Circadian Clock and Diabetes — Time for Action

According to most recent estimates from the U.S. Centers for Disease Control and Prevention (CDC), more than one third of the U.S. adult population has prediabetes. Early interventions that minimize the risk of progression to overt diabetes could therefore have a major impact on individual and population health. Emerging evidence supports an increasingly important role for circadian rhythms in human health and disease. Indeed, the 2017 Nobel Prize in Physiology and Medicine was awarded to Drs. Jeffry Hall, Michael Rosbash, and Michael Young “for their discoveries of molecular mechanisms controlling the circadian rhythm.” However, the role of circadian rhythms in diabetes pathogenesis remains poorly understood. Vijay Yecheor, MD, director of the Diabetes and Beta Cell (β-cell) Biology Center at the University of Pittsburgh, is deciphering the mechanisms linking the molecular clock to diabetes progression with the goal of identifying novel pathways to prevent and treat diabetes.

Circadian Disruption and Diabetes: An Emerging and Significant Problem

Disruption in circadian rhythms, as occurs in more than 8.6 million American shift workers, is strongly associated with obesity and related metabolic disorders, including β-cell dysfunction and type 2 diabetes (T2D). Overall, this circadian disruption accounts for a cumulative excess risk of up to 60 percent of T2D.5,6 However, this problem is not only limited to shift workers. “Social jetlag,” defined as a change of more than two hours between sleep/wake time between weekdays and weekends for any reason, has recently been shown to contribute to as much as a 33 percent excess risk of obesity.6 Furthermore, the prevalent and rapid transformation to more “modern” lifestyles (characterized by travel across time zones, ubiquitous exposure to screen-time from smart phones and tablets, light pollution, etc.) increases the exposure of the general population to circadian disruption, as well as its associated metabolic consequences.

The Molecular Clock

All living things have an internal timing system. This “circadian clock” has a rhythm of approximately 24 hours, roughly reflecting the day/night cycles associated with the rotation of the earth. In addition, all mammals, including humans, have a “molecular clock” in every cell. The molecular clock consists

Continued on Page 10
An Interesting Case of Secondary Hypertension

Case Presentation

The inpatient Endocrinology service was consulted for evaluation of new onset hypertension and hypokalemia in a previously healthy, 48-year-old, Caucasian female.

One month prior to admission, the patient developed a pruritic forearm rash following contact with a new tomato plant. She was treated for six days with an oral prednisone taper (40 mg for 1 day, 30 mg for 1 day, 20 mg for 2 days, and 10 mg for 2 days). Five days later, she developed severe right upper quadrant abdominal pain radiating to her right flank without any other associated symptoms. The pain was not influenced by eating, position, or other aggravating or alleviating factors. Despite several days of bland food and proton-pump inhibitor therapy, the pain persisted. The patient then sought further evaluation in the emergency department (ED). In the ED, her examination was nonfocal with negative Murphy’s sign. Her vital signs were normal, including a blood pressure (BP) of 136/74 mmHg. Laboratory evaluation revealed normal electrolytes, creatinine, alkaline phosphatase, bilirubin, pancreatic lipase, and complete blood count. However, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were elevated at 127 and 146 IU/L, respectively. Abdominal ultrasound revealed mild pericholecystic fluid with gall bladder wall thickening, which was not felt to be concerning. She remained stable and was discharged home with outpatient follow-up.

One day later, she was evaluated by her primary care provider (PCP). At that time, her BP had increased to 159/86 mmHg (similar in both arms), but liver enzymes had improved to AST of 45 IU/L and ALT of 105 IU/L. Electrolytes were notable for a sodium of 137 mmol/L and a potassium of 3.3 mmol/L. For further evaluation of her persistent symptoms, she underwent a CT scan of the abdomen and pelvis with intravenous and oral contrast, which did not reveal any concerning findings. One week later, she was again evaluated by her PCP. At that time, her blood pressure had increased to 190/98 mmHg (169/97 mmHg upon repeat measurement). Laboratory data revealed a sodium of 136 mmol/L and potassium of 3.0 mmol/L. The patient noted continued right flank pain, as well as a new onset mild headache. These new findings prompted a CT of the head, with CT angiogram/venogram, which were negative for vascular occlusion. Her PCP recommended hospital admission for further evaluation.

