

JUNE 2022

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

Endocrine news

Weight EXPECTATIONS

New studies from the Endocrine Society offer a variety of potential solutions for treating overweight and obesity.

- **MIDDLE MANAGEMENT:** Three new studies evaluate new insights to obesity and weight control options from the bench to the bedside and even into the streets.
- **TIPPING THE SCALES:** Recent research from Endocrine Society journals reveals new hope for novel, safe, and innovative weight loss methods.
- **FLESH AND BONE:** Has a new study in *The Journal of Clinical Endocrinology & Metabolism* upended conventional wisdom about obesity and bone density in men?

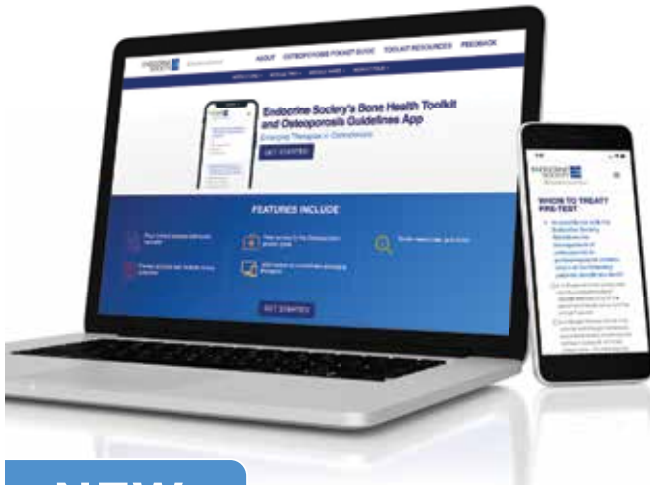


TREATING INPATIENT HYPERGLYCEMIA:
Q&A with the chairs of the latest Endocrine Society
Clinical Practice Guideline

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22 | Tipping the Scales: Noninvasive Obesity Breakthroughs

As the worldwide mortality rate linked to obesity and its comorbidities surpasses 4 million annually, new approaches to combating this condition are sorely needed. Thankfully, recent research from Endocrine Society journals shows promise in some surprisingly novel and safe noninvasive weight loss methods.

BY KELLY HORVATH

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New Research Upends the Conventional Wisdom About Body Weight and Bone Density in Men

For years, obesity was thought to have the ability to thwart the occurrence of osteoporosis, especially in men. However, a new study in *The Journal of Clinical Endocrinology & Metabolism* shows that men with obesity could be at a higher risk for osteoporosis than previously thought.

BY DEREK BAGLEY

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Evaluating New Insights to Obesity and Weight Control Options

As obesity continues to reach epidemic proportions, endocrine researchers are at the forefront of discovering new methods to help clinicians and patients alike to manage and even conquer obesity and its plethora of comorbidities. Here, we look at three recent studies that take these solutions from the bench to the bedside and even to the sidewalks.

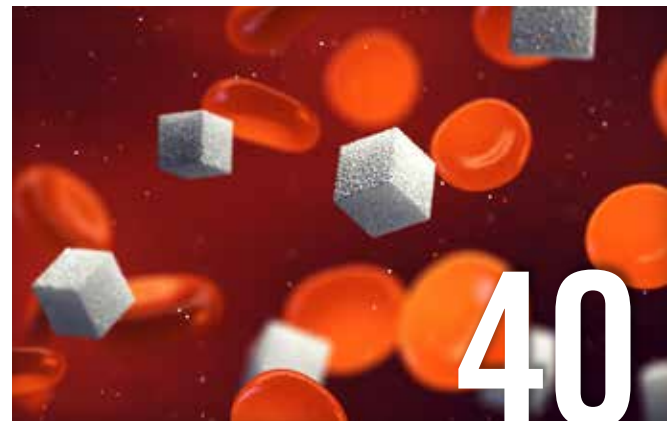
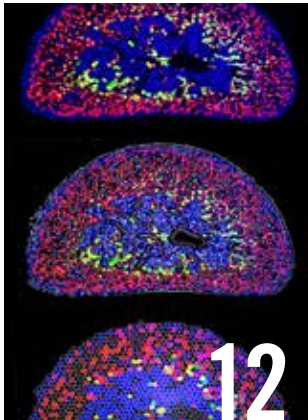
BY KELLY HORVATH

40 | Q&A: Mary Korytkowski, MD, and Ranganath Muniyappa, MD, PhD

Endocrine News talks with Mary Korytkowski, MD, and Ranganath Muniyappa, MD, PhD, chairs of the guideline development panel that created the latest Endocrine Society Clinical Practice Guideline on treating adult patients with hyperglycemia in a hospital setting.

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BEIGE FAT BENEFITS: Q&A WITH SHINGO KAJIMURA, PHD

Endocrine News talks to Shingo Kajimura, PhD, recipient of the Endocrine Society's 2022 Richard E. Weitzman Outstanding Early Career Investigator Laureate Award, about his research of brown and beige fat, challenges his lab faced during the pandemic, and why early-career researchers should just make sure the "science works out."

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Endocrine Society calls for increased NIH funding; Endocrine Society advises EU policymakers on chemicals strategy; and Learn how you can help the Endocrine Society advocate on behalf of endocrine science and practice.

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A Look Back at an Unforgettable Term

Although my presidential term has been 15 months, instead of the typical 12 months (due to ENDO moving from March to June this year), I have to say that this year has flown by. And I couldn't be prouder and more pleased with how we have created opportunities out of challenges and how we have risen to the occasion.

The past two years have been anything but ordinary, with everyone's lives disrupted due to the pandemic. We had to cancel ENDO 2020 just a few weeks before its start date and developed our first virtual meeting a few months later. We were able to plan a fully virtual ENDO 2021 the following year, which was a great success. We have learned

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I want to acknowledge the dedication and creativity of our members, who in strong partnership with our talented staff, have done remarkable things and produced amazing results.

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from adversity and have been flexible and open to adapt to these new situations. This year we will be holding our first hybrid annual meeting ever, and I am extremely pleased with the amazing program that our Annual Meeting Steering Committee (AMSC) members have put together. Many of us are very much looking forward to getting together in person to seeing our colleagues and friends. At the same time, we

understand that some of you are still unable to travel and hope you will be able to benefit from attending a virtual ENDO. I want to take this opportunity to thank our AMSC chairs Steve Hammes, Scott Dehm, Lauren Fishbein, and Bulent Yildiz for their leadership, creativity, and commitment to develop an outstanding program.

There are other areas that I want to briefly highlight as our great successes this past year. In the advocacy area, we have made great strides by having virtual Hill visits and thereby, benefiting from having a much larger number of members participating in these visits. We continue to focus on our advocacy agenda advocating for increased NIH research funding, reduction in the prevalence of diabetes and obesity, protecting access to care for women and transgender patients, ensuring access to adequate, affordable healthcare, and improved regulation of endocrine-disrupting chemicals (EDCs), just to name a few areas.

2021 marked the 100th anniversary of the discovery of insulin and how it transformed diabetes from a fatal disease to a chronic condition. We spent 2021 commemorating this important centennial with video interviews with diabetes experts and webinars delving into important issues around insulin and diabetes. We continue to advocate for access to affordable insulin products and to establish better diabetes management practices and guidelines.

We have recently launched a new open access journal: *JCEM Case Reports*, publishing reports on clinical cases and clinical problem solving from across the field of endocrinology. I am pleased to announce that the editor-in-chief is William Young, MD, a past president and one of the most engaged members in our Society. I am certain that under his leadership the journal will have a great impact.

For those wishing to publish their research, members of the Endocrine Society benefit from waived page charges for publication in *Endocrinology*.

On the education front, we have enhanced our Center for Learning, our online repository for on-demand education, for a more streamlined, productive, state-of-the-art online

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This has been an exceptional year as we continue to serve as global ambassadors for endocrine science and care.

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learning environment that is easier to use. You can gain access to a variety of resources from podcasts and webinars, to our premier case-based products including *Endocrine Self-Assessment Program (ESAP™)*, *Pediatric ESAP™*, and *Endocrine Board Review*.

Our commitment to diversity, equity, and inclusion continues through several of our programs. The Future Leaders Advancing Research in Endocrinology (FLARE) program is geared toward basic science, clinical research trainees, and junior faculty from underrepresented minority communities who have demonstrated achievement in endocrine research. FLARE program components provide structured leadership development and in-depth, hands-on training in topics ranging from grantsmanship to lab management. Earlier this year, we launched the Excellence in Clinical Endocrinology

Leadership (ExCEL) program, which offers comprehensive leadership training and mentorship to early-career physicians of communities underrepresented in medicine and science. Both programs are aimed to build leadership skills, explore opportunities for advancement, and expand your network of peers and colleagues.

Although there are many other achievements that I am not mentioning, I want to make sure I thank and acknowledge all those who have contributed to our success. I must begin by acknowledging our Executive Committee. Our presidential officers, Gary Hammer, immediate past president, and Ursula Kaiser, president-elect, as well as Dolores Shoback, secretary-treasurer, and Jeff Boord, secretary treasurer-elect, who have been my advisors, sounding board, and friends. I also want to thank our Board members for their commitment, dedication, and thoughtful engagement.

I want to thank our new CEO, Kate Fryer, for her partnership. Kate has provided the stability, support, and leadership that we needed to move our priorities forward. Importantly, I want to acknowledge the dedication and creativity of our members, who in strong partnership with our talented staff, have done remarkable things and produced amazing results. And last, but not least, we all owe a great debt of gratitude to the staff of the Endocrine Society, who have persevered under the many challenges of the past two years.

In closing, this has been an exceptional year as we continue to serve as global ambassadors for endocrine science and care. I feel honored and humbled to have been given the opportunity to serve this outstanding organization. Thank you for your trust and continued engagement. 

Carol H. Wysham, MD
President, Endocrine Society



FROM THE **EDITOR**

A Plethora of Obesity Research Courtesy of Endocrine Society Journals

This month's issue takes a concentrated look at another epidemic that predates COVID-19 and has even more far-reaching effects: obesity. More specifically, we are looking at the breakthroughs in the study of overweight and obesity, all from Endocrine Society journals.

"Tipping the Scales: Noninvasive Obesity Breakthroughs" by Kelly Horvath on page 22 looks at recent research from three different studies that show promise regarding novel, noninvasive, and safe weight loss methods that could help in easing the burden of obesity and its many comorbidities that are linked to over 4 million deaths each year. Christos S. Mantzoros, MD, ScD, chief, endocrinology, Diabetes, and Metabolism, Boston VA Healthcare System; director, Human Nutrition

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More specifically, we are looking at the breakthroughs in the study of overweight and obesity, all from Endocrine Society journals.

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Unit, Division of Endocrinology, Diabetes, and Metabolism, Beth Israel Deaconess Medical Center, Boston, Mass., and the lead author of "Novel Noninvasive Approaches to the Treatment of Obesity: From Pharmacotherapy to Gene Therapy," published in *Endocrine Reviews* last October, says that the root causes of obesity include environmental, psychological, as well as biological and genetic factors, all need to be studied in depth "utilizing new tools including artificial intelligence, and this will eventually deliver novel approaches to our therapeutic

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armamentarium that could result in tangible benefits for those of us who struggle to keep our body weight under control to avoid metabolic complications and thus live healthier and longer lives.”


Senior editor Derek Bagley looks at a new study from *The Journal of Clinical Endocrinology & Metabolism* (JCEM) that seems to take another step in understanding the impact of obesity on men’s bone health in “Flesh and Bone: New Research Upends the Conventional Wisdom About Body Weight and Bone Density in Men” on page 30. “While there are excellent studies looking at bone health and obesity, most studies have used body mass index as the indicator of obesity,” says one of the study’s authors, Rajesh K. Jain, MD, assistant professor of Medicine and Endocrinology Fellowship Program director at the University of Chicago Medicine, who adds that “BMI has its limitations and does not account for a person’s body composition and that most previous studies have shown positive or neutral effects of body fat mass on bone health, but “have been limited due to small numbers, referral bias, or lack of racial and ethnic diversity.”

In “Middle Management: Evaluating New Insights to Obesity and Weight Control Options” on page 34, Kelly Horvath reports on three more studies that highlight how endocrine scientists remain at the forefront of discovering new methods to help both clinicians and patients to not just manage but overcome obesity and its many comorbidities. Two of the studies specifically address the impacts of obesity on kidney diseases — “Obesity and Chronic Kidney Disease in U.S. Adults with Type 1 and Type 2 Diabetes Mellitus,” published in the May issue of JCEM and “Body Mass Index and Risk of Diabetic Nephropathy: A Mendelian Randomization Study,” published in the February issue of JCEM.

The third study, “The Weight of Place: Built Environment Correlates of Obesity and Diabetes” from the February issue

of *Endocrine Reviews*, shows that people who live in walkable neighborhoods with access to parks and other outdoor activities are more active and less likely to have diabetes or obesity. This research by Gillian L. Booth, MD, MSc, of the University of Toronto, St. Michael’s Hospital of Unity Health Toronto and ICES in Ontario, Canada, and team focuses on the built environment and how one’s living conditions can often have an outsized influence on his or her health. “We got interested in this area because of the large increase in obesity and diabetes over the last few decades, and so researchers and policymakers have been struggling to find out what we can do about it at a population level,” Booth says. “We might say, ‘walk 30 minutes five times a week,’ but we don’t always think about the context in which people live, which is crucial to actually getting them to make behavior changes and to maintain them. Understanding the barriers that people face and the sort of changes that they can make in terms of, for example, their transportation mode would be more effective.”

