

MARCH 2024

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

Endocrine news

A Special Focus on Treating Pediatric Obesity

Andrew O. Agbaje, MD, MPH, FESC, speaks to *Endocrine News* about his research that examines how obesity in adolescence has far-reaching impacts well into adulthood as well as why late adolescence could be the most critical time to interrupt the potential comorbidities so often associated with obesity.

“Need To Fight
FOR THE
KIDS.”

BAD RECEPTION:

Unlocking a confounding enigma behind monogenic obesity in children.

• MASS HYSTERIA:

How obesity in adolescence impacts cardiovascular and bone health

• HAVING A BALL:

An examination of pediatric dyslipidemia and how routine lipid screening could play a role

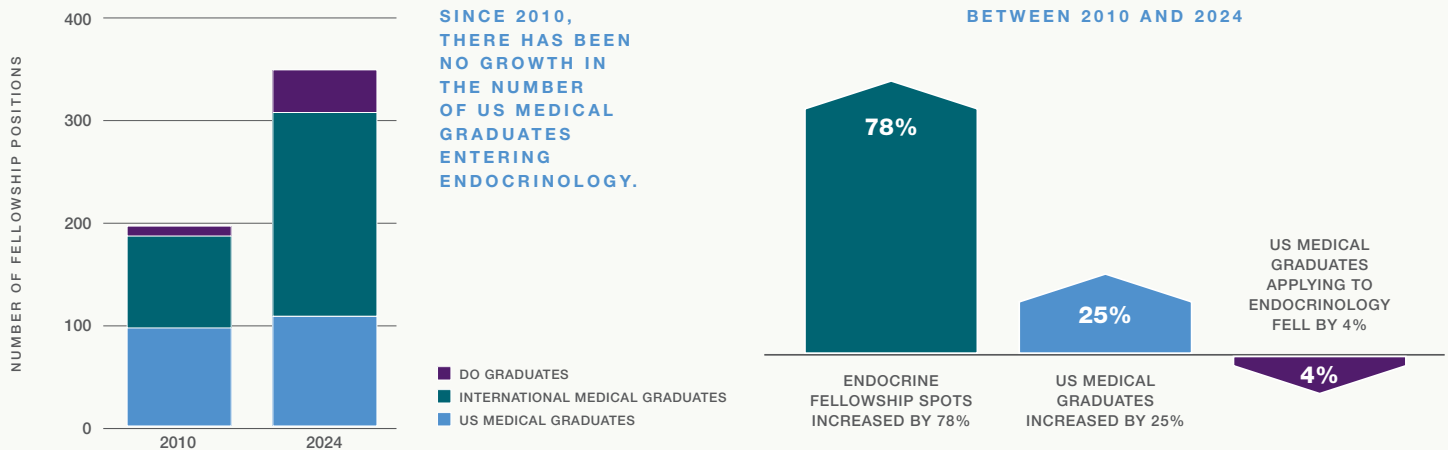
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BY DEREK BAGLEY

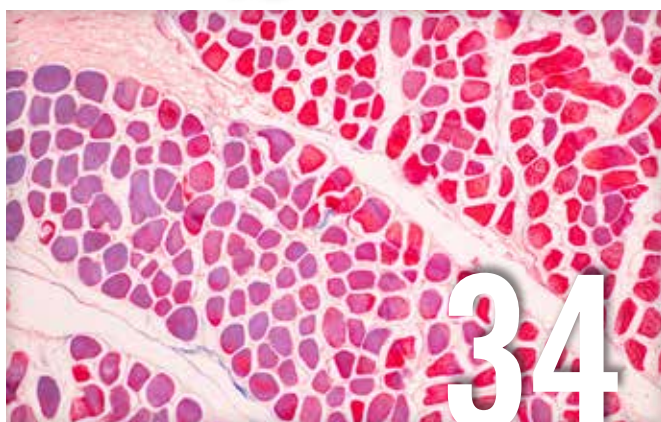
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ENDO 2024 Highlights

ENDO 2024

With springtime just around the corner (or perhaps still a little further around the corner if you live in Rochester, N.Y., like I do), our thoughts once again turn to sunshine, flowers, and **ENDO!**

This year's annual meeting in Boston, Massachusetts, June 1 – 4, promises to be one of our best yet. Members of the dedicated Annual Meeting Steering Committee, along with the Society's hardworking education and meetings staff, once again have outdone themselves in developing a program of cutting-edge educational sessions and exciting networking opportunities.

It's my pleasure to share a few highlights of this year's program. Right off the bat, it's instructive to see the numbers. This year's **ENDO** will include:

- ▶ **6,000-plus attendees** from around the world;
- ▶ **160-plus** education sessions;
- ▶ **40-plus** Meet the Professor sessions;
- ▶ **Four** basic science pathways: Diabetes and Metabolism; Neuroendocrinology; Nuclear Receptors and Signaling; and Reproduction;
- ▶ **30** oral abstract sessions and a poster hall with more than 2,200 scientific abstracts; and
- ▶ **72** industry exhibitors supporting our field in the **ENDOExpo** hall.

Such programming alone will keep you busy from morning until evening.

But you also won't want to miss our three plenary sessions taking place at 8:00 AM on the **ENDO** Main Stage. These unopposed sessions have been specially curated to offer the broadest appeal and insights into some of the hottest topics affecting endocrinology and the medical/science fields at large. They are:

June 1: Cardiovascular Disease in Diabetes: From Molecular Pathways to Populations — This session gets to the heart of the matter. Among other

things, this session will review advances in knowledge around mechanisms responsible for cardiometabolic disorders, which are informing novel approaches to therapy.

June 2: Artificial Intelligence (AI) in Health and Biomedical Research: The Future Is Now — Who doesn't both fear and respect AI? This session will include a discussion on ways that

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Our meeting presents an excellent opportunity for these young professionals to kickstart their careers, whether they decide to focus on amazing clinical care, teaching the next generation of physicians and scientists, or doing cutting-edge research.

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AI-based methods are being used to advance research and care. Hear from two experts on computational biology, precision medicine, genetics of complex traits, and machine learning.

June 3: Hormones and the Aging Brain — We aren't getting any younger! At this session, you will hear from experts leading initiatives to accelerate the advancement of evidence-based clinical care of brain disorders caused by disease, genetics, or trauma. Other areas of expertise include early detection and prevention of cognitive aging and Alzheimer's disease in at-risk individuals, especially women.

These plenaries are marque events that present the very latest in scientific knowledge. They also give us an opportunity to recognize leading figures in our field through the presentation of our Laureate Awards. I'm always inspired to see and hear from the “rock stars of endocrinology!” These are the people who have made significant contributions to improving the care and knowledge of hormone health, improving the lives of millions of patients.


At the same time, I'm even more inspired to meet the up-and-coming generation of endocrine clinicians and scientists

attending **ENDO**. Our meeting presents an excellent opportunity for these young professionals to kickstart their careers, whether they decide to focus on amazing clinical care, teaching the next generation of physicians and scientists, or doing cutting-edge research.

The Endocrine Society takes seriously the need to prepare the next generation of practitioners in our field. This was evident at **ENDO 2023**, when we held the inaugural Endocrinology Mentor Day. The program is designed to stoke interest in endocrinology among medical students and residents. Mentors introduced their mentees to **ENDO's** signature programs, including poster presentations, interesting case studies, and a plenary session. Already we're seeing a huge demand for the second iteration of Mentoring Day, so stay tuned to upcoming Society communications if you want to become a mentor or mentee.

Clearly, **ENDO** provides an intense dose of knowledge sharing and career betterment. But it's also a lot of fun! The meeting provides many opportunities to catch up with old friends and make new ones.

Networking, in fact, has always been a major component of **ENDO**. I can say, without a doubt, that I have met some of my best friends and colleagues at **ENDO**, and every year I look forward to seeing them again. I love the energy that comes from bumping into colleagues and peers in the hallways and at organized social events. One that you won't want to miss is the Opening Reception in the **ENDOExpo**, Saturday, June 1, from 6:15 PM to 7:45 PM. An even more targeted opportunity to network is at our Career Fair in the **ENDOExpo**, on Sunday, June 2, from 2:00 PM to 4:00 PM.

Bottom line: **ENDO** is far and away the best meeting for endocrine clinicians and researchers in the world. Stay abreast of the latest offerings and updates by visiting the **ENDO 2024** website at: www.endocrine.org/ENDO2024. I will see you in Boston, and, if you run into me wandering through the halls, please take a moment to come and introduce yourself! 

*Stephen R. Hammes, MD, PhD
President, Endocrine Society*



FROM THE **EDITOR**

MARCH 2024

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THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

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Endocrine News informs and engages the global endocrine community by delivering timely, accurate, and trusted content covering the practice, research, and profession of endocrinology.

Mom Was Right...

My mother was a nurse. She had a tendency to look at the world two ways: her way and the wrong way. The problem, such as it was, typically turned out to be that her way was the right way. It was both comforting and infuriating all at once. I feel like there are many of you out there who totally get where I'm coming from.

During the hot summers in southwest Alabama, when she would see me sitting on the couch, watching *Good Times* reruns with my hand jammed into a Golden Flake potato chip bag up to my elbow, she would encourage me to "go outside and play!" She told me I would feel better, and it was such nice weather, and it would be good for me, etc. To be honest, I didn't realize how wise she was until after the summer of my freshman year in high school wrapped up and I experienced my first band camp. I started my sophomore year lean, tanned, and only a marginally better trumpet player!

I relate this youthful tale of an abruptly ended life of sloth because so much of this issue focuses on the dangers of adolescent obesity, not to mention too much sedentary time for many adolescents with obesity. This month's cover features Andrew O. Agbaje, MD, MPH, FESC, from the Institute of Public Health and Clinical Nutrition, School of Medicine, Faculty of Health Sciences, at the University of Eastern Finland in Kuopio, whose research figures prominently in two studies published in the January 2024 issue of *The Journal of Clinical Endocrinology & Metabolism* that both address the dangers of the many complications associated with obesity in youth.

In "Having a Ball" on page 28, Kelly Horvath talks to Agbaje about his JCEM paper, "Associations of Sedentary Time and Physical Activity From Childhood With Lipids: A 13-Year Mediation and Temporal Study," and he details the study's findings, why some of the official guidelines are wildly arbitrary, and the need for more regular lipid screenings in pediatric patients. According to Agbaje, one out of five adolescents with obesity who eventually develop heart disease is "one too many, when this is preventable,"



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The mission of the Endocrine Society is to advance excellence in endocrinology and promote its essential and integrative role in scientific discovery, medical practice, and human health.

*Endocrine News** is published 12 times a year by the Endocrine Society, 2055 L Street, NW, Suite 600, Washington, DC 20036
Phone 202-971-3636 • Fax 202-736-9708
www.endocrine.org

Print ISSN 2157-2089 Online ISSN 2157-2097
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Editor's mom (center) helping to prepare for a health fair in Jackson, Ala., sometime in the 1980s.



he says. “Also, when many of these heart diseases eventually occur, we can’t cure them, we can only manage them for life, which increases healthcare costs, yet it’s so cheap to measure cholesterol levels.” Current guidelines recommending cholesterol screening at age 40 are woefully misguided because by the time middle age rolls around, the damage has already been done to the cardiovascular system, and the healthcare cost burden spirals.

In “**Critical Mass**” on page 22, Eric Seaborg speaks to Agbaje about his other JCEM study, “DXA-based Fat Mass With Risk of Worsening Insulin Resistance in Adolescents: A 9-Year Temporal and Mediation Study,” where he says that body mass index (BMI) measurements only tell part of the story; BMI does not give a true measure of the dangers of abdominal fat

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It’s not an antibody.