Upon hospital admission, she underwent further evaluation of her hypertension and electrolyte abnormalities. Plasma aldosterone concentration (PAC) was 12 ng/dl (normal range: upright 8 to 10 a.m. / 28 ng/dl, 4 to 6 p.m. / 21 ng/dl) while plasma renin activity (PRA) was pending. Treatment with amlopidine 5 mg once daily was initiated, but BP remained in the ranges of 160-170/100-110 mmHg despite therapy. A 24-hour urine study revealed the following: urine volume of 1900 ml, creatinine 0.98 g/24 hours (normal range: 0.63-2.5g/24h), sodium 160 mEq/24h (normal range: 40-220 mEq/24h), potassium 75 mEq/24h (normal range: 25-125 mEq/24h), and aldosterone 20.8 mcg/24h (normal range: 2.3-21 mcg/24h or random sodium diet). Additional blood pressure medications were sequentially added, and she was eventually discharged home three days later on amlopidine 5 mg once daily, clonidine 0.2 mg BID, hydralazine 50 mg QID, and potassium chloride supplements 60 mEq/day. Despite these multiple antihypertensive medications, her BP remained in the range of 148-168/86-102 mmHg in the 24 hours preceding discharge.

Two days later, the PRA from admission was reported to be 15.92 ng/mL/h (normal range: 0.25-82 ng/mL/h). Based on the elevated PRA, a renal artery Doppler was performed and revealed “tardus parvus waveforms in the segmental arteries of the right kidney relative to the normal waveforms in the left kidney, suggesting right renal artery stenosis.” Repeat laboratory data, with the patient in a seated position, revealed PAC of 66 ng/dl and PRA of 18.29 ng/mL/h. PAC/PRA ratio was 3.6. CT angiogram of the chest and abdomen revealed “a long segment of smooth, severe stenosis of the mid-right renal artery with minimum caliper of 1.8 mm and post-stenotic dilatation as the likely etiology for systemic hypertension; symmetric enhancement and normal size of both kidneys without cortical thinning or infarct; normal left renal artery and normal aorta.” See Figure 1-3 on Page 3 for CT angiogram of the abdomen and pelvis. See Table 1 for a summary of her BP and potassium levels.

Vascular surgery recommended anticoagulation over stenting due to concerns of renal artery thrombosis. A hypercoagulability evaluation was negative. Lisinopril 5 mg once daily was added to her discharge regimen. Renal artery Doppler, four weeks later, revealed small septations in the mid/distal renal artery with an associated severe stenosis (444 cm/sec, ratio 4.8) consistent with renal fibromuscular dysplasia. Anticoagulation was subsequently discontinued, and the patient was switched to lisinopril only. The dose was titrated until BP control was achieved. The patient elected to pursue conservative management with serial imaging, and her most recent renal artery Doppler was stable.

<table>
<thead>
<tr>
<th>Table 1. Blood Pressure and Serum Potassium Trends</th>
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<tr>
<td>Days after completing prednisone taper</td>
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<tr>
<td>BP (mmHg)</td>
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<tr>
<td>Serum potassium</td>
</tr>
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</table>
1. Review medication list and identify medications that can potentially affect testing.¹
   a. Beta-blockers can lower PRA and PRC, leading to rise of the PAC/PRA ratio.²
   b. Mineralocorticoid receptor (MR) antagonists (spironolactone and eplerenone) prevent aldosterone from activating the MR, resulting in a decrease in plasma volume, loss of sodium, an increase in PRA, and reduction of the PAC/PRA ratio. If a patient is hypokalemic despite treatment with one of these agents, the MR is not completely blocked and testing can proceed. If discontinued, spironolactone must be held for at least six weeks prior to testing.¹

2. Measure PAC and PRA, and calculate a PAC/PRA ratio.¹
   a. PAC is elevated, and PRA is low; PAC/PRA >/ = 20 AND PAC >/ = 15 ng/dL.³
      These results suggest primary hyperaldosteronism and further evaluation to identify the underlying cause should be pursued.
   b. PAC and PRA both elevated; PAC/PRA </ = 10.¹
      These results suggest hypotension or hypovolemia stimulating the juxtaglomerular apparatus, and differential diagnoses include:
      - Diuretic
      - Renin-secreting tumors
      - Coarctation of aorta
      - Malignant hypertension
      - Reno-vascular hypertension
   c. PAC and PRA low.¹
      These results suggest apparent mineralocorticoid excess
      - Congenital adrenal hyperplasia
      - Glucocorticoid resistance
      - Licorice ingestion
      - Deoxycorticosterone-producing tumor⁴
      - Liddle syndrome
      - Apparent mineralocorticoid excess
      - Cushing’s syndrome/ectopic ACTH syndrome
      - Exogenous mineralocorticoid ingestion
      - Hypertension exacerbated by pregnancy

Final Diagnosis
Fibromuscular dysplasia with acute thrombosis, possibly precipitated by steroid use.

