# ENDOCRINOLOGY UPDATE

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#### From the Division of Endocrinology and Metabolism

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# **Ready for the Emerging Diabetes Technologies**



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As the rates of diabetes mellitus (DM) continue to rise, health systems and providers are being challenged to meet the demands of high-quality, high-value care, particularly for those patients at highest risk. This is occurring while new tools for managing diabetes are being introduced to providers and patients at an exponential rate.

Continuous glucose monitoring (CGM) is among the most innovative of the technological advances now available and the basis for the future of diabetes technology. CGM devices generate nearly continuous blood glucose (BG) data and have the ability to provide useful information regarding BG variability.

This information is available not only to health care providers, but also to patients and their families. CGM

data can be used to identify BG trends and patterns to assist with insulin and other treatment adjustments, as well as to alert users when BG is out of the desired target range. Improvements in CGM technology,

Patients experiencing problems with their diabetes management often require additional time and expertise, which presents challenges in a busy clinic setting.

and changes that apply to users, are being made at a rapid pace that includes remote monitoring capabilities and transmission of data to personal electronic devices, such as phones, computers, and tablets. The U.S. Food and Drug Administration (FDA) recently expanded the approved use of a mobile CGM system to allow for replacement of fingerstick BG testing for diabetes treatment decisions in people 2-years-of-age and older with diabetes. This is the first FDA-approved CGM that can be used to make treatment decisions without confirmation from a traditional fingerstick test.¹ These devices are the foundation for the first closed-loop insulin delivery system (aka — "artificial pancreas"), <sup>2,3</sup> which is expected to come to market in 2017.

Insulin delivery is now possible through the use of continuous subcutaneous insulin infusion (CSII) insulin pumps. Programs now allow insulin pump and CGM devices to connect and send information



# Point-of-Care, Comprehensive Evaluation of **Thyroid Nodular Disease by Endocrinologists:** A New Paradigm for Controlling Health Care Costs



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According to the Centers for Medicare and Medicaid Services (CMS), health care costs in the United States reached \$3.2 trillion in 2015, accounting for 17.8% of the U.S. gross domestic product (GDP). Experts estimate that health care spending will continue to grow, by an average of 5.8% per year over the next decade, unless significant changes occur.<sup>1</sup> With this in mind, medical professionals must develop new

> paradigms that appropriately treat disease processes while limiting excessive, and often unnecessary, much to contribute to this task, particularly as it relates to thyroid

expenditures. Endocrinologists have nodular disease.

Thyroid nodules are exceedingly common. Research indicates that greater than 60% of randomly selected individuals have nodules when evaluated by high-frequency

ultrasound, with women and elderly patients more likely to be affected.<sup>2</sup> Not surprisingly, as highfrequency ultrasound has become more readily available, the discovery and evaluation of thyroid nodules have increased.3 This, in turn, has resulted in an explosion of newly diagnosed thyroid malignancy.3 For instance, in 2009, there were 37,200 new diagnoses of thyroid cancer in the United States, while in 2016 the NIH/NCI Surveillance, Epidemiology, and End Results (SEER) Program estimates that number will increase to approximately 64,300.<sup>4,5</sup> The vast majority of this increase is comprised of small (less than 2 cm) differentiated thyroid cancer (papillary and follicular).<sup>3</sup> One study suggests that by 2019, papillary thyroid cancer will be the third most common malignancy

among U.S. women, at a cost of \$20 billion annually.6 Ironically, despite the increased detection of what appears to be early thyroid cancer, there has been no appreciable impact on the already low rate of thyroid cancer-related mortality.<sup>3,5</sup> This raises the question, "Can endocrinologists develop a paradigm for thyroid nodule evaluation that provides appropriate care while limiting excessive and potentially unnecessary health care expenditures?"

Currently, there is no "gold standard" for the evaluation of thyroid nodules. In some instances, primary care physicians lead the way, ordering biochemical testing, radiologic imaging, and fine needle aspiration on their own. In these situations, primary care physicians consult specialists for cases they deem to be complicated. In other instances, a multidisciplinary team of medical and surgical specialists coordinates the evaluation but relies on other physicians, e.g., radiologists or pathologists, to perform some, or all, of the diagnostic testing, e.g., thyroid/neck ultrasound and ultrasound-guided fine needle aspiration (USG-FNA). While these two approaches yield satisfactory results for patients, thyroidologists at UPMC believe these approaches may result in excessive and/or unnecessary testing, and that endocrinologists play a critical role in the comprehensive evaluation themselves, during which they perform both the medical decision making and diagnostic testing.