It’s not an autoimmune antibody.

It’s a naturally occurring protein working as antagonist when you treat the patient with wild-type leptin, then you will see that it’s blocking the receptor.

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nor does it elucidate the benefits of muscle mass. “Fat mass drives insulin resistance, but muscle mass appears to reverse it in a very small way,” Agbaje says. “If we only use BMI, we will not be able to see that muscle mass is beneficial in lowering insulin resistance. ... Abdominal fat is twice as dangerous as total body fat. Every increase in abdominal fat raised the risk of insulin resistance, not just at the time point but progressively from age 15 to 24.”

The article also reports on a second JCEM study, “Insufficient Bone Mineralization to Sustain Mechanical Load of Weight

in Obese Boys: A Cross-Sectional Study,” which details the impact of pediatric obesity on bone mineral density and content compared to average-weight children. The study shows that those children with obesity have a 25% higher risk of extremity fracture than children of average weight.

Senior Editor Derek Bagley examines a *New England Journal of Medicine* study that looked into the cases of two very different children — one from Qatar and one from Austria — who presented with unusually high leptin levels that the researchers discovered were due to inadequate binding with receptors (“**Bad Reception**,” p. 16). It wasn’t until the young patients’ family history was considered that the researchers were finally able to put the pieces of the puzzle together. Once this binding “defect” was realized, it was like a totally new idea from a biological point of view that had never been described before, according to researcher Martin Wabitsch, MD, PhD, head of the Division of Pediatric Endocrinology and Diabetes, at Ulm University Medical Center in Germany. “It’s not an antibody. It’s not an autoimmune antibody. It’s a naturally occurring protein working as antagonist when you treat the patient with wild-type leptin, then you will see that it’s blocking the receptor. And that’s what we saw also in the patients.”

I hope you enjoy this issue with a special focus on adolescent obesity. It’s such an important issue that can be addressed in so many cases that will not only improve the current and future health of these kids but take the strain off of the healthcare systems around the world.

Just wish my mom was here to say, “I told you so!” **EN**

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

New Position Statement Focuses on Patient Experience in Diabetes Care



Healthcare providers who treat diabetes need to think beyond the clinical numbers, such as solely focusing on a person's glucose goals. Taking the patient experience into account can improve the quality of care and facilitate attainment of treatment goals, according to a new position statement published in the Endocrine Society's *Journal of Clinical Endocrinology & Metabolism*.

The position statement reflects the consensus of two virtual roundtables the Endocrine Society held in 2022. Participants included representatives from the American College of Cardiology; American College of Physicians; American Diabetes Association®; Association of Diabetes Care & Education Specialists; Diabetes Technology Society; the U.S. Centers for Disease Control and Prevention; the diabetes research organization dQ&A; and patient advocacy organizations DiabetesSisters, Close Concerns, and Taking Control of Your Diabetes.

More than 500 million people worldwide have diabetes. Managing this chronic disease requires making lifestyle changes throughout life, which can be burdensome for people living with diabetes and their caregivers. Daily tasks such as blood glucose monitoring, dietary and exercise management, routine preventive care scheduling, and medication management must be overseen by people living with diabetes themselves.

Effective two-way communication between people with diabetes and their healthcare providers helps establish a shared understanding of the treatment plan and goals. Healthcare providers who take the time to explain treatment options and discuss potential barriers can improve patient satisfaction and clinical outcomes. In addition, healthcare providers need to consider each individual patient's level of health literacy and cultural background when discussing treatment options.



“Many existing educational resources are available to help healthcare providers think through ways they can discuss diabetes treatment in a neutral and nonjudgmental way and practice using those strategies,” says Rita R. Kalyani, MD, MHS, professor of medicine in the Division of Endocrinology, Diabetes, and Metabolism at Johns Hopkins University School of Medicine, who chaired the position statement and represented the Endocrine Society during the consensus roundtables. “However, in the ever-changing landscape of diabetes and its management, both health care providers and people with diabetes will continue to need new and evolving tools to help address the common challenges they face.”

People with diabetes face an elevated risk of developing depression, anxiety, and other mental health disorders. This makes understanding the psychosocial impact of diabetes important. Addressing stressors in the healthcare setting and ensuring timely mental health referrals, when appropriate, can help individuals with diabetes feel more comfortable and help them participate more fully in their appointments and care.


Each section in the position statement begins with a common clinical scenario that illustrates key gaps in diabetes care. Readily accessible graphics and tools that can be used by healthcare providers to deliver patient-centered care in practice are also included.

The position statement offers a framework for leveraging the experiences of people with diabetes to optimize health outcomes in several important areas, including:

- ▶ Use of person-centered language in the healthcare setting
- ▶ Ensuring that referrals to diabetes self-management and support service programs are timely and accessible to all people with diabetes.
- ▶ Effectively navigating available therapeutic options together and explaining complex regimens to people with diabetes to encourage them to take medication as prescribed.
- ▶ Considering ways to adjust an individual's treatment plan in a timely manner if they aren't meeting therapeutic goals to prevent therapeutic inertia.

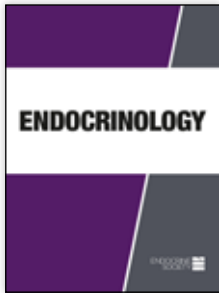
- ▶ Discussing strategies for assessment of hypoglycemia — low blood glucose episodes that can be dangerous — as well as prevention and treatment of hypoglycemia.
- ▶ Improving cardiovascular and renal outcomes using newer therapeutic options.
- ▶ Using telehealth in the appropriate clinical setting.
- ▶ Using and incorporating diabetes technologies such as insulin pumps and continuous glucose monitoring systems into the diabetes management plan, when appropriate.

The other authors of this study are Myriam Allende-Vigo of the University of Puerto Rico, Humacao, Puerto Rico, representing the American College of Physicians; Kellie Antinori-Lent of the University of Pittsburgh Medical Center Shadyside in Pittsburgh, Pa., representing Association of Diabetes Care & Education Specialists (ADCES); Kelly L. Close of Close Concerns, Inc., in San Francisco, Calif.; Sandeep R. Das of UT Southwestern Medical Center in Dallas, Texas, representing the American College of Cardiology; Phyllisa Deroze of dQ&A, The Diabetes Research Company in San Francisco, Calif.; Steven Edelman of the University of California at San Diego in San Diego, Calif., representing Taking Control of Your Diabetes (TCOYD); Nuha A. El Sayed of the American Diabetes Association of Arlington, Va., and Harvard Medical School in Boston, Mass.; David Kerr of the Diabetes Technology Society in Santa Barbara, Calif.; Joshua J. Neumiller of Washington State University of Spokane, Wash., representing the American Diabetes Association; and Anna Norton, on behalf of DiabetesSisters of Raleigh, N.C.

The roundtable meetings were supported by educational grants to the Endocrine Society from Abbott, Medtronic, Novo Nordisk, and Vertex. The position statement, which is a summary of the findings from those consensus roundtables, was developed by the authors independently. 



BY DEREK BAGLEY
Senior Editor



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While an imbalance of nutrition intake and energy expenditure is a primary cause of obesity, we are now aware that the perinatal and early postnatal environments can play a significant role in modifying disease risk.

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TRENDS & INSIGHTS

High Fat Diet Influences Milk Lipids in Lactating Women

Maternal exposure to a high fat diet (HFD) alters milk lipids in lactating women, enhancing adiposity and myeloid inflammation in offspring, even in early life, according to an animal study recently published in *Endocrinology*.

Researchers led by Kanakadurga Singer, MD, and Brigid Gregg, MD, both of the University of Michigan in Ann Arbor, point out that as of 2018, 43.4% of American adults over 20 years of age have obesity. And as the obesity epidemic grows, so does our knowledge and awareness of the complex disease. “While an imbalance of nutrition intake and energy expenditure is a primary cause of obesity, we are now aware that the perinatal and early postnatal environments can play a significant role in modifying disease risk,” the authors write.

The researchers write that infants are susceptible to programming effects through signals conveyed during lactation — the lactational programming hypothesis. “In both humans and mice, the lactation period is a time when adipocytes and the immune system continue to develop,” the authors write. “These systems then play a role in governing global metabolism. Suboptimal development of immune and adipose cells can put individuals at higher risk for obesity and its comorbidities, as well as impaired immune function.”

Previous studies have shown connections between maternal diet and how it affects adiposity in offspring. Indeed, the authors’ prior studies demonstrated that the adult meta-inflammation exaggerated by HFD during the postnatal lactation window (PN) was predominantly a phenotype of male offspring. “However, it is not clear if these programmed effects manifest early at the time of weaning,” the authors write.

For this study, the researchers hypothesized that altering the milk fat profile via changes in the maternal diet favoring omega-6 fatty acids would promote a pro-inflammatory milieu in offspring. “Previous lactational exposure studies have not performed detailed immune phenotyping in the offspring,” the authors write. “Our findings show that even early in life offspring of HFD dams had more adiposity and increased [bone marrow (BM)] myeloid inflammation with serum from these mice directly stimulating myelopoiesis.”

Mice were fed a high fat diet during the postnatal lactation window (HFD PN mice). Their offspring were evaluated at postnatal days 16 to 19 for tissue weight and gene expression. Profiling of adipose tissue and bone marrow immune cells was conducted through lipidomics, in vitro myeloid colony forming unit assays, and flow cytometry.

“HFD PN mouse infants showed not only heavier body and organ weights, but also presented with larger adipocyte sizes than control infants,” the authors write. “Lipidomic analysis revealed increased n6:n3 ratios and increased linoleic acid in milk from HFD dams as well as serum from suckling HFD PN mice. HFD PN mice also showed altered BM and adipose tissue immune cell profiles. Together, these results demonstrate a significant change in infant health profiles upon exposure to a maternal HFD, which can have detrimental effects toward their future health.”

The authors go on to conclude that these findings may hold significant implications for nutritional guidelines for pregnant women and nursing mothers. “Future studies are needed to understand the mechanisms driving this pro-inflammatory state of both BM and [adipose tissue macrophages], the causes of the sexually dimorphic phenotypes, and the feasibility of intervening in this window to improve metabolic health,” they write.

Potential Link Between High Maternal Cortisol and Unpredicted Birth Complications

A snippet of hair can reveal a pregnant person's stress level and may one day help warn of unexpected birth problems, according to a study recently published in *Psychoneuroendocrinology*.

Washington State University researchers measured the stress hormone cortisol in hair samples of 53 women in their third trimester. Of that group, 13 women who had elevated cortisol levels later experienced unpredicted birth complications, such as an early birth or hemorrhaging.

While more research is needed with larger groups, this preliminary finding could eventually lead to



a non-invasive way to identify those at risk for such complications. "There was otherwise nothing about these women that would suggest a disease or anything else complicating the pregnancy. This confirmed some hypotheses that levels of stress, related specifically to cortisol levels, might be associated with adverse birth outcomes," says Erica Crespi, PhD, a WSU developmental biologist and the study's corresponding author.

As part of the study, the participants all answered survey questions about their levels of psychological distress in addition to having cortisol measurements taken in the third trimester of pregnancy and after they gave birth. The women who experienced unexpected birth complications had elevated cortisol concentrations in their hair, a measure that indicates the stress hormone's circulating levels in the body during the three

months prior to collection. These women also reported feelings of stress, anxiety, and depression, but on average, only high cortisol levels during pregnancy showed a strong link to adverse birth outcomes.

Throughout pregnancy, cortisol levels naturally rise two to four times and peak during the third trimester, but the measurements in this study showed even more pronounced elevated cortisol levels among the women who had unexpected birth complications.

