FALL 2021

DIVISION OF ENDOCRINOLOGY AND METABOLISM

UPDATE IN

ENDOCRINOLOGY

Inside This Edition

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Dear Colleagues,

We are pleased to share our latest edition of Update in Endocrinology. The last year has brought so many changes to the academic health care environment. It has been truly humbling to witness the resilience and ongoing commitment of our colleagues to all aspects of the academic mission - research, education, quality, and clinical care. In this issue, we share some of the activities of our colleagues.

To highlight our research excellence, scientist **Yong Wan, PhD**, discusses novel, evidence-based treatments for osteoporosis. Dr. Wan was recently awarded a Samuel and Emma Winters Foundation grant to further his research regarding potential targets for the treatment of osteoporosis.

On the clinical front, School of Nursing Department chair **Denise Charron-Prochownik, PhD, RN, CPNP**, and research assistant professor **Andrea Fischl, PhD, CRNP, MPH**, along with **Sarah Stotz, PhD, RD, CDE**, and **Kelly Moore, MD**, of the Colorado School of Public Health, discuss the importance of preconception counseling for indigenous adolescents with diabetes.

Complex cases continue to challenge our expertise and provide fellows with transformative lessons in clinical care. Previous Endocrinology Clinical Fellow, **Nami Safai Haeri, MD**, who is now a Clinical instructor, and his mentor, **Hussain Mahmud, MD**, present two clinical cases discussing rare occurrences of spontaneous bilateral adrenal hemorrhages in pregnancy.

David Rometo, MD, Clinical Lead of the Endocrine Obesity Unit and Weight Management Program, discusses the UPMC Clinical Fellowship in Obesity Medicine. This fellowship program, which is supported by a grant from the Obesity Medicine Fellowship Council, is one of the few of its kind in the country and provides subspecialty training in the pathogenesis and treatment of obesity and its complications.

Our Division continues to grow with the addition of several new faculty including **Divya Sistla, MBBS, Katrina Han, MD**, **Margaret Zupa, MD**, and **Donna Lee, MD**, to our clinical faculty. We welcomed back Dr. Sistla and Dr. Han to UPMC, who previously completed their clinical fellowship and residency, respectively, at UPMC. Dr. Lee came to our Division following completion of a clinical fellowship at Albert Einstein College of Medicine.

In addition, we also celebrate many accomplishments of our faculty and trainees. **Ruya Liu, MD, PhD**, and **Yong Wan, PhD**, were each awarded a Samuel and Emma Winters Foundation Award. **Linda Siminerio, RN, PhD, DCES**, was the recipient of the 2021 Lois Jovanovic Transformative Woman in Diabetes Award.

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

Best wishes,

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

Exploring Novel Treatments for Osteoporosis: Lessons for Future Treatment Development

Yong Wan, PhD

Research Assistant Professor, Department of Medicine

Overview of Osteoporosis

Osteoporosis is the most common form of bone disease, affecting approximately 54 million Americans. According to data from the Centers for Disease Control and Prevention (CDC), osteoporosis-related morbidity for men above the age of 50 is 4.2%, while for women above the age of 50 the rate is much higher at 18.8%. Osteoporosis is an age-related disease caused by imbalanced bone remodeling with coupling of osteoblastic bone formation and osteoclastic bone resorption, causing "porous bone" with decreased bone mineral density. When the balance favors osteoclastic bone resorption, it leads to fragile bones with a high risk of bone fracture.[1-3] Osteoporosis is not a painful disease and, as a result, many patients do not seek treatment until a bone fracture occurs.

There has, however, been increased interest in seeking new osteoporosis therapies. In the past three decades, the United States Food and Drug Administration (FDA) has approved 11 drugs for osteoporosis treatment. These drugs target either osteoblasts or osteoclasts, if not both. Three major limitations of these medications include: (1) poor efficacy in preventing nonvertebral fractures; (2) long-term side effects; and (3) tight activity coupling of osteoblasts and osteoclasts.[4] As such, it is of great interest to explore novel targets to inhibit bone resorption and/or promote bone formation within bone context. These novel targets might serve as potential therapeutic targets to prevent age-related bone loss, and thus be relevant in the treatment of osteoporosis.

Cross-talk between Osteoblasts and Osteoclasts

Bone is a complex endocrine organ that secretes several hormones, including Osteocalcin (OCN),[5,6] Lipocalin 2 (LCN2),[7] Fibroblast Growth Factor 23 (FGF23),[8,9] and Sclerostin (SOST),[10] which have various endocrine effects on energy metabolism.[10] Osteoblastic bone formation starts during the embryonic stage and continuously regulates bone dynamics throughout life,[11] while osteoclasts activity is evident in embryonic bones, but also increases throughout the aging process.[12,13] In addition to the endocrine function of bone, both osteoblasts (osteocytes) and osteoclasts can secrete several cytokines and growth factors exerting an autocrine and paracrine effect on each other.[14] There are several proteins, Wnt, Notch, and Bone Morphogenetic Protein (BMP), secreted by osteoblasts that regulate osteoblast proliferation and/or differentiation in autocrine and paracrine manner.[14-17] In addition, osteoclasts secrete several cytokines, including BMP6, collagen triple helix repeat containing 1 (CTHRC1), EphrinB2 (EFNB2), Sphingosine 1-phosphate (S1P), Wnt10b, Semaphorin 4D (SEMA4D), and Cardiotrophin-1(CT-1) to regulate osteoblastogenesis.[14,18-22]

A bone remodeling unit (BMU) mainly consists of osteoblasts, osteoclasts, bone-lining cells, and osteocytes.[3] In healthy human adults, there are about 1 million active BMUs at any given moment.[23] As major components of a BMU, the cross-talk between osteoblasts and osteoclasts is critical to regulating bone remodeling. The functional coupling of osteoblasts and osteoclasts causes most osteoporosis medications to become less effective. Antiresorptive medications, which inhibit bone resorption, leads to decreased bone turnover, while anabolic medications improve bone turnover with increased bone formation, as well as bone resorption.[4] It would be ideal to target the functional activity of osteoblasts or osteoclasts instead of its differentiation ability.