Discussion
The evaluation and diagnosis of secondary hypertension can often be challenging. When evaluating a patient with hypertension and hypokalemia, it is important to consider multiple factors to make an accurate diagnosis. The following stepwise approach is recommended:
Addressing the Challenge of Inpatient Management of Hyperglycemia

Diabetes mellitus (DM) is a frequently encountered diagnosis among hospitalized adult patients ≥ 18 years of age, affecting 20 to 40 percent of inpatient populations depending on the geographic and demographic characteristics of the institution. Hyperglycemia is observed in another 12 percent or more of hospitalized patients without known DM prior to admission. The importance of recognizing and addressing hyperglycemia in hospitalized patients with and without known DM is based on studies demonstrating an increase incidence of infections, arrhythmias, and mortality with prolonged hospital length of stay (LOS) and risk for postdischarge disability and readmission. The good news is that the risk for these adverse clinical outcomes can be modified by attention to glycemic management and control during periods of hospitalization.

At UPMC, the unique challenges associated with inpatient diabetes and glycemic management are being addressed by a multidisciplinary Diabetes InPatient Safety Committee (DPSC) that includes representation from physicians, nurses, diabetes educators, pharmacists, and other key personnel. The first initiative of this committee was the development and implementation of a hospital-wide nurse-directed Hypoglycemia Treatment Protocol (HTP) to address the frequency of severe hypoglycemia with associated potential for adverse patient outcomes. The HTP guided and enabled nurses to treat patients immediately upon recognition of any hypoglycemic event (defined as any blood glucose (BG) < 70 mg/dL) with oral carbohydrates, intravenous (IV) glucose, or subcutaneous (SQ) glucagon according to the severity of the event and overall patient status. This protocol effectively reduced the occurrence of severe hypoglycemia events across the institution and is now incorporated as a safety measure into all protocols guiding the pharmacologic management of hyperglycemia in hospitalized patients with and without diabetes at UPMC.

The process of developing the HTP led to recognition of issues contributing to not only hypoglycemia but also hyperglycemia in hospitalized patients. For example, there was recognition of the fact that there were over 20 different physician-specific “sliding scale insulin (SSI)” algorithms in use on any one day. These SSI protocols defined variable glucose levels for initiation of different doses of short acting insulin, contributing to errors in both insulin dosing and administration. Standardization of these SSI order sets with predefined patient-specific insulin dosing according to assessment of insulin sensitivity effectively decreased the frequency of these errors, as well as the frequency of hypoglycemia and hyperglycemia.

The standardization of SSI protocols was immediately followed by the development of an Insulin Order Set that provided guidance for use of scheduled basal and basal bolus insulin therapy as a way of decreasing the over-dependence on SSI alone, which is ineffective at achieving desired glycemic targets. Each guideline, protocol, and order set directed at glycemic management in the hospital protocol was developed and implemented using quality improvement (QI) strategies that focused on user input and patient safety (Table 1).

Incoming resident and fellow physicians receive a guide outlining the protocols and tools that are now available in the electronic medical record (EMR) that can assist them with managing their patients with diabetes and hyperglycemia. In addition to the Insulin Order Set described above that includes a step by step guide for initiation of scheduled insulin therapy, guidance is provided for modification of diabetes therapies during periods of fasting or in response to implementation of medications known to provoke hyperglycemia, such as glucocorticoid therapy.

