REMEMBERING JOEL HABENER, MD, A "PIONEER IN MOLECULAR ENDOCRINOLOGY"

FEBRUARY 2026

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

Endocrine news

WEIGHT OF THE WORLD

This special edition of *Endocrine News* examines recent research surrounding GLP-1s, their benefits, and the side effects, both positive and negative.

COMPARE AND CONTRAST: As glucagon-like peptide-1 receptor agonist access expands, comparative heart outcomes matter.

SIDE EFFECTS: Endocrine Society journals look at GLP-1RAs and the positive and negative unintended impacts.

BEYOND THE SCALE: Sure, they help with weight loss, but what else can glucagon-like peptide-1 receptor gonists do?

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ENDOCRINE SOCIETY
Hormone Science to Health

Society Boosts Support for Researchers to Attend **ENDO 2026** and Provides Career Development Opportunities

As an endocrine scientist and long-time Society member, I'm proud of the many programs our organization offers to both our basic and clinical researchers. The Endocrine Society, of course, represents professionals across the full range of our field, from bench to bedside. But I want to take this opportunity to highlight some of the work we do specifically for endocrine scientists.

Our initiatives in this area rest on three prongs: Presenting, Publishing, and Mentorship.

Presenting

For the first prong, Presenting, I was pleased to announce in January a one-year expansion of our **ENDO 2026** travel grant programs. This move provides significant additional financial support that will allow more researchers to attend our annual meeting, taking place June 13 – 16, 2026, in Chicago, Ill.

Approved unanimously by the board of directors, this initiative:

- Increases to $1,500 the grant amount for each recipient of the Early Investigator Awards, Outstanding Abstract Awards, and Early Career Forum.
- Provides up to 200 additional grants of $1,500 per award recipient for the Outstanding Abstract Awards ($1,750 per award for international recipients).

We hope this allows more scientists to submit their abstracts for presentation in our ENDOExpo. Always a highlight of **ENDO**, the hall features more than 2,500 abstracts on display during the poster sessions.

Members who submit their abstracts also may be selected to share highlights of their research via video interviews posted on the Society's social media channels. Last year, these research videos received thousands of views.

Publishing

Another key aspect of submitting an abstract to **ENDO** is the opportunity for the research to be published in a supplement of our open access journal, *Journal of the Endocrine Society* (JES). Each abstract is assigned a digital object identifier (DOI), a unique string assigned to online journal articles, ensuring the research is accessible and citable worldwide.

> "We recognize that in today's funding climate, many researchers face increased financial uncertainty, making the Society's support more important than ever. I'm proud of the many things we're doing to unite and grow the global endocrine research community."

This is just one way we help research members publish their work.

The Society's entire suite of top-ranked journals have been on the forefront of publishing major developments and discovery milestones in endocrine science since 1917.

Researchers are encouraged to submit their manuscripts to the Society's prestigious journals. Members receive special rates on production costs for accepted manuscripts.

Each submission receives consideration by thought leaders in the field, with rigorous attention to research integrity throughout the peer review and publication process. Our team of expert editors and editorial board members adhere to the strictest publishing standards.

Mentorship

The third prong on our research stool is Mentorship. As noted, we are committed to growing our field, both in terms of researchers and clinicians. The Society offers several crucial programs for early-career researchers.

One of them is the Research Experiences for Graduate and Medical Students (REGMS), which offers promising students a chance to engage in collaborative lab work, receive expert mentorship, build professional networks, and enhance their professional skills through year-round activities.

Our staff is currently reviewing applications. This year, REGMS participants will:

- Receive funding for a summer research project with an Endocrine Society mentor;
- Participate in virtual career-development training;
- Present their work at **ENDO 2027** with a travel grant; and
- Receive a $2,500 honorarium (in addition to the $1,500 travel grant).

Another wonderful opportunity for early endocrine researchers is our Future Leaders Advancing Research in Endocrinology (FLARE) program. FLARE participants, composed of graduate students, postdoctoral fellows, clinical fellows, and junior faculty, receive training in how to establish independent research careers and develop leadership skills.

We look forward to hosting this year's FLARE participants at a workshop March 26 – 28. It is so rewarding to see how the participants' confidence grows during the course of this event.

Bonus: Knowledge Development

On top of these three specific research prongs, we continue to offer an array of outstanding educational programs for researchers. At **ENDO**, these include:

- Basic Science Pathways offering curated content tracks in Diabetes and Metabolism, Neuroendocrinology, Nuclear Receptors and Signaling, and Reproductive Endocrinology.
- Meet-the-Professor and Meet-the-Scientist sessions providing insights from experts on treating a variety of endocrine conditions as well as the latest in scientific research.