Aside from these three feature articles (covering seven different studies, in case you’re keeping track), we also have a Laboratory Notes Q&A with the 2022 Endocrine Society Richard E. Weitzman Outstanding Early Career Investigator Laureate Award recipient Shingo Kajimura, PhD, (p. 44) who discusses his research regarding beige and brown fats, as well as advice for other early-career scientists.

This issue is just a small sampling of the amazing work featured each month in the Endocrine Society’s peer-reviewed journals. If you’re part of a team that has had its research published recently, be sure to let us know and it could very well be featured in an upcoming issue of *Endocrine News!* 

— **Mark A. Newman**, Editor, *Endocrine News*

Hammer Wins Inaugural Endocrine Images Art Competition

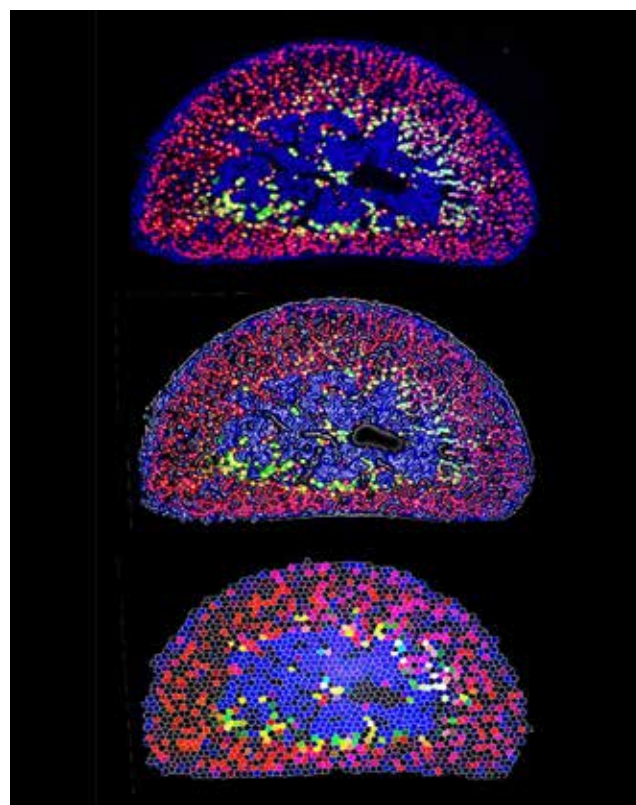
Gary Hammer, MD, PhD, Millie Schembechler Professor of Adrenal Cancer at the University of Michigan in Ann Arbor, Mich., won the Endocrine Society's Endocrine Images Art Competition, a contest celebrating the beauty of endocrine science.

Entries were judged based on aesthetic value and significance to endocrine research.

Hammer's image of the adrenal gland took the top prize this year out of more than 40 entries. Federico Salas-Lucia, PhD, of the University of Chicago in Chicago, Ill., and Jennifer Richer, PhD, Lyndsey Crump, PhD, and Nicole Spoelstra of

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The goal of showing the art of science is to educate, inspire, and illustrate the beauty of discovery and biology itself. And, of course, endocrinology epitomizes the beauty of integrative biology in action.
 ”

the University of Colorado School of Medicine in Aurora, Colo., tied for a close second. Salas-Lucia's image featured the pituitary gland, while Richer's team entered a staining of multiple hormone receptors in breast cancer.



“The iterative process of discovery and translation into care is both science and art. Specifically, medical care is a science. Medical care is an art. Medical care informs science. Science can be artful, too and science creates medicine,” Hammer tells *Endocrine News*. “The goal of showing the art of science is to educate, inspire, and illustrate the beauty of discovery and biology itself. And, of course, endocrinology epitomizes the beauty of integrative biology in action. Maybe Albert Einstein said it best: “The most beautiful thing we can experience is the mysterious. It is the source of all true art and science.”

Hammer, the Endocrine Society's 2020 – 2021 past-president, declined the prize of complimentary ENDO 2022 registration, so the judges awarded the prize to Salas-Lucia.

Top entries will be shared with scientists and researchers from all over the world via a special display at ENDO and will also be featured in *Endocrine News*, on the Endocrine Society website, and on social media.

Visit the Endocrine Images Art Competition website to see the top endocrine images and gather more details for submitting next year at: www.endocrine.org/awards/endocrine-images-award.



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We are accepting seeking dedicated member leaders to serve on our Board of Directors for the 2023-2024 term. Nominate yourself or a colleague for one of the following positions:

- **President-Elect**
- **At-Large Directors (4 open positions)**
- **Early Career Member**

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Endocrine Society Announces 2022 Early Investigator Award Winners

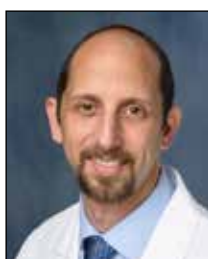
The Endocrine Society has selected five recipients for its Early Investigators Awards.

The Early Investigators Awards were established to assist in the development of early-career investigators and to recognize their accomplishments in endocrine-related research. The Endocrine Society's 2022 Early Investigators Award winners are:



OMAR BELLO-CHAVOLLA, MD, PHD, INSTITUTO NACIONAL DE GERIATRÍA, MEXICO CITY, MEXICO

Bello-Chavolla is an associate professor at the National Institute for Geriatrics, where his research has focused on understanding the interaction between cardiometabolic diseases and aging, characterizing the epidemiology of cardio-metabolic disorders in low and middle-income countries as well as characterizing metabolic phenotypes linked to increased risk of severe COVID-19.



FERNANDO BRIL, MD, UNIVERSITY OF ALABAMA AT BIRMINGHAM, BIRMINGHAM, ALA.

Bril is currently a clinical fellow in the Division of Endocrinology at University of Alabama at Birmingham. His main research interest has been to understand the metabolic mechanisms that promote the progression of nonalcoholic fatty liver disease (NAFLD) in obesity and diabetes, identify markers for early diagnosis, and assess pharmacological approaches that may be able to change the natural history of the disease.



LAWRENCE KAZAK, PHD, MCGILL UNIVERSITY, QUEBEC, CANADA

Lawrence joined McGill University as an assistant professor in 2018. His lab is broadly focused on defining the molecular control of energy expenditure using thermogenic fat as a model system.



ESTELLE EVERETT, MD, MHS, UNIVERSITY OF CALIFORNIA LOS ANGELES, LOS ANGELES, CALIF.

Everett is an endocrinologist and health services researcher at Geffen School of Medicine at UCLA. Her research involves exploring and addressing barriers to care in vulnerable populations with type 1 diabetes. She has a particular interest in addressing inequities in access and use of diabetes technology.



TIM KOREVAAR, MD, PHD, ERASMUS UNIVERSITY MEDICAL CENTER, ROTTERDAM, NETHERLANDS

Korevaar is a postdoctoral fellow at the Endocrinology Department and Academic Center for Thyroid Disease of the Erasmus University Medical Center. His research focuses on thyroid function and glucose homeostasis during fertility and pregnancy.

Look for a roundtable interview with these five outstanding early-career researchers in an upcoming issue of *Endocrine News*.

Additional information about these awards and when the new application cycles open can be found at: <https://www.endocrine.org/awards>.



Rimesh Pal Receives C. Wayne Bardin International Travel Award

Rimesh Pal, MD, DM, is the 2022 winner of the C. Wayne Bardin International Travel Award. The Endocrine Society established this award to pay tribute to Bardin, who passed away in 2019 and made remarkable research contributions to both reproductive physiology and contraception throughout his long career.

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The award recognizes Bardin's passion for recognizing and nurturing young researchers by covering the costs to send a young, outstanding endocrinologist to ENDO, the annual meeting of the Endocrine Society.

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The award recognizes Bardin's passion for recognizing and nurturing young researchers by covering the costs to send a young, outstanding endocrinologist to ENDO, the annual meeting of the Endocrine Society. Candidates for the award are chosen based on the quality of their ENDO abstract and the overall quality of their science.

Pal, of the Postgraduate Institute of Medical Education and Research in Chandigarh, India, is an assistant professor in the Department of Endocrinology and a physician at the Postgraduate Institute of Medical Education and Research (PGIMER).


Pal completed his MBBS degree in 2013, MD degree in internal medicine in 2016, and DM degree in endocrinology from PGIMER in 2019. An astute and dedicated physician, he is also a highly motivated academician and a keen researcher with a particular interest in the fields of metabolic bone diseases, osteoporosis, primary hyperparathyroidism, sarcopenia, type 2 diabetes, and the endocrinological aspects of COVID-19.

In his relatively short career, Pal has published more than 85 PubMed indexed articles, including publications in *The Lancet Diabetes and Endocrinology*, *Diabetes Research and Clinical Practice*, *Osteoporosis International*, and *Endocrine Connections*, among others. His publications are a result of collaborative work with researchers from PGIMER as well as throughout India and around the world.

Pal received complimentary registration and a travel award to attend ENDO 2022 in Atlanta. The travel award covered up to \$3,000 in travel, hotel, and per-diem costs.

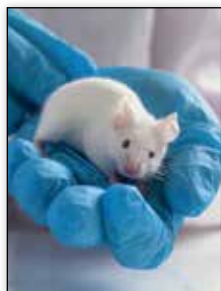
The new application cycle will open December 1, 2022. To be considered for the award, applicants must be an endocrine fellow currently in training or a junior faculty member for less than five years and submit an abstract to ENDO 2023.

More information on the award and application requirements can be found at: www.endocrine.org/bardinaward. Contact awards@endocrine.org with any questions.

To contribute to this award, donate to the “In Memory of C. Wayne Bardin Fund” at www.endocrine.org/donation. 



BY DEREK BAGLEY
Senior Editor



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This study shows that the heart is ‘programmed’ by the nutrients it receives in fetal life. Changes in the expression of genes alter how the heart normally metabolizes carbohydrates and fats. They shift the heart’s nutrient preference further toward fat and away from sugar.

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Obesity in Pregnancy Increases Risk of Lifelong Cardiovascular Disease in Offspring

Maternal obesity impairs heart health and function of the fetus according to a new mouse study published in *The Journal of Physiology*. The study found that maternal obesity causes molecular changes in the heart of the fetus and alters expression of genes related to nutrient metabolism, which greatly increases offspring’s risk of cardiac problems in later life.

The authors point out that the global prevalence of obesity in women of reproductive age is continuing to increase at a rapid pace and that children born to women with obesity during pregnancy are at a 30% greater risk for cardiovascular disease in adulthood. This study shows that the heart is “programmed” by the nutrients it receives in fetal life. Changes in the expression of genes alter how the heart normally metabolizes carbohydrates and fats. They shift the heart’s nutrient preference further toward fat and away from sugar. As a result, the hearts of fetuses of obese female mice were larger, weighed more, had thicker walls, and showed signs of inflammation. This impairs how efficiently the heart contracts and pumps blood around the body.

Researchers from University of Colorado used a mouse model that replicates human maternal physiology and placental nutrient transport in obese women. Female mice (n=31) were fed a diet with a high fat content together with a sugary drink, which is equivalent to a human regularly consuming a burger, chips, and a fizzy drink (1,500 kcal). The female mice ate this diet until they developed obesity, putting on about 25% of their original body weight. Fifty female mice were fed a control diet.

Mouse pups (n=187) were studied in utero, as well as after birth at three, six, nine, and 24 months using imaging techniques, including echocardiography and positron emission tomography (PET)

scans. Researchers analyzed genes, proteins, and mitochondria of the offspring.

The changes in offspring cardiac metabolism strongly depended on sex. The expression of 841 genes were altered in the hearts of female fetuses, and 764 genes were altered in male fetuses, but less than 10% genes were commonly altered in both sexes. Interestingly, although both male and female offspring from mothers with obesity had impaired cardiac function, there were differences in the progression between sexes; males were impaired from the start, whereas females’ cardiac function got progressively worse with age.

The sex-difference in the lasting impairments of cardiovascular health and function could be due to estrogen. Higher levels in young females may protect cardiovascular health, the protection diminishes as estrogen levels deplete as the females age. The molecular cause for the sex difference is not yet understood.

Mice have shorter pregnancies, more offspring, and different diets to humans so further studies in human volunteers would be required to extrapolate the findings to women’s health. Loss-of-function studies also need to be carried out to prove this mechanism linking maternal obesity and offspring heart function and pinpoint the exact molecules responsible.



New Study Makes Case for Culturing Embryos Up to Seven Days Post-Insemination for Selected Patients

Ending embryo culture at 144 hours (six days) post-insemination (h.p.i.) would involve 7.3% and 4.4% relative reductions in the number of patients obtaining euploid blastocysts and live birth(s) (LBs), respectively, according to a study published in *Human Reproduction*. The study results were announced recently by Fairtility, a company using artificial intelligence to enhance in vitro fertilization (IVF) for improved outcomes.

The authors point out that about 20% of women in the U.S. experience fertility challenges and that currently there is no available tool to confer competence to an oocyte or an embryo. “The only strategies in our hands to improve the prognosis of IVF patients are (i) tailoring the ovarian stimulation to obtain at least one euploid blastocyst...and (ii) preventing treatment discontinuation any time the residual chance of success after a failure is not negligible,” the authors write.

This observational study reviewed 1,966 blastocysts cultured in a time-lapse incubator between 2013 and 2020 at private Italian IVF center, GeneraLife, demonstrating the benefit of expanding blastocyst assessment to Day 7 (168 h.p.i.). The study also highlighted the advantage of Fairtility’s transparent AI-powered embryo quality assessment assistant, CHLOE EQ™, the use of which enabled clinicians to limit embryo assessment bias and expand embryo viability prediction.