All insulin orders include instructions to implement an alternative source of glucose in the event of abrupt discontinuation of enteral (EN) or parenteral nutrition as a way of minimizing risk for hypoglycemia in patients receiving insulin therapy. Members of the DPSC conducted one of the first studies investigating the use of insulin pump therapy in the hospital setting. The protocols and guidelines are amended according to evolving guidance from

<table>
<thead>
<tr>
<th>Table 1. UPMC Guidelines, Order Sets, and Protocols for Inpatient Glycemic Management</th>
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<tbody>
<tr>
<td>Hypoglycemia Treatment Protocol</td>
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<tr>
<td>Consistent Carbohydrate Meal Plan</td>
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<tr>
<td>DKA PowerPlan</td>
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<tr>
<td>IV Insulin Infusion Protocols 130-160 mg/dL, SICU, CTICU</td>
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<tr>
<td>Insulin Pump Order Set and Guideline Insulin Pump Assessment Form</td>
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<tr>
<td>Subcutaneous Insulin Order Set</td>
</tr>
<tr>
<td>U-500 Order Set and Guideline</td>
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<tr>
<td>Preoperative Diabetes Management Instructions</td>
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<tr>
<td>Perioperative Insulin Order Sets for SQ and IV Insulin</td>
</tr>
<tr>
<td>Guideline for Perioperative Insulin Pump Management</td>
</tr>
<tr>
<td>Patient Discharge Instructions for Insulin</td>
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</tbody>
</table>
professional organizations, such as the American Diabetes Association, the American Association of Clinical Endocrinologists, and the Endocrine Society, as well as others.9

There are areas of hospital care that have unique issues that present specific challenges to inpatient glycemic management. These include the same-day surgical suite, the operating and recovery rooms, and medical and surgical critical care areas.10-12 Partnerships have been formed in each of the areas to develop pre- and perioperative glycemic management order sets and guidelines, intravenous insulin infusion protocols targeting a blood glucose range of 110 to 180 mg/dL, and protocols for transitioning patients from IV back to SQ insulin therapy.

The multidisciplinary DPSC began at the university-based hospital (UPMC Presbyterian Shadyside) which has now evolved into an integrated health care system of more than 30 hospitals. Many of these partner institutions adopt and contribute to the refinement of the currently available glycemic management protocols, providing representation at each of the larger bimonthly DPSC meetings in person or by teleconferencing that allows active participation from representatives from geographically distant hospitals. These partner hospitals, with their own multidisciplinary teams, are integral members of the DPSC. An example of this engagement was the introduction of a specific PowerPlan in the EMR that addressed problematic areas in the management of patients with diabetic ketoacidosis (DKA) — identified as ongoing management of the IV insulin infusion following acute fluid resuscitation and transitioning from IV to SQ insulin therapy. It was one of the satellite hospitals that took the initiative of testing these revisions which were then rapidly adopted by other UPMC hospitals following demonstration of both efficacy and safety of these modifications.

Despite the accomplishments to date, the inpatient glycemic management program at UPMC continues to confront ongoing and new challenges. Some of these challenges result from the introduction of new insulin preparations and new diabetes medications, and others from the rapidly evolving technology advances in diabetes care. For example, it is anticipated that as more patients use continuous glucose monitoring devices, these devices will be encountered more commonly in the hospital setting. This raises questions as to who will have the responsibility for monitoring these devices and ensuring their accuracy during periods of hospitalization. The integration of CGM devices with automated insulin delivery via an insulin pump device is now being used clinically, and is expected to grow, providing additional challenges in management to care providers who may not always have experience with this technology. These latter devices pose challenges even to institutions with established policies guiding inpatient use of insulin pump therapy.8

Members of the UPMC DPSC are active participants in a national movement that investigates efficacy and safety of protocols and guidelines with publication of results from quality improvement and research studies that address these ongoing issues.13 A lesson that has been learned over the years of work by the DPSC is that the existence of protocols and guidelines are not sufficient for success of an inpatient glycemic management program. Clinical judgement is an important component of any protocol or guideline, which may be appropriate for many but not all patients, as there are situations that require individualized input from a team with expertise in hospital glycemic management.

At UPMC, an Inpatient Diabetes Consultation Service was established in 2007 by several physicians in the Division of Endocrinology and Metabolism. This service rapidly grew and now includes two certified registered nurse practitioners (CRNPs) with expertise in hospital glycemic management on medical and surgical services. Physicians from the Division of Endocrinology and Metabolism provide overnight and weekend coverage for patients followed on the diabetes service, and provide support for the CRNPs when the need arises. This service has been very successful, averaging a census of 15 to 20 patients per day, and is expanding to cover patients with specific needs that traverse the inpatient and outpatient settings, such as those coming in for pulse steroid therapy or same-day surgery. Diabetes service CRNPs play an active role in education of clinical fellows and hospital nursing staff, serve as a resource for questions relating to hyperglycemia management, and provide assistance with discharge planning of patients new to insulin or who have major modifications to their preadmission diabetes regimen.