Two months after giving birth, the group that experienced birth complications continued

to show elevated cortisol and gave survey answers indicating continued stress, anxiety, and depression. At six months, their cortisol remained elevated, but they started to report lower psychological distress on the survey, which the authors noted might be a sign of recovery.

Finding ways to reduce stress around birth could help improve outcomes for both infants and mothers, the researchers say. They point out that adverse birth outcomes are rising in the country. The U.S. also notoriously has one of the highest maternal mortality rates among developed countries, with deaths disproportionately impacting Black women and other people of color.



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Metals, including arsenic and cadmium, possess endocrine-disrupting characteristics and may be potentially toxic to the ovaries. We need to study the younger population as well to fully understand the role of chemicals in diminished ovarian reserve and infertility.

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Women Exposed to Toxic Metals May Experience Earlier Aging of Their Ovaries

Middle-age women who are exposed to toxic metals may have fewer eggs in their ovaries as they approach menopause, according to new research published in *The Journal of Clinical Endocrinology & Metabolism*.

Researchers led by Sung Kyun Park, ScD, MPH, associate professor of epidemiology and environmental health sciences at the School of Public Health at the University of Michigan in Ann Arbor, point out that Anti-Müllerian hormone (AMH) is a member of the TGF- β superfamily produced by granulosa cells of preantral and early antral follicles and is detectable in circulation. AMH is a promising serum biomarker of ovarian reserve, since measuring AMH has the advantage of being noninvasive and relatively stable over the menstrual cycle, contrary to antral follicle count and ovarian morphology, which are best measured during the follicular phase. “Although genetic and lifestyle factors, such as smoking, are known to affect ovarian reserve, the impact of environmental exposures remains inconclusive,” the authors write.

Studies have linked heavy metals measured in urine with women’s reproductive aging and diminished ovarian reserve. Heavy metals such as arsenic, cadmium, mercury, and lead are commonly found in our drinking water, air pollution, and food contamination and are considered endocrine-disrupting chemicals.

“We attempted to address this gap by examining the associations of heavy metals including arsenic, cadmium, mercury, and lead, with longitudinal trajectories of serum AMH concentrations as

markers of ovarian reserve during the menopausal transition from samples collected in the Study of Women’s Health Across the Nation (SWAN),” the authors write. “We hypothesized that higher metal concentrations were associated with lower AMH concentrations and accelerated rates of decline in AMH during the menopausal transition.”

The researchers studied 549 middle-age women from the Study of Women’s Health Across the Nation (SWAN) who were transitioning to menopause and had evidence of heavy metals — including arsenic, cadmium, mercury, or lead — in their urine samples. They analyzed data from AMH blood tests from up to 10 years before the women’s final menstrual periods. They found women with higher levels of metal in their urine were more likely to have lower AMH levels, an indicator of diminished ovarian reserve.

“Widespread exposure to toxins in heavy metals may have a big impact on health problems linked to earlier aging of the ovaries in middle-aged women, such as hot flashes, bone weakening and osteoporosis, higher chances of heart disease, and cognitive decline,” Park says. “Our study linked heavy metal exposure to lower levels of AMH in middle-aged women. AMH tells us roughly how many eggs are left in a woman’s ovaries — it’s like a biological clock for the ovaries that can hint at health risks in middle age and later in life.”

“Metals, including arsenic and cadmium, possess endocrine-disrupting characteristics and may be potentially toxic to the ovaries,” Park continues. “We need to study the younger population as well to fully understand the role of chemicals in diminished ovarian reserve and infertility.” ^{EN}



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Adipose tissue impacts so many diseases — type 2 diabetes, of course, but also obesity, lipodystrophy, MASLD, hyperlipidemia, atherosclerosis, cancer, and more. All of these conditions could potentially benefit from therapies that manipulate adipose tissue biology. Despite the fact that there are already many medications for these diseases, they continue to cause a huge amount of suffering. **So, there is absolutely a need for new treatments, and adipose tissue offers potential opportunities for tissue-based therapeutics. In many ways, we have just scratched the surface of what's possible.”**

— 2024 Roy O. Greep Laureate for Outstanding Research recipient **Evan D. Rosen, MD, PhD**, on better options for treating diabetes in **“Scratching the Surface,”** on page 34.



The percentage of adults with type 2 diabetes who discontinued their second-line medication within a year of starting it.

— SOURCE: AMERICAN JOURNAL OF MANAGED CARE



Number of U.S.-based medical and nursing students who view their current studies as a “steppingstone” to a healthcare career that does not involve treating patients.

— SOURCE: CLINICIAN OF THE FUTURE 2023 EDUCATION EDITION/ELSEVIER



Patients this age and older who receive thyroid hormone therapy and experience low thyrotropin are at increased risk for dementia and other cognitive problems.

— SOURCE: JAMA INTERNAL MEDICINE



The percentage by which telehealth utilization increased in three out of four U.S. census regions.

— SOURCE: FAIR HEALTH'S MONTHLY TELEHEALTH REGIONAL TRACKER.



PCOS-diagnosed patients had an 8.47-fold higher risk of attempted suicide compared with women without PCOS.

— SOURCE: ANNALS OF INTERNAL MEDICINE



The number of patients removed from Medicaid over the past year in a process known as the “unwinding,” which is aimed to bring the number of Medicaid enrollees back to pre-pandemic levels.

— SOURCE: KFF HEALTH NEWS

16,000,000+

ENDO 2024

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We hope to see you at **ENDO 2024**, taking place June 1 – 4, 2024, in Boston, Mass. With more than 7,000 attendees, nearly 2,000 abstracts, and more than 200 other sessions, **ENDO** is the top global meeting on endocrinology research and clinical care. **ENDO** provides the opportunity to collaborate with an unparalleled list of endocrinologists, healthcare practitioners, and leading scientists from around the world. Through sharing our experience, advice on patient care, and new advances in research, we move the needle forward in hormone health and science. Our outstanding slate of world-renowned speakers will showcase the most cutting-edge advances in research and medicine, with presentations spanning the spectrum of science, clinical care, and social implications. <https://www.endocrine.org/meetings-and-events/endo-2024>

AAES 2024 Annual Meeting

Dallas, Texas

April 20 – 22, 2024

American Association of Endocrine Surgeons 2024 Annual Meeting attendees can look forward to dynamic speakers, presentations of innovative research,



opportunities to connect with colleagues, and informative panel discussions. This year's pre-meeting Advanced Course in Endocrine Surgery will include outstanding faculty and a wide range of topics. In addition, sponsors will be on site to showcase cutting-edge technological advancements pertinent to the practice of endocrine surgery. The AAES Annual

Meeting is dedicated to the advancement of the science and art of endocrine surgery through exchange of knowledge and fostering collaboration. The upcoming 2024 event promises to deliver innovative programming that will enrich attendees' clinical practices, provide networking opportunities, and facilitate scholarly pursuits. We cordially invite you to join us in Dallas for this exciting event. It will be an excellent opportunity to dive into new topics, share expertise, and connect with peers who share similar interests.

<https://www.endocrinesurgery.org/2024-annual-meeting>

2024 Lab Manager Leadership Summit

Denver, Colorado

April 29 – May 1, 2024

The Lab Manager 2024 Leadership Summit will offer actionable advice on the management, business, safety, and staffing challenges facing today's lab managers. The program's expert speakers will provide you with the tools you need to reach higher levels of engagement and efficiency among your lab teams. Topics will range from dealing with burnout, to incorporating automation into your lab, to lab operations, to effective communication,



and much more — an interactive Q&A will follow each session. Attendees will also be able to participate in hands-on workshops and roundtable discussions, where they will receive focused advice and learn from real-life examples of leadership success.

<https://www.labmanager.com/lab-manager-leadership-summit-30946>

Pediatric Endocrine Society 2024 Annual Meeting

Chicago, Illinois

May 2 – 5, 2024

The Pediatric Endocrine Society's Annual Meeting brings together our diverse international community of over 1,000 clinicians, researchers, and trainees to share

the excitement of new ideas, establish new friendships, and learn the latest insights covering the wide scope of our diverse field.

<https://pedsendo.org/education-events/pes-2024-annual-meeting/>

19th International Adrenal Meeting

Boston, Massachusetts

May 29 – 31, 2024

Adrenal researchers and clinicians from around the world will convene for the 19th International Adrenal meeting, which will feature the Keith Parker Memorial Award and Lecture and the Alastair Brownie and Bernie Schimmer Early Career Awards & Lectures. This year's conference will see the addition of pheochromocytoma and paraganglioma to the program along with presentations in each session selected from submitted abstracts.

<https://www.eventsquid.com/mobileapp.cfm?id=22293>

ADA 84th Scientific Sessions

Orlando, Florida

June 21 – 24, 2024

The American Diabetes Association's (ADA) Scientific Sessions offers researchers and healthcare professionals the unique opportunity to share ideas and learn about the significant advances and breakthroughs in diabetes. Participants will receive exclusive access to more than 190 sessions and 2,000 original research presentations, take part in provocative and engaging exchanges with leading diabetes experts, expand their professional networks, and so much more.

<https://professional.diabetes.org/scientific-sessions>

ADCES24

New Orleans, Louisiana

August 9 – 12, 2024

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 ADCES24 in New Orleans, La. Connect, collaborate, and educate yourself and others on the latest in diabetes care and education.

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

ASBMR 2024

Toronto, Ontario, Canada

September 27 – 30, 2024

The ASBMR Annual Meeting boasts nearly 100 education sessions and 1,100 poster presentations in four information-filled days. The conference includes hands-on workshops focused on the latest technologies and research tools using model data sets, meet-the-professor sessions, the ASBMR Discovery Hall, an exhibition hall that provides attendees with a truly immersive experience, with access to new science, new knowledge, new tools, and new contacts all in one location.

<https://www.asbmr.org/annual-meeting>

INTERNATIONAL ITINERARY

Diabetes Meet 2024

Rome, Italy/Virtual

March 11 – 12, 2024

This Diabetes Meet 2024 Conference invites all the academic scientists, endocrinologists, surgeons, primary healthcare specialists, pediatricians, pharmaceutical industrial delegates, talented young scientists, and student communities across the globe to attend this meeting where all the aspects of diabetes mechanism, disorders, and treatment will be discussed under a single roof.

<https://www.diabetesmeet.com>

12th Seoul International Congress of Endocrinology and Metabolism (SICEM 2024)

Seoul, Korea

April 11 – 13, 2024

The Korean Endocrine Society (KES) will explore new frontiers in the realms of endocrinology and metabolism at SICEM 2024, the 12th Seoul International Congress of Endocrinology and Metabolism, in conjunction with the 43rd Annual Scientific Meeting of the KES. This prestigious congress will take place at Grand Walkerhill Seoul in Korea and is hosted by KES. This year, there will be joint symposiums in the SICEM program: ESROC-KES will explore the intricate nuances of the thyroid; JES-KES will concentrate on the field of bone; AFES-KES will delve into the clinical aspects of diabetes, obesity, and lipid disorders; and ENDO-ESE-KES will provide valuable insights into the field of pituitary, adrenal, and gonad studies.

<https://www.sicem.kr/about/overview.php>

ECE 2024: 26th European Congress of Endocrinology

Stockholm, Sweden

May 11 – 14, 2024

Attracting more than 4,000 delegates, from more than 100 countries, ECE continues to develop as a world-leading congress for endocrine specialists. Given that our community works on diverse research topics and sees patients with a wide range of conditions, ECE enables access to a comprehensive program, covering the breadth of endocrinology. Whatever your area of interest, there will be sessions that are of direct relevance, as well as extensive networking opportunities.

