulin preparation administered before meals in patients who are eating, or every four to six hours in patients who are not eating. Correctional insulin is administered as a part of a scheduled SC insulin regimen to treat BG levels above desired targets.

Dexamethasone, a glucocorticoid that can lead to higher BG levels in people with and without diabetes, has emerged as a standard of care for patients with moderately severe COVID-19 as a way of reducing mortality.[6] The majority of

patients receiving dexamethasone or other glucocorticoids will experience higher insulin requirements while on these therapies. At UPMC, glucose monitoring at regular intervals is performed for any patient receiving high dose glucocorticoids independent of a known history of diabetes. For the majority of patients who develop hyperglycemia with use of glucocorticoids, it is recommended to titrate SC or IV insulin doses to maintain BG levels in the target range.

Not all hospitalized patients with COVID-19 are critically ill. Based on several earlier reports demonstrating the efficacy of dipeptidyl peptidase 4 inhibitors (DPP4i) in carefully selected patients with type 2 diabetes, modified protocols for glycemic management have included use of these agents in clinically stable, non-critically ill patients with COVID-19. These agents typically require additional correctional insulin in the hospital setting.[2] Some patients may be able to achieve glycemic targets with a DPP4i, which have the advantage of avoiding risk of hypoglycemia. A recent observational study from Italy demonstrated significant improvement in clinical outcomes including mortality in hospitalized patients with type 2 diabetes and COVID-19 who received the DPP4i sitagliptin as part of their treatment regimen.[7] More research is needed to confirm the results from this promising study.

Once patients are stabilized and discharged to home, it is important to continue to provide ongoing support and guidance as it is highly likely that insulin doses will need to be decreased over time, particularly in those discharged home on glucocorticoid therapy. Glycemic control continues to be an important component for achieving favorable outcomes in these patients. Close post-hospital discharge follow-up helps to maintain desired levels of glycemic control.

Synchronous video conferencing was started at UPMC in 2019 as a pilot project allowing patients to connect with their physician via phone or home computer. The U.S. Department of Health and Human Services now provides reimbursement for both video and phone visits under the CARES Act Provider Relief Fund. This resulted in the emergence of telemedicine as an essential component of care for patients with diabetes, with and without COVID-19 infection, in the outpatient setting, including post hospital discharge visits. These virtual visits overcome geographic barriers to care, protect health care personnel from exposure to COVID-19, and help preserve PPE for inpatient use.

Diabetes technologies such as Tidepool, Dexcom Clarity, and Freestyle Libre View provide tools for patients to download home BG meters or continuous glucose monitors (CGM) prior to a virtual visit, contributing to delivery of effective, high-quality care. At UPMC, Freestyle Libre CGM devices are provided at the time of hospital discharge for selected patients. CGM devices provide metrics including Time in Range and Glucose Management Indicators (GMI) that are highly correlated with HbA1c values.[8] These metrics reduce the need for patients to travel to outside laboratories for measures of HbA1c, circumventing potential COVID-19 exposure.

It is important to note that not all patients will have access to telemedicine. This increases existing disparities in health care delivery to more vulnerable patient populations with COVID-19. Programs such as Lifeline of the Federal Communications Commission can help provide reduced-cost phone or internet service to low-income patients and their families as one way of addressing this important issue.[10]

In conclusion, glycemic control is important for ensuring favorable outcomes in the hospital and outpatient settings for people with diabetes who develop COVID-19 infection. Telemedicine alone, or in combination with emerging diabetes technologies, provides an important alternative to office visits for many patients who are able to access high quality care remotely.

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UPMC Guidance for Management of Hospitalized COVID-19 Patients with Diabetes and Hyperglycemia

Glycemic Targets	100-180 mg/dl
Blood Glucose Monitoring	Patients who are eating: Before meals and bedtime If blood sugars are all < 180 mg/dL, decrease frequency to once or twice a day Patients who are not eating: Check BG every 4- 6 hours
Treatment of Hyperglycemia Critical Illness	Critically ill patients: SC basal-bolus preferred over insulin drips to decrease the need for frequent blood glucose monitoring Starting Dose* Basal insulin: 0.1-0.2 units/kg Prandial Insulin (if eating): 0.1-0.2 unit/kg in divided doses Correction sliding scale insulin IV Insulin Therapy is indicated for patients not achieving glucose targets with SC insulin therapy If patient has persistent hyperglycemia for >24 hours, consult diabetes service
Treatment of Hyperglycemia Non-Critical Illness	Mild hyperglycemia (BG < 140-180 mg/dl): Start a DPP4i if there are no contraindications (history of pancreatitis or pancreatic tumors) Correctional sliding scale insulin Moderate-to-severe hyperglycemia (BG >180-200 mg/dl): Basal insulin: 0.1-0.2 unit/kg Correctional sliding scale insulin Prandial insulin: If BG > 140-180 mg/dl persists 0.1-0.2 units/kg/day in divided doses

**Initial insulin doses need to be adjusted at regular intervals based on BG levels*

Abbreviations: BG Blood Glucose, DPP4i Dipeptidyl Peptidase 4 inhibitor, IV Intravenous, SC Subcutaneous

Notable Publications

Fazeli PK, Zhang Y, O'Keefe J, Pesaresi T, Lun M, Lawney B, Steinhauser ML. Prolonged fasting drives a program of metabolic inflammation in human adipose tissue. *Mol Metab*. 2020 Dec;42:101082. PMID: 32992039.