There is currently a national shortage of endocrinologists that is not likely to change in the near future. This makes it unlikely that there can be an endocrinologist as part of an inpatient glycemic management team at every acute care hospital. However, given the large percentage of hospitalized patients with diabetes and/or hyperglycemia who would benefit from a program of inpatient glycemic management, it is important that alternative methods of providing this support be investigated and examined with attention to the efficacy and safety of these programs. This includes use of certified diabetes educators, advanced practice providers (CRNP and Physician Assistants), and use of telemedicine and teleconsultation as potential methods of expanding the process of inpatient glycemic management programs beyond the confines of university-based hospital settings.

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Prepar ing the Next Generation of Physicians and Scientists to Tackle Our Nation’s Greatest Threats in Endocrinology and Metabolism

Program History

The Division of Endocrinology and Metabolism at UPMC, being an important unit of one of the largest academic medical centers in the country, is committed to the mission of training clinicians and researchers for the needs of the medical community of today and the future. With respect to our research mission, a central component of our training revolves around a National Institutes of Health (NIH) Ruth L. Kirschstein Institutional National Research Service Award (NRSA; T32 program) that provides structured research training to qualified MD and PhD fellows. The overall purpose of Ruth L. Kirschstein Institutional National training programs is to provide fellowships to allow institutions with proven training track records, such as the University of Pittsburgh School of Medicine, to recruit and fund qualified individuals for research training. The goal of our specific T32 program, which is the longest continuously funded T32 training program at the University of Pittsburgh (currently 42 years), is to prepare trainees for careers that will impact the health-related research needs of the United States into the future. In this respect, we are immensely proud of our history of success in providing trainees with the research and career skills necessary for developing independent academic careers.

During the 40 years of our program, the research landscape has changed dramatically, and our training program has adapted to complement those changes. One notable and relatively recent change is the increased complexity of medical research, requiring cross-discipline integration of research programs. This evolution of the research landscape has necessitated that researchers operate in an environment that provides a thorough grounding in the translational focus of medical research.

Added to that has been the development of the need for ever greater competency in the ancillary skills that are required to complement the core research skills — including project, group, and multidisciplinary collaboration management, grant writing, public presentations, transitioning to independence, and others. Historically, these skills were often learned “on the fly” but now require a more organized approach, which is reflected in the structural evolution of our T32 program.

Program Structure

The structure of our T32 program is centered on three research hubs (Figure 1), each of which has a membership of a minimum of seven NIH-funded training faculty, complemented with didactic courses, workshops, and educational opportunities offered through the Division of Endocrinology and Metabolism and other complementary training programs throughout the University of Pittsburgh Schools of the Health Sciences. The largest representation of our training faculty comes from the Division of Endocrinology and Metabolism (~30 percent), as has been the case throughout the life of the training program. However, it also always has been the goal of the training program to draw on the best and brightest researchers, within the University of Pittsburgh and beyond, to enable trainees to be exposed to the most outstanding research environment possible. Furthermore, there is a wealth of research that is based in a variety of departments and schools across the University of Pittsburgh that fits perfectly into the focus of our training program. Thus, the remaining 70 percent of the training faculty (and nearly 50 percent of the management committee) is drawn from outside the Division. Similarly, as mentioned above, our program draws on numerous initiatives throughout the Health Sciences Schools that present abundant and relevant didactic and educational opportunities to our trainees. These range from an extensive conference schedule within the School of Medicine, through didactic courses in areas such as translational research, concepts of basic research, and certificate programs offered through the Clinical and Translational Science Institute (CTSI). Furthermore, there are professional development courses that cover such areas as grant writing, laboratory and project management, and responsible conduct of research (RCR) offered through the Office of Academic Career Development (OACD) and other programs. These represent just a fraction of the training opportunities available in our program.