<https://www.es-hormones.org/events-deadlines/european-congress-of-endocrinology/ece-2024>



BY DEREK BAGLEY

Obesity is an extremely complex disease, especially in young children. If a child younger than the age of five has severe obesity, it's highly probable that the cause is genetic rather than being overfed by the parents.

BAD

Unlocking a Confounding Enigma Behind Monogenic Obesity in Children

reception

When two very different pediatric patients with obesity presented with unusually high leptin levels, endocrine researchers took notice and discovered that leptin was not adequately binding with receptors. When the young patients' familial history was considered, solutions were finally forthcoming.

About three years ago, a 19-month-old girl presented to Sidra Medicine — a women's and children's hospital, medical education, and biomedical research center located in Doha, Qatar — with severe obesity, the signs of which began developing at just three months of age.

Khalid Hussain, MD, division chief of Endocrinology at Sidra Medicine, which is a member of the Qatar Foundation, and his team took on the case of this child who weighed almost 60 pounds before reaching the age of two. Hussain says the child could hardly walk or even breathe, so she also came under the care of a respiratory team since the physicians thought her asthma may be related to the obesity as well.

"I became very interested," Hussain says. "I wanted to understand why she had such severe obesity at

this age. We did some tests in Qatar, and I think the family at some stage went to the U.K., as well. To cut a very long story short, between the U.K., Qatar, and Germany, we found that this child had a genetic cause for the obesity — a defect in the hormone called leptin, which regulates your feeding satiety.”

Monogenic obesity is a rare early-onset, and severe form of obesity resulting from a mutation or deficiency of a single gene, e.g., leptin.

But this case was unusual in that children who have problems with leptin have a deficiency; this child had very high levels of leptin. After running some tests at the University Medical Center in Ulm, Germany, Hussain and his team were able to show that the child was producing leptin, but it wasn’t working as well in the body because it would not properly activate the leptin receptor.

An Increase in Pediatric Leptin Deficiency

In June 2023, Hussain and his colleagues and co-authors published a paper in the *New England Journal of Medicine*, detailing the case of the above patient (Patient B) and another unrelated adolescent, a 14-year-old boy (Patient A), who also had characteristics of leptin dysfunction including intense hyperphagia, impaired satiety, and severe, early-onset obesity. The authors point out that Patient A is of European descent, while Patient B is of Arab descent.

Martin Wabitsch, MD, PhD, head of the Division of Pediatric Endocrinology and Diabetes at Ulm University Medical Center in Ulm, Germany, and senior author of the *NEJM* paper tells

Wabitsch says that 2015 was a milestone because that’s when he and his team found that even though high levels of leptin are secreted in the body, there was a defect in binding.



**MARTIN WABITSCH,
MD, PHD**

HEAD, DIVISION
OF PEDIATRIC
ENDOCRINOLOGY AND
DIABETES,
ULM UNIVERSITY
MEDICAL CENTER,
ULM, GERMANY

“This is, from a biological point of view, a totally new idea, new finding, never been described before, that human nature can present a mutated protein which is acting as an antagonist. It’s not an antibody. It’s not an autoimmune antibody. It’s a naturally occurring protein working as antagonist when you treat the patient with wild-type leptin, then you will see that it’s blocking the receptor. And that’s what we saw also in the patients.”

Endocrine News that after the first description of congenital leptin deficiency by Stephen O’Rahilly and Sadaf Farooqi, most experts agreed that leptin deficiency was only found in consanguineous families from Pakistan, Turkey, and possibly some Arabic countries.

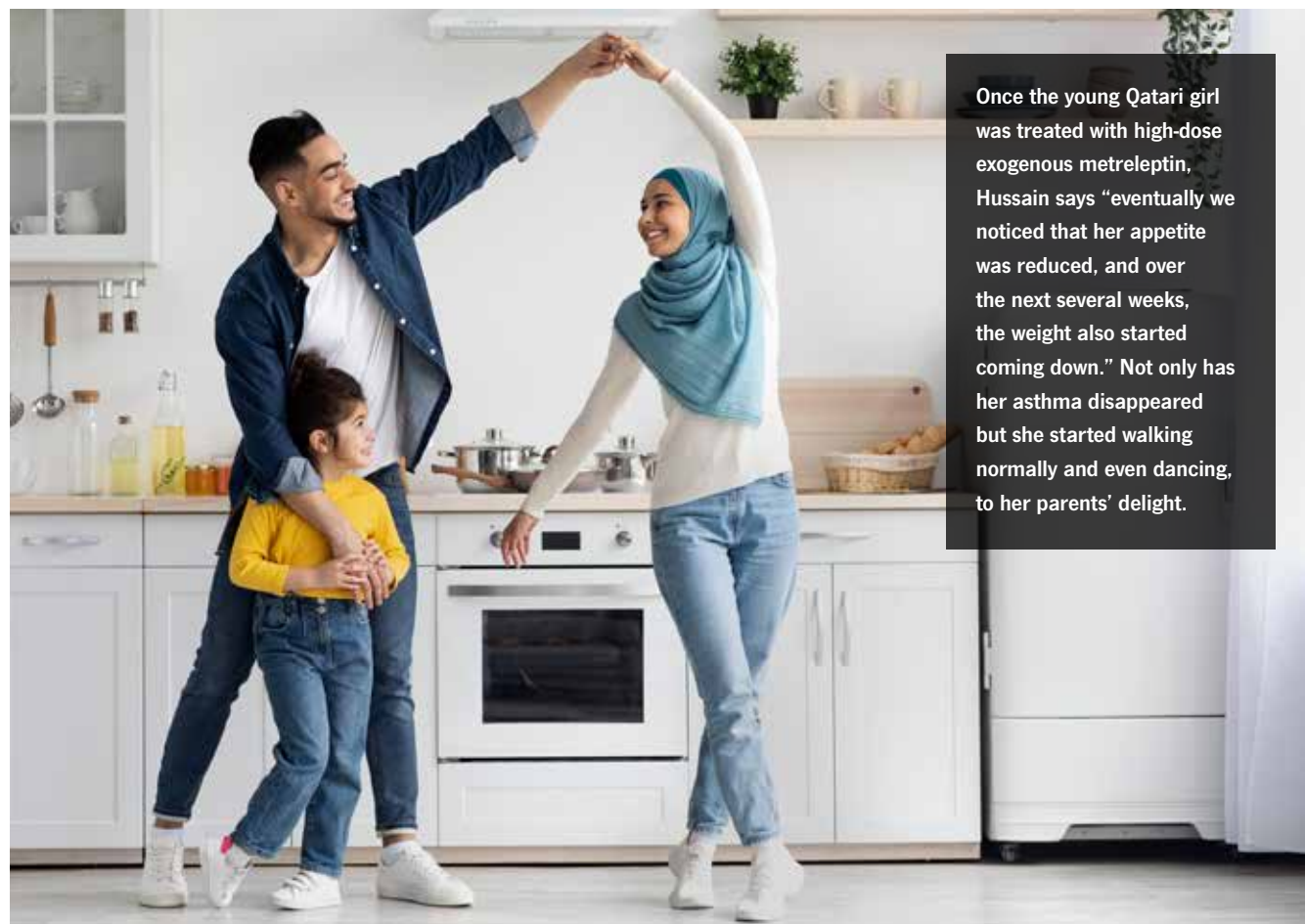
But then an adolescent girl from a family in Austria without known consanguinity with severe, early-onset obesity and leptin deficiency presented to the clinic in Ulm. Wabitsch runs a lab that focuses on children and adolescents with genetic obesity and leptin deficiency. He and his team tested this girl’s adipose tissue-derived stem cells and differentiated adipocytes, and found proof that the patient did indeed have adipocytes that do not secrete leptin. Congenital leptin deficiency in this girl has been shown to be due to a biallelic variant in the leptin gene.

“The phenotype was different to the Pakistani patients,” Wabitsch says, “no immunological phenotype at all and the

weight was much lower than that of the published patients. We treated the patient with metreleptin, which was very difficult to get at the time.”

Wabitsch says that from that point on, they had several new patients with congenital leptin deficiency. Then in 2015, a two-year-old patient from Germany presented with the classical phenotype of leptin deficiency — severe obesity, hyperphagia — so the team measured serum leptin levels, but this time found the patient had high levels of leptin, in the 40s. “After excluding other forms of genetic obesity, we said, ‘We don’t know what this patient has,’” he recalls.

Around that time, another colleague of Wabitsch’s did leptin sequencing in this child (which Wabitsch admits he wouldn’t have done because the leptin levels were so high) and detected a biallelic variant in the leptin gene. “I was reminded of Kowarski syndrome,” Wabitsch says, “growth hormone deficiency with



Once the young Qatari girl was treated with high-dose exogenous metreleptin, Hussain says “eventually we noticed that her appetite was reduced, and over the next several weeks, the weight also started coming down.” Not only has her asthma disappeared but she started walking normally and even dancing, to her parents’ delight.

high growth hormone levels due to a defect in the binding of the growth hormone, so bio-inactive growth hormone. And then I said, 'It seems to me that we have congenital leptin deficiency with high leptin levels due to bio-inactive leptin.'"

A "Eureka!" Moment

Wabitsch marks 2015 as a milestone — the time they found that even though high levels of leptin are secreted in the body but there's a defect in binding. They also found that these patients could be treated with metreleptin as well. (These results were also published in *NEJM* in 2015.) Wabitsch and his team screened more patients and found they had bio-inactive leptin.

Wabitsch explains that bio-inactive hormones have been known to endocrinologists for a while, from the aforementioned growth hormone to luteinizing hormone to thyroid-stimulating hormone. But this was new for leptin, and it told the researchers that leptin measurements are not enough; gene sequencing to exclude leptin was also required.

The team in Ulm also looked at the interaction between leptin and its receptor. There are three binding sites with which leptin engages with its receptor. Wabitsch says that binding site one's function is unclear; site two is for high-affinity binding of leptin to its receptor; and site three is for receptor activation. They theorized that a genetic variant could also affect the code for binding site three, and thus a naturally occurring antagonist could be impacting the receptor.

Factoring in Family History

That brings us back to the most recent *NEJM* paper. Hussain, Wabitsch, and the co-authors of the paper found that while both Patient A and Patient B had high levels of leptin, they both had variants in binding site three. "That's what we were waiting for, humans with variants in this binding site, and both of them, in our in vitro assessments, showed that these variants behaved as antagonists on the level of the leptin receptor," Wabitsch says. "And we needed much higher amounts of metreleptin to overcome the antagonism."

From a biological point of view, this is a totally new finding that has never been described before where "human nature can present a mutated protein which is acting as an antagonist," according to Wabitsch. "It's not an autoimmune antibody," he says. "It's a naturally occurring protein working as antagonist when you treat the patient with wild-type leptin, then you will see that it's blocking the receptor. And that's what we saw in the two patients."

"We realized that we needed to treat the children with high dose exogenous metreleptin," Hussain says. "We admitted [Patient B], and we followed a particular protocol by escalating the dose of metreleptin every few days. And eventually we noticed that her appetite was reduced, and over the next several weeks, the weight



AT A GLANCE

- ▶ **Monogenic obesity can result from rare mutations in the leptin gene usually resulting in congenital leptin deficiency, which can be treated with the human leptin analogon metreleptin.**
- ▶ **Young children who presented with severe obesity and high leptin levels, which is unusual, led researchers to discover leptin was not binding with receptors as it should.**
- ▶ **Recent study findings detail two cases of children with severe obesity and high leptin levels treated with high doses of metreleptin.**



KHALID HUSSAIN, MD

DIVISION CHIEF OF
ENDOCRINOLOGY,
SIDRA MEDICINE,
DOHA, QATAR

“If they present extremely early, that’s mostly suggestive of a genetic cause. And they should either discuss this with a specialist, an endocrinologist, or a geneticist who has an interest in this area, because if you find the cause, you can actually make a complete difference to the child’s management.”

also started coming down. She’s down to about 18 or 19 kilos at the age of about four or five now.”