In addition, the next focused Basic Science Summit on Nuclear Receptors will be held this fall in Chicago, Ill. Stay tuned for further announcements and a call for abstracts.

We recognize that in today's funding climate, many researchers face increased financial uncertainty, making the Society's support more important than ever. I'm proud of the many things we're doing to unite and grow the global endocrine research community.

We are committed to our members, the field of endocrinology, scientific discovery, and hormone health while we invest in improving the endocrine research pipeline for a healthier tomorrow.

Carol A. Lange, PhD
President, Endocrine Society

Miracle Drugs or Too Good to Be True?

Obviously, from that headline I'm referring to GLP-1s and their many similar glucagon-like peptide-1 receptor agonist cohorts that have become a medical, healthcare, and even cultural zeitgeist over the course of the past couple of years. In fact, I bet every single person reading these words can sing the Ozempic jingle right now!

This month's issue features a wealth of information on the studies that are spilling out of every peer-reviewed journal you can think of. Truly, an embarrassment of riches, and yet we barely scratched the surface with what we discuss on the following pages as more and more studies are released every day. So, while no means an exhaustive list — and if you check this month's Endocrine Society journals, you'll see even more recently released research! — but it's what we had to work with at the time of planning this issue.

On page 12, Kelly Horvath looks at the cardiac outcomes in patients taking these obesity conquering drugs in **"Compare and Contrast."** Specifically, she talks to the researchers about their recent studies to get more insights into how this new class of pharmaceuticals could affect the user's cardiac health. "It is important to understand whether the cardiovascular benefits of GLP-1RAs are limited to those who also experience glycemic and/or weight benefits, or we see benefits in hard outcomes more broadly," according to Rozalina G. McCoy, MD, MS, from the University of Maryland School of Public Health THRIVE (Transforming Health through Real-world Insights, Values, and Evidence) Lab, in Baltimore, Md., and Stacey M. Sklepinski, MD, from the Advocate Lutheran General Hospital, Park Ridge, Ill. "Current indirect evidence from the cardiovascular outcomes trials suggests that cardiovascular benefits are at least partly independent of glucose-lowering, but the same analysis was not done for weight loss."

In **"Beyond the Scale: What Else Glucagon-like Peptide-1 Receptor Agonists Can Do,"** on page 22, Kelly takes a look at a variety of journal studies that examine the impact of incretin-based therapies on cardiovascular health, as well as how they affect the liver, quality of life, insulin resistance, and much more. According to Ambarish Pandey, MD, MSCS, from the University of Texas Southwestern Medical Center in Dallas, clinicians shouldn't hesitate to administer semaglutide because a patient with obesity-related heart failure with preserved ejection fraction (HFpEF) looks too frail. "They're the ones who stand to benefit most," he explains. "In our analysis, the frailest patients saw the largest symptom gains, were far more likely to improve their frailty status, and experienced

FEBRUARY 2026

Endocrine news

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

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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- Product print and product online display advertising, by Pharmaceutical Media, Inc., contact Joe Schuldner, *jschuldner@pminy.com*, or John Alberto, *jalberto@pminy.com.*
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fewer serious adverse events on semaglutide than on placebo. If you've been hesitant because a patient seems fragile, reconsider. That's exactly who should be getting this therapy."

Endocrine News Senior Editor Derek Bagley takes a look at some recent studies published in Endocrine Society journals in **"Side Effects,"** on page 18, that examine both the positive and negative unintended impacts of GLP-1RAs. On the positive side, GLP-1RAs have apparently been shown to reduce consumption of alcohol and drugs as well as curtailing addictions to sex and gambling. However, there are cases of fatal, albeit rare, complications that endocrinologists need to be aware of. "Although GLP-1 receptor agonists show impressive efficacy and favorable side-effect profiles, it is necessary that we determine all risks and side effects, particularly rare ones, to minimize chances of poor outcomes," says Endocrine Society member Eli J. Louwagie, MD, PhD, of the Department of Internal Medicine at LewisGale Hospital Montgomery in Blacksburg, Va., and one of the authors of a study discussed. "This is especially important considering the increasing use of these medications."

Derek has also written a tribute to the life and career of **Joel Habener, MD**, on page 30. Habener died in December at the age of 88, but he left behind a legacy that has certainly led to where we are today in terms of these GLP-1s and many other obesity-fighting drugs. According to Daniel J. Drucker, MD, senior investigator, Lunenfeld-Tanenbaum Research Institute, Sinai Health; professor, Department of Medicine, University of Toronto's Temerty Faculty of Medicine, Ontario, Canada, and a former member of Habener's lab, Habener will be "remembered as a visionary scientist whose discoveries transformed the field of metabolic medicine and as a highly sought after mentor who trained generations of independent investigators."