The study revealed that the low euploidy rate among Day 7 blastocysts had more to do with morphology and oocyte age than the rate of development — a slower-growing blastocyst was

not definitively indicative of poor viability. In fact, in each instance of full culture up to 168 h.p.i. (Day 7) as opposed to 144 h.p.i. (Day 6), researchers found increased numbers related to blastocysts, euploid blastocysts, pregnancy, and LBs.

Significantly, 14.6% of blastocytes reached the fully expanded stage beyond the 144 h.p.i. threshold in the study. While both embryologists and CHLOE EQ™ agreed that such embryos were of lower quality, researchers concluded that

poor prognosis couples, couples less compliant toward other attempts in case of a failure, and couples wishing for more than one child could still benefit from these embryos. In such cases, CHLOE EQ™ can contribute to embryo viability prediction up to Day 7.

“This investigation is useful (i) to understand the blastulation and blastocyst expansion dynamics, (ii) for the management of IVF clinics daily workload and (iii) for a more objective clinical evaluation of Day 7 culture,” the authors conclude. “Clearly, the patients should be informed that Day 7 embryos are less competent than faster-growing ones. Still, poor prognosis patients, patients less compliant toward other attempts after a failure and patients wishing for second children may benefit from Day 7 blastocysts.”



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These data demonstrate that increases in circulating FGF21 mediate the extension of lifespan and improvement in healthspan during dietary protein restriction, and thereby identify a novel mechanism that drives the increase in longevity in response to dietary protein restriction in mammals.

”

Mouse Study Finds FGF21 Directs Body's Responses to Low-Protein Diet

Reducing the amount of protein in the diet produces an array of favorable health outcomes, including an extension of lifespan, and that these effects depend on Fibroblast Growth Factor 21 (FGF21), according to a study recently published in *Nature Communications*.

It has long been known that reducing the amount you eat improves health and extends lifespan, and there has been increasing interest in the possibility that reducing protein or amino acid intake contributes to this beneficial effect. “Epidemiological data suggest that lowering dietary protein content supports metabolic improvements and resilience, while high protein



intake correlates with increased mortality,” the authors write. “Protein restriction (PR) is a form of dietary restriction in the absence of energy restriction that extends lifespan and improves general health measures in various organisms, including rodents, fruit flies, and yeast.”

A few years ago, Pennington Biomedical’s Neurosignaling Laboratory discovered that the metabolic hormone FGF21 was a key signal linking the body to the brain during protein restriction. Without this signal, young mice failed to change their feeding behavior or metabolism when placed on a low-protein diet.

The group’s newest work demonstrates that low-protein diets produce beneficial metabolic effects in aged mice, improving metabolic health, reducing frailty, and extending lifespan. These beneficial effects were also apparent when protein intake was reduced in middle-age mice, even protecting against the detriments of obesity. Importantly, these beneficial effects were lost in mice that lacked FGF21, suggesting that its action in the brain is critical for the increase in health and lifespan.

The authors write that their work collectively supports multiple overarching conclusions: First, in male C57BL/6J mice the restriction of dietary protein intake exerts beneficial effects on body weight gain, adiposity, glucose homeostasis, physical performance, and metabolic health, with these effects ultimately reducing frailty and increasing lifespan. Second, these beneficial effects can be reproduced if the diet is initiated in middle age, where PR also protects against the harmful effects of diet-induced obesity during aging. “Finally, and most importantly,” the authors write, “nearly all these PR-induced beneficial effects depend on the liver-derived hormone FGF21. The inability to detect

protein restriction in *Fgf21*-KO mice is initially benign but ultimately leads to negative outcomes in late life, such that *Fgf21*-KO mice on LP die earlier than their controls. Collectively, these data demonstrate that increases in circulating FGF21 mediate the extension of lifespan and improvement in healthspan during dietary protein restriction, and thereby identify a novel mechanism that drives the increase in longevity in response to dietary protein restriction in mammals.” **EN**



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CLINICAL ENDOCRINOLOGY UPDATE

SEPTEMBER 8-10, 2022

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[ENDOCRINE.ORG/CEU2022](https://www.endocrine.org/CEU2022)

2022 Clinical Endocrinology Update/Endocrine Board Review

CEU 2022

CLINICAL ENDOCRINOLOGY UPDATE

Sept. 8 – 10, 2022/ Miami, Fla. & Virtual

The Endocrine Society's Clinical Endocrinology Update (CEU) provides an annual update on the latest diagnosis and treatment recommendations for various endocrine conditions, delivering educational value for clinicians, and ensuring optimal patient care worldwide.

Our program is the best way to stay updated on the latest developments in patient diagnosis and treatment in endocrinology. Esteemed faculty from across the globe will present a comprehensive, case-based agenda to help you gain knowledge to improve your practice in an intimate atmosphere where you have direct access to experts in hormone health. Sessions are organized around nine core topics, including diabetes and glucose metabolism, obesity, adrenal and cancer, pituitary and thyroid diseases, bone disorders, and transgender care.

Those interested in meeting in person can join us in Miami, Fla. We will also provide the majority of this year's program online via our virtual meeting platform.

<https://ceu2022.endocrine.org/Home>



EBR 2022

ENDOCRINE BOARD REVIEW

Sept. 16 – 18, 2022/Virtual Only

Endocrine Board Review (EBR) is an essential course for endocrinologists preparing to take the boards or practicing physicians seeking an intensive knowledge assessment. The virtual program is designed as a mock exam, with rapid-fire case-based questions emulating the format and subject matter of the ABIM's Endocrinology, Diabetes, and Metabolism Certification Examination. Attendees will have early access to topical on-demand presentations with detailed answer rationale (available in late August).

<https://www.endocrine.org/ebr2022>



The Phospholipids Conference: Dynamic Lipid Signaling in Health and Disease

Jupiter, Florida

July 31 – August 4, 2022

Launched in 1988, this FASEB Science Research Conference (SRC) is one of the longest-running lipid research meetings. This year's SRC explores all aspects of the biology and biochemistry associated with lipid signaling, lipid metabolism, lipid-protein interactions, and lipids in health and disease. A special workshop will highlight lipids in aging. This conference brings together leading investigators in lipid metabolism and signaling and helps train the next generation of U.S. investigators to bring new advances to lipid and aging discovery.

<https://www.faseb.org/>

ADCES22

Baltimore, Maryland

August 12 – 15, 2022

The Association of Diabetes Care & Education Specialists (ADCES) Annual Conference is the premier diabetes care and educational event of the year. More than 3,000 diabetes care and education specialists and other healthcare professionals are expected to participate at ADCES22 in Baltimore, Md. Connect, collaborate, and educate yourself and others on the latest in diabetes care and education in person for the first time in two years!

<https://www.diabeteseducator.org/home>

91st Annual Meeting of the American Thyroid Association

Montreal, Quebec, Canada

October 19 – 23, 2022

The ATA Annual Meeting is the world's preeminent event for those interested in thyroid diseases and disorders. Clinicians and researchers from around the world participate in ATA's Annual Meeting. Whether you're an endocrinologist, a surgeon, an advanced practice provider, a fellow in training, or a medical student, the topics covered during the meeting will provide you with in-depth information about thyroid diseases and disorders. With a diverse program planned, attendees can customize their experience by attending sessions that are most important to their professional development.

<https://www.thyroid.org/91st-annual-meeting-ata/>

INTERNATIONAL ITINERARY

10th International Congress of Neuroendocrinology (ICN2022)

Glasgow, Scotland

August 7 – 10, 2022

ICN2022 is sponsored by the International Neuroendocrine Federation (INF) and is combined with the annual meeting of the following societies: the British Society for Neuroendocrinology (BSN), the French Society of Neuroendocrinology (SNE), the Hypothalamic Neuroscience and Neuroendocrinology Australasia (HNNA), and the Pan-American Neuroendocrine Society (PANS). The aim for ICN2022 is to have a fully inclusive congress that will promote networking and interaction between all members of the international neuroendocrine community.

<https://icn2022.org/>

6th International Symposium on Pheochromocytoma

Prague, Czech Republic

October 19 – 22, 2022

Leading international experts in basic, clinical, and translational pheochromocytoma research will present their latest discoveries, guidelines, clinical trials results, collaborative efforts, and future visions for studying this tumor. Four plenary sessions will focus on the latest discoveries and perspectives in genetics and epigenetics, biochemistry and metabologenomics, theranostics, and mitochondrial function. The symposium will have several sessions devoted to patient management, including unique case presentations and in-person discussions with expert physicians on their approach to the workup, diagnosis, and treatment of patients with this tumor. All healthcare professionals, scientists, students, patients, and allies are welcome to attend this symposium, which will undoubtedly outline new focuses and avenues for early diagnosis, treatment, and ultimately prevention of pheochromocytoma.

<http://www.isp2022prague.com/>

EndoBridge 2022

Antalya, Turkey

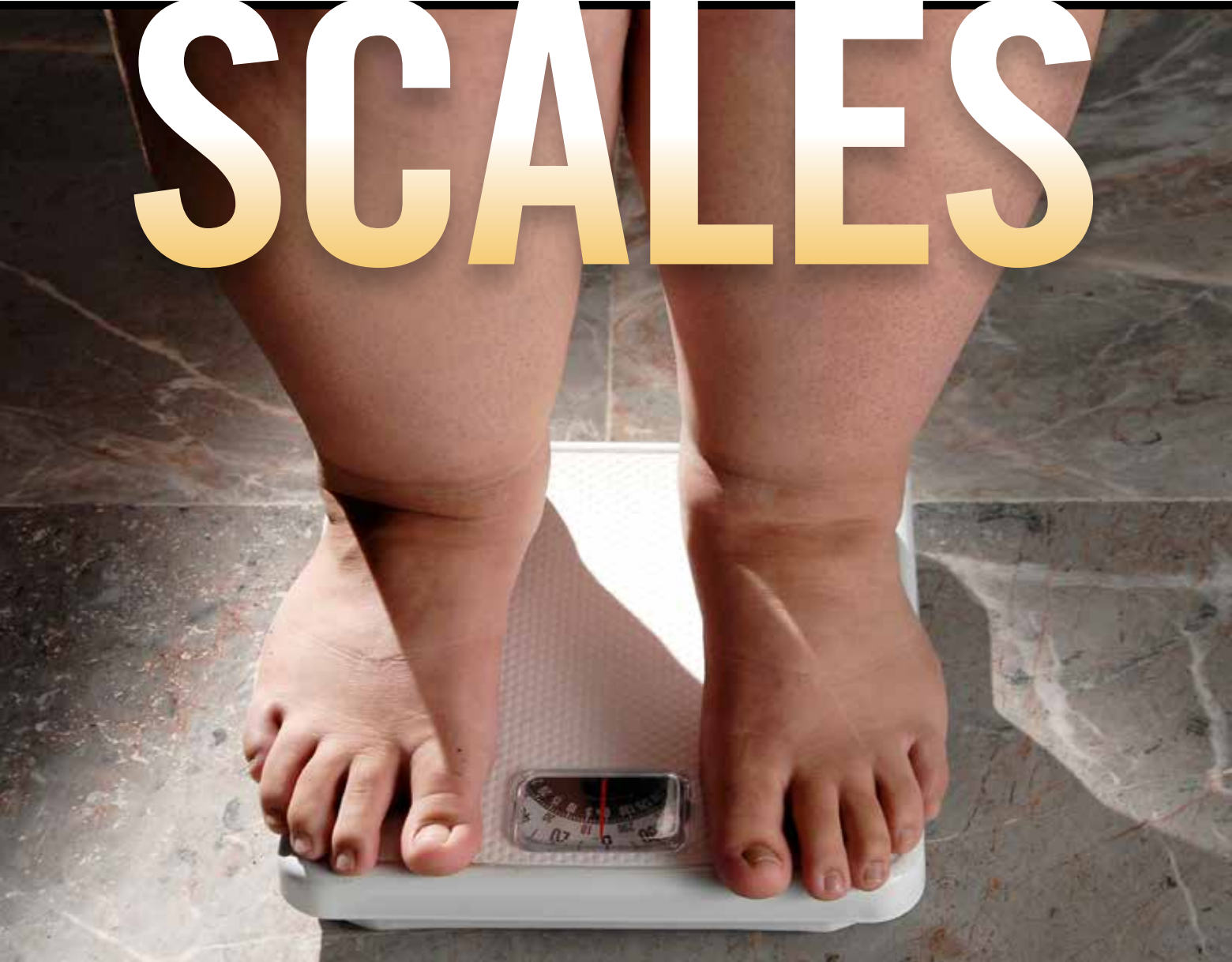
October 20 – 23, 2022

EndoBridge® is a unique initiative with the vision of bridging the world of endocrinology. The annual meeting of EndoBridge is co-hosted by the Endocrine Society and the European Society of Endocrinology in collaboration with the Society of Endocrinology and Metabolism of Turkey. EndoBridge will be held in English with simultaneous translation into Russian, Arabic, and Turkish. Accredited by the European Accreditation Council for Continuing Medical Education (EACCME), this three-day scientific program includes state-of-the-art lectures delivered by world-renowned faculty and interactive sessions covering all aspects of endocrinology. EndoBridge® provides a great opportunity for physicians and scientists from around the world to interact with each other, share their experience and perspectives, and participate in discussions with global leaders of endocrinology.

www.endobridge.org

BY KELLY HORVATH

TIPPING **the** SCALES



Noninvasive Obesity Breakthroughs



As the worldwide mortality rate linked to obesity and its comorbidities surpasses 4 million annually, new approaches to combating this condition are sorely needed. Thankfully, recent research from Endocrine Society journals shows promise in some surprisingly novel and safe noninvasive weight loss methods.