Hussain says that the girl’s asthma has disappeared, she’s walking normally and even dancing, with no medical issues at all. “It’s been absolutely revolutionary managing her and seeing her go from a child that couldn’t breathe in my clinic to someone who is starting to dance around,” he says.

The girl’s parents are delighted, and Hussain says that the interesting thing was that there were three other aunts in this family who are adults and have severe obesity, so clinicians investigated them, and the aunts have the same genetic problem.

“They’re being treated by my adult colleagues in the adult hospital here in Qatar,” he says. “They’re responding very well, so it’s not just the child. We eventually managed to treat the rest of the family here, and they’re doing extremely well.”

Indeed, both patients experienced a return to normal weight, and Patient A reached mature Tanner stage at age 16.5. “After the two patients had extensive weight loss, which was presumably accompanied by reductions in the endogenous production of leptin variants, we reduced the metreleptin dose in both patients,” the *NEJM* paper authors write.

“Here, we provide in vitro and in vivo evidence for the existence of leptin variants that orthosterically bind to, but do not fully activate the leptin receptor, hence acting as competitive antagonists in the presence of non-variant leptin,” Wabitsch says.

Overcoming the Antagonist

And again, these findings speak to the absolute complexity of a disease like obesity. If a child younger than the age of five has severe obesity, it’s highly probable that the cause is genetic. The general tendency is to think the parents are over-feeding the child, but that tendency falls apart in the case of a 19-month-old.

“If they present extremely early, that’s mostly suggestive of a genetic cause,” Hussain says. “And they should either discuss this with a specialist, an endocrinologist, or a geneticist who has an interest in this area, because if you find the cause, you can actually make a complete difference to the child’s management. If we had not discovered the cause, this poor child would continue to gain weight, suffer from asthma, unable to walk or participate in any of her life activities.” **EN**

— BAGLEY IS THE SENIOR EDITOR OF *ENDOCRINE NEWS*. IN THE FEBRUARY ISSUE, HE SPOKE TO ENDOCRINE SOCIETY MEMBER KEMAL AGBAHT, MD, ABOUT HOW HE MANAGED TO PRACTICE ENDOCRINOLOGY IN THE WAKE OF THE 2023 EARTHQUAKE THAT DEVASTATED PORTIONS OF TURKEY.

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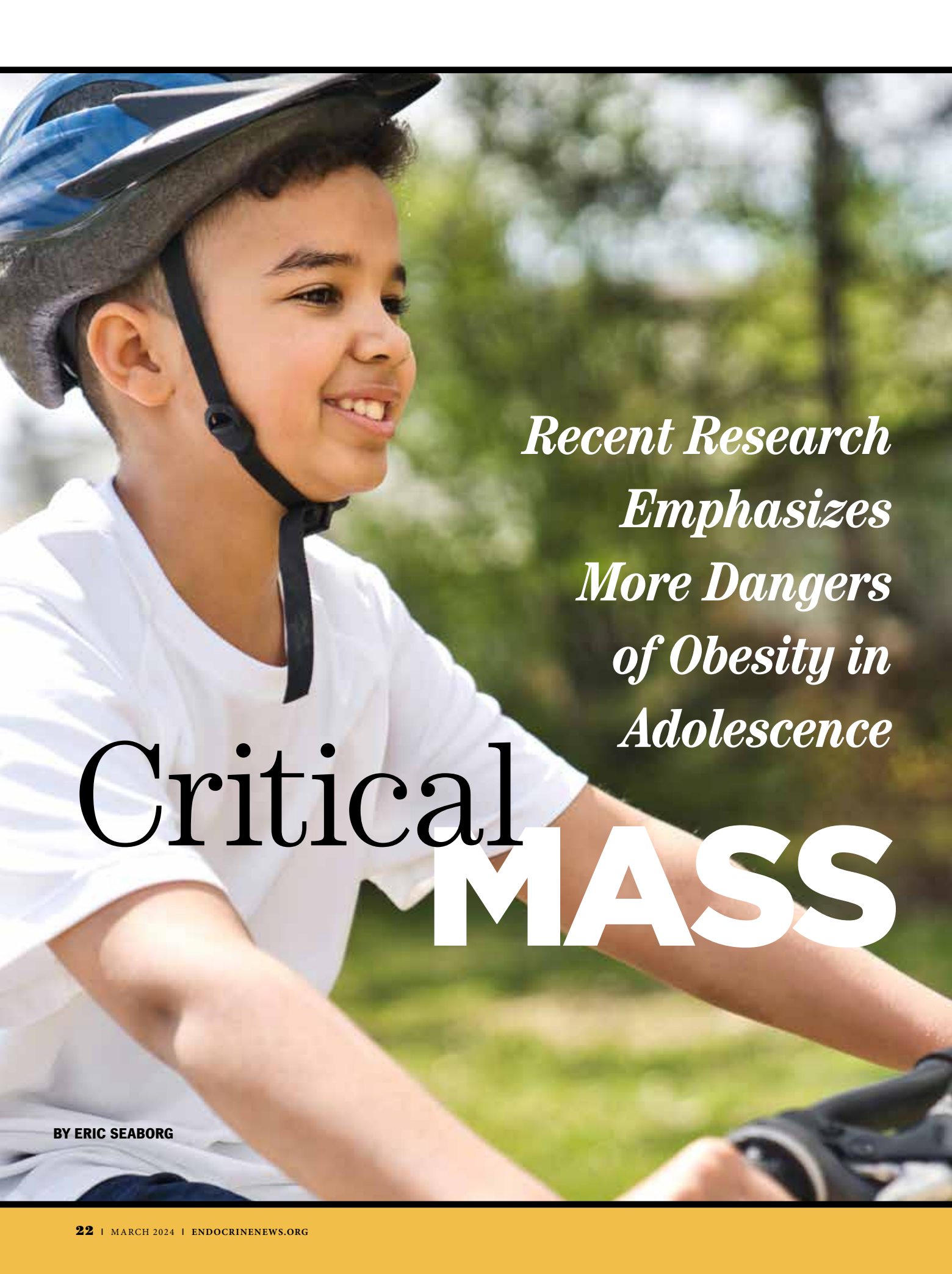
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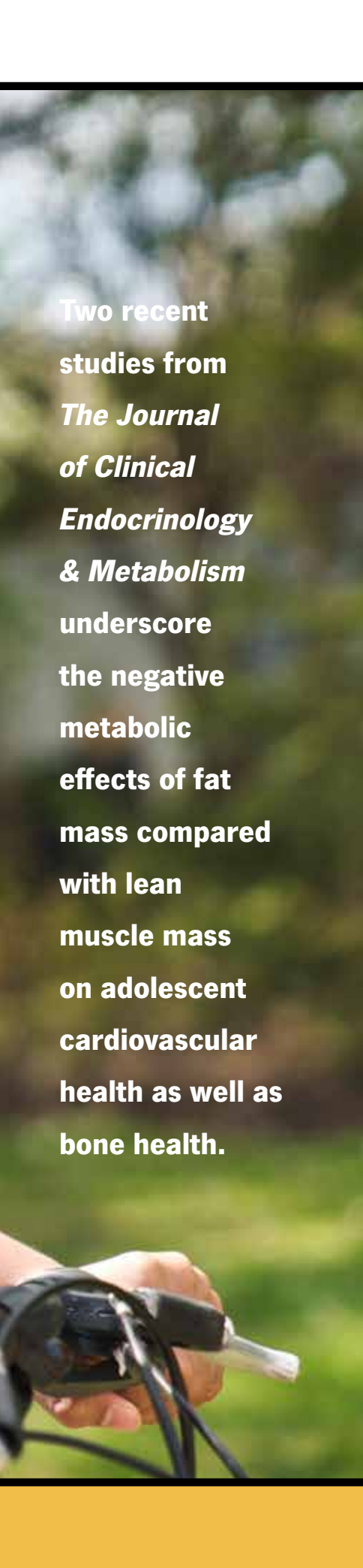
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*Recent Research
Emphasizes
More Dangers
of Obesity in
Adolescence*

Critical MASS

BY ERIC SEABORG



Two recent studies from *The Journal of Clinical Endocrinology & Metabolism* underscore the negative metabolic effects of fat mass compared with lean muscle mass on adolescent cardiovascular health as well as bone health.

Several recent studies have highlighted the importance of lean muscle mass versus the dangers of fat mass in children and adolescents — and suggest that adolescence could be a particularly important time to interrupt an individual's trend toward the morbidities associated with obesity.

Studies often rely on body mass index (BMI) alone as a measure of obesity, but BMI can be misleading because it does not differentiate lean mass from fat mass, according to Andrew O. Agbaje, MD, MPH, a pediatric clinical epidemiologist at the Institute of Public Health and Clinical Nutrition at the University of Eastern Finland.

To differentiate the effects of muscle mass versus fat mass, Agbaje led a team that studied more than 3,000 adolescents from the U.K. Avon Longitudinal Study of Parents and Children (ALSPAC) who had complete dual-energy x-ray absorptiometry measurements and fasting blood samples taken at ages 15, 17, and 24 years.

The study, “DXA-based Fat Mass With Risk of Worsening Insulin Resistance in Adolescents: A 9-Year Temporal and Mediation Study,” was published in the January 2024 issue of *The Journal of Clinical Endocrinology & Metabolism* and analyzed the longitudinal association of total fat mass, trunk fat mass, lean mass, and BMI with the cumulative risk of hyperglycemia, hyperinsulinemia, and high insulin resistance at those ages.

“Each 1-kilogram cumulative increase in total fat mass from ages 15 through 24 years was associated with a progressively worsening risk of high insulin resistance as well as hyperglycemia and hyperinsulinemia,” the study found.

“Fat mass drives insulin resistance, but muscle mass appears to reverse it in a very small way,” Agbaje says. “If we only use BMI, we will not be able to see that muscle mass is beneficial in lowering insulin resistance.”

Agbaje added that the study was also able to differentiate the effects of kinds of fat, such that “abdominal fat is twice as dangerous as total body fat. Every increase in abdominal fat raised the risk of insulin resistance, not just at the time point but progressively from age 15 to 24.”

A Key Time to Intervene?

The temporal nature of the study — following each subject for nine years — enabled Agbaje to conclude that “this age 15 to 17 is a very critical point, where physiology appears to become pathology. The vicious cycle of insulin resistance and fat mass reinforcing each other begins at the age of 17 years.”

The timing of the start of this “vicious cycle” led the study authors to conclude: “Mid-adolescence may be an optimal time for interrupting the worsening fat mass-insulin resistance pathologic cycle and attenuating the risk of progressively worsening metabolic dysfunction before young adulthood.”

“One critical point is that when people with obesity lose weight, it is very important that they do so by exercise to keep up the lean body mass. **By keeping the lean body mass, they will protect their bones.**”

— REGIS COUTANT, MD, SPECIALIZED CENTER FOR OBESITY,
UNIVERSITY HOSPITAL, ANGERS, FRANCE

Cardiovascular Evidence

Agbaje says that a study he published in *Atherosclerosis* on the effects of lipids on the cardiovascular system provides further evidence of how early pathological damage can begin.