Until next month, if you have any story ideas that you think Endocrine Society members would be interested in, feel free to drop me a line at: **mnewman@endocrine.org.**

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

Novo Nordisk's OASIS 4 Study Validates Daily Oral Pill for Chronic Weight Management

> "Oral pills do not require refrigeration, a factor that could widen the reach of obesity care in many regions of the world where lack of refrigeration is a barrier to access."

A new year brings a new therapeutic milestone for weight management: Following its recent U.S. Food and Drug Administration approval, the 25 mg oral semaglutide tablet (brand name: Wegovy), a once-daily pill became available in the United States in early January 2026 for chronic weight management and for reducing the risk of major adverse cardiovascular events in adults living with obesity or overweight and established cardiovascular disease.

According to results from the OASIS (Oral Semaglutide Treatment Effect in People with Obesity) 4 clinical trial recently published in the *New England Journal of Medicine*, a daily 25 mg dose leads to significant weight reduction and improved physical function. The study positions this mid-dose oral option as a potent alternative for patients who prefer the convenience of a pill over standard weekly injections or higher-dose oral formulations.

"The reasons patients may prefer oral administration over the subcutaneous route are most often needle aversion and local skin reactions," the authors write. They further noted that oral pills do not require refrigeration, a factor that could "widen the reach of obesity care in many regions of the world where lack of refrigeration is a barrier to access."

The 71-week, double-blind, randomized trial enrolled 307 participants without diabetes across four countries. Eligible participants had a body mass index (BMI) of 30 or higher, or a BMI of 27 with at least one obesity-related complication, such as hypertension, dyslipidemia, or obstructive sleep apnea. Results revealed that participants taking 25 mg of oral semaglutide achieved an estimated mean weight loss of 13.6% from baseline, compared to just 2.2% in the placebo group. This offers a strategic "middle-ground" therapeutic window for patients who may not require the maximum 50 mg dose but seek more robust results than those offered by lower-dose oral options.

Beyond primary weight loss, the study measured several confirmatory secondary endpoints, including waist circumference reduction and improvements in systolic blood pressure. Participants in the semaglutide group were significantly more likely to reach major milestones than those on placebo, achieving weight reductions of 10%, 15%, and even 20% or more. Furthermore, patients reported a marked improvement in their physical function scores via the IWQOL-Lite-CT assessment. These scores indicate that the weight loss translated into tangible improvements in mobility and quality of daily life.

"The weight loss and improvements in metabolic markers seen with oral semaglutide is significant and will positively impact the field of obesity medicine and metabolic conditions," says Sean Wharton, primary author and head of the Wharton Weight Management Clinic in Burlington, Canada.

As a GLP-1 receptor agonist, oral semaglutide works by mimicking a natural hormone that regulates appetite and caloric intake. While highly effective, the 25-mg dose was associated with a higher frequency of side effects than the placebo. Gastrointestinal adverse events — primarily nausea and diarrhea — were reported by 74.0% of the semaglutide group, compared to 42.2% of the placebo group. These findings remain consistent with the established safety profile of the GLP-1 class. — *Jackie Oberst*

Lilly's Oral GLP-1 Orforglipron Demonstrates Superiority in Phase 3 Diabetes Trials

Eli Lilly's "Ozempic-in-a-pill" candidate just cleared its most significant clinical hurdle to date. The pharmaceutical giant announced that its experimental once-daily pill, orforglipron, met all primary and secondary endpoints in two pivotal Phase 3 trials: ACHIEVE-2 and ACHIEVE-5. Data indicate that this oral treatment provides superior glycemic control compared to both a standard SGLT-2 inhibitor and a placebo. If approved, this small-molecule agonist could fundamentally disrupt the diabetes landscape by offering the high-potency results of injectables in a convenient daily tablet.

The findings, released in October 2025, show that orforglipron achieved significant reductions in A1C levels — the standard measure of average blood sugar — and body weight over a 40-week period. Unlike current oral GLP-1 options, orforglipron is a non-peptide, small-molecule drug. This chemical structure is clinically significant; while "peptide" drugs are proteins usually digested by stomach enzymes, this non-peptide version is sturdy enough to be absorbed as a pill without restrictive food or water requirements.