Wnt Signal in Osteoporosis

The most recently FDA approved medication is romosozumab, an anti-Sclerostin (SOST) antibody. SOST, mainly secreted by osteocytes, can bind with the LRP5/6 receptor, thus inhibiting the Wnt/beta-catenin signal. The primary biological function of SOST is to inhibit osteoblast differentiation.[24,25] Even though SOST is not expressed in osteoclasts, SOST is capable of regulating osteoclastogenesis in a direct and indirect manner. As the only medication that promotes bone formation and inhibits bone resorption, the molecular and cellular mechanism of SOST sets a good example for the development of anabolic medications with antiresorptive activity.

Wnt/beta-catenin signal is a conserved signal that regulates adult tissue homeostasis. Wnt/beta-catenin

signal might positively regulate osteoblastogenesis, while negatively regulating osteoclastogenesis. As such, it is still of interest to target Wnt signal specifically in the bone context to treat osteoporosis.

Beyond Osteoporosis, Treating Osteoporosis as an Aging Disease

Aging leads to the time-dependent functional decline of all tissues, including bone. At least nine separate hallmarks are reported to contribute to aging, such as telomere shortening and cellular senescence.[29] Recent publications have shown links to mitochondrial dysfunction[30-32] and cellular senescence[33] with aging-related bone loss. Findings like these have piqued investigators' interest in seeking new osteoporosis treatment options as part of the aging process. For example, Sirtuins 6 (SIRT6), one member of the Sirtuins (1-7) family, has been reported to extend the lifespan of mice by approximately 15%[34,35] while deletion of SIRT6 in mice leads to osteoporosis phenotype with decreased bone formation and enhanced bone resorption.[36-38] As bone closely interacts with other tissues, such as muscle and adipose tissue, the potential anti-aging medication will not merely improve bone quality, but also improve the function of bone related tissues, which in turn is beneficial to bone functions.

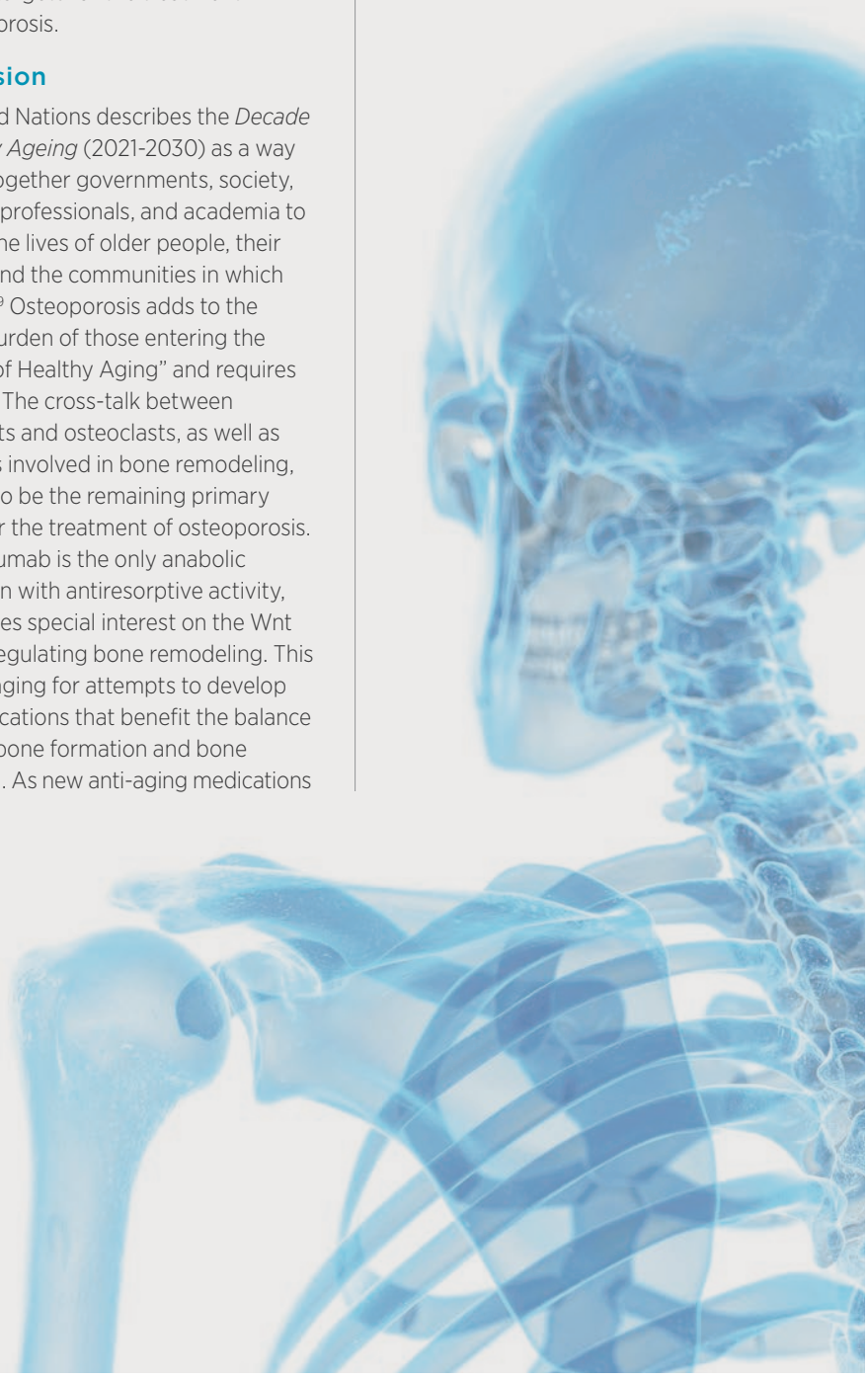
Exploring Novel Targets through Secretome Analysis for the Treatment of Osteoporosis