This study analyzed findings from almost 1,600 adolescents in the ALSPAC cohort who had their lipids levels measured at ages 17 and 24 along with echocardiography measurements. The study found that “each 1 mmol increase in total cholesterol was associated with higher odds of worsening left ventricular hypertrophy progression over seven years.”

The study concluded: “Increasing lipid levels from adolescence through young adulthood independently associated with the risk of progressively worsening changes in cardiac structure and function and premature cardiac damage in asymptomatic youth. Evidence of cardiac damage attributable to high lipid levels may be seen two decades earlier in the mid-twenties than the current level of evidence in the mid-forties. Increased fat mass, systolic blood pressure, and insulin are potential pathways through which increased lipids may contribute to cardiac damage.”

Agbaje noted that these findings could indicate a need for lipid screening to begin at a much earlier age than called for in current guidelines.

Bone Mass Can't Keep Up

Looking at another part of the body that obesity can affect, children with obesity have higher bone mineral density and bone mineral content compared with children of average weight, yet those with obesity have a 25% higher risk of extremity fracture than children of average weight.

RESOURCES

Agbaje AO, Saner C, Zhang J, et al. DXA-based fat mass with risk of worsening insulin resistance in adolescents: A 9-year temporal and mediation study. *J Clin Endocrinol Metab*. 2024 Jan 4:dgae004. doi: 10.1210/clinem/dgae004. Online ahead of print.

Emeriau F, Amsellem-Jager J, Bouhours-Nouet N, et al. Insufficient bone mineralization to sustain mechanical load of weight in obese boys: a cross-sectional study. *J Clin Endocrinol Metab*. 2024 Jan 2:dgad760. doi: 10.1210/clinem/dgad760. Online ahead of print.

Agbaje AG. Increasing lipids with risk of worsening cardiac damage in 1595 adolescents: a 7-year longitudinal and mediation study. *Atherosclerosis*. 2024 Feb;389:117440. doi: 10.1016/j.atherosclerosis.2023.117440. Epub 2023 Dec 27.

Intrigued by this paradox, researchers led by pediatric endocrinologist Regis Coutant, MD, of the Specialized Center for Obesity at University Hospital in Angers, France, explored the underlying mechanisms in “Insufficient Bone Mineralization to Sustain Mechanical Load of Weight in Obese Boys: A Cross-Sectional Study,” also published in the January 2024 JCEM.

The researchers used dual energy x-ray absorptiometry (DXA) to measure the bone mineral content and bone mineral density of about 250 boys with obesity between the ages of 8 and 18 years at Angers Hospital.

They matched them by height and age with boys without obesity (whom the researchers termed “lean boys”) using data from the U.S. National Health and Nutrition Examination Study (NHANES).

The study found that each 1-point increase in BMI (1 kg/m^2) was associated with an average 39-gram increase in bone mineral content in lean boys compared with a 25-gram increase in boys with obesity — a 40% difference. Each 1-point increase in lean BMI was



While fat mass drives insulin resistance, muscle mass appears to reverse it, albeit in a seemingly small way, according to Agbaje. He adds that if BMI is the only tool used to measure fat mass, it's difficult to see the benefits of muscle mass or the dangers of abdominal fat.



AT A GLANCE

- ▶ Late adolescence could be a critical time to interrupt the march toward the comorbidities associated with obesity.
- ▶ Too much fat mass could begin affecting the cardiovascular system at an early age.
- ▶ Children with obesity do not add bone mass at a rate adequate to keep up with the added load caused by their weight.



Andrew O. Agbaje, MD, MPH, FESC

“Fat mass drives insulin resistance, but muscle mass appears to reverse it in a very small way. If we only use BMI, we will not be able to see that muscle mass is beneficial in lowering insulin resistance. **Abdominal fat is twice as dangerous as total body fat. Every increase in abdominal fat raised the risk of insulin resistance, not just at the time point but progressively from age 15 to 24.**”

— ANDREW O. AGBAJE, MD, MPH, FESC, INSTITUTE OF PUBLIC HEALTH AND CLINICAL NUTRITION, SCHOOL OF MEDICINE, FACULTY OF HEALTH SCIENCES, UNIVERSITY OF EASTERN FINLAND, KUOPIO



Children with obesity tend to have a higher bone mineral density and bone mineral content than children of average weight. However, those with obesity could have a 25% higher risk of extremity fracture than average-weight children.

associated with an average 78-gram increase in bone mineral content in both boys of average weight and boys with obesity, whereas a 1-point increase in fat mass index was associated with an average decrease of 9 grams of bone mineral content.

“When you increase the mechanical load with the weight, you have to increase the bone mineral content,” Coutant says. “But the increase in the bone mineral content in boys with obesity is significantly less than it is in lean boys. So our study suggests that the increase in the bone mineral content associated with the increased weight in obese boys is not enough to support the mechanical load, so it may explain the relative bone frailty of obese boys.”

Although the study did not address treatment, Coutant says that the results suggest the importance of ensuring that children with obesity receive enough calcium and vitamin D to support bone health.

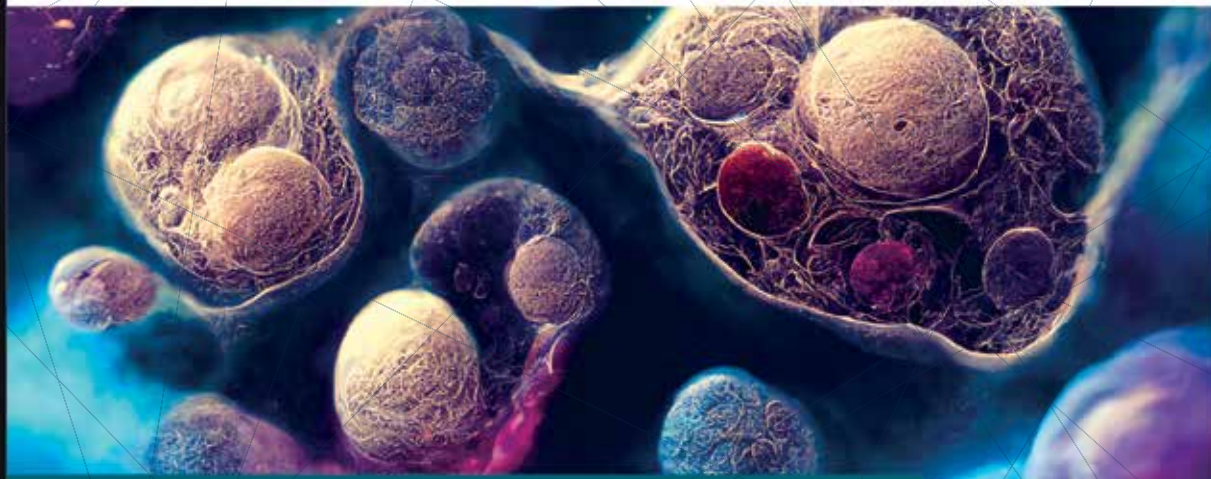
He also highlighted the important association between lean body mass and bone mineral content:

“One critical point is that when people with obesity lose weight, it is very important that they do so by exercise to keep up the lean body mass. By keeping the lean body mass, they will protect their bones.” ^{EN}

— SEABORG IS A FREELANCE WRITER BASED IN CHARLOTTESVILLE, VA. IN THE NOVEMBER 2023 ISSUE, HE WROTE ABOUT EFFORTS TO REDUCE THE RISK OF HYPOGLYCEMIA IN OLDER ADULTS WITH DIABETES.

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HAVING *a*

Can Solving Pediatric Dyslipidemia
Really Be as Simple as Child's Play?

BY KELLY HORVATH



As parents constantly tell their kids to “go outside and play,” new research published in *The Journal of Clinical Endocrinology & Metabolism* basically proves that mothers and fathers really do know best, even when it comes to good cardiovascular health!

For generations, moms and dads have been urging their children to “go outside and play!” Although those well-meaning parents probably just wanted to get their kids out into the fresh air, little did they know that they were also giving their kids sound cardiovascular health tips.

However, what a study published in the December 2023 issue of *The Journal of Clinical Endocrinology & Metabolism* does show for certain is that high levels of cholesterol during childhood have been associated with early signs of heart disease when sedentary kids reach their mid-twenties, as well



Andrew O. Agbaje, MD, MPH, FESC, questioned the WHO's 2020 guidelines stating that children should get at least an hour of exercise every day. "Why 60 minutes?" he asks. "Why not 75? Or 50? Then I also recognized that telling adolescents that 80% of you do not meet the guideline is telling them that they are failures, when they are not."

“ We [recently] found that increasing cholesterol level within the space of seven years [between ages 17 and 24 years] increased the risk of premature heart damage by 20%. We now realize that sedentary time was at the root of all of the problems, not even the cholesterol itself. The cholesterol now looks like an intermediate.”

— ANDREW O. AGBAJE, MD, MPH, FESC, INSTITUTE OF PUBLIC HEALTH AND CLINICAL NUTRITION, SCHOOL OF MEDICINE, FACULTY OF HEALTH SCIENCES, UNIVERSITY OF EASTERN FINLAND, KUOPIO

as an increased risk of premature cardiovascular death when they are in their mid-forties. Furthermore, several clinical trials aimed at lowering cholesterol levels in the youth population have had minimal or no effect.

In “Associations of Sedentary Time and Physical Activity From Childhood With Lipids: A 13-Year Mediation and Temporal Study,” study author Andrew O. Agbaje, MD, MPH, FESC, of the Institute of Public Health and Clinical Nutrition, School of Medicine, Faculty of Health Sciences, University of Eastern Finland in Kuopio, and a Harvard-certified clinical researcher makes child’s play of how to prevent dyslipidemia. In the process, Agbaje turns entrenched beliefs about physical activity on their heads.

Origin Story

Using data from 792 “children of the ‘90s” from the University of Bristol’s Avon Longitudinal Study of Parents and Children (ALSPAC), in England, Agbaje’s study aims to fill a gap in the current understanding of the relationship between physical activity in childhood and adult cardiovascular health. While we have long suspected that sedentary time has deleterious effects on lipid indices, insufficient research has been done on the optimal way to reduce sedentary time (i.e., increase physical activity).

According to the World Health Organization’s (WHO’s) “WHO guidelines on physical activity and sedentary behaviour,” from 2020, “Children and adolescents should do at least an average of 60 minutes per day of moderate-to-vigorous-intensity, mostly aerobic, physical activity, across the week.” The Centers for Disease Control and Prevention recommend the same.

The WHO also points out that current evidence suggests that 80% of children and adolescents do not meet this guideline. These metrics sent Agbaje on a quest. “Why



To restrict dangerous sedentary time for children, a combination of light and moderate-to-vigorous-intensity physical activity could be the perfect solution.

60 minutes?” he asked. “Why not 75? Or 50? Then I also recognized that telling adolescents that 80% of you do not meet the guideline is telling them that they are failures, when they are not. People don’t naturally accumulate 60 min/day of moderate-to-vigorous-intensity physical activity (MVPA). Specialized athletes *choose* to do this, but we are not *designed* to do this. What we are designed to do is to walk.” Agbaje says that in addition to the adolescent mental health hit this message delivers, it also affects parents, who likewise feel like failures for not succeeding in pushing their children to achieve 60 min/day of MVPA.

“I began to see the problems of the 60-minutes-per-day guideline — how ineffective, arbitrary, and unsustainable it is and the consequences of this negative publicity to adolescents. So what is the benefit? There must be a paradigm shift,” he concludes, “but before I can speak about paradigm shifts, there must be evidence.”