Orforglipron belongs to the GLP-1 (glucagon-like peptide-1) receptor agonist class, mimicking a gut hormone that triggers insulin release and slows digestion. In contrast, SGLT-2 inhibitors work through the kidneys by flushing excess sugar out through urine. Lilly's latest data suggest that orforglipron's hormonal pathway offers more robust glycemic lowering than this renal-focused approach.

The ACHIEVE program evaluates orforglipron across five global registration trials. While earlier studies outperformed oral semaglutide, the results from ACHIEVE-2 and ACHIEVE-5 provide the definitive evidence of superiority over existing standards of care.

In the ACHIEVE-2 trial, which compared orforglipron directly to the SGLT-2 inhibitor dapagliflozin, patients inadequately controlled on metformin who received a 36 mg dose of orforglipron saw an A1C reduction of 1.7%. This more than doubled the 0.8% reduction observed in the SGLT-2 group. "Orforglipron has now demonstrated superiority over two active comparators," states Jeff Emmick, senior vice president of product development at Lilly Cardiometabolic Health, reinforcing its potential as a new standard of care.

The ACHIEVE-5 trial evaluated a more complex population: adults using titrated insulin glargine. In this trial, the glargine dose was constantly adjusted to find the exact amount needed to keep fasting blood sugar stable. The study was significant because it showed that adding orforglipron to insulin glargine helped patients lower their A1C by an additional 2.1%, compared to 0.8% in the placebo group. This is important because many patients find that insulin alone is not enough to reach their health goals, or it causes unwanted weight gain. Adding orforglipron helped manage blood sugar more aggressively while also promoting weight loss.

Beyond glycemic control, orforglipron delivered improvements in cardiovascular risk factors. The safety profile remained consistent with the broader GLP-1 class; mild-to-moderate gastrointestinal events were the most common side effects, with no liver safety concerns observed. Lilly plans to submit orforglipron for regulatory approval in 2026. If authorized, it would remove the logistical barriers of injections and strict fasting, offering a flexible, "no-restriction" oral option for the global diabetes community. — *Jackie Oberst*

"Beyond glycemic control, orforglipron delivered improvements in cardiovascular risk factors. The safety profile remained consistent with the broader GLP-1 class; mild-to-moderate gastrointestinal events were the most common side effects, with no liver safety concerns observed."

New Research Challenges Fears of Semaglutide-Linked Thyroid Cancer Risk

The "black box" warning on the popular diabetes and weight loss drug semaglutide may be shifting from a cautionary black to a reassuring gray. A landmark study published in *The Journal of Clinical Endocrinology & Metabolism* reveals that semaglutide does not promote thyroid cancer; instead, it may suppress tumor growth by "reprogramming" the immune system to fight it.

Thyroid cancer is the most common endocrine malignancy, consisting primarily of papillary thyroid carcinoma (PTC) — which accounts for the vast majority of cases — and medullary thyroid cancer (MTC), a rarer form making up about 3% of diagnoses. Early rodent studies showed increased MTC incidence, leading the U.S. Food and Drug Administration to mandate a black box warning for patients with a family history of the disease. However, human data remained mixed, leaving a gap between preclinical fears and clinical reality.

This latest study provides the mechanistic evidence needed to alleviate these concerns. Using mouse models implanted with PTC tumors and cell cultures, researchers found that semaglutide significantly reduced tumor size. Crucially, the drug did not directly affect cancer cell proliferation. Instead, it targeted the tumor microenvironment (TME) — specifically, immune cells known as tumor-associated macrophages (TAMs).

TAMs often make up more than 50% of a tumor's mass. In a typical cancer setting, they act as a "double-edged sword" favoring the tumor by adopting a "supporter" (M2) phenotype. The research team discovered by their experiments that semaglutide forces these cells to undergo a "polarization shift," increasing "attacker" (M1) macrophages that actively inhibit tumor growth.

This immune reprogramming occurs through the GLP-1R/PPARG/ACSL1 signaling pathway. Semaglutide downregulates PPARG, modifying lipid metabolism within macrophages. By modulating downstream genes such as ACSL1 and RSAD2, the drug prevents the lipid accumulation required for M2 macrophage survival. This effectively "flips the switch" to an M1 state, enhancing anti-cancer activity.

The study concludes that this metabolic modulation represents a promising frontier for semaglutide. Beyond its established roles in blood sugar and weight management, semaglutide could eventually be explored as an adjunctive therapy in oncology.

"These findings suggest that semaglutide may improve therapeutic strategies, reduce unnecessary screenings, and broaden its clinical applications," the authors write in **"Semaglutide Reprograms Macrophages via the GLP-1R/PPARG/ACSL1 Pathway to Suppress Papillary Thyroid Carcinoma Growth."** If validated in human trials, this research could fundamentally change care for millions of patients, moving semaglutide from a perceived risk to a potential protective asset in thyroid health.