Investigators in the Wan Lab have established that osteoblasts/osteocytes secrete Wnt proteins that regulate osteoblasts and osteoclasts.[16,17] In order to explore novel secreted proteins from osteoblasts/osteocytes that exert paracrine and/or endocrine effect on bone metabolism, the Wan Lab research team is currently conducting secretome analysis of osteoblasts/osteocytes both *in vitro* and *in vivo*. For that purpose, they have been capable of overexpressing biotin ligase in endoplasmic reticulum of bone cells, which will biotinylate proteins through conventional secretion. These secreted biotinylated proteins allow for rapid purification and mass spectrometry analysis. The Wan Lab researchers will further screen the top hits from mass spectrometry analysis through the functional study of bone cells and neonatal bone cultures. The candidate targets will be further validated by their ability to prevent osteoporosis in aged mice. This hypothesis, if validated, will help to find novel target(s) to prevent age related bone loss, thus serving as potential targets for the treatment of osteoporosis.

Conclusion

The United Nations describes the *Decade of Healthy Ageing* (2021-2030) as a way to bring together governments, society, agencies, professionals, and academia to improve the lives of older people, their families, and the communities in which they live.[39] Osteoporosis adds to the societal burden of those entering the "Decade of Healthy Aging" and requires attention. The cross-talk between osteoblasts and osteoclasts, as well as other cells involved in bone remodeling, continue to be the remaining primary targets for the treatment of osteoporosis. Romosozumab is the only anabolic medication with antiresorptive activity, which raises special interest on the Wnt signal in regulating bone remodeling. This is encouraging for attempts to develop new medications that benefit the balance between bone formation and bone resorption. As new anti-aging medications emerge, it will be of general benefit to approach osteoporosis as part of the aging process. Given the aging population, it is more critical than ever to ensure that people not only live longer, but that they remain healthy, mobile, and functional longer. Having healthy bones is an essential component of healthy aging, and Dr. Wan's research will help achieve this goal.

Please refer to the Update in Endocrinology Fall 2021 CME course on UPMCPhysicianResources.com for a full list of references featured in this article.



Preconception Counseling Starts at Puberty for Child-Bearing Women: An Essential Tool in Diabetes Care

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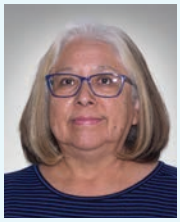

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While risks related to pregnancy for women with diabetes are well-known, a persistent need remains for evidence-based clinical approaches that take into account the specific needs of childbearing aged women. National organizations, like the American Diabetes Association (ADA),[1] have responded by supporting research in this area and now recommend starting preconception counseling at puberty and repeating it often to help women plan their pregnancies when it's safe and wanted as a standard of care. Investigators at the University of Pittsburgh School of Nursing, along with nationwide collaborators, have been pioneers and leaders in this field. With research supported by the ADA and National Institutes of Health, the goals of their research studies are to develop, examine, and implement developmentally appropriate and culturally relevant preconception counseling programs, and find, through research initiatives, the best ways to help support and guide a successful future pregnancy for women and their families.

Preconception counseling (PC) has been shown to reduce the risk of pregnancy-related complications in women with diabetes by preventing unplanned pregnancies and planning healthy pregnancies. Early in their efforts, the research team, led by **Denise Charron-Prochownik, PhD, RN, CPNP** surveyed teens with diabetes. They were concerned when they learned that teens were unaware of PC and reproductive complications, had sexual intercourse before the age of 16 years, had some unsafe sexual practices, and were at high risk for an unplanned pregnancy.[2–4] In their studies, it was found that the first sexual experience of participants was 15 years[6] and 40% had at least one occurrence of unprotected sex.[2–4] They found that young adolescents, starting at puberty (~13 years old), needed developmentally appropriate and culturally relevant information with a sensitive, proactive, and preventative approach before becoming sexually active to empower them to make informed choices regarding reproductive health.

In response, the research team developed *READY-Girls* (Reproductive-health Education and Awareness of Diabetes in Youth for Girls)[4–6], a developmentally appropriate, theory-based,[7] and cost-effective PC program for teens with either Type 1 or Type 2 diabetes, and culturally modified it to specifically meet the needs of African American and Latina adolescent women. *READY-Girls* is designed to engender "awareness" that includes information on several topics including the importance of tight control before conception, diabetes and pregnancy/risk of complications, importance of planning a pregnancy with PC, how to prevent an unplanned pregnancy, and family planning advice.[4-6] The *READY-Girls* preconception counseling program is endorsed and distributed by the ADA to raise awareness and prevent unplanned pregnancies and pregnancy complications.

Research on *READY-Girls* has demonstrated the feasibility and efficacy of a PC intervention for teens,[4,8,9] the benefit of "booster" interventions,[3] and the feasibility and benefits of a mother-daughter intervention[10,11] and communication.[11] *READY-Girls* has been shown to be a useful resource for health care providers (HCPs) in providing prevention-focused pregnancy counseling to parents of adolescents with diabetes[12] with an economic benefit (costs $18 per participant).[2] Long-term (15 year follow up) results showed that initiating PC during adolescence was associated with the use of more effective family planning and postponing a participant's first sexual experience.[3,8] These studies served as the evidence-based platform to support the statement, "Starting at puberty, PC should be incorporated into routine diabetes care for all girls of child bearing potential."[1] For example, PC and reproductive health is one of four modules provided to adolescents with diabetes in the Diabetes Transition Program at UPMC Children's Hospital of Pittsburgh. The modules serve as the stimulus for group discussions led byHCPs who focus on issues relevant to teenagers within the context of diabetes, leading to group decision-making and peer support. *READY-Girls* is presented to female adolescents with diabetes and *READY-Guys*[13] is offered to male adolescents with diabetes who participate in the Diabetes Transition Program. The team's next goal was to develop a PC program for adolescent females at risk for diabetes.[1,3] The *READY-Girls* book[5] is available free to families and providers on the ADA website (www.diabetes.org/

ReadyGirls) for adolescents and health care providers.