Another problem with the WHO guideline — one they cite as a limitation — is that the threshold at which sedentary time becomes harmful is not known, so they simply advise reducing it. “This is not a guideline,” Agbaje says. “You don’t leave people in limbo; we must be concrete.”

Universal Pediatric Lipid Screening

Agbaje says that ALSPAC data showed sedentary time measured by accelerometer worn for seven days at three time points increasing from six hours per day in childhood to eight hours per day in adolescence and to nine hours per day by young adulthood, an increase driven largely — no

surprise — by screen time. He also analyzed measurements of complete fasting plasma high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and total cholesterol taken at each of three follow-up visits at ages 15, 17, and 24 years. “When we cumulatively looked at that sedentary time and its impact on cholesterol level, it was alarming to see that sedentary time independently contributed nearly 70% to the total increase in cholesterol level from the age of 15 to the age of 24.”

Add this to the findings from Agbaje’s previous studies that: 1) elevated pediatric lipid levels are linked to subclinical atherosclerosis in the mid-twenties; 2) a simulated intervention in late adolescence (around age 17) was shown to ameliorate the pathophysiologic mechanisms driving atherosclerosis; and 3) other researchers have reported pediatric dyslipidemia-related premature cardiovascular mortality in the mid-forties, and an important takeaway for clinicians emerges: “there should be universal pediatric lipid screening,” Agbaje says.

But there’s more. “We [recently] found that increasing cholesterol level within the space of seven years [between ages 17 and 24 years] increased the risk of premature heart damage by 20%,” Agbaje says. The current study, however, revealed some additional unpleasant surprises. “We now realize that sedentary time was at the root of all of the problems, not even the cholesterol itself. The cholesterol now looks like an intermediate,” he explains.

“The one out of five who develop heart disease is one too many, when this is preventable. Also, when many of these heart diseases eventually occur, we can’t cure them, we can only manage them for life, which increases healthcare costs, yet it’s



**Andrew O. Agbaje,
MD, MPH, FESC**

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— ANDREW O. AGBAJE, MD, MPH, FESC,
INSTITUTE OF PUBLIC HEALTH AND CLINICAL
NUTRITION, SCHOOL OF MEDICINE, FACULTY
OF HEALTH SCIENCES, UNIVERSITY OF
EASTERN FINLAND, KUOPIO

so cheap to measure cholesterol levels.” Current guidelines recommending cholesterol screening at age 40 are woefully *misguided*. At that point, any damage to the cardiovascular system that has occurred is probably irreversible, and the healthcare cost burden spirals.

Finding Middle Ground

So, sedentary time is profoundly harmful, yet 60 min/day of MVPA is an unrealistic target — where do we go from here? Fortunately, there is an extremely effective — yet systematically overlooked — middle ground: *light* physical activity (LPA). For children and adolescents, LPA can take many easy-to-come-by forms like walking, riding a bike, and even playing on the playground. The irony will be lost on no one that this is precisely what childhood used to look like.

Agbaje’s study showed that time spent in MVPA does not change significantly from childhood to young adulthood, but what does change is the amount of time spent sedentary, and this extra time has been “stolen” from time that had been spent in LPA. “Our study showed that we need at least three to four hours of light exercise every day to be able to counter the effects of sedentary time. Up to six hours of light exercise every day is the optimal amount, but, realistically, as we grow and get involved in classes and work, our time is being fought for by many responsibilities. So our studies have shown that if we can get three to four hours of light exercise every day, we can antagonize all the negative effects of sedentary time.” In other words, LPA completely reverses that 70% increase in total cholesterol level from age 15 to 24 and therefore also obviates its negative downstream effects, such as subclinical atherosclerosis and premature heart damage.

LPA has other advantages as well, such as being accessible to most people, whereas not everyone can participate in MVPA for various health reasons. LPA also can be implemented gradually and systematically until it becomes what Agbaje called an “autopilot of positivity” (as compared to the “autopilot of negativity” that sedentary time induces).

That this is great news is clear, but why no recommendation exists for a specific sedentary threshold, which equates to increasing LPA, is not. This is where Agbaje’s paradigm shift is critical. “What we have been pushing does not work. MVPA is not the right solution for sedentary time.”

“I Need to Fight for the Kids”

To be clear, Agbaje is not decrying MVPA, which certainly has many overall health benefits, but he is saying that it is not going to improve cholesterol parameters as effectively as LPA can because increased sedentary time is driving cholesterol increases, and the increase in sedentary time was bought at the expense of time spent in LPA. LPA also has the upper hand because its effects on cholesterol reduction are long-lasting, whereas the effects of MVPA diminish soon after exercise ceases, mediated by fat mass.



While too much sedentary time is harmful and 60 minutes of physical activity is unrealistic, the middle ground appears to be light physical activity such as walking, bike riding, or playing on the playground.


Ultimately, spending time in both MVPA and LPA while reducing time spent sedentary is the optimal approach to overall health from a physical activity standpoint. These findings are also true for adults — increasing LPA improves several health parameters and lowers the risk of various diseases — but Agbaje will keep his research focus on younger populations. “They don’t have many voices. I need to fight for the kids.” Prevention, he believes, through decreasing sedentary time and instituting pediatric cholesterol screening, is the turning point in this fight against dyslipidemia.

The study was funded by the Finnish Cultural Foundation, the Finnish Foundation for Cardiovascular Research, the Yrjö Jahnsson Foundation, the Jenny and Antti Wihuri Foundation, the Orion Research Foundation, the Aarne Koskelon Foundation, the Paulo Foundation, the Paavo Nurmi Foundation, and the Ida Montinin Foundation. ^{EN}

At A Glance

- In a 13-year study of activity and lipid levels in participants ages 11 through 24, increasing sedentary time was associated with increasing low-density lipoprotein cholesterol, triglyceride, and total cholesterol.
- Increased light physical activity (LPA) (i.e., reduced sedentary time) reduced total cholesterol by five- to eight-fold and was significantly less subject to the effect of fat mass than was moderate-to-vigorous intensity exercise.
- Recommending instituting cholesterol screening in adolescence, when reversing damage is still possible, and engaging in at least three to four hours per day of LPA could be helpful to include in future guidelines.

— HORVATH IS A FREELANCE WRITER BASED IN BALTIMORE, MD. IN THE FEBRUARY ISSUE, SHE TALKED WITH 2024 TRANSATLANTIC AWARD WINNER FELIX BEUSCHLEIN, MD, ABOUT HIS CAREER AND RESEARCH.



Adipose tissue as seen from under a microscope lens.



Evan D. Rosen, MD, PhD

Scratching the **SURFACE**

**Q&A with
2024 Roy O. Greep
Laureate for
Outstanding Research
Evan D. Rosen,
MD, PhD**

BY GLENDA FAUNTLEROY SHAW

His significant contributions to unlocking the mysteries of adipose biology are numerous, yet Evan D. Rosen, MD, PhD, offers that he and his fellow researchers have just scratched the surface of possibilities in treating the diseases most impacted by adipose tissues.

Rosen has been recognized as the Endocrine Society's 2024 Laureate for Outstanding Research — an annual award that honors the work of the late Roy O. Greep, PhD, recognizing meritorious contributions to research in endocrinology.

Rosen is the chief of the Division of Endocrinology, Diabetes, and Metabolism at Beth Israel Deaconess Medical Center and professor of medicine at Harvard Medical School in Boston, Mass. His team of laboratory researchers aim to define novel targets that can be manipulated to improve outcomes in metabolic disease. They research the transcriptional pathways that underlie metabolic diseases like obesity and type 2 diabetes. They use genomic and epigenomic approaches to identify novel

When Evan D. Rosen, MD, PhD, first began researching adipose biology many years ago, not much was known about it and its impacts on so many diseases. He talks to *Endocrine News* about how far the science has advanced regarding adipose tissue as well as his own lab's research, the importance of collaboration, and why a laboratory is a lot like a submarine!

transcription factors and pathways that regulate processes such as adipogenesis, lipid handling, insulin resistance, and metabolic memory. His lab also created many mouse models that are widely used by the research community to study adipose tissue.

Endocrine News wanted to learn more about Rosen's laboratory's goals and the future of adipose research.

***Endocrine News:* What did hearing the news of the recognition for Outstanding Research mean to you?**

Evan D. Rosen: It was such a lovely feeling — so much of our work as scientists can feel isolating and self-contained. In many ways, the lab is like a submarine. We go dark for long periods of time as we puzzle through a project, surfacing every so often to communicate our results to the rest of the community. Winning the Greep award meant that someone was tracking our submarine, which is very gratifying and validating.

***EN:* Your work in helping to understand adipose biology is well recognized. How did you find yourself delving into this type of research?**



In Honor of Roy O. Greep, PhD

The Endocrine Society honors Roy Orval Greep, PhD, (1905 – 1997) a Harvard University endocrinologist and scholar renowned for his seminal observations related to reproduction. Greep spent most of his career at Harvard, teaching anatomy, dental science, and endocrinology and histology, and serving as dean of the Graduate School of Dental Health. He was editor-in-chief of *Endocrinology* and edited two widely used textbooks on endocrinology and histology. Greep served as the 45th president of the Endocrine Society from 1965 to 1966.

Rosen: I was attracted to adipose biology because, when I started working in the field, so little was known. The first scientific meetings I attended only had a hundred people or so (compared to thousands now), and there was a sense that this was a really important area that had been overlooked for a long time.

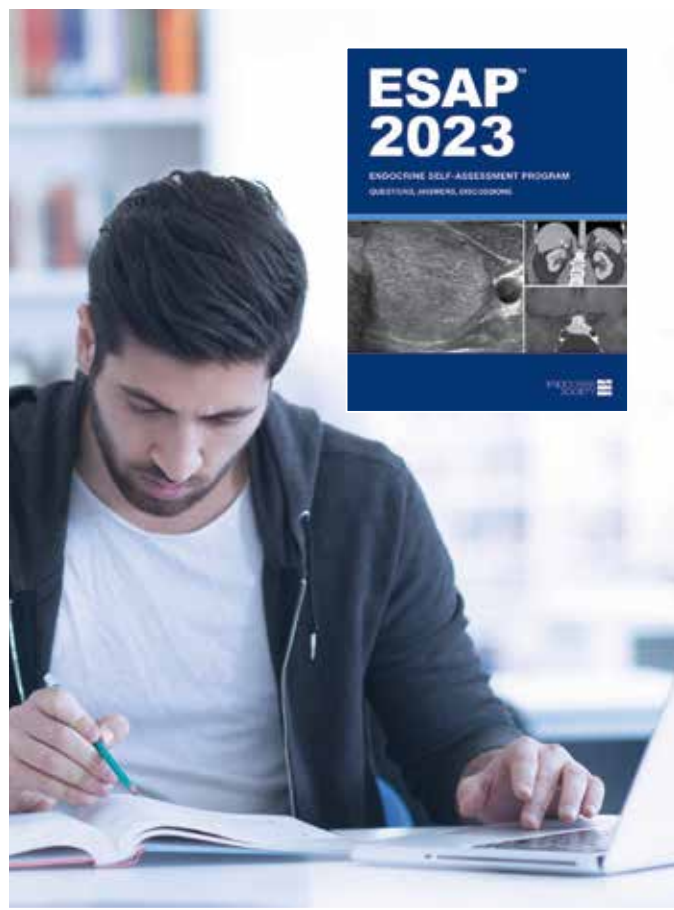
EN: I'm curious about your view on the progress that has been made since your early scientific meeting experience? Is it correct that the growth in numbers of researchers has led to promising collaborations, both nationally and globally? Are young researchers in your lab excited about their future in the field?