The human adaptive fasting response enables survival during periods of caloric deprivation. A crucial component of the fasting response is the shift from glucose metabolism to utilization of lipids, underscoring the importance of adipose tissue as the central lipid-storing organ. The objective of this study was to investigate the response of adipose tissue to a prolonged fast in humans. Collectively, this study demonstrates an unexpected role of metabolic inflammation in the human adaptive fasting response.

Carty SE, Ohori NP, Hilko DA, McCoy KL, **French EK**, Manroa P, **Morariu E**, Sridharan S, Seethala RR, Yip L. The Clinical Utility of Molecular Testing in the Management of Thyroid Follicular Neoplasms (Bethesda IV Nodules). *Ann Surg*. 2020 Oct:272(4): 621-627. PMID: 32773640.

Follicular neoplasms (FN) present a management quandary as they are often benign but may also be aggressive thyroid cancer (TC). Consensus recommendations have historically advised thyroidectomy for definitive diagnosis. Although molecular testing (MT) has robust benefit in hypothetical cost analyses, under current management guidelines a real-time study of their clinical utility in FN is awaited. We investigate if MT for FN directs appropriate thyroidectomy for TC while triaging to surveillance nodules that are likely benign. MT use for FN increased the surgical yield of cancer by four-fold, identified all potentially aggressive malignancies, and allowed apparently safe nonoperative surveillance for >80% of MT-negative patients. Thyroid nodule MT optimizes patient outcomes sufficiently to justify its incorporation into routine practice.

Awards and Accomplishments

Vijay Yechoor, MD, was awarded a NIDDK R01 supplement titled "Therapeutic strategies to test the mitigation of the cytokine storm syndrome and coagulopathy in patient cell-derived vLAMPS with type 2 diabetes and COVID-19 infections" in collaboration with the team headed by Lans Taylor, PhD, of the University of Pittsburgh Drug Discovery Institute.

Frederico G.S. Toledo, MD, was awarded a NIDDK U01 grant titled "UPMC Clinical Center for the Study of Diabetes After Acute Pancreatitis" in collaboration with Dhiraj Yadav, MD from the University of Pittsburgh Division of Gastroenterology, Hepatology and Nutrition.

Erin E. Kershaw, MD, was awarded a NIA R01 grant titled "Investigating the role of adipose tissue in mobility and aging (SOMMA-AT)" in collaboration with Lauren Sparks, PhD, from AdventHealth Orlando, and Jamie Justice, PhD, from Wake Forest School of Medicine.

Linda Siminerio, RN, PhD, DCES, was awarded a 25th Anniversary Recognition Award by the Foundation of European Nurses in Diabetes Federation. This award is presented to nurses for their distinguished international service in diabetes care, research, or education.

Michael Jurczak, PhD, was awarded a NIAID R56 grant titled "Molecular mechanisms and novel biological-based therapies for anthrax lethal toxin-induced mortality" in collaboration with Shihui Liu, MD, PhD, from the University of Pittsburgh Aging Institute.

R Harsha Rao, MD, achieved Emeritus Professor of Medicine status. Dr. Rao joined the University of Pittsburgh in 1988 and has held many roles during his time with the University, including Fellowship Program Director. Dr. Rao is currently the Chief of the Endocrine Division at the Veterans Administration Pittsburgh Healthcare System.

Linda Siminerio, RN, PhD, DCES, Jodi Krall, PhD, and **Jason Ng, MD**, were awarded Sanofi research support for their project titled "My Dose Coach And Connected Ecosystem Titration & Maintenance In Patients With Type 2 Diabetes Mellitus On Basal Insulin".

NEW FACULTY

Janet Leung, MD

Dr. Leung received her medical degree from the University of Michigan Medical School in 2010. In 2013, she completed an internal medicine residency at Stanford University, VA Palo Alto Health System. Dr. Leung completed her fellowships in endocrinology and endocrine hypertension at Brigham and Women's Hospital, Harvard Medical School in 2016. Dr. Leung's clinical interests include all aspects of endocrinology, with a special interest in the care of transgender and gender-diverse people. Dr. Leung joined our division as a Clinical Assistant Professor, the Associate Program Director for Quality, and the Clinical Lead for Quality and Value in November 2020.

Roy Brett Guinto, DO

Dr. Guinto received his medical degree from the New York College of Osteopathic Medicine in 2010. In 2013, he completed an internal medicine residency at the Tripler Army Medical Center. Dr. Guinto went on to complete an endocrine fellowship at Walter Reed National Military Medical Center in 2015. Dr. Guinto's clinical interests include general endocrinology, metabolic diseases (i.e. obesity, diabetes), and lifestyle medicine. Dr. Guinto joined our division as a Clinical Assistant Professor in February 2021.

ALUMNI

If you trained at one of UPMC's Residency or Fellowship programs, you'll want to stay up-to-date on our innovations in clinical care and cutting-edge research. Join our email and mailing list to stay connected at upmc.com/alumni.

ADDRESS CORRESPONDENCE TO:

Division of Endocrinology and Metabolism
200 Lothrop St.
W1055 BST
Pittsburgh, PA 15213
Phone: 412-648-9770

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