The authors acknowledge shortcomings. For instance, immunocompromised mice used in the PTC xenograft model may not fully reflect human patients. Secondly, macrophages obtained were stimulated in vitro with growth factors and cytokines, which might not reflect how TAMs switch in vivo. Lastly, due to its rarity, MTC cells were not used, so findings may not apply beyond PTC.

Ultimately, the research indicates that semaglutide could revolutionize the way clinicians think about GLP-1 receptor agonists in oncology. While further research is required to translate these preclinical findings into clinical practice, the identification of the GLP-1R/PPARG/ACSL1 pathway provides a clear roadmap for future investigations into the intersection of metabolic drugs and cancer immunotherapy in the future. — *Jackie Oberst*

"Ultimately, the research indicates that semaglutide could revolutionize the way clinicians think about GLP-1 receptor agonists in oncology. While further research is required to translate these preclinical findings into clinical practice, the identification of the GLP-1R/PPARG/ACSL1 pathway provides a clear roadmap for future investigations into the intersection of metabolic drugs and cancer immunotherapy in the future."

> “Although GLP-1 receptor agonists show impressive efficacy and favorable side-effect profiles, it is necessary that we determine all risks and side effects, particularly rare ones, to minimize chances of poor outcomes. **This is especially important considering the increasing use of these medications.”**

Eli J. Louwagie, MD, PhD, Department of Internal Medicine, LewisGale Hospital Montgomery, Blacksburg, Va., on the potential benefits of using GLP-1RAs to treat alcohol or drug abuse in **“Side Effects”** on page 18

People with a high BMI are more than 50% more likely to go on to be diagnosed with thyroid cancer during their lifetime compared to individuals with a healthy BMI. **SOURCE:** BBC

The percentage of children worldwide who do not receive enough iodine, putting them at increased risk for thyroid dysfunction, goiter, and preventable cognitive impairment. **SOURCE:** *THYROID*

Glucose levels below 70 mg typically harm the retina and kidney more than elevated glucose and may lead to blindness. **SOURCE:** THE RETINA SOCIETY

Of the millions eligible, only about 9,000 people have enrolled in Medicare’s Diabetes Prevention Program. **SOURCE:** *CENTER FOR MEDICARE AND MEDICAID SERVICES EVALUATION OF THE MEDICARE DIABETES PREVENTION PROGRAM FINAL EVALUATION REPORT*

The increased percentage in risk for developing diabetes during pregnancy in women who stopped taking GLP-1 before or during pregnancy as compared to those who never used the medication. **SOURCE:** *JAMA*

Obesity-linked cancer deaths in the U.S. have tripled over the past 20 years. **SOURCE:** *JOURNAL OF THE ENDOCRINE SOCIETY*

ENDO 2026

Chicago, Ill. • June 13 – 16, 2026

We hope to see you at **ENDO 2026**, taking place June 13 – 16, 2026, in Chicago, Ill. 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-2026-save-the-date

BPS2026

San Francisco, California
February 21 – 22, 2026

BPS2026 will showcase the exciting advances in science and technology brought forth by big data and AI. This year's program offers a strikingly diverse and forward-looking slate of symposia that captures the dynamic, multiscale nature of our field. From the controlled chaos of intrinsically disordered proteins to the emergent properties of life's assemblies, our sessions illuminate the physical organizing principles underlying biology. Symposia revisit new perspectives in classics such as membrane transport and calcium signaling, while also spotlighting new frontiers such as the biophysics of immunity, cancer, and protein design.

https://www.biophysics.org/2026meeting#/

ACLA Annual Meeting 2026

Washington, D.C.
February 25, 2026

The 2026 American Clinical Laboratory Association Annual Meeting will bring together the nation's leading clinical laboratories with influential healthcare policy leaders, including invited administration officials for a day of insights and timely inside-the-beltway analysis relevant to the field. Sessions will delve into the latest political dynamics in the mid-term election year and explore reimbursement and regulatory policy priorities critical to ACLA members' mission of expanding patient access to the next generation of innovation diagnostic services, and more.

www.acla.com

NASIT 2026

Portland, Oregon
March 6 – 7, 2026

The North American Society for Interventional Thyroidology (NASIT) is the largest, multidisciplinary group in the United States dedicated to the field of interventional thyroidology.