Building on their PC work with adolescents and parents, the research team expanded their program to address the needs of adolescent women at risk for gestational diabetes mellitus (GDM). GDM is among the most common medical complications of pregnancy, affecting 7-18% of all pregnancies in the U.S.[14] with rates that have doubled in the last two decades, paralleling the obesity epidemic.[15] GDM and obesity can increase maternal and fetal morbidity and mortality[16,17] and are associated with severe complications for both the mother and baby. In addition, GDM is a significant risk factor for both mother and baby developing type 2 diabetes (T2D).[15] GDM and obesity complications during pregnancy include maternal high blood pressure, preeclampsia,[18] fetal macrosomia, birth trauma, hypoglycemia, hyperbilirubinemia, and hypocalcemia.[15,19] Increasing the risk of obesity and T2D in the offspring creates a vicious cycle.[20]

Women are more likely to develop GDM if they are Indigenous,[21,22] have high pre-pregnancy weight, weight gain in young adulthood, a history of GDM or hypertension,[19] a family history of diabetes, or a sedentary lifestyle.[23] Compared to Caucasians, American Indian (AI), Alaska Native (AI/AN)[24], and Native Hawaiian (NH) youth[25,26] have more risk factors for GDM and higher rates of GDM and pregnancy-related complications, including higher preterm delivery[22] and neonatal mortality rates.[25,26] Indigenous females have twice the risk of GDM than non-Hispanic White females and 52-74% of women with GDM develop T2D.[27] The prevention of GDM is imperative for breaking the generational cycle of T2D in Native populations. The widely referred to *Diabetes Prevention Program (DPP)*, translated for AI/AN adults[28] with prediabetes from diverse AI/AN community settings, showed that a lifestyle intervention can prevent or delay the onset of diabetes for those at risk.[29] Additionally, the most effective intervention, the lifestyle program, was also effective in reducing progression to diabetes among women with a history of GDM who participated in the DPP study.[30] However, neither the DPP nor post-partum GDM T2D risk reduction interventions[31] have been developed to specifically target the primary prevention of GDM or focus on high risk adolescents.[32]

To reduce GDM in youth in Indigenous populations, *Stopping GDM*, a PC program built upon *READY-Girls*, was created.[4,6,33] The adapted *Stopping GDM* program focuses on GDM-at-risk AI adolescent females and their mothers. *Stopping GDM* combines the DPP healthy lifestyle elements with PC to reduce the risk of GDM prior to the first pregnancy and to reduce the risk of T2D in both the AI adolescent and her future offspring. The aim is to break the intergenerational cycle of diabetes in Indigenous communities starting at puberty, and prior to conception, by raising awareness of adolescent females' risks and GDM risk-reduction strategies using culturally grounded, community-inclusive, and strengths-based holistic health messages to promote healthy family planning.

To culturally inform *Stopping GDM* development, a robust qualitative needs assessment with key stakeholders was performed that revealed that AI women with a history of GDM lamented a lack of resources tailored for AIs, stories from AI women who had GDM, a focus on instilling traditional values with family and community involvement, and culturally empowering messages for AI girls.[32,34,35] *Stopping GDM* is an online PC/education program that relies on healthy lifestyle behaviors to reduce risk for GDM in at-risk AI adolescents with support from a female adult family member prior to pregnancy. *Stopping GDM* includes an online eBook,[36] video,[37] mother-daughter communication booklet, and an online resource toolkit. The online eBook includes two parts, "GDM and GDM Prevention" and "Taking Care of Your Body: Balancing Mind, Body, and Spirit". The video, produced by a female AI-owned production company, is ~45 minutes in length and narrated by a female AI physician with real stories from AI women. *Stopping GDM* is available online at no charge.[38] An online delivery method was implemented to reach a wider AI audience during the project dissemination phase and ensure widespread free access after the study was completed. Supported by the literature, online learning has been shown to be a feasible method of providing health education and information to Indigenous audiences.[39–43]

With additional NIH funding, a series of focus groups were conducted with AI/AN tribal leaders, HCPs who care for AI/AN women and teens, AI mothers, AI women with T2D and/or a history of GDM, and AI teen girls to adapt *READY-Girls* for use in AI communities. Focus group findings found that AI women did not know about GDM or GDM risk reduction principles before they were diagnosed, or that they were at higher risk of developing GDM.[34] In a pre-post pilot study, results showed *Stopping GDM* enhanced knowledge, health beliefs, and the intention to engage in behaviors to reduce the risk of GDM.[44] In addition, the study team compiled data from a 5-site randomized control trial (RCT) with AI daughters (12-24 years old) and mothers (or other adult female caregiver) (N=149 dyads). *Stopping GDM* findings are currently being analyzed in the RCT to determine the early effects of engagement on GDM and reproductive health knowledge, health beliefs, self-efficacy, and GDM risk reduction behaviors, such as healthy eating and physical activity, reproductive health choices, family planning, and mother-daughter communication. This RCT had also tested *Stopping GDM's* effect on adolescent-initiated discussions with HCPs.