The obesity epidemic continues to pose serious health threats to populations worldwide. In the past 50 years, the prevalence of obesity has more than doubled in dozens of countries (and overall tripled worldwide), and the overall number of adults and children with obesity approaches 1 billion.

What this means in terms of morbidity and mortality is grave: Comorbidities like type 2 diabetes mellitus, nonalcoholic steatohepatitis (NASH), cardiovascular disease, obstructive sleep apnea, and obesity-related malignancies are all-too common, and about 4 million people die from obesity-related conditions annually. Scientists and researchers have searched for mechanisms to explain and therapies to combat this colossal health problem for decades, and their breakthroughs are hard won.

But two new studies are lightening the load. “Novel Noninvasive Approaches to the Treatment of Obesity: From Pharmacotherapy to Gene Therapy,” by Christos S. Mantzoros, MD, ScD, chief of Endocrinology, Diabetes, and Metabolism, Boston VA Healthcare System; director, Human Nutrition Unit, Division of Endocrinology, Diabetes, and Metabolism, Beth Israel Deaconess Medical

Center in Boston, Mass., and team, published in *Endocrine Reviews* in October, and “Diet-induced Fasting Ghrelin Elevation Reflects the Recovery of Insulin Sensitivity and Visceral Adiposity Regression,” by Gal Tsaban MD, MPH, of the Soroka University Medical Center and the Ben-Gurion University of the Negev, in Beer-Sheva, Israel, and team, published in *The Journal of Clinical Endocrinology & Metabolism* (JCEM) in November, come at obesity from promising new angles.

Novel Obesity Therapies

Mantzoros and team saw unmet clinical needs in obesity comorbidities, which prompted their review of potential new therapeutic approaches. “We have no U.S. Food and Drug Administration–approved medications for several comorbidities such as NASH, which affects 25% of the population, and treatment options for obesity itself remained truly suboptimal until very recently,” Mantzoros says. “We need to better understand the underlying mechanisms and leverage them to create optimal solutions for clinical conditions that have reached epidemic proportions in our societies.”



The overall number of adults and children worldwide with obesity approaches 1 billion.

Although bariatric and other invasive procedures are available and effective, they come with significant risks and side effects. “After observing a significant number of patients with obesity for more than 10 years after bariatric surgery (mainly Roux en Y and sleeve gastrectomy), we found that they largely maintain their weight loss up to 10 years,” Mantzoros says. “This is one of the longest observation periods to date, which has allowed us to monitor and report changes of hormonal mediators over time. We believe that if we can make and administer these hormones alone or in combination to obese people, we could induce a degree of weight loss similar to what we achieve with bariatric surgery. This is the direction we and several pharmaceutical companies are taking.”

Given the complexity of the pathways involved in the pathophysiology of obesity, the pharmacotherapeutic targets included in their exhaustive analysis run the gamut: the central nervous system, gastrointestinal hormones, adipose tissue, the kidney, liver, and skeletal muscle. They also explored novel drug delivery systems, chronotherapy, vaccines, modulation of the gut microbiome, and gene therapy. Here are some highlights.

With drugs, the researchers tease out the biochemical circuits involved in energy homeostasis, then discuss the agents that

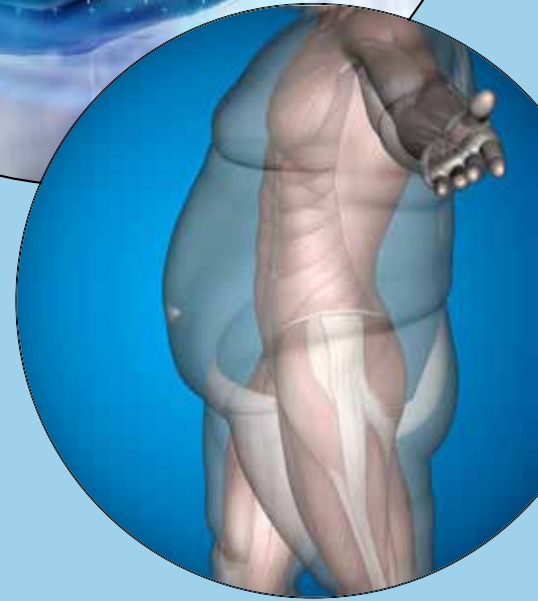
may agonize or antagonize receptors in those specific areas. Importantly, these agents are not intended to supplant lifestyle modification but should potentially be useful adjuncts.

In states of leptin deficiency, for example, setmelanotide, metreleptin, and methylphenidate act to physiologically replace leptin and, in addition, as Mantzoros puts it, “should, by definition, be the most appropriate and natural replacement therapy. For those obese subjects whose condition is due to mutations downstream of leptin (leptin receptor, melanocortins, etc.), it is reasonable to expect that setmelanotide, which acts to activate the MC4R (a receptor located downstream of the above molecules in the leptin pathway to regulate energy homeostasis), would have beneficial results.” He emphasizes that these conditions are rare, but for these patients, “a ‘personalized medicine’ approach with genetic-based diagnostics and targeted therapy would be expected to work very well.”

For the majority of patients with obesity, however, leptin has not proven effective. “Obesity in most humans,” says Mantzoros, “is a leptin-tolerant state, the exact nature of which remains to be fully elucidated.”

“ The root causes of obesity, which include not only biological and genetic but also environmental, psychological, and other factors, remain to be studied in depth, utilizing new tools including artificial intelligence, and **this will eventually deliver novel approaches to our therapeutic armamentarium that could result in tangible benefits for those of us who struggle to keep our body weight under control** to avoid metabolic complications and thus live healthier and longer lives.”

— CHRISTOS S. MANTZOROS, MD, SCD, CHIEF, ENDOCRINOLOGY, DIABETES, AND METABOLISM, BOSTON VA HEALTHCARE SYSTEM; DIRECTOR, HUMAN NUTRITION UNIT, DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM, BETH ISRAEL DEACONESS MEDICAL CENTER, BOSTON, MASS.



Although targeting the endocannabinoid system had seemed an intuitive approach until recently, unintended side effects have thwarted these aims. “Until and unless specific compounds act only to decrease body weight without any concomitant cross talk and activation of other pathways activated by the endocannabinoid system, this approach appears to hold limited promise,” Mantzoros says.

So-called “WAT browning,” however, is achieving some success. Removal of white adipose tissue (WAT), such as with liposuction, is only a temporary measure, as WAT grows back. Browning the WAT with various agents to become brown adipose tissue (BAT) in animal experiments has demonstrated that the resulting increased energy expenditure may decrease body weight. “This notion has been extremely difficult to replicate in humans, similar to many other hypotheses raised on the basis of observations in animal models, using standard drug-based approaches,” Mantzoros says. “It remains to be seen whether nanotherapeutic or other approaches targeting specifically WAT browning could overcome existing obstacles and lead to progress on that front.”

Another approach with potential is delivering anti-obesity peptides orally, which may enhance patient adherence. “Oral peptide delivery promises to be a revolution in obesity treatment and in medicine in general. Until recently this was not possible, but several novel technologies have delivered some results (positive outcomes, but at a very high cost of goods needed), and, with time, we hope that advances in this area will continue to lead to improvements in

AT A GLANCE

- ▶ With more than 4 million people dying annually from obesity and its comorbidities, the need for therapies is urgent.
- ▶ New approaches to combating obesity will be noninvasive but just as effective and with fewer side effects.
- ▶ Diet-induced fasting ghrelin level elevation improves insulin sensitivity and degree of visceral adiposity in men, independent of weight loss.

The Mediterranean Diet



“ In my view as a clinician, this study highlights the importance of fasting ghrelin as a marker of insulin sensitivity recovery and adiposity regression during lifestyle interventions, which is often not reflected by weight loss alone. The findings of this study support the use of FGL as a laboratory marker to estimate the metabolic responsiveness of an individual to specific lifestyle interventions.”

— GAL TSABAN MD, MPH, SOROKA UNIVERSITY MEDICAL CENTER, BEN-GURION UNIVERSITY OF THE NEGEV, BEER-SHEVA, ISRAEL

technology that allows us to deliver bioactive peptides orally. These strides in the delivery methods field promise to make this approach a more viable possibility in the near future,” Mantzoros explains.

Overall, in drug therapy, the news is good, with recently approved medications leading to 15% weight loss when combined with behavioral modification therapy. “This is significant progress versus what was available until a year ago, and dual or triple agonists currently in development promise to result in even higher weight loss in the near future,” Mantzoros says.

The team is further investigating the physiology of adipose tissue, muscle, and gastrointestinal tract–secreted peptides for their potential as druggable targets that will revolutionize how we treat obesity in the near future.

Apart from drug therapies, the researchers also looked at manipulating the gut microbiome, but with less-than-encouraging results. “Although this is a major focus of research by many investigators, most of the studies to date are observational and thus cannot prove causality,” Mantzoros says. “Any intervention causes many changes in many species at the same time, and this non-specificity creates ‘noise’ that confuses our interpretation of the data. Finally, empirical evidence (e.g., from patients taking antibiotics for several conditions) does not support the notion that we could have material weight loss by manipulating the microbiome. I am thus very cautious and still waiting to see the breakthrough in this field that would be making me more enthusiastic.”

Although the results of their extensive analysis were mixed depending on the therapy, any advancement in the understanding of the pathophysiologic basis of obesity counts as progress. Progress, says Mantzoros, “that will hopefully lead to multimodal, personalized approaches to obesity treatment that result in safe, effective, and sustainable weight loss, which, in turn, would also result in the decreased prevalence of obesity comorbidities.”

Ultimately, taming the many-headed Hydra that is obesity will take sustained effort. “The root causes of obesity, which include not only biological and genetic but also environmental, psychological, and other factors, remain to be studied in depth,

utilizing new tools including artificial intelligence, and this will eventually deliver novel approaches to our therapeutic armamentarium that could result in tangible benefits for those of us who struggle to keep our body weight under control to avoid metabolic complications and thus live healthier and longer lives,” Mantzoros concludes.

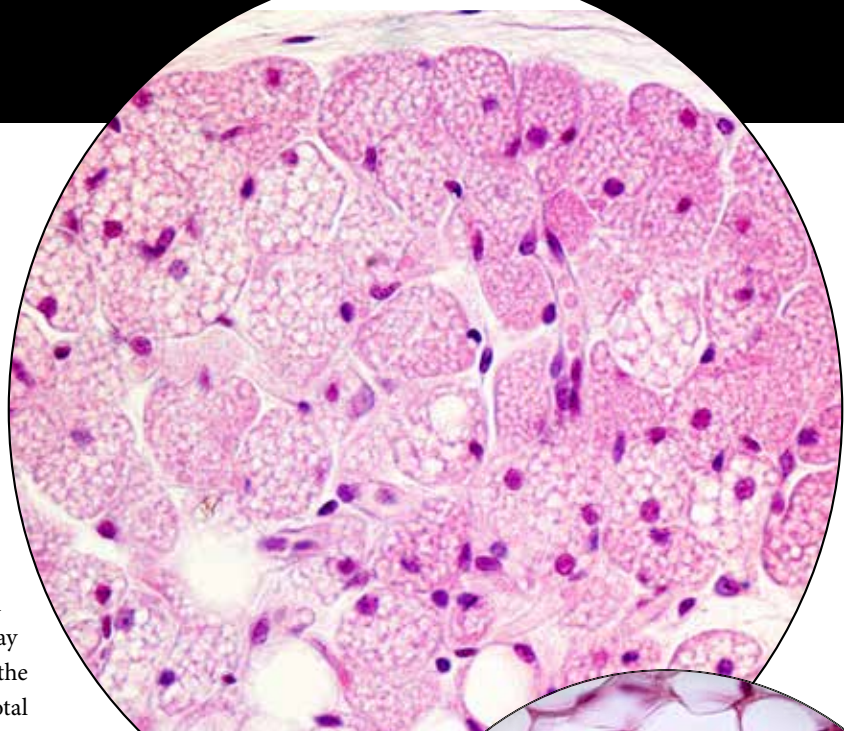
Fasting Ghrelin Levels

Tsaban and team homed in on the “hunger hormone” for their study: a secondary analysis of the DIRECT-PLUS clinical trial in Israel that took place over 18 months starting in May 2017. DIRECT-PLUS was specifically designed to address the effects of the green-MED diet on adiposity and obesity. A total of 294 participants (mostly male) were evenly divided into three intervention groups: 1) healthy dietary guidance plus physical activity; 2) the vegetable-heavy and lean-protein Mediterranean diet plus physical activity and 28 g/day of walnuts; or 3) the Mediterranean diet (including everything from group 2) plus 3 to 4 cups/day of green tea and 100 g of frozen duckweed called Mankai (green-MED diet). The two Mediterranean diet groups were additionally restricted to under 1,800 calories a day for males and under 1,400 calories a day for females.

In Tsaban and team’s substudy, they sought to determine the relationship between fasting ghrelin levels (FGL), obesity, adiposity, and insulin resistance during the intervention. “We performed this analysis because the role of ghrelin in metabolic regulation of insulin sensitivity during prolonged (12 hours) fasting and its role in adiposity promotion is sparsely explored so far,” Tsaban explains. “We aimed to define the associations between FGL and adiposity and insulin resistance determinants to shed light on FGL’s possible role in this aspect of metabolism during weight loss-directed dietary intervention strategies.”