The society was created to promote safe integration of ablative thyroid technologies into clinical practice and a collaborative environment that supports education and research efforts in interventional thyroidology. NASIT holds an annual meeting that includes one and a half days of expert panel sessions, scientific presentations, and the most up-to-date information on innovative technologies in the field.
https://www.nasit.org/Annual-Meeting

AAES 2026

Lexington, Kentucky
April 18 – 20, 2026

The American Association of Endocrine Surgeons 46th Annual Meeting centers around the theme "Strengthening Connections" — reflecting our commitment to deepening professional relationships, fostering interdisciplinary collaboration, and building a stronger, more inclusive endocrine surgery community. The highly rated breakout sessions return with immersive, expert-led content, designed to spark dialogue and collaboration among attendees. The AAES Annual Meeting is dedicated to advancing the science and art of endocrine surgery through knowledge exchange, collaboration, and community, and promises innovative programming, networking opportunities, and scholarly enrichment — all designed to strengthen the connections that make the field thrive.
https://www.endocrinesurgery.org/2026-annual-meeting-home

2026 Lab Manager Leadership Summit

Phoenix, Arizona
April 20 – 22, 2026

The 2026 Lab Manager Leadership Summit is an exclusive event for laboratory leaders and decision makers across clinical, forensic, environmental, food and beverage, pharmaceutical, and life science fields. The Summit offers interactive sessions, hands-on workshops, and insightful presentations designed to elevate your leadership skills. Discover the latest advancements from technology and service providers showcasing innovative lab solutions, connect with industry peers, gain actionable insights, and bring transformative ideas back to your organization. Don't miss this chance to drive your lab forward with confidence and vision!
https://summit.labmanager.com/leadership/home

INTERNATIONAL **ITINERARY**

World Endocrine, Diabetes & Cardiovascular Conference (EDCC26)

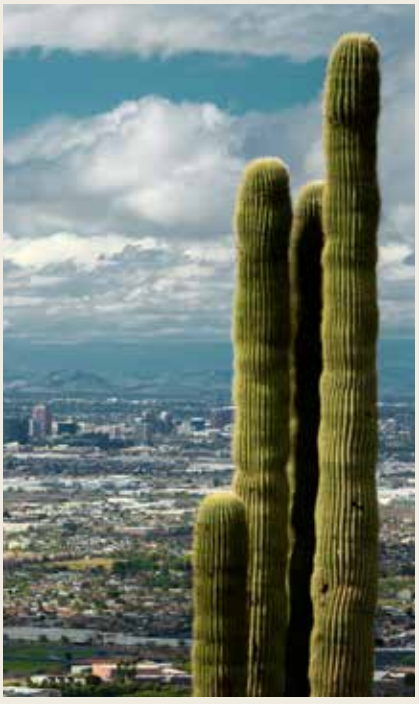
Bangkok, Thailand
March 6 – 7, 2026

The World Endocrine, Diabetes & Cardiovascular Conference 2026 (EDCC26) will be organized around the theme of "Interdisciplinary Approaches to Endocrine Health." The program includes local and international speakers with inspiring insights to share on advancing endocrinology, diabetes, cardiovascular health, and metabolism quality improvement through patient and family experiences. EDCC26 will feature leading experts, researchers, and healthcare professionals from around the globe and will serve as a platform for the exchange of knowledge, ideas, and insights in the fields of endocrinology, diabetes, obesity, and more.
https://endocrine.episirus.org/bangkok/

ATTD 2026

Barcelona, Spain
March 11 – 14, 2026

The landscape of diabetes care is evolving fast, and the 19th International Conference on Advanced Technologies & Treatments for Diabetes (ATTD) 2026 is where technology, innovation, and research converge to shape the next era of treatment. From AI-driven solutions to the latest in digital health, smart devices, and groundbreaking therapies, this is the conference that defines what's next in diabetes management. Connect with global experts, industry leaders, and visionaries pushing the boundaries of what's possible.
https://attd.kenes.com/



PES 2026

San Francisco, California
April 30 – May 3, 2026

The Pediatric Endocrine Society's (PES's) Annual Meeting brings together a diverse international community of more than 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 this diverse field.
https://pedsendo.org/

BY KELLY HORVATH

Compare and CONTRAST

As glucagon-like peptide-1 receptor agonist access expands, comparative heart outcomes matter.

As the onslaught of anti-obesity drugs hit the market in recent years, more research is being released about their potential side effects as well as their benefits. *Endocrine News* investigates two of these studies to gain more insight to how these "miracle drugs" could affect cardiac health.

Rozalina G. McCoy, MD, MS, University of Maryland School of Public Health THRIVE (Transforming Health through Real-world Insights, Values, and Evidence) Lab, Baltimore, Md. (pictured) and **Stacey M. Sklepinski, MD,** Family Medicine Resident Physician (PGY1), Advocate Lutheran General Hospital, Park Ridge, Ill.