Endocrinologists have specific training and a unique experience in the epidemiology and pathophysiology of thyroid neoplasms. This perspective makes them perfectly suited to provide comprehensive management of thyroid nodules. With the increased portability and decreased cost of high-frequency ultrasound equipment, neck ultrasound and USG-FNA are now accessible to most clinical endocrine practices.

Can endocrinologists develop

a paradigm for thyroid nodule

evaluation that provides

appropriate care while

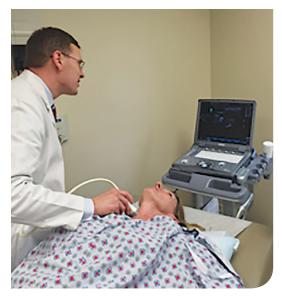
limiting excessive and

potentially unnecessary

health care expenditures?

In addition, the American Association of Clinical Endocrinologists (AACE) offers an Endocrine Certificate in Neck Ultrasound (ECNU) program, which verifies that certificate holders have completed an appropriate amount of training and are capable of performing and interpreting high-quality imaging studies, as well as ultrasound-guided fine needle aspiration. Therefore, endocrinologists who have completed the ECNU program can perform diagnostic ultrasound, discuss the findings with patients in real time, and apply the American Thyroid Association (ATA) Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer to each case, deciding whether evaluation with USG-FNA is indicated or if radiologic follow-up is preferrable.7 This point-of-care, comprehensive approach by a single provider specialized in thyroid disease may result in a more consistent application of the ATA guidelines, which now focus on risk stratification combining sonographic characteristics and nodule size.7 This approach may result in a decrease in the number of nodules that undergo USG-FNA, a decrease in the number of thyroid cancers that are unnecessarily diagnosed and, hopefully, a decrease in health care expenditures related to thyroid nodular disease while continuing to provide excellent patient care.

The UPMC Division of Endocrinology and Metabolism appreciates the escalating costs of health care related to thyroid nodular disease and is committed to providing state-of-the-art care for patients in a manner that is convenient, patient-oriented and cost conscious. Currently, the UPMC Division of Endocrinology and Metabolism participates in a multidisciplinary thyroid center where endocrinologists work together with physicians from surgery, radiology, and pathology to care for patients with thyroid nodules and cancer. In addition, endocrinologists within the Division who are ECNU certified offer a comprehensive approach to thyroid nodule evaluation, during which patients are seen by a physician, undergo diagnostic neck ultrasound, and discuss their results in real time with the endocrinologist, who outlines the appropriate course of action based on the latest medical research. Finally, UPMC thyroidologists have developed a program through which all endocrine fellows are trained in this comprehensive approach and are able to achieve ECNU certification, with the hope that they incorporate this new paradigm into their practices as they begin their careers managing thyroid disease.



Dr. Lebeau performing ultrasound exam in clinic.

#### References

- Centers for Medicare and Medicaid Services. Available on www.cms.gov/Research-Statistics-Data-and-Systems/Statistics.
- 2. Guth S, Theune U, Aberle J, Galach A, Bamberger CM. Very High Prevalence of Thyroid Nodules Detected by High Frequency (13MHz) Ultrasound Examination. *Eur J Clin Invest.* 2009; 39: 699-706.
- 3. Davies L, Welch HG. Current Thyroid Cancer Trends in the United States. *JAMA*. 2014; 140: 317-322.
- Cooper DS, et al. Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2009; 19(11): 1167-1214.
- NIH: National Cancer Institute Surveillance, Epidemiology, and End Results Program. Available on http://seer.cancer.gov/statfacts/html/thyro.html.
- 6. Aschebrook-Kilfoy B, et al. The Clinical and Economic Burden of a Sustained Increase in Thyroid Cancer Incidence. *Cancer Epidemiol Biomarkers Prev.* 2013; 22: 1252-1259.
- Haugen BR, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer. *Thyroid*. 2016; 26(1): 1-133.