Figure 1: Organizational Structure of T32 Research Training Program.
### Application and Training Details

How, then, does one enter our program, and how does an individual’s training experience evolve? To address the first question, entry to the program is through a competitive application process. Those with MD degrees enter the pool of applicants as part of the larger Endocrinology MD Fellowship Program. Those with PhD degrees, and periodically MD applicants who are not part of the Endocrinology MD fellowship, apply through the T32 website (EndocrineResearchTraining.pitt.edu). It is worthwhile to highlight this relatively unique strength of our program: its emphasis on providing the highest level of training to both MD and PhD trainees. Thus, PhD trainees work alongside MD trainees, and are exposed to a medical and human disease learning environment that they are unlikely to see in programs that only train PhD fellows. Conversely, MD trainees work alongside PhD trainees, and are exposed to a research culture that is likely more intensive than that of programs that offer research training to MDs alone. Once accepted into our program, MD trainees within the three-year Endocrinology MD fellowship are required to complete a clinical component (12 months total) in Adult Endocrinology for certification for Board Eligibility by the Residency Review Committee (RRC) of the American College of Graduate Medical Education (ACGME) and the American Board of Internal Medicine. However, the T32 program is designed to ensure that these requirements minimally impact the research training program in two ways and vice versa. First, the clinical component is financially supported by UPMC hospital or U.S. Department of Veterans Administration endocrine fellowship positions. This means that in our program, in contrast to many other programs that lack hospital training slots, our T32 is used exclusively for research training. Second, the clinical training component occurs in Year 1 (~10 months) and only to a small extent in Years 2 and 3 (~1 month/year) to fulfill the RRC requirements. Since our training program is a three-year program, this ensures virtually two years of uninterrupted research training for MD trainees (Figure 2), thereby providing them with the greatest possible opportunity for career development and success. PhD trainees are recruited for a minimum of a two-year postdoctoral fellowship that includes their research project and didactic/educational courses. During this time, they have a pure research agenda for their entire training period. From a practical standpoint, this means that PhD fellows commence full-time research on day one of their arrival in the program. (In respect to Figure 2, Years 1 and 2 for MD fellows is collapsed into a single year for PhD fellows.) To devise an individual training experience, the MD and PhD trainees work with a primary mentor and the director of the T32 program to assemble a multidisciplinary mentoring team and develop an Individual Career Development Plan (ICDP). This ICDP includes three critical components — a statement of career goals, a detailed description of the project to be undertaken under the primary mentor’s supervision, and the identification of the didactic and educational courses that are most suited to the individual trainee. Accomplishment of these goals establishes a solid foundation for the subsequent training experience (Figure 2).

<table>
<thead>
<tr>
<th>Year 1 — VA/UPMC Funded</th>
<th>Year 2 — T32 Funded</th>
<th>Year 3 — T32 Funded</th>
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<tbody>
<tr>
<td>Identify Primary Mentor</td>
<td>Begin Full-Time Research Project</td>
<td>Complete Full-Time Research Project</td>
</tr>
<tr>
<td>Assemble Mentoring Team</td>
<td>Begin Individual Prescribed Didactic and Educational Course Work</td>
<td>Complete Individual Prescribed Didactic and Educational Course Work</td>
</tr>
<tr>
<td>Complete Fundamentals of Research Course</td>
<td>Write/Submit Abstract, Present at ADA or Endo Soc Meeting</td>
<td>Write/Submit Manuscript(s), Submit Abstract(s), Present at ADA or Endo Soc Meeting</td>
</tr>
<tr>
<td>Produce Individual Career Development Plan</td>
<td>Write/Submit Individual NRSA</td>
<td>Write/Submit K Application</td>
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<tr>
<td>Predominantly Clinical Training</td>
<td>Predominantly Exclusively Research Training</td>
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**Figure 2:** Research Training Schedule.

### Conclusion

The Division of Endocrinology and Metabolism has a longstanding commitment to, and success in, research training that is buttressed by a highly structured NRSA T32 training program. This program offers (i) outstanding research opportunities that range from the molecular to the public health arenas; (ii) exceptional NIH-funded training faculty with expertise in basic, clinical, and public health research; (iii) access to a range of didactic courses, workshops, and educational experiences that complement research opportunities; (iv) structured career development courses that impart skills ranging from managing group projects to presentation skills, through the T32 to K to R grant transition; (v) a continuous assessment program for trainees, reinforced by an ICDP, a mentoring team, and progress evaluations that focus on the individualized professional development of trainees, and (vi) a program management structure that efficiently oversees the ever-increasing complexity of research training in medical research. We believe that our program offers a high probability for the future academic success of our trainees.