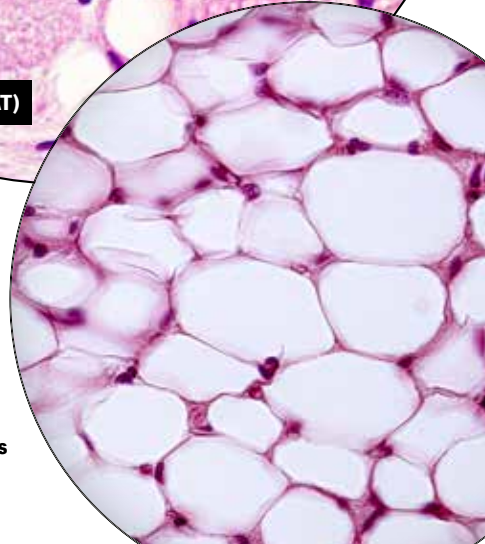
A healthy diet and exercise are the cornerstones of weight loss, but the addition of walnuts (Mediterranean diet and green-Med groups) was intentional and based on the results of some of their former studies. “Walnuts are rich in alpha-linolenic acid and polyunsaturated fats and are a fundamental ingredient in the Mediterranean diet we studied previously. The Mediterranean diet has many versions, but the inclusion of legumes or walnuts in this diet is associated with many cardiometabolic benefits in previous studies,” Tsaban says. The current study represents their best evidence-based version of the Mediterranean diet.

And Mankai? “We looked for an edible plant rich in bioavailable protein and polyphenols that can be consumed as a dinner



Brown Adipose Tissue (BAT)

Removal of white adipose tissue (WAT), such as with liposuction, is only a temporary measure, as WAT grows back. Browning the WAT with various agents to become brown adipose tissue (BAT) in animal experiments has demonstrated that the resulting increased energy expenditure may decrease body weight.



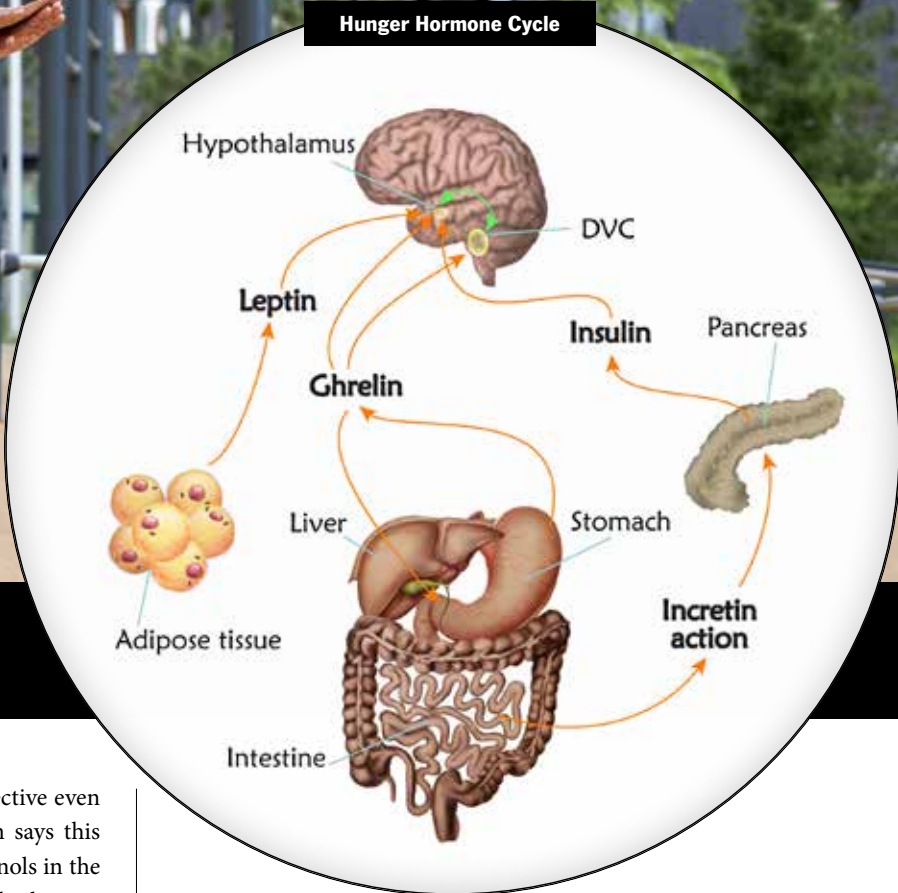
White Adipose Tissue (WAT)

substitute (meaning satiable and palatable),” Tsaban explains. “After a long search, we found Mankai (*Wolffia globosa*), which answered our expectations. We do not have any commercial relationship with the manufacturer of Mankai and do not advertise it.” Moreover, the company that markets Mankai was not involved in the design or handling of the study, had no access to the study’s data, and was not involved in the data analysis or publications from the study.

Baseline FGL were similar among the three intervention groups, and 52% were normo-glycemic, 37% had prediabetics, and 11% had type 2 diabetes. After 18 months, the FGL increased with weight loss and was associated with improvement in insulin sensitivity and reduced visceral adiposity in the two Mediterranean diet groups, but with FGL being twice as high in the green-MED group. Importantly, these changes persisted even after adjusting for weight loss, suggesting a dietary influence.



Hunger Hormone Cycle



Overall, in drug therapy, the news is good, with recently approved medications leading to 15% weight loss when combined with behavioral modification therapy.

As for why the green-MED diet was so markedly effective even compared to the regular Mediterranean diet, Tsaban says this may be attributable to the higher amounts of polyphenols in the green-Med diet, compounds well known to benefit the human body and even fight disease. “We have also shown that the green-MED diet promoted distinct changes in the gut microbiome associated with some of the observed metabolic benefits,” he adds. These are just observations for now and remain to be specifically investigated.

To explain the seeming paradox that fasting levels of ghrelin (which is orexigenic) are lower in insulin resistance, Tsaban explains that ghrelin has different functions in short and prolonged fasting conditions. “We and others (as elaborated in the paper) show that ghrelin plays a vital role in metabolic and energy regulation during long fasting conditions (meaning more than eight hours), and higher levels of fasting ghrelin are associated with increased insulin sensitivity. This is the first study to show that fasting ghrelin is related to the recovery of sensitivity to insulin and adiposity regression during lifestyle intervention and that different dietary interventions have other effects on FGL increase.”

These findings burst with positive implications. “In my view as a clinician, this study highlights the importance of fasting ghrelin as a marker of insulin sensitivity recovery and adiposity regression during lifestyle interventions, which is often not reflected by weight loss alone. The findings of this study support the use of FGL as a laboratory marker to estimate the metabolic responsiveness of an individual to specific lifestyle interventions,” Tsaban says. The team has already undertaken additional sub-studies of DIRECT-PLUS under the leadership of Iris Shai (a coauthor of the current study), and they plan to continue investigating the effects of the green-MED diet on different aspects of human health.

The important leads by Mantzoros’s and Tsaban’s teams have brought us much closer to trimming the fat. The more we understand about obesity, the better our ability to develop effective therapies. ^{EN}

– HORVATH IS A FREELANCE WRITER BASED IN BALTIMORE, MD. IN THE FEBRUARY ISSUE, SHE WROTE ABOUT THE DIABETES RISK OF GENDER-AFFIRMING HORMONE THERAPY IN TRANSGENDER WOMEN.



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New Research *Upends the Conventional Wisdom* About Body Weight and Bone Density in Men.

For years, obesity was thought to have the ability to thwart the occurrence of osteoporosis, especially in men. However, a new study in *The Journal of Clinical Endocrinology & Metabolism* shows that men with obesity could be at a higher risk for osteoporosis than previously thought.

Flesh and **Bone**

BY DEREK BAGLEY

Earlier this year, a paper in *The Journal of Clinical Endocrinology & Metabolism* looked at the relationship between body composition and bone mineral density (BMD) in patients with a wide range of body mass index (BMI).

In their introduction, the authors state that while there have been several studies that show a strong positive relationship between body weight and BMD, the relationship has not been well studied in the current obesity epidemic. The authors go on to note that obesity has been linked to fractures in the humerus and other sites, and these findings “challenge conventional thinking and require a re-examination of our understanding of how weight may affect BMD.”

“While there are excellent studies looking at bone health and obesity, most studies have used body mass index as the indicator of obesity,” says one of the study’s authors, Rajesh K. Jain, MD, assistant professor of medicine and Endocrinology Fellowship Program director at the University of Chicago Medicine. “As we know, BMI has its limitations and does not account for a person’s body composition. Studies have demonstrated that lean mass (which includes muscle mass) and fat mass have differing relationships to bone density, but the exact relationship of fat mass and bone density was not clear.”

Most previous studies have shown positive or neutral effects of body fat mass on bone health, but “have been limited due to small numbers, referral bias, or lack of racial and ethnic diversity,” says Jain.

What’s more, studies in men are scarcer and have had conflicting results. According to Jain, the main reason for this gap is that many studies chose to focus on women. “Because osteoporosis is more common in women, many research questions are asked first in women before considering men,” Jain says. “Unfortunately, this means that the discovery of novel risk factors in men may be delayed.”

Inconsistent Effects of Fat Mass

For this study, researchers analyzed the bone mineral density and body composition data of 10,814 people younger than 60 years old from the National Health and Nutrition Examination Survey (NHANES) 2011 – 2018. They found a strong positive



“ It is important to ensure that associations we see in lower weight individuals are still present in obese individuals. **For example, BMI has been strongly associated with bone density in many studies; however, if you look at just the subjects with BMI over 30 kg/m² in our study, there was no relationship between BMI and bone density.**”

— RAJESH K. JAIN, MD, ASSISTANT PROFESSOR OF MEDICINE AND ENDOCRINOLOGY FELLOWSHIP PROGRAM DIRECTOR, UNIVERSITY OF CHICAGO MEDICINE, CHICAGO, ILL.

“ There have not been enough studies in bone health and osteoporosis looking at racially and ethnically diverse people. While we do know there are substantial differences in fracture rates by race or ethnicity, we have very little understanding about how risk factors may vary. For example, there is evidence that some of our most basic osteoporosis risk factors, such as age and body mass index, differ in Black people.”

— RAJESH K. JAIN, MD, ASSISTANT PROFESSOR OF MEDICINE AND ENDOCRINOLOGY FELLOWSHIP PROGRAM DIRECTOR, UNIVERSITY OF CHICAGO MEDICINE, CHICAGO, ILL.

association between lean mass and bone mineral density in both men and women. Conversely, fat mass had a moderately negative association with bone mineral density, and these effects were particularly prominent in men and those with the highest levels of fat mass.

Jain and co-author Tamara J. Vokes, MD, write that their work contrasts with prior studies that found inconsistent effects of fat mass — positive, neutral, or slightly negative. “Furthermore, previous studies, some of which are 15 to 20 years old, may not reflect current trends in severe obesity, which has been increasing substantially in the United States and projected to worsen,” they write.

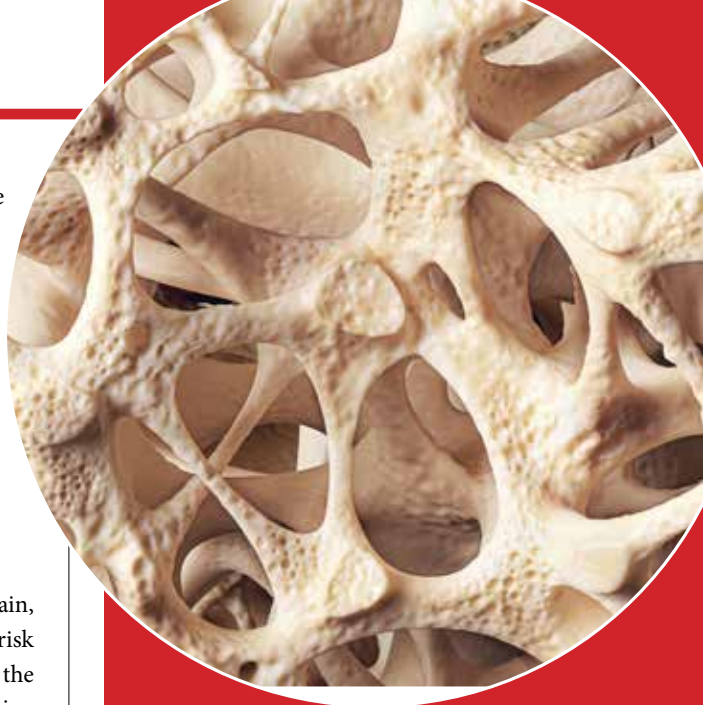
Jain tells *Endocrine News* that as obesity — and especially high levels of obesity — become more common, providers need to fully understand all of the health effects. “It is important to ensure that associations we see in lower weight individuals are still present in obese individuals,” he says. “For example, BMI has been strongly associated with bone density in many studies; however, if you look at just the subjects with BMI over 30 kg/m² in our study, there was no relationship between BMI and bone density.”

A More Diverse Sampling

Jain and Vokes also point out that their study differs from previous ones in that they were able to analyze data from a diverse population. They write that very few studies have included as many men or racial and ethnic minorities, but the NHANES uses “a complex, multistage probability sampling design to represent the U.S. population as a whole.”

“Studying racially and ethnically diverse people is so important and one of the focuses of my research,” Jain says. “There have not been enough studies in bone health and osteoporosis looking at racially and ethnically diverse people. While we do know there are substantial differences in fracture rates by race or ethnicity, we have very little understanding about how risk factors may vary. For example, there is evidence that some of our most basic osteoporosis risk factors, such as age and body mass index, differ in Black people. I’ve also done work (also published in *JCEM* [“Diabetes-Related Fracture Risk Is Different in African Americans Compared With Hispanics and Caucasians,” August 2019]) looking at diabetes-related fracture risk that also demonstrated differences by race and ethnicity.”