# **An Unusual Case of Hypercalcemia**



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#### **Clinical Case**

An 85-year-old woman with a history of type 2 diabetes, hypertension (HTN), and osteopenia was admitted to an outside hospital with generalized weakness and altered mental status. Her family reported that she had experienced significant weight loss in the preceding two months. Her medications at home included amlodipine 5 mg daily, gabapentin 400 mg t.i.d., ezetimibe/simvastatin 10/40 mg daily, olmesartan 40 mg once a day, nadolol 40 mg once a day, saxagliptin 2.5 mg once a day, glipizide XL 10 mg twice a day, and metformin 1000 mg twice a day. The family also reported that she was a heavy smoker but did not use alcohol. A laboratory evaluation performed at the time of presentation revealed a blood glucose of 108 mg/dL and a corrected serum calcium of 14.4 mg/ dL with hypercalciuria (Table 1). Based on an elevated parathyroid hormone (PTH) level, she was diagnosed with primary hyperparathyroidism and treated with V hydration with normal saline, which resulted in a decrease in her serum calcium to 13 mg/dL. As she was not deemed a surgical candidate, she was discharged to home with a prescription for cinacalcet 30 mg twice daily. The patient was readmitted two days later with increasing lethargy, further decline in her mental status, and poor oral intake. Her corrected calcium at the time of readmission was 15.1 mg/dL, with a PTH

of 141 pg/mL. She was again treated with IV hydration, furosemide, subcutaneous (SC) calcitonin, and 4 mg of zoledronic acid with gradual improvement in her serum calcium and mental status. Her corrected serum calcium was 10 mg/dL at time of hospital discharge to home.

The patient presented again two weeks later with altered mental status, a corrected serum calcium of 15.7 mg/dL, an intact PTH of 636 pg/mL, and acute kidney injury with creatinine of 1.6 mg/dL. She was again treated acutely with IV fluids, furosemide, and a second dose of 4 mg zoledronic acid before transfer to our facility. Upon arrival, she was lethargic with spontaneous movements, but was minimally responsive to voice and was unable to follow commands. On physical examination, she had a blood pressure of 168/92 mmHg, heart rate of 66 bpm, respiration of 14 breaths per minute, O2 saturation of 98% on room air, a weight of 49 kg, and a BMI of 19.1. There were no palpable neck masses or thyromegaly. The patient's serum calcium was 13.7 mg/dL, PTH 385 pg/mL, phosphorus 2.1 mg/dL, magnesium 1.7 mg/dL, a 25(OH)D 33 ng/mL, 1,25(OH)<sub>2</sub>D level of 46 pg/mL, a PTHrP of 0.5 pmol/L (< 2.0 pmol/L), normal hepatic function panel, and normal thyroid function tests. An SPEP was normal. IV hydration with NS and SC calcitonin were continued in anticipation of a reduction in her serum calcium following the bisphosphonate infusion.

Given the significant elevations in her PTH levels and poor responsiveness to bisphosphonate therapy, there was clinical suspicion for parathyroid carcinoma, and surgical exploration was considered. A neck ultrasound demonstrated the presence of a 2.1 cm exophytic left-sided, mixed solid-cystic nodule within the thyroid gland without evidence of parathyroid enlargement or mass. A sestamibi scan did not provide any definitive evidence of a parathyroid adenoma.

Surgical neck exploration revealed the presence of three normal and viable-appearing parathyroid glands with several firm white nodules in the left lower neck and left cervical thymus, the latter of which were resected with minimal reduction in intraoperative PTH levels (403 pg/mL at baseline, 365 pg/mL post resection, 372 and 373 pg/mL post-continued exploration and resection). Intraoperative frozen

section suggested the presence of a high-grade malignancy. A left thyroid lobectomy was performed for possible intra-thyroidal parathyroid gland. Further surgical exploration into the upper mediastinum revealed significant fixed nodules retrosternally that were not resectable by cervical incision.

Surgical pathology was negative for parathyroid carcinoma, and instead demonstrated the presence of a small cell neuroendocrine carcinoma, with positive staining for pankeratin and rare TTF-1 positivity, suggesting possible lung versus upper aerodigestive tract origin. Immunohistochemical staining of the available tumor tissue for PTH was negative. A normal-sized, but mildly hypercellular, intra-thyroidal parathyroid gland was noted within the resected left lobe of the thyroid.