Robert M. O’Doherty, PhD  
Professor of Medicine  
Director, T32 Diabetes and Endocrinology Training Program
An Interesting Case of Secondary Hypertension (Continued from Page 3)

In this case, the PAC and PRA were both elevated. Thus, underlying etiologies that could result in true or perceived hypertension or hypovolemia, leading to stimulation of the juxtaglomerular apparatus and the renin-angiotensin-aldosterone system (RAAS), were considered. The patient was not taking diuretic medications, and no renal masses suggestive of reninoma were identified by imaging. BP was equal in both arms, making coarctation of aorta unlikely. There was no evidence of organ dysfunction, so malignant hypertension was excluded (note that ophthalmoscopy was not performed). In this way, the differential diagnoses was narrowed to renovascular hypertension. Findings on imaging were consistent with right renal artery fibromuscular dysplasia (FMD).

FMD is a noninflammatory, nonatherosclerotic disorder that results in arterial stenosis, occlusion, aneurysm, and/or dissection, which can occasionally be unilateral. It is more common in women, with a mean age at diagnosis of 52 years. Pathogenesis is not definitively known, but acute ischemia is implicated as one of the possibilities. Appearance on renal artery Doppler may be characterized by a “string of beads” or “tubular stenosis” appearance. Treatment modalities include ACE-inhibitors, surgery, or angioplasty. In this case, there was no evidence at acute presentation of unilateral fibromuscular dysplasia as secondary hyperaldosteronism. Clinical evidence suggests that the rapid development of hypertension and hypokalemia could have been caused by an acute thrombotic event that may have been precipitated by one or more factors, including recent steroid exposure, RAAS activation, viral infection, and/or dehydration (as noted by epigastric pain and transient transaminits during the patient’s initial ED visit). Any of these factors could have contributed to a transient hypercoagulable state. However, while both corticosteroids and RAAS activation can promote hypercoagulability, it is not known whether they predispose to acute arterial thrombosis. In a recent study, even short-term steroid use was associated with an increased risk of development of venous thromboembolism within five to 30 days of acute steroid exposure. A higher medication dose was associated with more risk.

Conclusion

The details of this case strongly suggest a diagnosis of fibromuscular dysplasia with acute thrombosis, possibly precipitated by steroid use. Fibromuscular dysplasia is a common cause of renal artery stenosis in middle-aged females, and it can lead to secondary hypertension with secondary hyperaldosteronism. Steroids have been associated with multiple side effects, including hypercoagulability (specifically venous thromboembolism), and their use should be undertaken judiciously. Hypertension and hyperaldosteronism require accurate diagnosis and a thorough evaluation of the underlying causes and precipitating factors.

References

Department News

New Faculty

Jagdeesh Ullal, MD, clinical associate professor of medicine, received a Master of Science in Biomedical Research from Eastern Virginia Medical School (EVMS). He then completed his residency in Internal Medicine in 2008, and a fellowship in Endocrinology in 2010 at the EVMS Health System before becoming faculty there in 2010. He joined the UPMC Division of Endocrinology and Metabolism in January 2018 as the clinic lead for Inpatient and Subspecialty Diabetes. His scholarly work focuses on understanding how electronic and computer-based glycemic management systems impact inpatient diabetes care.

Pittsburgh Innovation Challenge Award

A multidisciplinary team led by UPMC Endocrinology faculty received an award from the Pittsburgh Innovation Challenge (PiNC) for their project titled “REMIT-DM: Using Continuous Glucose Monitoring to Promote Diabetes Remission.” Congratulations to Linda Siminerio (2nd from left), Sandra Sobel (3rd from left), David Rometo (4th from left), Patrick McCarthy (5th from left). Not pictured: Emily Timm and Kristine Ruppert. The award was presented by Steven Reis (far left), Director of the University of Pittsburgh Clinical and Translational Science Institute.

Announcement

Save the Date: The UPMC Division of Endocrinology and Metabolism will be hosting their annual Alumni and Friends Reception at the 78th American Diabetes Association Scientific Sessions in Orlando, Florida (June 22–26, 2018). The reception will be held on the evening of June 24. Please contact Chelsea Dempsey for further details (cad183@pitt.edu).