The research team's future plans include exploring ways to address the needs of childbearing women with a focus on those women at highest risk. AI/AN/NH are federally recognized as the three major Indigenous populations of the U.S. While culturally distinct and geographically-based, these three diverse populations are all at increased risk for GDM and this known risk is so high that many in Indigenous communities believe that the development of diabetes is "all but inevitable."[34,45–47] Since *Stopping GDM* was uniquely tailored to AI teens, the research team plans to expand their program to all adolescents in U.S. Indigenous populations at high risk for GDM. The model will be expanded to include Ancestral Knowledge Systems

(AKS)[48,49,] which is traditional ecological knowledge for Indigenous people. A movement toward holistic health or holistic wellness will include a focus on a healthy lifestyle and reproductive health, such as planning future pregnancies with a healthier body weight to decrease risk for GDM. Technological approaches that are evidence-based, relevant, and regularly utilized by Indigenous communities will be implemented.[50–54] The goal is to improve Indigenous health by empowering Indigenous adolescents and their families, building the resilience of Indigenous peoples, and decreasing maternal/fetal morbidity and mortality by lowering the risk of GDM.[20]

Most importantly, the investigators will continue to use a strong community engagement approach to obtain perspectives from AI/AN/NH adolescent females at risk for GDM and members of their support network, HCPs, and Indigenous community members who are local 'keepers' of traditional knowledge. The program will rely on innovative, easy to scale methods, e.g., a mHealth platform, making it relevant for a larger number of Indigenous females across the U.S.[55] The research team brings a strong background in diabetes research, along with engagement in Indigenous communities. Over 60% of the research team are AI/AN/NH and cumulatively bring decades of academic-Indigenous community partnership experience achieved through strong and thoughtful collaborations with target communities and community leaders.

Preconception counseling needs to be considered as a critical component of routine care for childbearing women with diabetes. While it is important that conversations start early at puberty and prior to sexual activity, all women with diabetes (and those at risk of diabetes) need to be made aware of preconception counseling and its importance. Preconception counseling should be raised at every clinic visit. Women with diabetes need to know that it's more than preventing an unplanned pregnancy, it's also knowing how to plan a pregnancy when it's safe and wanted. It takes knowledge, positive health beliefs, and social support to change health behavior. While counseling must be individually tailored, resources should be available that are culturally adapted for specific populations. Preconception counseling and support leads to empowerment.

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Obesity Medicine Fellowship

The Division of Endocrinology at the University of Pittsburgh and its affiliated medical center UPMC is proud to be one of the few institutions in the United States that offers an Obesity Medicine Fellowship. The Obesity Medicine Fellowship provides subspecialty training in the broad range of diseases that cause, are affected by, or are a result of obesity, as well as the treatment of obesity. Those eligible to apply to the fellowship are physicians who are board-certified, or eligible for board certification, in internal medicine or family medicine. Fellows receive clinical training in both the inpatient and outpatient settings while working with a collegial community of faculty, trainees, and staff who are part of the UPMC Center for Obesity Medicine. The UPMC Center for Obesity Medicine is comprised of colleagues from the Departments of Medicine, Bariatric Surgery, Hepatology, Sleep Medicine, Nutrition, Exercise Physiology, and Psychiatry/Psychology. Fellows in training also have the opportunity to collaborate with expert researchers to conduct clinical and/or basic obesity-related research. Fellows in training are also required to prepare and implement a quality improvement project intended to offer a significant contribution to the understanding and/or improving clinical care/obesity-related outcomes. The quality improvement project can overlap or be distinct from the clinical and/or basic research the fellow conducts with a research mentor.

If you or a colleague are interested in learning more about the Obesity Medicine Fellowship, contact Lorrie Fox at johnsonla2@upmc.edu.

Spontaneous Bilateral Adrenal Hemorrhage in Pregnancy

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Introduction

Acute hemorrhage of the adrenal gland, without prior history of trauma or anticoagulation, is known as spontaneous adrenal hemorrhage (SAH). SAH usually presents with nonspecific symptoms such as fatigue, dizziness, nausea, abdominal pain, and anorexia. SAH can easily be mistaken for other conditions that present with shock or acute abdominal pain. While 90% of SAH cases are unilateral, and statistically more common in the right adrenal gland, there are rare occurrences of bilateral SAH.[1] Two cases of bilateral SAH that occurred during the third trimester of pregnancy are discussed in this report.

Case 1

A 28-year-old female with a history of irritable bowel syndrome (IBS) and asthma presented to a UPMC emergency room with nausea, vomiting, and right sided abdominal pain during the 35th week of her first pregnancy. An abdominal MRI revealed a 4.7 x 2.8 cm right adrenal hemorrhage (see Image 1).

Her vital signs were stable on presentation. Laboratory results revealed sodium 134 mEq/L, potassium 3.4 mEq/L, hematocrit 33.4%, and a random cortisol level of 26 mcg/dL. She was admitted to the hospital for observation. Over the next 24 hours her symptoms improved and she remained clinically stable. She was discharged and advised to follow up with an endocrinologist and her obstetrician within four weeks.

She returned to the emergency room four days after discharge with similar abdominal pain, this time occurring on the left side. A second MRI, however, did not show adrenal bleeding. Due to the patient's blood pressure (BP) of 90/70 mmHg, hydrocortisone IV 50 mg was administered every eight hours. Thirty-six hours following the inpatient admission, the patient became tachycardic and tachypneic.

A CT angiogram (CTa) ruled out a pulmonary embolus (PE), but revealed an interval development of a 5.3 x 3 cm left adrenal hemorrhage (see Image 2).

The patient had normal sodium and potassium levels with no findings indicative of Primary Adrenal Insufficiency (PAI) and was discharged to home on a physiologic dose of hydrocortisone.

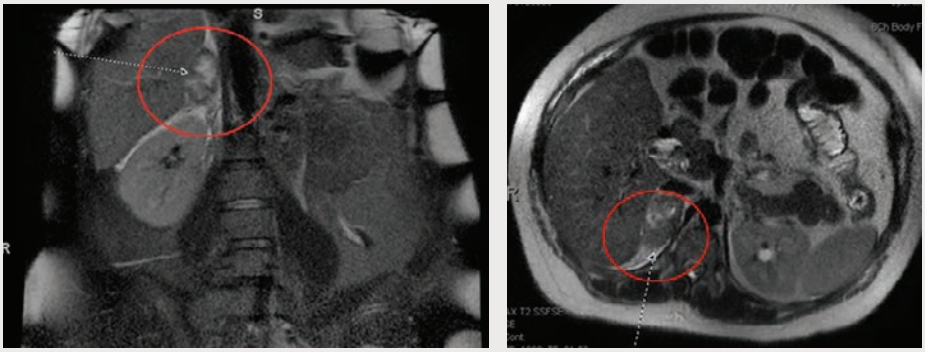

Image 1. MRI without contrast remarkable for a 4.7 x 2.8 cm indeterminate right adrenal lesion with associated perinephric fluid. This finding is concerning for adrenal hemorrhage.