The patient's serum calcium normalized within four days of receiving zoledronic acid, without improvement in her mental status. The decision was made to transfer her to a facility close to her home. After transfer, an abdominal CT performed for suspected ileus revealed numerous lesions suspicious for metastases of liver and bone. Her calcium again was rising. She was evaluated by oncology, however, given her declining functional status, chemotherapy was deferred. Her code status was changed to comfort measures only, and the patient passed away within two weeks of her neck exploration.

#### Discussion

This case illustrates a very rare presentation of PTHmediated hypercalcemia. The patient had PTH-mediated hypercalcemia without confirmation of the source of PTH production. There was no evidence of a parathyroid cancer or adenomatous enlargement. The mechanism of hypercalcemia may have been multifactorial, with possible contribution from osteolytic bone metastases, which were identified later in her course. An ectopic PTH-secreting neuroendocrine carcinoma is strongly suspected as the etiology of hypercalcemia in this patient. There was minimal drop in intraoperative PTH levels following removal of the suspected parathyroid tissue. Staining for PTH on the available tumor tissue was negative, which may have been due, in part, to heterogeneity of the tumor and variability in the site of PTH hypersecretion.

Cases of ectopic PTH-producing nonparathyroid tumors have been previously reported.<sup>1-5</sup> Ectopic sources include cases of lung carcinomas, including

TABLE 1. PTH and Calcium Levels

	PTH (pg/mL)	Corrected Calcium (mg/dL)	Creatinine (mg/dL)
7/2014	_	9.7 (uncorrected)	1.04
Admission #1 11/20/14	110	14.4	1.38
Admission #2 11/23/14	141	15.1	1.19
Admission #3 (2 weeks post zoledronate dose #2) 12/17/14	636	15.7	1.6
2 days post zoledronate dose #2 12/19/14	385	13.7	1.4
3 days post zoledronate dose #2, day 1 of calcitonin 12/20/14	-	9.5	1.1
2 weeks after zoledronate dose #2 12/30/14	-	13.6	1.1

both small cell neuroendocrine lung carcinomas and squamous cell carcinomas; four pancreatic malignancies; two papillary thyroid cancers; one medullary thyroid cancer; one tonsillar squamous cell carcinoma; a nasopharyngeal rhabdomyosarcoma; a neuroendocrine tumor of the head and neck; two cases of ovarian carcinoma; and two cases of hepatocellular carcinoma. In most, but not all, reported cases, ectopic PTH secretion was demonstrated by positive immunohistochemical staining for PTH or detection of PTH mRNA in the tumor.

In one case, a 73-year-old woman with clinical and biochemical findings suggestive of primary hyperparathyroidism with negative sestamibi scintigraphy and neck ultrasound was found to have normal parathyroid glands and a 1.5 cm mass in the thyrothymic ligament at the time of surgical neck exploration. Excision of this mass was accompanied by an appropriate intraoperative PTH drop from 126 to 12 pg/mL. Pathology was consistent with a neuroendocrine tumor with positive immunohistochemical staining for PTH.

In another case, a 73-year-old woman with severe PTH-mediated hypercalcemia (calcium 15.3 mg/dL, PTH 399 pg/mL) was found to have a poorly

# **Understanding the Mechanisms of Physical Activity-Induced Health Benefits**



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A University of Pittsburgh research team that includes members from the Division of Endocrinology will contribute to a multi-institutional, collaborative effort to understand the molecular mechanisms underlying the health benefits of physical activity.

Physical activity, in addition to a healthful diet, is widely accepted as among the most beneficial lifestyle measures to promote health and wellness. Indeed,

The link between physical activity and improved health holds extraordinary promise for discovery of novel therapeutic targets and development of personalized exercise medicine.

physical activity exerts a multitude of beneficial effects on both physical and emotional health, including promoting strength and fitness, improving mental health and mood, prolonging lifespan, and preventing chronic disease.\(^1\)
Conversely, a lack of physical inactivity is detrimental to health and is one of the most important causes of many chronic diseases, including obesity, diabetes, cardiovascular disease, and even cancer.\(^2\) Despite this critical role of physical activity in health

and wellness, the molecular mechanisms mediating the beneficial effects of physical activity remain largely unknown.