One of the more surprising findings was that sex hormones don’t seem to fully explain the sex differences in the results. Indeed, other hormones could be playing a role, but Jain says it might



still be too early to tell which ones, and what exactly they're up to. "When we think about differences in bone health by gender, we often think about sex hormones since they play such a crucial role for bone health," he says. "We also know that men with high levels of obesity can develop hypogonadism. We, therefore, thought it was important to investigate that as a potential cause of the sex differences. However, we did not find that sex hormones fully explained the differences we saw in bone density. More work is needed. For example, there could be effects of adipokines (released by adipose tissue) on bone."


Obesity Is No Guarantee Against Osteoporosis

These findings may serve to shake up how things are done in the clinic. Again, the assumption among providers is that patients with obesity are at a lower risk of fracture. And for a time, that made sense; in clinical practice many of the patients with osteoporosis are underweight, and there are many studies showing an association of higher body weight or BMI with higher bone density. "However, higher body weight or BMI does not reflect a person's body composition, which we found varied substantially even within BMI categories," Jain says.

There are several screening recommendations in place, depending on the organization, but Jain says as far as he knows, no organization has different recommendations based on whether a patient has obesity. "For example, the United States Preventive Task Force recommends that all women over age 65 get bone density screening," he says. "In reality, the general rate of screening is low, and more targeted screening is done for people physicians think are at risk. In general, higher BMI is associated with higher bone density so patients with obesity may be less likely to be screened."

But this study suggests that people with high body fat may be at higher risk for low bone density or fractures. Unfortunately, as of now, there is no routine way (outside of a research study) to measure body fat and appropriately identify who may be targeted for screening. "Rather than measure body fat, I would suggest clinicians consider factors that correlate with high body fat, such as the presence of diabetes, or low lean mass, such as poor performance on physical activity measures, such as grip strength," Jain says. "These factors, in addition to their associations with body composition, are also associated with osteoporosis or fractures, and their presence should prompt clinicians to consider osteoporosis screening."

Jain and Vokes conclude the paper by writing that further work is necessary to understand the effects of high fat mass on the risk of fracture, devise appropriate osteoporosis screening strategies in obese patients, and determine whether negative effects of fat on bone mass are reversible with weight loss.

For now, healthcare providers should consider osteoporosis screening for patients with high body weight, especially if they have other risk factors like older age, previous fracture, family history, or steroid use, Jain says. "While higher BMI is generally associated with higher bone density," he continues, "our study demonstrates that lean and fat mass affect bone density differently and that obesity is not a guarantee against osteoporosis." 

AT A GLANCE

- ▶ As the obesity epidemic worsens, the relationship between body weight and bone mineral density becomes less clear.
- ▶ A recent study in *The Journal of Clinical Endocrinology & Metabolism* suggests that men with obesity may be at higher risk for osteoporosis than previously thought.
- ▶ Providers should consider screening patients with high body weight for osteoporosis, especially if they have other risk factors.

— BAGLEY IS THE SENIOR EDITOR OF *ENDOCRINE NEWS*. IN THE MAY ISSUE, HE WROTE ABOUT THE **ENDO 2022** SESSION, "CLINICAL YEAR IN REVIEW: ALL THINGS ADRENAL."



MIDDLE *management*

Evaluating New Insights into Obesity and Weight Control Options

As obesity continues to reach epidemic proportions, endocrine researchers are at the forefront of discovering new methods to help clinicians and patients alike to manage and even conquer obesity and its plethora of comorbidities. Here, we look at three recent studies that take these solutions from the bench to the bedside and even to the sidewalks.

BY KELLY HORVATH

Obesity and its sequelae continue to jeopardize patients' health and keep our healthcare system in a tailspin. But researchers are doing their utmost to bring new insights into this complex disease to help clinicians and patients better manage obesity and its comorbidities and maybe even prevent them.

In addition, as dedicated as researchers and clinicians have been in battling this public health epidemic, some help from policymakers and stakeholders outside the medical sphere would bring us much closer to winning this war.

Three recent studies provide three different viewpoints on obesity: two examine obesity, diabetes, and renal function from two different angles and study methods, and a third explores the relationship between physical environment, obesity, and diabetes.

Obesity, Diabetes, and Renal Function

In "Obesity and Chronic Kidney Disease in U.S. Adults With Type 1 and Type 2 Diabetes Mellitus," published in the May issue of *The Journal of Clinical Endocrinology & Metabolism* (JCEM), Elizabeth Selvin, PhD, MPH, of the Johns Hopkins Bloomberg School of Public Health in Baltimore, Md., and team take a look at how renal function is affected in patients with obesity and type 1 diabetes.

The link among obesity, type 2 diabetes, and chronic kidney disease (CKD) is well characterized, but that association in the setting of type 1 diabetes has not been fully investigated, leading the team to try to fill that gap. In addition, despite improvements in treatment, people with type 1 diabetes have a life expectancy 12 years lower than the general population, which studies suggest is due to chronic diseases, including CKD. Even so, the kidney function of patients with diabetes of either type is undertested, despite guidelines recommending testing annually.

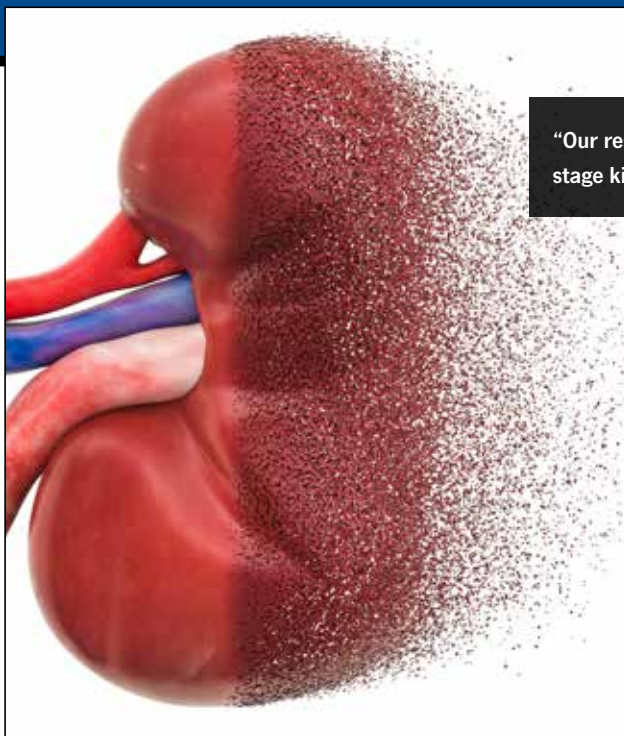
For their study, Selvin and team compared how the association of obesity, type 1 diabetes, and CKD in a cohort of 4,060 patients measured up against a cohort of 135,458 patients with obesity, type 2 diabetes, and CKD, using data from patients for both cohorts ages 18 years old and older receiving primary care from the Geisinger Health System serving central and northeastern Pennsylvania between January 1, 2004, and December 31, 2018. Data from 47,611 patients without diabetes taken from the 1999 – 2018 National Health and Nutrition Examination Survey

“ We might say, ‘walk 30 minutes five times a week,’ but we don’t always think about the context in which people live, which is crucial to actually getting them to make behavior changes and to maintain them. **Understanding the barriers that people face and the sort of changes that they can make in terms of, for example, their transportation mode would be more effective.**”

— GILLIAN L. BOOTH, MD, MSC, UNIVERSITY OF TORONTO,
ST. MICHAEL'S HOSPITAL OF UNITY HEALTH TORONTO AND ICES, ONTARIO, CANADA



“People who live in walkable neighborhoods with access to parks and other outdoor activities are more active and less likely to have diabetes or obesity.”



“Our results highlight the need for interventions to prevent weight gain and end-stage kidney disease in people with type 1 diabetes”

(NHANES) served as a control. Outcome measurements were obtained from routine clinical care and included body mass index (BMI) and estimated glomerular filtration rate (eGFR). Obesity = mean BMI ≥ 30 kg/m², and low eGFR = mean eGFR < 60 mL/min/1.73 m².

“Obesity in type 1 diabetes is turning out to be just as big of a problem as in the general population,” Selvin says, despite the historical presumption that these patients have lower rates of obesity. In fact, rates are trending upward, rising from a 32.6% prevalence in 2004 to 36.8% in 2018. (Rates of obesity in type 2 diabetes remained troublingly high throughout the study period: 58.1% prevalence in 2004 to 61.6% in 2018.)

Also concerning, CKD also turns out to be a larger problem in type 1 diabetes than once believed. The prevalence of low eGFR in type 1 diabetes (17.5% in 2004 to 16.1% in 2018) was higher than in both the general population and the type 2 diabetes population, after adjusting for age. “Kidney disease is often considered a bigger problem in type 2 diabetes,” Selvin explains, “but our study shows that adults with type 1 diabetes actually have a higher risk of kidney disease.” This may be due to the fact that CKD tends to be a disease of older age, and the population of patients with type 2 diabetes is much older than those with type 1 diabetes. Obesity, of course, plays a significant role in the link between CKD and either type 1 diabetes or type 2 diabetes, but with a stronger effect in type 1 diabetes: Obesity was associated with 50% higher odds of low eGFR in the population with type 1 diabetes.

“

Previous epidemiological studies have suggested that obesity is associated with an increased risk of [diabetic nephropathy], but some studies have also suggested that higher BMI is a protective factor for renal function deterioration in patients with type 2 diabetes. **Identification of potentially modifiable pathogenic factors is essential for the prevention and treatment of [diabetic nephropathy.]”**

— ZHI-HONG LIU, MD, JINLING HOSPITAL AND NANJING UNIVERSITY SCHOOL OF MEDICINE, NANJING, CHINA

“Our results highlight the need for interventions to prevent weight gain and end-stage kidney disease in people with type 1 diabetes,” Selvin concludes. Such interventions include regular screening and renal testing.

Obesity, Diabetes, and Renal Function in Women

In a related study, a team led by Zhi-Hong Liu, MD, of Jinling Hospital and Nanjing University School of Medicine in Nanjing, China, zeroed in on the link between obesity and diabetic nephropathy (DN) in type 2 diabetes to clarify mechanisms and

causality. “Previous epidemiological studies have suggested that obesity is associated with an increased risk of DN, but some studies have also suggested that higher BMI is a protective factor for renal function deterioration in patients with type 2 diabetes,” Liu says. “Identification of potentially modifiable pathogenic factors is essential for the prevention and treatment of DN.”

“Body Mass Index and Risk of Diabetic Nephropathy: A Mendelian Randomization Study,” published in the February issue of *JCEM*, reports how Mendelian randomization (MR) can facilitate this identification and evaluates the causal effect of BMI on DN and kidney traits. The 56 BMI-associated genetic variants used in the study came from the BioBank Japan discovery genome-wide association studies analyses; their effects on DN risk, eGFR, and proteinuria were estimated in 3,972 patients with type 2 diabetes, and then sex-stratified MR analysis was performed between BMI and DN.

To back up a bit to what prompted the researchers to explore these particular associations, Liu says, “[studies show] obesity was related to chronic inflammation and may activate the inflammatory cascade response, which, in turn, leads to insulin resistance. This may be a pathway that higher BMI increases risk of DN.” Moreover, he continues, “gender differences in sex hormone levels and fat distribution result in higher estrogen levels and fat deposit in the kidney for women with the same BMI, which affect renal hemodynamics and intrarenal regulation, thus possibly leading to a higher risk of DN in women.”

Their results showed that one standard deviation increase in BMI was causally associated with higher DN risk and lower eGFR level (but not with proteinuria), an effect stronger in women than in men. The team plans to study this causal association between BMI and DN more deeply in the future as well as the dynamic causal association between BMI and DN.

“This study helps strengthen clinicians’ focus on lifestyle interventions,” Liu says. “In clinical practice, lower BMI levels have important therapeutic benefits in preventing the onset and delaying the progression of DN, especially in women.”

Weight Management with Smart Growth

In “The Weight of Place: Built Environment Correlates of Obesity and Diabetes,” published in the February issue of *Endocrine Reviews*, Gillian L. Booth, MD, MSc, of the University of Toronto, St. Michael’s Hospital of Unity Health Toronto and ICES in Ontario, Canada, and team show that people who live in walkable neighborhoods with access to parks and other outdoor activities are more active and less likely to have diabetes or obesity.

“We got interested in this area because of the large increase in obesity and diabetes over the last few decades, and so researchers and policymakers have been struggling to find out what we can do about it at a population level,” Booth says. While genetics and biologic factors play enormous roles in increasing rates of obesity, so too might manmade environmental factors that make driving from place to place more desirable



AT A GLANCE

- ▶ A U.S. study from Johns Hopkins Bloomberg School of Public Health showed that patients with type 1 diabetes now have rates of obesity similar to that of the general population, magnifying their risk for renal disease and highlighting the need for screening and prevention in these patients.
- ▶ In a study from Nanjing University in China, genetic evidence showed that higher BMI levels were causally associated with increased risk of diabetic nephropathy (DN) and decreased eGFR levels, and this increase in BMI had a greater impact on DN risk in women.
- ▶ A study from the University of Toronto in Canada explored the research on the relationship between the built environment and metabolic health, concluding that living in an environment that facilitates physical activity reduces risk of obesity and diabetes and building more such environments could greatly improve population health.

than walking, such as improvements in road infrastructure and zoning policies that increase distance between locations.