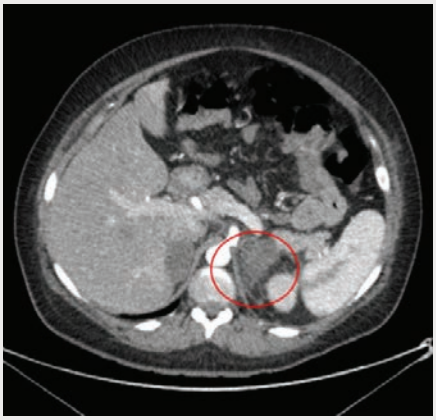

Image 2. CT angiogram remarkable for interval development of a 5.3 x 3 cm left adrenal mass with subtle infiltration of adjacent fat, consistent with left adrenal hemorrhage.

Case 2

A 30-year-old female with a history of hypertension, cerebral aneurysm, and polycystic kidney disease presented to a UPMC emergency room with nausea and left side abdominal pain during the 31st week of her second pregnancy. An abdominal CT scan showed a 2.3 x 3.1 cm left adrenal hemorrhage (see Image 3).

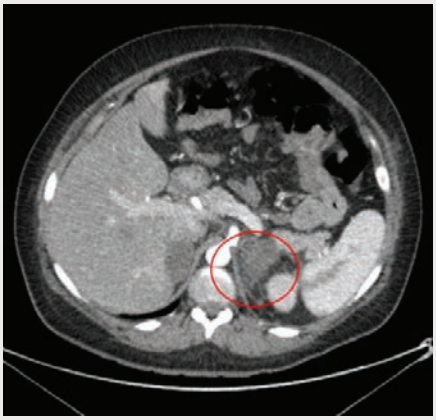

Image 3. CT without contrast remarkable for enlarged left adrenal gland with adjacent fat stranding. Findings are concerning for left adrenal hemorrhage.

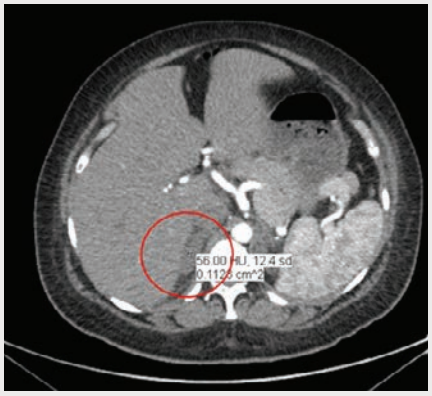

Image 4. CT Angiogram remarkable for increased soft tissue bulkiness and partial obliteration of fat planes within the region of the right adrenal gland with Hounsfield units measuring 56 suspicious for new right adrenal hemorrhage.

At the time of the patient's hospital admission, her BP was 85/50 mmHg. Therapy with IV hydrocortisone was initiated at an initial dose of 50 mg, followed by 25 mg administered every eight hours. Her BP subsequently improved (112/68 mmHg) within 24 hours. Three days after the initial presentation, the patient developed new right flank pain. The MRI was remarkable for features indicative of adrenal hyperplasia but did not confirm presence of hemorrhage.

The following day, the patient developed hypoxia and tachycardia. A follow-up CTa was remarkable for the development of a new right adrenal hemorrhage (see Image 4).

She did not have hyperkalemia or other findings indicative of PAI and was discharged to home on 30 mg total daily dose of hydrocortisone.

Discussion

SAH is extremely rare with an estimated incidence of 0.03% to 1.8% based on autopsy reports in patients with complaints of abdominal pain. Spontaneous adrenal hemorrhage in pregnancy can lead to adrenal crisis, often associated with a high rate of fatality in both the mother and fetus. Some pregnancy-related causes for adrenal hemorrhage are spontaneous abortion, ovarian cyst torsion, pre-eclampsia, antepartum or postpartum hemorrhage, and coagulation disorders, such as antiphospholipid syndrome.[1]

During pregnancy, there is adrenal cortex hyperplasia and hypertrophy secondary to physiological elevation of the adrenocorticotropic hormone (ACTH) that may predispose a patient to adrenal venous congestion. Increased catecholamine release also constricts the venules and enhances platelet aggregation. The synergistic effect of these two mechanisms increases pressure within the venous sinusoids, especially as the pregnancy progresses, and serves as the likely etiology for increased risk of SAH during pregnancy.[2]

Common manifestations of SAH include those similar to what is described with an adrenal crisis, including abdominal pain, fever, fatigue, dizziness, arthralgias, myalgias, anorexia, nausea, vomiting, and hypotension. Laboratory findings may reveal anemia, prolonged International Normalized Ratio (INR), and leukocytosis. If SAH is unilateral, it usually does not cause adrenal insufficiency. In patients with bilateral SAH, the presentation is consistent with an acute adrenal crisis. Features of PAI such as hyponatremia and hyperkalemia and a non-anion gap metabolic acidosis can be anticipated when over 90% of adrenal cortices are affected.[2]

Ultrasonography is usually the initial imaging modality ordered during pregnancy if SAH is suspected, though sonographic features of adrenal hemorrhage are very nonspecific. CT scans have higher sensitivity to detect hemorrhage in the acute phase. MRI has high sensitivity and specificity for SAH although it is a more expensive detection method as compared to other testing modalities. Both MRI or CT scans can also be used to evaluate potential underlying etiology for hemorrhage, such as pheochromocytoma or presence of an adrenal mass.[3]