Over the past several decades, scientists have struggled to unravel the "molecular mysteries" underlying the beneficial effects of physical activity on the human body. These benefits have been attributed to a variety of factors, including reducing body weight, improving serum lipids, increasing muscle mass, and influencing other factors that generally promote cardiorespiratory fitness. However, not until recently have scientific advances uncovered the increasingly important role of intertissue crosstalk in mediating the beneficial

effects of physical activity. In this regard, one of the most transformative advances has been the discovery that physically active muscle undergoes a variety of molecular changes that ultimately result in the release of circulating factors knows as "myokines" and "myometabolites." These molecular changes and circulating factors have far-reaching systemic metabolic effects. The number of studies addressing these issues is increasing exponentially (see Febbraio, 2017 for review of the most impactful studies from 2016), and yet the understanding of these mechanisms is still in its infancy. Such knowledge could reveal novel therapeutic targets for disease prevention and treatment.

To address these knowledge gaps, the National Institutes of Health (NIH) convened a workshop in late October 2014 entitled, "Understanding the Cellular and Molecular Mechanisms of Physical Activity-Induced Health Benefits." This workshop addressed current challenges (i.e., different types and duration of physical activity, differences in study design and patient populations, and lack of infrastructure and collaborative expertise to incorporate large-scale mechanistic outcomes into physical activity clinical trials), as well as new advances that could overcome some of these challenges (i.e., development of "-omics" and bioinformatics technology, advances in systems biological approaches, and new platform technologies.) The conclusion of this workshop was: "The identification of the mechanisms underlying the link between physical activity and improved health holds extraordinary promise for discovery of novel therapeutic targets and development of personalized exercise medicine."7

As a result, the National Institute of Health Common Fund submitted a request for applications to identify the Molecular Transducer of Physical Activity (MoTrPAC). Approximately \$170 million has been devoted to this study over the next six years. The overarching goals of the MoTrPAC study are, "to catalogue the biological molecules affected by exercise in people, to assemble a comprehensive map of the molecular changes that

occur in response to movement and, when possible, to relate these changes to the benefits of physical activity. This map will contain the many molecular signals that transmit the health effects of physical activity, and indicate how they are altered by age, sex, body composition, fitness level, and exposure to exercise. The program also aims to develop a user-friendly database that any researcher can access to develop hypotheses regarding the mechanisms whereby physical activity improves or preserves health, facilitating investigator-initiated studies and catalyzing the field of physical activity research." (See MoTrPAC website link on Page 11.)

To achieve this goal, the program includes five components: adult clinical centers (6), a child clinical center (1), preclinical animal study sites (3), and chemical analysis sites (7), as well as a bioinformatics center (1), and a consortium coordinating center (1). The University of Pittsburgh has been selected as one of the adult clinical centers in this 19-center collaborative consortium. John J. Jakicic, PhD, chair of the Department of Health and Physical Activity

within the School of Education, at the University of Pittsburgh, will lead this effort with his executive team. This team consists of several other faculty members from throughout the University of Pittsburgh community, including Daniel E. Forman, MD, chair of the Section of Geriatric Cardiology within the Department of Medicine; Erin E. Kershaw, MD, chief of the Division of Endocrinology and Metabolism within the Department of Medicine; Anne B. Newman, MD, chair of the Department of Epidemiology within the Graduate School of Public Health; Bradley C. Nindl, PhD, director of the Neuromuscular Research Laboratory in the Department of Sports Medicine and Nutrition within the School of Health and Rehabilitation Sciences; Lindsay C. Page, PhD, assistant professor of Research Methodology within the School of Education, and a research scientist within the Learning Research and Development Center; and Renee J. Rogers, PhD, assistant professor of Health and Physical Activity within the School of Education.



### An Unusual Case of Hypercalcemia (Continued from Page 5)

differentiated neuroendocrine tumor of the pancreas with metastases to the liver and retroperitoneal lymph nodes.<sup>2</sup> The tumor tissue demonstrated positive immunohistochemical staining for PTH. Tumor cells were found to express the PTH gene by activating regulatory sequences in the PTH promoter. Nussbaum, et al. described a case of a PTH-secreting ovarian clear cell carcinoma, with tumor cells positive for PTH

Control of hypercalcemia due to ectopic PTH production relies on the ability to treat the underlying neuroendocrine tumor.