“So, we’ve been looking at how neighborhoods can be designed to help promote activity on a broader level,” Booth says.

They scoured the available literature and synthesized their findings to make some conclusions about the benefits of living in a walkable neighborhood. It will surprise no one that the benefits are vast, including reducing rates of obesity, diabetes, and hypertension and other cardiovascular diseases, but the real impact of their research is how they have enumerated the ways we can act on it to improve population health.

“One way is transit expansion,” Booth says, “because you can actually increase what we call ‘active transportation’ by being able to walk or cycle to a transit hub and not be dependent on cars, which is a win-win because this will also decrease emissions and align with other policies.”

Another potential way is to build mixed-income neighborhoods, so that poor neighborhoods are not subject to food deserts, while affluent neighborhoods have access to a variety of healthy food options. A third is creating “complete streets,” a transportation policy and design approach that allows for multiple modes of transportation — cycling, walking, and so on



“In clinical practice, lower BMI levels have important therapeutic benefits in preventing the onset and delaying the progression of DN, especially in women.”


“ Kidney disease is often considered a bigger problem in type 2 diabetes. **But our study shows that adults with type 1 diabetes actually have a higher risk of kidney disease.**”

— ELIZABETH SELVIN, PHD, MPH,
JOHNS HOPKINS BLOOMBERG SCHOOL OF PUBLIC HEALTH, BALTIMORE, MD.

— to exist alongside driving and public transit to facilitate the active transportation Booth describes. “Cities like Barcelona and Copenhagen are looking at innovative ways to create corridors for pedestrian activities or cycling,” she explains. So-called “greening interventions” are yet another way to both encourage moderate to vigorous activity and reduce pollution by expanding parks and other green spaces.

Even this look at how policy can help improve population health has implications inside the clinic. Although clinicians are certainly aware of the importance of being physically active as a cornerstone of weight-loss strategies and diabetes prevention, just giving that advice is not always adequate. “We might say, ‘walk 30 minutes five times a week,’ but we don’t always think about the context in which people live, which is crucial to actually getting them to make behavior changes and to maintain them,” Booth says. “Understanding the barriers that people face and the sort of changes that they can make in terms of, for example, their transportation mode would be more effective.”

Booth says clinicians can suggest that their patients park their cars farther away from their destination point or getting there by transit. “Think about how you can incorporate those little adjustments and find those opportunities for physical activity in daily life. Understanding that is key,” she adds.

And, if you build it, they will come. 

— HORVATH IS A FREELANCE WRITER BASED IN BALTIMORE, MD. IN THE FEBRUARY ISSUE, SHE WROTE ABOUT THE DIABETES RISK OF GENDER-AFFIRMING HORMONE THERAPY IN TRANSGENDER WOMEN.



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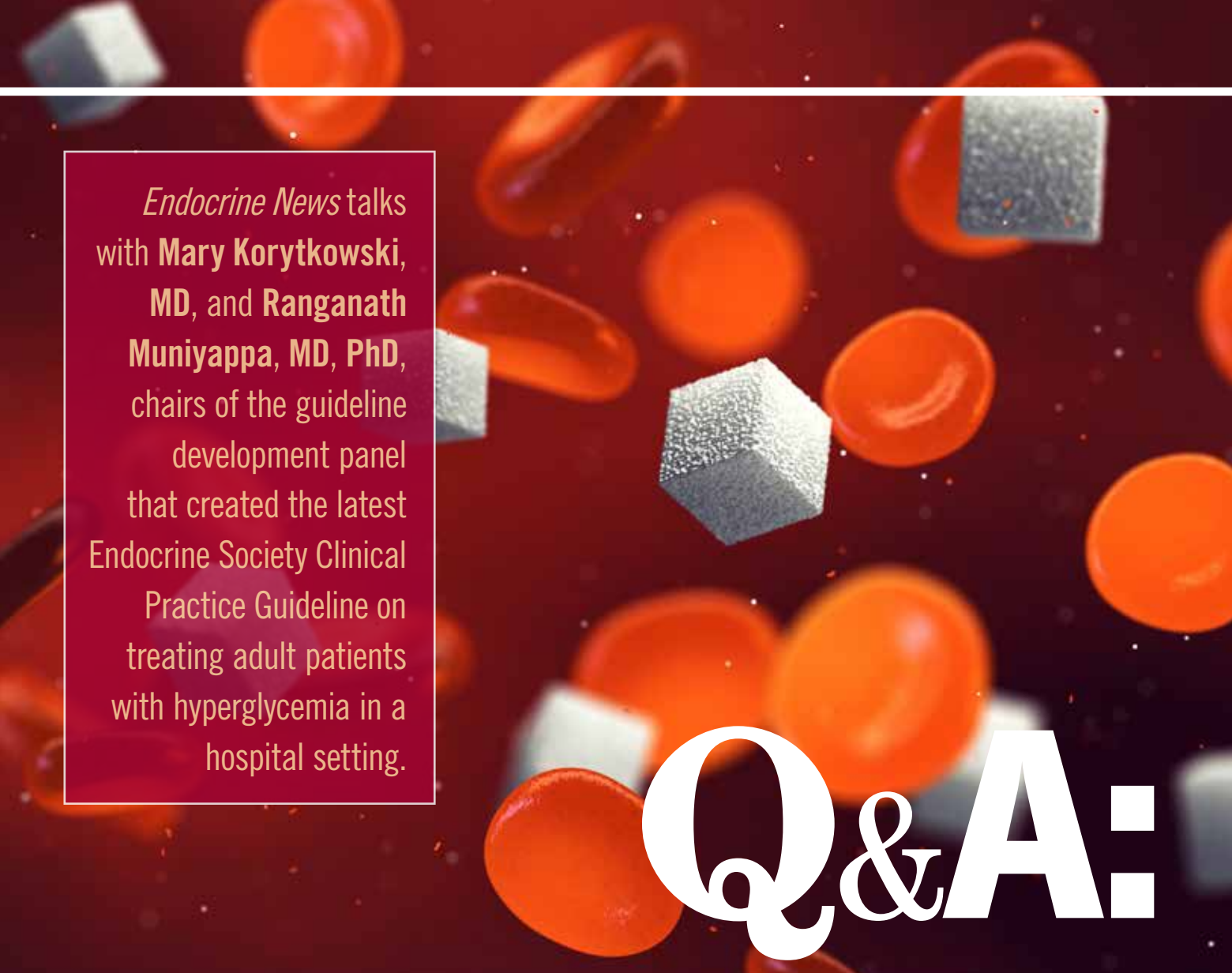


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Endocrine News talks with **Mary Korytkowski, MD**, and **Ranganath Muniyappa, MD, PhD**, chairs of the guideline development panel that created the latest Endocrine Society Clinical Practice Guideline on treating adult patients with hyperglycemia in a hospital setting.

Q&A:

Mary Korytkowski, MD, *and* Ranganath Muniyappa, MD, PhD

This month, the Endocrine Society plans to issue a Clinical Practice Guideline on treating hospitalized patients with hyperglycemia. Titled “Management of Hyperglycemia in Hospitalized Adult Patients in Non-Critical Care Settings: An Endocrine Society Clinical Practice Guideline,” this guideline serves as an update to the last guideline addressing glycemic management in a hospital setting from 2012. The guideline was published online June 13 and will appear in the print issue of *The Journal of Clinical Endocrinology & Metabolism*.

Mary Korytkowski, MD, professor of medicine, Division of Endocrinology, University of Pittsburgh Medical Center, Pittsburgh, Pa., and Ranganath Muniyappa, MD, PhD, senior research physician, Clinical Endocrinology Section, Diabetes, Endocrinology, and Obesity Branch; director, Inter-Institute Endocrinology Fellowship Program, National Institute of



Mary Korytkowski, MD



Ranganath Muniyappa, MD, PhD

Diabetes and Digestive and Kidney Diseases, Bethesda, Md., are the chairs of the guideline development panel that authored the guideline. They shared their thoughts with *Endocrine News* about how they hope this guideline will aid healthcare professionals who treat hospitalized adult patients with hyperglycemia as well as prove to be a vital resource for professionals in other specialties.

Endocrine News: What were the main reasons for the publication of the inpatient hyperglycemia guideline – what drove the decision and why now?

Mary Korytkowski:

- ▶ Management of inpatient hyperglycemia is an important aspect of patient care that contributes to clinical outcomes. There is wide variability in the attention provided to inpatient glycemic management in many hospital settings.
- ▶ There are ongoing developments in technologies for diabetes care in the outpatient setting that have relevance to inpatient glycemic management. There are increasing numbers of patients who use continuous glucose monitoring (CGM) devices and continuous subcutaneous insulin infusion (CSII) devices (i.e., insulin pumps) either alone or in combination who are admitted to the hospital with these devices in place. In addition, CGM is being investigated for guiding glucose-lowering therapies in hospitalized patients with hyperglycemia who were not using this prior to hospital admission.
- ▶ There are many questions regarding the use of non-insulin therapies in the inpatient setting.
- ▶ The last Endocrine Society Clinical Guideline addressing glycemic management in non-critically ill hospitalized patients was published in 2012. Many of the recommendations in this earlier guideline were based on consensus of panel members without systematic reviews.

“ There are several therapies that are commonly used in the hospital setting, including use of glucocorticoids or enteral nutrition, which can either exacerbate hyperglycemia in patients with established diabetes or cause hyperglycemia in patients with no prior history of diabetes. **These patients are at higher risk for adverse outcomes when glycemic management is not addressed.**”

— MARY KORYTKOWSKI, MD, PROFESSOR OF MEDICINE, DIVISION OF ENDOCRINOLOGY, UNIVERSITY OF PITTSBURGH MEDICAL CENTER, PITTSBURGH, PA.

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“The guideline also acknowledges that hospitalization provides an opportunity for providing self-management education to patients, many of whom do not have access to this education in the outpatient setting. **The practice of providing this information to patients can help improve glycemic measures following hospital discharge and reduce need for readmissions.**”

— RANGANATH MUNIYAPPA, MD, PHD, SENIOR RESEARCH PHYSICIAN, CLINICAL ENDOCRINOLOGY SECTION, DIABETES, ENDOCRINOLOGY, AND OBESITY BRANCH; DIRECTOR, INTER-INSTITUTE ENDOCRINOLOGY FELLOWSHIP PROGRAM, NATIONAL INSTITUTE OF DIABETES AND DIGESTIVE AND KIDNEY DISEASES, BETHESDA, MD.

EN: What are your hopes for the impact of the guideline on endocrine-performed standards of care for hospitalized patients in non-critical care setting with hyperglycemia?

Ranganath Muniyappa: There are several:

- ▶ That the use of CGM in hospitalized patients with diabetes who are at high risk for hypoglycemia will receive approval by the FDA with guidance and consideration for safe implementation of these devices by hospitals;
- ▶ That pre-operative glycemic management and targets for elective surgical procedures will be more consistent;
- ▶ That hospitals will acknowledge the importance of hiring knowledgeable diabetes care and education specialists (DCES) (either certified or eligible for certification) to:
 - Provide ongoing staff education regarding many of the recommendations for inpatient use of DM technologies (CGM, CSII);
 - Provide oversight for patients using technologies for glycemic management in the hospital;
 - Empower/educate staff nurses to provide standardized diabetes self-management education to patients prior to discharge as a way of minimizing risk for hospital readmission.
- ▶ Resolve the debate regarding appropriate and inappropriate use of correctional insulin therapy (previously referred to as SSI) for inpatient glycemic management.
- ▶ Stimulate funding for research protocols for aspects of inpatient glycemic management for which there is little or no data available to guide clinical practice (e.g., the use of meformin, SGLT2 inhibitors, or other therapies in the hospital setting).

EN: How do you expect other medical specialties to be affected by the Guideline Development Panel’s recommendations?

MK: Patients with diabetes are admitted to every service in a hospital setting, which means that all medical specialties will

encounter this group of patients. It is important that all medical specialties be aware of the importance of glycemic management as a contributor to either positive or negative clinical outcomes. We do not anticipate that all medical specialties will have the expertise necessary for safe glycemic management, but that awareness of this will serve as an incentive for hospitals to provide personnel — clinicians, certified registered nurse practitioners, physician's assistants, certified DCEs, pharmacists — who are knowledgeable in this practice.

There are several therapies that are commonly used in the hospital setting, including use of glucocorticoids or enteral nutrition, which can either exacerbate hyperglycemia in patients with established diabetes or cause hyperglycemia in patients with no prior history of diabetes. These patients are at higher risk for adverse outcomes when glycemic management is not addressed.

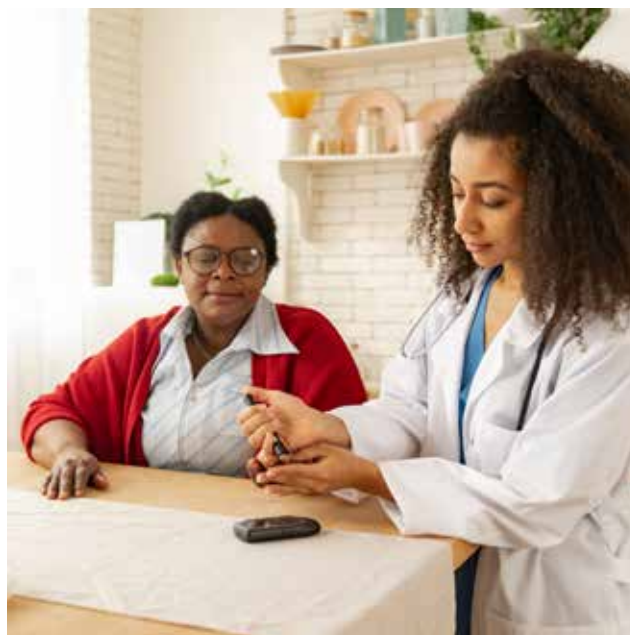
Examples of settings where this guideline may affect patient care include surgical subspecialties, some of which recommend tight glycemic control prior to elective surgical procedures, and others for which there is little or no thought given to pre-operative glycemic control. Together with surgeons, another group that may be affected are anesthesiologists, who are most likely to make decisions regarding use of pre-operative ingestion of oral carbohydrates, which can exacerbate risk for hyperglycemia in some patients.