Notable Publications


of two transcription factors, BMAL1 and its partner CLOCK, which activate the expression of two other important sets of genes, PERIOD (PER1 & PER2) and CRYPTOCHROME (CRY1 & CRY2). The protein products of PER and CRY accumulate slowly and, in a negative feedback loop, inhibit their own gene activation. This entire process of activation and inhibition takes approximately 24 hours, thereby forming the basis of the molecular clock.

Targeted disruption of clock genes in mice cause striking metabolic disturbances, highlighting their central role in circadian regulation of cellular metabolism. Likewise, evidence supports a role for clock genes in human metabolism. For example, the essential core clock gene ARNTL (commonly referred to as BMAL1) was significantly downregulated in diabetic human islets, and two BMAL1 haplotypes were associated with increased susceptibility to T2D. In addition, genome-wide association studies (GWAS) have implicated MTNR1B, another circadian rhythm-related gene, in T2D and impaired β-cell function. All cell types, including pancreatic islet cells, display robust clock oscillations. The molecular clocks controlling these oscillations are influenced by different entrainment signals in central and peripheral cells and tissues. For example, the central clock in the hypothalamic suprachiasmatic nucleus (SCN) is primarily influenced by light/dark signals. This central clock then synchronizes peripheral clocks via neurohormonal pathways. In contrast, other signals, such as feeding cues, serve as the dominant entrainment signal that drive peripheral clocks, including the clock in pancreatic islets.

This is a consequence of impaired β-cell function with impaired glucose-stimulated insulin secretion by the pancreatic β-cells. The circadian clock appears to control multiple critical pathways in β-cells, including glucose sensing, substrate metabolism, mitochondrial function, vesicular transport and exocytosis, and cellular stress responses. A disruption of any of these could contribute to β-cell failure and diabetes. Indeed, even a minor shift in the normal light/dark cycle is sufficient to cause significant impairment in mitochondrial adenosine triphosphate (ATP) production and glucose-stimulated insulin secretion, similar to that observed with deletion of BMAL1 in mice. These data demonstrate the powerful effect of circadian disruption on β-cell function. In preclinical mouse models, Dr. Yechoor’s group has recently shown that antioxidants reduce oxidative stress and restore β-cell function in islets with circadian disruption. These findings suggest possible ways to ameliorate β-cell dysfunction and protect against diabetes in the context of circadian disruption.

Dr. Yechoor’s research group at the University of Pittsburgh Division of Endocrinology and Metabolism recognizes the opportunities that lie in these recent discoveries. These new insights provide a deeper understanding of β-cell function and the pathogenesis of diabetes, and also provide valuable clues about potential novel therapeutic strategies. To further pursue this important research and assist other investigators in pursuing diabetes research, Dr. Yechoor has established a β-cell biology core as part of the Diabetes Center at the University of Pittsburgh. As a next step in this research, Dr. Yechoor is working collaboratively with other investigators to study novel approaches to mitigating the deleterious effects of circadian disruption on substrate metabolism, cellular stress, and β-cell function by identifying “druggable” targets in circadian-regulated pathways. In collaboration with the University of Pittsburgh Center for Metabolism and Mitochondrial Medicine (C3M) and the University of Pittsburgh’s Sleep and Chronobiology Center, Dr. Yechoor’s group is expanding the research team to address circadian disruption and its effect on diabetes in preclinical models with the ultimate goal of translating these findings to clinical practice.

With diabetes reaching epidemic proportions, the Division of Endocrinology and Metabolism at the University of Pittsburgh recognizes the need to invest in basic and translational research related to diabetes. Fundamental discoveries underlying the molecular pathogenesis of diabetes are critical for developing new therapies for this devastating disorder. Toward this goal, with investment from the University of Pittsburgh Department of Medicine and the Division of Endocrinology and Metabolism, the Diabetes Center also is actively recruiting faculty to address fundamental research questions in β-cell/islet biology and diabetes. The Division remains committed to its mission to be at the leading edge of scientific research and to create new knowledge that will improve the prevention and treatment of diabetes, while cultivating the next generation of leaders in diabetes research.

Circadian Control of β-cell Function

Disruption of the molecular clock genes, especially BMAL1 (the only nonredundant core clock gene), leads to significant metabolic perturbations. Dr. Yechoor’s group, and others, have shown that deletion of BMAL1 in mouse β-cells leads to progressive glucose intolerance, hypoinsulinemia, and diabetes.1-5
Inpatient Management of Hyperglycemia

References


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

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

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