mRNA.³ There was documentation of PTH gene rearrangement involving an upstream regulatory sequence. Vacher-Coponat, et al. described a 58-year-old female with severe PTH-mediated hyper-calcemia (calcium of 22.4 mg/dL, PTH of 394 pg/mL at presentation).⁴ Cervical parathyroid exploration was negative for a parathyroid tumor, however sestamibi scintigraphy showed a hepatic lesion confirmed by subsequent CT imaging, which demonstrated multiple liver nodules

and diffuse neoplasia of the liver. A biopsy of the liver lesion showed a highly undifferentiated neuroendocrine neoplasm of the pancreas. A gradient of PTH levels was observed between the suprahepatic veins and peripheral veins. Similar to the patient in our case, PTH immunohistochemical staining was not demonstrated in tumor tissue. However, the observed hepatic-peripheral vein gradient, as well as the drop in PTH levels correlating to tumor regression with chemotherapy, strongly suggested an ectopic PTH-producing neuroendocrine tumor of the pancreas.

Ectopic PTH-secreting tumors are rare, with limited available information to guide management. Control of hypercalcemia often depends on the ability to treat the underlying tumor. In cases of nonresectable tumor burden, intravenous bisphosphonates have had limited and transient effects. 1,2,4 Consideration can be given to treatments used for hypercalcemia due to parathyroid carcinoma, such as cinacalcet, which has been shown to be effective. 6 Bisphosphonates have been shown to improve hypercalcemia in individual cases of parathyroid carcinoma, but again, the effect is usually transient. Denosumab was demonstrated to be effective in parathyroid cancer-mediated hypercalcemia refractory to bisphosphonates.<sup>7</sup> This may reflect the different mechanisms of action of denosumab and bisphosphonates. Denosumab, a monoclonal antibody, binds RANK ligand (RANKL), thus inhibiting

the RANKL pathway, which is important in osteoclast formation, differentiation, and action. Bisphosphonates, however, only inhibit the action of mature osteoclasts at the site of bone resorption, but do not affect osteoclast development or differentiation.<sup>8</sup> Thus, denosumab may be more effective in cases of very high levels of PTH, which increases RANKL signaling and osteoclast development and activity, and thus could have been considered in our patient.

In summary, we report a rare and challenging case of PTH-mediated hypercalcemia in the setting of a neuroendocrine tumor, where ectopic PTH production by the neuroendocrine tumor was strongly suspected. Control of hypercalcemia due to ectopic PTH production relies on the ability to treat the underlying neuroendocrine tumor. The use of denosumab could be considered in nonresectable cases.

#### References

- 1 Kandil E, Noureldine S, Khalek M, Daroca P, Friedlander P. Ectopic Secretion of Parathyroid Hormone in a Neuroendocrine Tumour: A Case Report and Review of the Literature. Int J Clin Exp Med. 2011; 4(3): 234-240.
- VanHouten JN, Yu N, Rimm D, et al. Hypercalcemia of Malignancy Due to Ectopic Transactivation of the Parathyroid Hormone Gene. J Clin Endocrinol Metab. 2006: 91(2): 580-583.
- 3. Nussbaum SR, Gaz RD, Arnold A. Hypercalcemia and Ectopic Secretion of Parathyroid Hormone by an Ovarian Carcinoma With Rearrangement of the Gene for Parathyroid Hormone. *N Engl J Med*. 1990; 323(19): 1324–1328.
- Vacher-Coponat H, Opris A, Denizot A, Dussol P, Berland Y. Hypercalcemia Induced by Excessive Parathyroid Hormone Secretion in a Patient With a Neuroendocrine Tumour. Nephrol Dial Transplant. 2005; 20(12): 2832–2835.
- Doyle MA, Malcolm JC. An Unusual Case of Malignancyrelated Hypercalcemia. Int J Gen Med. 2014; 7: 21–27.
- Silverberg SJ, Rubin MR, Faiman C, Peacock M, Shoback DM, Smallridge RC, Schwanauer LE, Olson KA, Klassen P, Bilezikian JP. Cinacalcet Hydrochloride Reduces the Serum Calcium Concentration in Inoperable Parathyroid Carcinoma. J Clin Endocrinol Metab. 2007; 92(10): 3803–3808.
- Vellanki P, Lange K, Elaraj D, et al. Denosumab for Management of Parathyroid Carcinoma-mediated Hypercalcemia. J Clin Endocrinol Metab. 2014; 99: 387-90.
- 8. Baron R, Ferrari S, Russell RG. Denosumab and Bisphosphonates: Different Mechanisms of Action and Effects. *Bone.* 2011; 48: 677–92.