EN: What are the key take-home messages for patients in this guideline?

RM: A patient representative served as a contributing member of the writing panel providing important insights to each of the questions addressed regarding issues of patient satisfaction and preferences as well as equity of glycemic management strategies during hospitalization and at time of hospital discharge. This representative expressed the hope that these guidelines will serve as the beginning of a conversation that will allow inpatient caregivers to provide individualized care to patients, some of whom may be self-sufficient with their glycemic management and others who may need additional assistance. The importance of these conversations cannot be overstated.

Having a patient voice for each of the recommendations represents a change in the way recommendations for clinical care were made in the past.

This guideline will help to empower patients with diabetes prior to admission to discuss continuation of technologies,



such as CGM or CSII, that they were using prior to admission while in the hospital. The guideline places an emphasis on targeted glycemic management strategies that avoid both hypoglycemia and hyperglycemia in the hospital setting. This includes specific guidance as to when it is either appropriate or inappropriate to discontinue or modify glucose-lowering therapies used prior to admission. Clear guidance is provided regarding use of correctional insulin previously referred to as sliding scale insulin (SSI).

Patients may be relieved to know specific glycemic targets prior to surgical procedures that can help avoid canceling surgical procedures due to hyperglycemia.

The guideline also acknowledges that hospitalization provides an opportunity for providing self-management education to patients, many of whom do not have access to this education in the outpatient setting. The practice of providing this information to patients can help improve glycemic measures following hospital discharge and reduce need for readmissions. ^{EN}

Editor's Note: This article could not have happened without Andrea Hickman, the Endocrine Society's manager of clinical practice guidelines, who coordinated and created this Q&A.



Shingo Kajimura, PhD

Endocrine News talks to Shingo Kajimura, PhD, the Endocrine Society's 2022 Richard E. Weitzman Outstanding Early Career Investigator Laureate Award recipient, about his research of brown and beige fat, challenges his lab faced during the pandemic, and why early-career researchers should just make sure the "science works out."

BY GLENDA FAUNTLEROY SHAW

beige fat benefits

With his significant contributions to changing how endocrinologists understand the function of brown/beige fat in improving metabolic health, Shingo Kajimura, PhD, has been bestowed as this year's recipient of the Endocrine Society's Outstanding Early Career Investigator Laureate Award.

Kajimura is a Howard Hughes Medical Institute (HHMI) investigator at Beth Israel Deaconess Medical Center in Boston, Mass., and his groundbreaking work has transformed the field's understanding of how brown/beige fat controls energy homeostasis in physiology and disease. His investigations continue to unlock how brown/beige fat cells might affect new therapies for controlling obesity and type 2 diabetes.

Endocrine News spoke with Kajimura to learn more about the promising future impact of his work as well as his advice for other young researchers at the blossoming stages of their careers.

***Endocrine News:* Can you share your impressions when you heard the news of your Laureate honor.**

Shingo Kajimura, PhD: I was honored and also humbled. It is a tremendous honor. I want to thank Gregory Steinberg (McMaster University) and Peter Tontonoz (UCLA) who nominated me for the award. They are terrific scientists who were both former honorees of this award, and I respect them very highly.

***EN:* A lot has been written about how the past two years of the pandemic has impacted the work of researchers around the globe. What were the biggest challenges your lab faced, and how did you best get through it?**

Kajimura: We were about to move from San Francisco to Boston around the time the pandemic started so we had to delay our move, and there was a lot of anxiety around the delay. But I really thank my lab members who took risks and moved together with me and my family. We finally moved in the summer of 2020 — in the middle of the pandemic. I tried to think that, well, this is tough for everyone so I need to just take time to think through what

we should do next, how we can transform our science. So, yes, it was difficult, but that led to challenging new questions that we never thought about before.

EN: Let's talk about brown and beige fat cells. The basis of your research is around the science that we already know — that our bodies' brown and beige fat cells are "good" because they can help us burn calories. And that we can make more brown cells by not only dietary changes and exercising, but also by exposing our body to cold temperatures?

Kajimura: The research field of brown fat has been many years centered around thermogenesis. The best well-known function of brown fat is making heat. So, the field has really tried to study the mechanism of thermogenesis, but in the last 10 years, this field has completely changed because of the link to metabolic disease in humans.

Cold is one of the best well-known stimulants of brown fat because of some of the previous knowledge about its links to thermogenesis. But it turns out, there are many ways to stimulate brown fat without cold exposure. The reason why this is important is, as you know, cold is not comfortable. I learned that being in Boston in the wintertime. Beyond that, cold is not actually good for your heart. It increases blood pressure, so cold or stimulation of the sympathetic nervous system may be detrimental to people who have risks of cardiovascular disease. What we really tried to do is to find a new way to activate brown fat without cold.

EN: It's been mentioned that your discoveries have the potential of influencing new therapies for preventing obesity or lead to new weight loss therapies. What would you say is on the horizon for weight loss therapy that could come out of your work?

Kajimura: Well, initially the field, including us, thought that anti-obesity was the way to go, but that may not be the case. First, if you look at the epidemiological studies in humans, the main health benefit of brown fat in humans really is the prevention from type 2 diabetes and dyslipidemia. The field thinks this is a consequence of elevated energy expenditure simply because of the well-known function of thermogenesis, but we still need to figure out why brown fat is

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If you look at the epidemiological studies in humans, the main health benefit of brown fat in humans really is the prevention from type 2 diabetes and dyslipidemia. **The field thinks this is a consequence of elevated energy expenditure simply because of the well-known function of thermogenesis, but we still need to figure out why brown fat is metabolically beneficial.**”

— SHINGO KAJIMURA, PH.D, HOWARD HUGHES MEDICAL INSTITUTE (HHMI) INVESTIGATOR, BETH ISRAEL DEACONESS MEDICAL CENTER, BOSTON, MASS.

metabolically beneficial. I even argue that probably the most potent promising aspect, if you think about therapeutic areas, is probably type 2 diabetes.

EN: Are there any words of advice that you would pass along to other young investigators? You have 12 lab members who work with you. How do you motivate them to continue the hard research work?

Kajimura: This is something my mentor, Bruce Spiegelman (Dana-Farber Cancer Institute), told me and I always keep this in my life. For basic scientists, like me, “if science works out, the rest will follow.” Well, the rest means sometimes promotion, fellowship, or grant, or some other things. So, really, I try to spend as much energy as possible on science. I try to work on unexplored areas of science and then I try not to think about the rest. I understand the anxiety that trainees and early-career scientists have. I felt exactly the same way when I was a post doc and assistant professor. But if the science works out, you'll get the rest. Don't worry about it. **EN**

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Endocrine Society Advocates for Increased NIH Funding

Join our online campaign to share our message with your representative and senators

The U.S. Congress is currently considering funding for fiscal year (FY) 2023, which begins October 1. The Endocrine Society is urging Congress to provide \$50 billion for the National Institutes of Health (NIH) for fiscal year (FY) 2023, a 7.9% increase from the FY 2022 funding level.

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The Endocrine Society is one of the leading advocates for NIH funding, helping Congress to understand that steady funding is essential to maintain momentum from previous investments and support new opportunities for life-saving medical research.

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To increase funding for the NIH, it is critical that all U.S. representatives and senators hear from their constituents about this issue. We encourage all U.S. Endocrine Society members to join our campaign by visiting www.endocrine.org/takeaction. Taking action will only take a minute of your time, but it will have an impact as all congressional offices constantly monitor and count constituent mail.

The Endocrine Society is one of the leading advocates for NIH funding, helping Congress to understand that steady funding is essential to maintain momentum from previous investments and support new opportunities for life-saving medical research. Last year, we helped secure a \$2.25 billion increase for the NIH, continuing a seven-year trend of increases to the NIH budget. This year's increase would support early-career researchers who have been impacted by the pandemic and fund innovative investigator-initiated research projects.

We also continue to share with Congress the importance of securing a base funding increase for the NIH exclusive of funding for the new Advanced Research Projects Agency for Health (ARPA-H). While the ARPA-H may have benefit for endocrine-related research, we have advocated that its funding must not siphon funds from investigator-initiated research at the NIH.

If the research community can amplify these messages, we can secure a significant increase in FY 2023. Take action today!

Endocrine Society Advises EU Policymakers on Chemicals Strategy



As part of our global advocacy for science-based policies to reduce exposure to harmful endocrine-disrupting chemicals (EDCs), the Endocrine Society has a seat on an advisory body to the European Commission on the implementation of the Chemicals Strategy for Sustainability (CSS). On May 18, members of the advisory met in Brussels, Belgium, to adopt a report and recommendations to the Commission on a Strategic Research and Innovation Plan (SRIP) and framework for Safe and Sustainable by Design (SSbD).

Endocrine Society member Anne-Simone Parent, MD, PhD, who represents the Society with this effort, delivered remarks emphasizing the need for the SRIP to support research on the harmful effects of chemicals on endocrine system. She called on the Commission to ensure that the SRIP and SSbD framework work synergistically to ensure that new discoveries on chemical hazards can be integrated into design frameworks for new chemicals to improve the predictive power of such frameworks. She highlighted the example of bisphenol-A (BPA), where a failure to integrate data developed by academic scientists about hazards associated with BPA exposure has created a situation where BPA exposure continues to be widespread and well above levels that are known to be harmful, according to a recent draft opinion by the European Food Safety Agency (EFSA). Moreover, replacement chemicals with similar structures to BPA have recently been found to often have similar effects. Our position is that a forward-

thinking strategy for SSbD would have utilized knowledge about endocrine hazards to better predict such effects.

On June 1, Parent joined Endocrine Society member Angel Nadal, PhD, for an Endocrine Society webinar highlighting the harmful effects of BPA and the importance of finalizing the draft EFSA opinion lowering the acceptable levels of BPA, consistent with scientific evidence, and developing group-based restrictions for bisphenols to prevent further regrettable substitutions. Also participating in the webinar were members of the European Parliament, Sarah Wiener, Jytte Guteland, and Martin Hojsik, who were tested for their exposure to bisphenols, among other groups of EDCs, and spoke about their personal concerns given their exposure to these chemicals. Finally, Jürgen Arning from the German Environment Agency described a proposal from the Agency to restrict a group of bisphenols due to their endocrine-disrupting properties.

These activities are another step in the Endocrine Society's ongoing work to encourage the Commission and EU institutions to move quickly to develop effective legislative proposals that reduce exposure to EDCs as part of the CSS. We will continue to keep members apprised of developments by the EU Commission, including discussion on the transition to safer chemicals and substitutions.

The Endocrine Society is Advocating for You

Learn more about our advocacy and how you can get involved.



Today's political environment is partisan, turbulent, and hard to navigate. Despite this challenge, the Endocrine Society works with the U.S. Congress, the White House, federal agencies, and global policymakers to influence the legislative and regulatory policies affecting endocrine-related research and practice.

We advocate for our members and the work that you do. Our policy priorities include:

- ▶ Increasing funding for biomedical research;
- ▶ Improving regulation of endocrine-disrupting chemicals (EDCs);
- ▶ Increasing physician payment;
- ▶ Reducing the prevalence of diabetes and obesity;
- ▶ Identifying solutions to make insulin more affordable;
- ▶ Protecting access to care for women and transgender people; and
- ▶ Understanding the impact of climate on health.

We encourage our member clinicians, clinical researchers, and basic scientists to use your voices to advocate for these policy priorities.

Here are some ways that you can make your voice heard:

- ▶ **Participate in an online campaign** — *Join our online advocacy campaigns (US and EU) to send a letter to your elected officials.*

Sending a message takes a minute but will have a significant impact — receiving 10 messages about an issue can result in a policymaker prioritizing it.

- ▶ **Meet with your elected officials** — *We bring our members to meet virtually or in person with their elected officials in Washington, D.C., and in Brussels about timely legislative issues.*

These meetings are an opportunity to call for action, form a relationship with a policymaker, and increase the visibility of the Endocrine Society.

- ▶ **Write a letter to the editor** — *Letters to the editor are an opportunity to comment on articles, editorials, and advertisements appearing in local newspapers.*

Letters to the editor are read by lawmakers and community leaders to gauge public sentiment about current issues in the news.

- ▶ **Join our social media campaigns** — *Visit @TheEndoSociety on Twitter for posts that you can retweet.*

Policymakers are active on Twitter and see when you tag them in a post. We create social media toolkits with sample posts that you can share to reach your members of Congress.

- ▶ **Sign-up for advocacy news and updates** — *To stay up to date on our advocacy activities and learn how you can get involved, read our weekly advocacy update www.endocrine.org/advocacy-in-action. To have weekly updates sent directly to you, email advocacy@endocrine.org.*

Please visit www.endocrine.org/advocacyaccomplishments to learn more details about our advocacy accomplishments and for ways to make your voice heard.