Rosen: Yes, there have been some terrific and productive collaborations, both within the adipose community and between adipose researchers and workers in other fields. One example of the former is the Human Cell Atlas Adipose Bionetwork (which I co-lead), and which is pulling the community together to develop standards for methodology and nomenclature. A lot of young scientists are interested in adipose tissue, so it certainly seems there is excitement in the field.

EN: We know how to treat diabetes (and, in most cases, prevent it), but what is the most important discovery still to be unlocked in treating the disease? Meaning, is there a need for better medications or better treatment options?

Rosen: Adipose tissue impacts so many diseases — type 2 diabetes, of course, but also obesity, lipodystrophy, MASLD, hyperlipidemia, atherosclerosis, cancer, and more. All of these conditions could potentially benefit from therapies that manipulate adipose tissue biology. Despite the fact that there are already many medications for these diseases, they continue to cause a huge amount of suffering. So, there is absolutely a need for new treatments, and adipose tissue offers potential opportunities for tissue-based therapeutics. In many ways, we have just scratched the surface of what's possible. ^{EN}

— FAUNTLEROY SHAW IS A FREELANCE WRITER BASED IN CARMEL, IND. SHE WRITES THE MONTHLY LABORATORY NOTES COLUMN.



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Endocrine Society Advances Women's Health Through Research and Advocacy

As leaders in women's health research, our members appreciate how persistent underinvestment in women's health research has impacted our ability to understand and treat conditions that only affect women such as polycystic ovarian syndrome and menopause; and those that affect men and women differently such as thyroid disease, osteoporosis, diabetes, and infertility. We also know how basic science can help us understand how diseases may affect women differently through sex differences. We are therefore encouraged by the establishment of an ad hoc committee of the National Academies of Sciences, Engineering, and Medicine (NASEM) charged with addressing the persistent gaps that remain in the knowledge of women's health research across all National Institutes of Health (NIH) institutes and centers (ICs).

The NASEM Committee has ambitious objectives and sought expertise from our Society to inform their discussions and thinking as they develop recommendations for the NIH to consider and potentially adopt. Working with a group of member women's health experts, we developed a detailed statement delivered to the committee in which we emphasized important endocrine-relevant issues. For instance, we urged the committee to consider a life course approach to the definition of women's health from in utero development through advanced age; to consider gender and biological sex as essential components of women's health; and to encourage the NIH to encourage and support women's health researchers in fields across all institutes and centers at the NIH.

NASEM also invited us to deliver prepared remarks during the committee's open session on March 7. Research Affairs Core Committee member Monica Laronda, PhD, shared the Endocrine Society's priorities and insights, giving committee members the opportunity to ask questions and engage with us further as it seeks to fulfill its charge. We look forward to continuing to share our members' perspective

with the committee and working with the NIH to implement the recommendations arising from the report.

The week prior to the NASEM meeting saw the Endocrine Society participate in another event emphasizing women's health. On February 29, during the 6th session of the United Nations Environment Assembly (UNEA6), the Endocrine Society participated in a meeting sponsored by the Women's Major Group on how chemicals are affecting women's health. Recognizing endocrine-disrupting chemicals (EDCs) as major contributors to women's health issues such as breast and ovarian cancer, Marina Fernandez, PhD, was invited to share the latest scientific information about the impacts of EDCs in plastic on women's health and our recommendations on how member states can improve public health by limiting exposure to hazardous chemicals.

Following this event, the Endocrine Society and the International Pollutants Elimination Network (IPEN) joined together to announce the launch of our latest collaborative report, "Endocrine-Disrupting Chemicals: Threats to Human Health." The report summarizes the latest scientific information on EDCs and their links to disease, including information on regulatory policies that have been updated in recent years to reduce exposures. The lead author on the report, Endocrine Society member Andrea Gore, PhD, participated in a media event during UNEA6 to share some of the key points raised in the report. The report is intended to inform policymakers and civil society organizations in their work to raise awareness and develop policies to minimize exposures to hazardous chemicals.

UNEA is the world's most influential decision-making body on environmental issues, and we are thrilled to collaborate with the Women's Major Group and IPEN to share our members' scientific expertise with the assembled delegations.

Clinical Endocrinology Mentorship Opportunity at ENDO 2024



Endocrine Society past-president Carol Wysham, MD, was an active participant in Endocrinology Mentor Day at **ENDO 2023** in Chicago, here instructing a mentee on the proper placement of a continuous glucose monitor (CGM).

The Endocrine Society will host the second annual Endocrinology Mentor Day (eMD) at **ENDO 2024** in Boston, on Sunday, June 2.

During the event, medical students and residents will be paired with an Endocrine Society member as their “mentor” for the day. Mentors will guide attendees around **ENDO** and introduce them to **ENDO**’s signature programs, including poster presentations, interesting case studies, and a plenary session. The event at **ENDO 2023** in Chicago last year was a big success, due in large part to our terrific mentors.

If you are interested in joining us for this program as a mentor, or would like to learn more about the event, please email Ellie Cliff at: ecliff@endocrine.org.



Endocrine Society Advocates to Protect and Increase Funding for the NIH

On March 5, the Endocrine Society conducted a Researcher Hill Day to advocate for the importance of the National Institutes of Health (NIH).

We asked Congress to complete work on a funding bill for the remainder of fiscal year (FY) 2024, before funding expires March 8, that will maintain paylines and protect early-stage investigators and trainees, and for \$51.3 billion for the NIH in FY 2025. On Hill Day, we will also advocate for the extension of the Special Diabetes Program (SDP) for two years with a 13% increase in funding.

TAKE ACTION

Amplify our message by joining in our online campaigns for research funding and SDP by visiting: endocrine.org/advocacy/take-action. Even if you cannot join us in Washington, D.C., for Hill Day, you can make your voice heard by your congressional delegation. In just three clicks, you can send a letter template to your senators and representatives and support Endocrine Society priorities.

EU Proposes Science-Based Restrictions on Bisphenols

Following the European Food Safety Authority's (EFSA) updated opinion on bisphenol-A (BPA), which indicated a concern for human health at extremely low levels of exposure, the European Commission announced a proposal to ban BPA in food contact materials (FCM) including plastic packaging and coatings. The Commission's proposal also goes a step further by introducing restrictions on derivatives of BPA to prevent substitutions with other bisphenols with potentially similar hazardous properties.

The Endocrine Society welcomes the new proposal, which is based on a systematic review of the latest science on BPA, including results from the Consortium Linking Academic and

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We enthusiastically support the provisions to address BPA derivatives, which is consistent with our recommended approach for group-based restrictions on similar chemicals.

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Regulatory Insights on BPA Toxicity (CLARITY-BPA). The Society's EU EDCs Task Force has provided expert guidance to European agencies and the Commission on every step



of this process, from suggesting studies to inform EFSA's systematic review, to providing commentary on the draft opinion, and finally encouraging the Commission to prioritize this important regulation. We enthusiastically support the provisions to address BPA derivatives, which is consistent with our recommended approach for group-based restrictions on similar chemicals.

The proposal is open for a public consultation through early March, and our task force will carefully review the draft regulation and offer further suggestions to ensure that the final restrictions achieve the intended health protections and can be swiftly implemented.

How to Incorporate the New Medicare Complex Code G2211 into Your Practice

The Endocrine Society has long advocated the need for Medicare to pay endocrinologists appropriately.

Due to our advocacy efforts, the 2024 Physician Fee Schedule includes an increase for endocrinology partly because of the opportunity to use a new complex add-on code. On January 29, the Endocrine Society hosted a members-only webinar

explaining how clinicians can integrate the G2211 code into their practices. The recording of the webinar and additional resources can be found on our Physician Payment web page at: www.endocrine.org/improving-practice/macra. We also collected the questions asked during the webinar and created a “FAQ” document that can be found on the Physician Payment web page as well. ^{EN}



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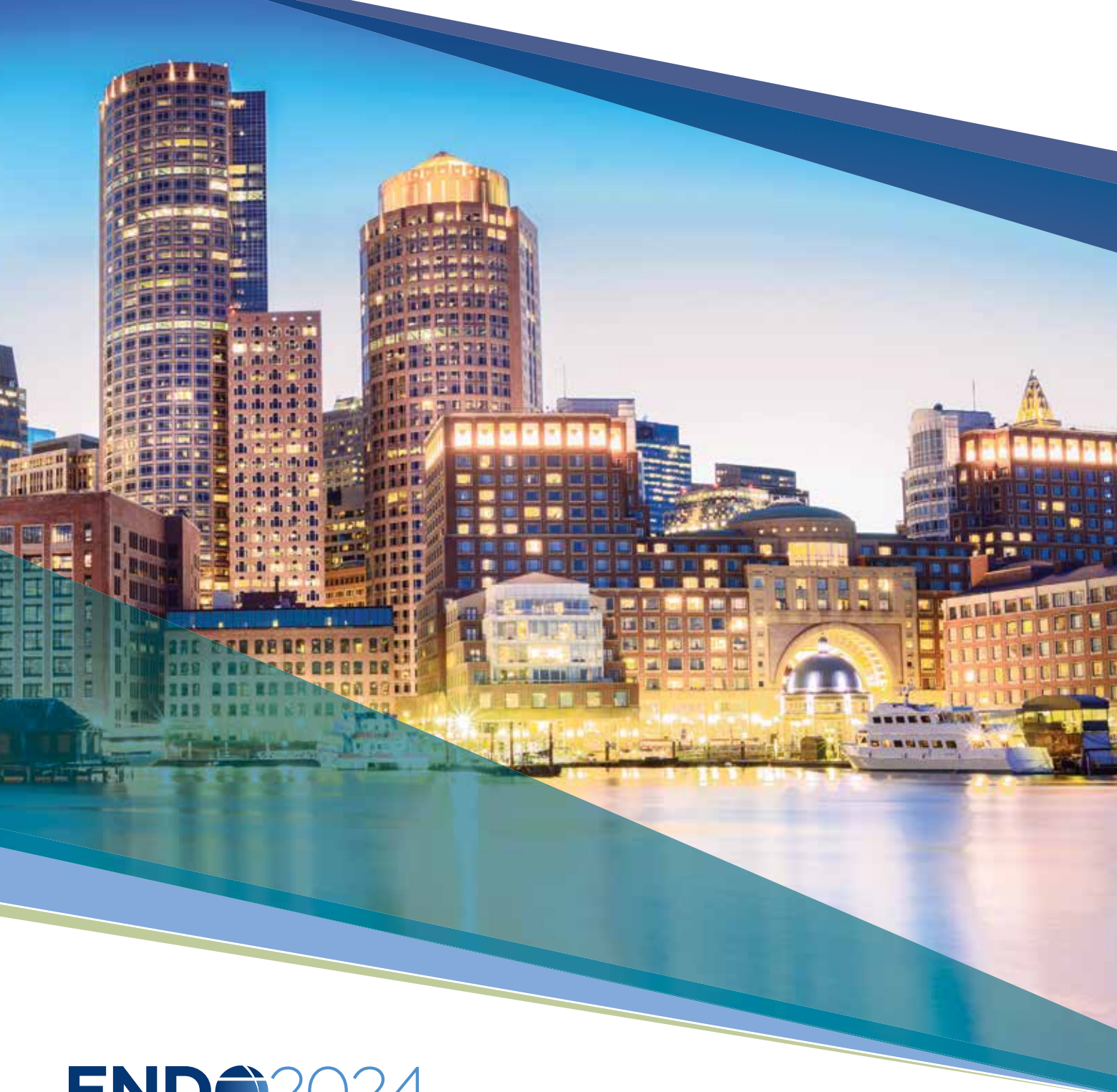
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