For management, patients need to be closely monitored by an endocrinologist and a maternal fetal medicine specialist. Patients are usually conservatively managed with oral glucocorticoid therapy, with or without mineralocorticoid replacement. If indicated, however, intravenous fluid resuscitation and pain control should be administered. Additional management methods include correction of electrolytes, close continued monitoring of hemoglobin, correction of coagulopathy as needed, and careful observation for features of adrenal crisis, such as circulatory collapse, generalized weakness, hypoglycemia, and altered mental status. In pregnant patients, frequent fetal monitoring and obstetric exams are also necessary.[2,4]

Conclusion

The possibility of the development of bilateral SAH should always be considered among patients presenting with unilateral SAH. If left unrecognized, SAH is associated with poor outcomes and complications for both mother and fetus.

Please refer to the Update in Endocrinology Fall 2021 CME course on UPMCPhysicianResources.com for a full list of references featured in this article.

Notable Publications

Rao RH, Perreiah PL, Cunningham CA. Monitoring the Impact of Aggressive Glycemic Intervention during Critical Care after Cardiac Surgery with a Glycemic Expert System for Nurse-Implemented Euglycemia: The MAGIC GENIE Project. J *Diabetes Sci Technol*. 2021 Mar;15(2):251-264. PMID: 33650454.

A novel, multi-dimensional protocol named GENIE has been in use for intensive insulin therapy (IIT, target glucose <140 mg/dL) in the surgical intensive care unit (SICU) after open heart surgery (OHS) at VA Pittsburgh since 2005. Despite concerns over increased mortality from IIT after the publication of the NICE-SUGAR Trial, it remains in use with ongoing monitoring under the MAGIC GENIE Project showing that GENIE performance over 12 years aligns with the current consensus that IIT with target blood glucose <140 mg/dL is advisable only if it does not provoke severe hypoglycemia. Two studies have been conducted to monitor glucometrics and outcomes during GENIE use in the SICU. One compares GENIE with a traditional IIT protocol during four years of contemporaneous use. The other compares GENIE's impact overall with a cohort of patients who maintained euglycemia after OHS extending across 12 years. GENIE performed significantly better than FORMULA during contemporaneous use, maintaining lower time-averaged glucose, provoking less frequent, severe, prolonged, or repetitive hypoglycemia, and achieving 50% lower one-year mortality, with no deaths from mediastinitis (0 of 8 cases vs 4 of 9 on FORMULA). Those benefits were sustained over the subsequent eight years of exclusive use in OHS patients, with an overall one-year mortality rate (4.2%) equivalent to the ENo-I cohort (4.5%). The results of the MAGIC GENIE Project show that GENIE can maintain tight glycemic control without provoking SH in patients undergoing OHS, and may be associated with a durable survival benefit. The results, however, await confirmation in a randomized control trial.

Beppu LY, **Mooli R**, Qu Z, Marrero G, Finley CA, Fooks AN, Mullen ZP, Frias AB Jr, **Sipula I**, **Xie B**, Helfrich KE, Watkins SC, Poholek AC, **Ramakrishnan SK**, **Jurczak MJ**, D'Cruz LM. Tregs facilitate obesity and insulin resistance via a Blimp-1-IL-10 axis. *JCI Insight*. 2021 Feb 8;6(3):e140644. PMID: 33351782.

Interleukin-10 (IL-10) is a critical cytokine used by immune cells to suppress inflammation. Paradoxically, immune cell-derived IL-10 can drive insulin resistance in obesity by suppressing adipocyte energy expenditure and thermogenesis. However, the source of IL-10 necessary for the suppression of adipocyte thermogenesis is unknown. We show here that CD4+Foxp3+ regulatory T cells (Tregs) are a substantial source of IL-10 and that Treg-derived IL-10 can suppress adipocyte beiging. Unexpectedly, Treg-specific loss of IL-10 resulted in increased insulin sensitivity and reduced obesity in high-fat diet-fed male mice. Mechanistically, we determined that Treg-specific loss of the transcription factor Blimp-1, a driver of IL-10 expression by Tregs, phenocopied the Treg-specific IL-10-deficient mice. Loss of Blimp-1 expression in Tregs resulted in reduced ST2+KLRG1+, IL-10-secreting Tregs, particularly in the white adipose tissue. Blimp-1-deficient mice were protected from glucose intolerance, insulin resistance, and diet-induced obesity, through increased white adipose tissue browning. Taken together, our data show that Blimp-1-regulated IL-10 secretion by Tregs represses white adipose tissue beiging to maintain adipose tissue homeostasis.

Awards and Accomplishments

Erin E. Kershaw, MD, was awarded a NIA R01 in collaboration with Becca Levy, PhD, and Nicola Hawley, PhD, from Yale University and Ryan Mister, PhD, from the University of Pittsburgh. The grant is titled "Cognitive Resilience Among Older Samoans".

Michael J. Jurczak, PhD, was awarded Generian Pharmaceuticals research support for the project titled "GA200 and NAFLD".

Clinical and T32 Fellow, **Nami Safai Haeri, MD**, received the Endocrine Society Helmsley Charitable Trust Abstract Award in Type 1 Diabetes for his abstract titled "Paraneplastic Hypoglycemia Leading to Insulin Independence in a Patient with Type 1 Diabetes". Dr. Safai Haeri and his mentors, Mary Korytkowski, MD, and Hussain Mahmud, MD, presented this abstract the 2021 Endocrine Society Annual Meeting.

Mary Korytkowski, MD, Mara Horwitz, MD, David Rometo, MD, Helena Levitt, MD, and **Susan Greenspan, MD**, were named 2021 Top Doctors by Pittsburgh Magazine. Dr. Korytkowski and Dr. Greenspan were also named Castle Connolly America's Top Doctors.