Two studies published in late 2025 examined cardiovascular outcomes among patients with type 2 diabetes treated with various glucagon-like peptide-1 receptor agonists (GLP-1RAs), providing real data suggesting that, although they clearly have multiple therapeutic benefits, not all agents within this drug class are created equal.

With recent federal policy changes aiming to make the GLP-1RAs and related drugs more affordable to potentially reach millions more patients who could see significant health improvements with treatment, this is a good time to scrutinize their safety and efficacy profiles. Collectively, these studies advance our understanding of within-class differences among GLP-1RAs, which may allow more individualized therapy, depending on patient-specific factors.

Tirzepatide Versus Dulaglutide

In **"Cardiovascular Outcomes with Tirzepatide versus Dulaglutide in Type 2 Diabetes,"** from *NEJM* in December, Stephen J. Nicholls, MB, BS, PhD, of Monash University in Clayton, Australia, and team compared tirzepatide and dulaglutide head-to-head. They conducted the Study of Tirzepatide Compared with Dulaglutide on Major Cardiovascular Events in Participants with Type 2 Diabetes (SURPASS-CVOT) to settle a couple of questions, explains Nicholls: "Given that there is a lot of interest in developing new incretin therapies, can we achieve better outcomes (metabolic or clinical) with combination therapy, and can we develop agents that are better tolerated? For all of these agents, there will ultimately be interest in knowing their effect on cardiovascular events."

For their active comparator–controlled, double-blind, noninferiority trial that began in 2020, 6,586 patients with type 2 diabetes were randomized to a tirzepatide (dual glucose-dependent insulinotropic polypeptide [GIP]/GLP-1RA) treatment group and 6,579 to a dulaglutide (selective GLP-1RA) group and followed for four years. The primary end point was time to first major cardiovascular adverse event (MACE), a composite of death from cardiovascular causes,

"It will also be important to examine use of GLP-1RAs and SGLT2is together. Both classes are highly effective in reducing cardiovascular events in patients with type 2 diabetes across the spectrum of CVD risk (notably, our prior work comparing across medication classes suggests that SGLT2is may be even more favorable than GLP-1RAs for some outcomes, and are comparable on others), ***and we assume that taking both together is likely to be even more beneficial. But we do not have direct evidence to back this up."***

According to Stephen J. Nicholls, MB, BS, PhD, of Monash University in Clayton, Australia, the benefits on mortality and major cardiovascular events highlight tirzepatide's potential utility and gives patients more treatment options.

myocardial infarction (MI), or stroke. Secondary outcomes included cardiovascular and all-cause death; additional composite cardiovascular outcomes (including coronary revascularization and heart-failure events), kidney function change over 36 months; and changes in A1c, weight, blood pressure (36 months), and triglycerides/low-density lipoprotein cholesterol (24 months). Tirzepatide proved as safe and effective as dulaglutide for MACEs (death, MI, or stroke) in high-risk patients with type 2 diabetes (noninferior, not clearly superior), with more gastrointestinal (GI) side effects, but better A1c and weight loss. However, the broader composite including revascularization was lower with tirzepatide, as was all-cause mortality.

Nicholls says they were not surprised that tirzepatide demonstrated noninferiority, but he underscores the significance of the latter findings. "While we expected that tirzepatide would have better metabolic benefits (weight loss, glycemic control)," he says, "we didn't know if it would have better effects on clinical outcomes. The benefits on extended MACE including coronary revascularization and all-cause mortality are important. They highlight that people with CVD and type 2 diabetes are at risk of a range of complications. Tirzepatide fared well from that perspective." Digging a little deeper into why and how tirzepatide prevented more deaths, Nicholls says, "the death benefit is really interesting and appears to involve a reduction in non-cardiovascular death. The degree to which that is less death in the setting of infection has been reported previously. We need to do more investigation."

A big question remains: What is it about the incretin agonists' mechanism of action that makes them effective against CVD/MACEs? "I think we're still trying to work that out from all of the studies," says Nicholls. "It is likely to be a combination of factors. It's not all about the weight loss or the improved glycemic control. The combined metabolic benefits are likely to be important, direct effects on blood vessels and the heart may be important, and there may be additional factors that remain unknown. It highlights that there is more research needed — we need to understand this data to a greater degree." For example, he cites an ongoing placebo-controlled trial of tirzepatide in high-risk patients with CVD but without type 2 diabetes. "That will be an important study to follow," he says. He adds that researchers should continue to strive for diversity in the makeup of study participants, "so our findings more reflect the diversity of patients we see in the clinic."