#### Ready for the Emerging Diabetes Technologies (Continued from Page 1)

through devices (some the size of a car key fob) to smartphone applications. With this technology, patients can quickly view their BG information. Furthermore, some of these devices display BG trends associated with food and activity levels. This creates opportunities for real-time adjustments in insulin delivery, allowing for quick responses to situations or environments in which BG levels change rapidly. Technologies that aid in the acquisition and processing of glucose information to a person with DM can be shared with their diabetes care team and have the potential to prove invaluable, but health care systems need to be prepared to handle all of the additional data that is becoming increasingly available.

While all of these innovations are life-changing for the patients and their families, training patients on the skills necessary to use these tools, and learning to interpret all of this available data, requires a prepared diabetes care team. The complexity of diabetes management requires that health care providers support their patients with the appropriate amount of time and education that are necessary for effective self-management and adherence. Patients experiencing problems with their diabetes management often require additional time and expertise, which presents challenges in a busy clinic setting. As diabetes therapies and technology are quickly advancing, health care systems need to be prepared to help patients use these tools and translate information for positive health outcomes.

The Multidisciplinary Diabetes Clinic was conceived in collaboration with the diabetes specialists at the Falk Center for Diabetes and Endocrinology at UPMC. Faculty and staff recognized limitations in providing the necessary care and time required for high-risk patients with glycemic management problems. Although the benefits of our highly-trained team members — which includes diabetes educators and dietitians — are numerous, their services for care and education, like many programs, are underutilized.5-7 Through a review of our patient database, we realized that although there were on-site educators and dietitians, for a variety of reasons patient visits to team members "fell through the cracks." Referral was not done in a systematic way, and care and education delivery were fragmented.



The Multidisciplinary Diabetes Clinic was designed to proactively identify patients experiencing challenges with glycemia, e.g., high hemoglobin A1C, recurrent unplanned care, hypoglycemia unawareness, new comorbidities and/or therapies, special needs related to diabetes technology, and other issues. These patients were scheduled for a visit that included all of the members of the Multidisciplinary Diabetes Clinic team. Through this patient-centered approach, members of the team have an opportunity to meet with the patient to individually assess, and collaboratively organize, a treatment plan that attends to all of the complex elements of diabetes care, including nutrition, medication management, and psychosocial, and behavioral issues. Ongoing patient follow-up is provided by a familiar member of the clinic team.

The UPMC Division of Endocrinology and Metabolism offers a full range of DM technologies to assist patients

# **Continuing Medical Education**

The free courses listed below are currently available for CME credit by visiting UPMCPhysicianResources.com/Endocrinology.

#### Med Grand Rounds: Endocrinology Year in Review

Presented by Erin Kershaw, MD, and David Rometo, MD

Drs. Kershaw and Rometo discuss current obesity statistics and the latest research in endocrinology.

# Type 1 Diabetes Complications: 30 Year Pittsburgh Retrospective

Presented by Trevor Orchard, MD

Dr. Orchard presents the 2016 Kenny Drash lecture, and discusses some of the work that has been done over the past 30 years in the Pittsburgh EDC study.

#### **Negotiating Diabetes Management in the Elderly**

Presented by Mary T. Korytkowski, MD

Dr. Korytkowski's presentation focuses on the scope of the burden and complications in the elderly who are dealing with diabetes. Dr. Korytkowski discusses ways to maintain and improve the health status of older adults with diabetes.

#### Ready for the Emerging Diabetes Technologies (Continued from Page 9)

with diabetes in achieving their optimal glycemic control and overall improved health. Technologies offered in our program include professional CGM and interpretation, CSII initiation, and real-time CGM initiation. Through the combined efforts of



our physicians, certified diabetes educators, advanced practice nurses, and staff, we have a comprehensive diabetes care and self-management education program that utilizes and integrates these technologies with lifestyle, physical activity, and dietary choices to help patients begin to understand the complex nature of glycemic management and obtain optimal glucose control. With all of the innovative tools and technology being introduced in diabetes care,

the Multidisciplinary Diabetes Clinic is being used to accommodate all of these rapid advances in diabetes care, and it is ready for all of the innovations ahead.