Linda Siminerio, PhD, RN, DCES, was the recipient of the American Diabetes Association's 2021 Lois Jovanovic Transformative Woman in Diabetes Award. The award recognizes a woman scientist, clinician, educator, or professional who has made a significant impact in the field of diabetes and/or in the lives of people affected by the disease.

Janet Leung, MD, was elected to the 2021-2024 American Association of Clinical Endocrinology (AACE) Board of Directors. In this role, Dr. Leung will be contributing to strategic planning and setting and providing oversight for AACE's mission and vision.

Alison Kohan, PhD, received a Pittsburgh Autoimmunity Center of Excellence in Rheumatology (PACER) Innovative Discovery Award. Dr. Kohan also received a 2021 University of Pittsburgh Cystic Fibrosis Research Center RDP Award in collaboration with Rachel Gottschalk, PhD, from the University of Pittsburgh Department of Immunology.

Aneseh Adeshirlarijaney, PhD, an Immunology T32 fellow under the mentorship of **Alison Kohan, PhD**, was awarded a University of Pittsburgh Cystic Fibrosis Research Center Impact grant. The project supported by this funding is titled "Are plasma lipoprotein profiles an extra-pulmonary contributor or consequence of Cystic Fibrosis?"

Alay Gandhi, a University of Pittsburgh undergraduate, was awarded a Summer 2021 Brackenridge Research Fellowship under the mentorship of **Ruya Liu, MD, PhD**. The project supported by this funding is titled "Let's Mend the Heart: Identification of a Potential Target for Cardiac Regeneration".

Assistant Professor of Medicine and previous T32 and Clinical Fellow **Margaret Zupa, MD**, has been awarded an Institute for Clinical Research Education Clinical Translational Scholars/KL2 Program Career Development Award. The project supported by this funding is titled "Enhancing Telemedicine Care Quality to Improve Outcomes for Adults with Type 2 Diabetes". Dr. Zupa's primary mentors are Anne-Marie Rosland, MD, MS, Linda Siminerio, RN, PhD, DCES, and Mary Korytkowski, MD. Co-mentors include Archana Bandi, MD, and Jason Ng, MD.

Ruya Liu, MD, PhD, has been awarded a Samuel and Emma Winters Foundation Award and a UPMC Competitive Medical Research Fund Award for her research with the previously uncharacterized gene, C5X, and its regulation of cardiogenesis.

Yong Wan, PhD, has been awarded a Samuel and Emma Winters Foundation Award for his project titled "Exploring Novel Targets Through Secretome Analysis for the Treatment of Osteoporosis".

Karen Selk, DO, has been named UPMC Mercy Chief of Endocrinology effective July 1, 2021. Dr. Selk completed her internal medicine residency at UPMC Mercy and her endocrinology fellowship at UPMC. She joined the UPMC Mercy medical staff in 2017. Dr. Selk is certified by the American Board of Internal Medicine in both internal medicine and endocrinology, as well as by the American Board of Obesity Medicine.

Leonie Finke, a University of Pittsburgh undergraduate, was awarded the Chancellor's Undergraduate Research Fellowship under the mentorship of **Ruya Liu, MD, PhD**. The project supported by this funding is titled "Dying of a Big Heart: The Role of C5X in Cardiac Hypertrophy and Heart Failure".

Vijay Yechoor, MD, has been awarded a NIDDK R01 in collaboration with Mariana Figueiro, PhD, of Mount Sinai and Antoni Paul, PhD, of Albany Medical Center. The title of this grant is "Clock modulation in circadian desynchrony induced diabetes and atherovascular disease – mechanisms and interventions."

NEW FACULTY

Katrina Han, MD

Dr. Han obtained her medical degree at the University of Pittsburgh in 2016. She went on to complete an internal medicine residency at UPMC in 2019. Following completion of her residency, Dr. Han completed an endocrinology fellowship at Washington University. Dr. Han has an interest in obesity, diabetes mellitus, and dyslipidemia. Dr. Han will see patients at the UPMC Center for Diabetes and Endocrinology located in the Falk Medical Building and Monroeville. Dr. Han joined our Division as a clinical assistant professor in July 2021.

Donna Lee, MD

Dr. Lee obtained her medical degree at the University of Rochester in 2016. She went on to complete an internal medicine residency in 2019 and an endocrinology fellowship in 2021 at Albert Einstein College of Medicine. Dr. Lee has an interest in general endocrinology, diabetes, thyroid, and osteoporosis. Dr. Lee will see patients at the UPMC Center for Diabetes and Endocrinology located in the Falk Medical Building and South Hills. Dr. Lee joined our Division as a clinical assistant professor in August 2021.

Divya Sistla, MBBS

Dr. Sistla obtained her MBBS at Kamineni Institute of Medical Science in 2013. She went on to complete an internal medicine residency at UPMC in 2019. Following completion of her residency, Dr. Sistla completed an endocrinology fellowship within our Division. Dr. Sistla has an interest in general endocrinology, telemedicine, diabetes management, and obesity management. Dr. Sistla will see patients at UPMC Mercy, UPMC McKeesport, and the UPMC Center for Diabetes and Endocrinology in West Mifflin. Dr. Sistla joined our Division as a clinical assistant professor in July 2021.

Margaret Zupa, MD

Dr. Zupa obtained her medical degree at the Jacobs School of Medicine and Biomedical Sciences at the University of Buffalo in 2015. She then went on to complete an internal medicine residency and clinical endocrinology fellowship at UPMC in 2018 and 2020, respectively. In 2021. Dr. Zupa completed a T32 postdoctoral fellowship in endocrinology, as well as obtained her MS from the University of Pittsburgh Institute on Clinical Research Education. Her clinical and research interests focus on improving diabetes quality of care through telemedicine, family, and heath supporter involvement. Dr. Zupa joined our Division as an assistant professor of medicine in July 2021.

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