#### References

- U.S. Food & Drug Administration (FDA) News Release. FDA Expands Indication for Continuous Glucose Monitoring System, First to Replace Fingerstick Testing for Diabetes Treatment Decisions. Dec. 20, 2016.
- 2. Garg S. The Future of Glucose Monitoring. *Diabetes Technol Ther.* 2016; 18(2): S2-iv-S2-2.
- Bergenstal RM, Garg S, Weinzimer SA, et al. Safety of a Hybrid Closed-loop Insulin Delivery System in Patients With Type 1 Diabetes. *JAMA*. 2016; September 15. Epub ahead of print.
- 4. American Diabetes Association. Strategies for Improving Care. *Diabetes Care*. 2016; 39 (Suppl. 1): S4-5.
- Rui L, Sundar S, Lipman R, Burrows N, Kolb L, Rutledge S. Diabetes Self-management Education and Training Among Privately Insured Persons With Newly Diagnosed Diabetes. The CDC Morbidity & Mortality Report. 2014; 63(46): 1045-1049.
- Duncan I, Ahmed T, Li QE, Stetson B, Ruggiero L, Burton K, Rosenthal D, Fitzner K. Assessing the value of the diabetes educator. *Diabetes Educ.* 2011 Sep-Oct;37(5):638-57. doi: 10.1177/0145721711416256. Epub 2011 Aug 30.
- 7. Ruppert K, Uhler A, Siminerio LM. Examining Patient Risk Factors, Comorbid Conditions, Participation, and Physician Referrals to a Rural Diabetes Self-management Education Program. *Diabetes Educ.* 2010; 36(4): 603-12.

#### Physical Activity-Induced Health Benefits (Continued from Page 7)

The University of Pittsburgh, including the Division of Endocrinology and Metabolism, has a long and strong tradition of contributing important knowledge to the understanding of physical activity and its impact on health. This study provides an important opportunity to better understand the fundamental mechanisms underlying the health benefits of physical activity, with the goal of preventing and treating human disease. These important studies will lay a strong foundation for translational research that we can ultimately bring to both individuals and the population as a whole.

Subsequent issues of this publication will provide updates on our progress, as well as additional information about this exciting study. If you are interested in participating in this study, or any University of Pittsburgh research study, please register at Pitt+Me™ (https://pittplusme.org/).

#### References

- 1. CDC (2017). Centers for Disease Control and Prevention: Physical Activity and Health.
- Booth FW, Roberts CK, Laye MJ. Lack of Exercise Is a Major Cause of Chronic Diseases. Compr Physiol. 2012; 2: 1143-1211.
- Petriz BA, Gomes CP, Almeida JA, de Oliveira GP Jr, Ribeiro FM, Pereira RW, Franco OL. The Effects of Acute and Chronic Exercise on Skeletal Muscle Proteome. J Cell Phys. 2017; 232: 257-269.
- Rai M, Demontis F. Systemic Nutrient and Stress Signaling Via Myokines and Myometabolites. *Annu Rev Physiol.* 2016; 78: 85-107.
- Whitham M, Febbraio MA. The Ever-expanding Myokinome: Discovery Challenges and Therapeutic Implications. Nat Rev Drug Discov.. 2016; 15: 719-729
- Febbraio MA. Exercise Metabolism in 2016: Health Benefits of Exercise — More Than Meets the Eye! Nat Rev Endocrinol. 2017 Feb: 13(2):72-74.
- Neufer PD, Bamman MM, Muoio DM, Bouchard C, Cooper DM, Goodpaster BH, Booth FW, Kohrt WM, Gerszten RE, Mattson MP, et al. Understanding the Cellular and Molecular Mechanisms of Physical Activity-induced Health Benefits. *Cell Metabolism*. 2015; 22: 4-11.



#### **Important Links for More Information**

# https://www.youtube.com/watch?v=wA\_7konZPTo &feature=youtu.be

NIH Director Francis S. Collins, MD, PhD, discussion of the MoTrPAC on YouTube

# https://commonfund.nih.gov/MolecularTransducers/overview

National Institutes of Health Announcement

https://www.nih.gov/news-events/news-releases/ nih-awards-aim-understand-molecular-changesduring-physical-activity

#### http://www.news.pitt.edu/news/understandingwhy-we-should-exercise

University of Pittsburgh Announcement

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