The bottom line here is that tirzepatide has proven its worth. Regarding the increased incidence of GI side effects, Nicholls points out that overall tirzepatide was similar to dulaglutide in terms of adverse events and drug discontinuation and thus tolerability. "Tirzepatide has good metabolic benefits and is at least comparable to dulaglutide regarding cardiovascular events," he says. "The benefits on mortality and extended MACE further highlight its potential utility. This is good for patients as it suggests we have more choice of therapies."

Dulaglutide, Exenatide, Liraglutide, and Semaglutide

From the September issue of *Diabetes Research and Clinical Practice*, **"Comparative effectiveness of GLP-1 receptor agonists on cardiovascular outcomes among adults with type 2 diabetes and moderate cardiovascular risk: emulation of a target trial"** compared the cardiovascular outcomes of four GLP-1RAs among adults with type 2 diabetes at moderate cardiovascular risk. Stacey M. Sklepinski, MD, family medicine resident physician (PGY1) at Advocate Lutheran General Hospital in Park Ridge, Ill., and Rozalina G. McCoy, MD, MS, of the University of Maryland School of Public Health THRIVE (Transforming Health through Real-world Insights, Values,

and Evidence) Lab in Baltimore, Md., and team sought to address a research gap: comparing cardiovascular outcomes following initiation of GLP-1RAs among people with type 2 diabetes at moderate cardiovascular risk (recalling Nicholls' stated research need), which they defined as individuals whose predicted risk of experiencing a MACE-like MI or stroke, or dying from any cause, was 1% to 5% in the coming year. "More fundamentally," say Sklepinski and McCoy, "there has been no head-to-head evidence comparing different GLP-1RAs for cardiovascular outcomes. Clinicians and patients often select agents based on insurance formulary preferences rather than comparative efficacy or effectiveness data. Payors make formulary decisions based, in large part, on manufacturer rebates and contract negotiations, particularly when comparative efficacy/effectiveness information is limited. With dramatic increases in GLP-1RA prescribing, potential shortages of semaglutide, in particular, and the recent availability of generic options for liraglutide, evidence-based guidance on preferential agents within this drug class became even more important."

They chose to emulate a target trial as their study design because such a framework provides the closest approximation to randomized-controlled trial (RCT)-level evidence when head-to-head trials are unlikely to be conducted due to time, cost, and feasibility constraints.

Their study included adults with type 2 diabetes and moderate CVD risk who initiated dulaglutide (35,572), exenatide (4,376), liraglutide (8,843), or semaglutide (33,063) between 2019 and 2021. Semaglutide and liraglutide fared best: Semaglutide was associated with lower risk of MACE, expanded MACE, all-cause mortality, acute stroke, and arterial revascularization compared to dulaglutide. Liraglutide was also associated with a lower risk of MACE and all-cause mortality compared to dulaglutide.

Possible mechanisms include differences in receptor-binding and pharmacokinetic properties, say Sklepinski and McCoy. "While all GLP-1RAs activate the same receptor, they differ in their structures (e.g., semaglutide has 94% homology to native GLP-1 with specific amino acid substitutions and fatty acid side chain allowing albumin binding) and half-life (~1 week for semaglutide, five days for dulaglutide, and 13 hours for liraglutide). Longer engagement with the receptor may translate to more sustained signaling effects. Beyond glycemic control and weight loss, GLP-1RAs exert direct cardiovascular effects, including endothelial function improvement, reduction in inflammatory markers and inflammatory cytokines, anti-atherosclerotic effects, blood pressure reduction, and potential direct myocardial effects. The magnitude of these effects may vary by agent based on receptor pharmacology and tissue penetration."

> *"Given that there is a lot of interest in developing new incretin therapies, can we achieve better outcomes (metabolic or clinical) with combination therapy,* ***and can we develop agents that are better tolerated? For all of these agents, there will ultimately be interest in knowing their effect on cardiovascular events."***
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> — STEPHEN J. NICHOLLS, MB, BS, PHD, MONASH UNIVERSITY, CLAYTON, AUSTRALIA

Of note, exenatide showed noninferiority to each of the other three agents, a finding that surprised the team, as it had not demonstrated cardiovascular benefits in the EXSCEL trial. Sklepinski and McCoy explain that treatment contamination in the EXSCEL trial could be diluting exenatide's effects, specifically, higher rates of open-label use of other GLP-1RAs and sodium-glucose cotransporter 2 inhibitors (SGLT2is) in the placebo arm. However, post-hoc analyses revealed statistically significant benefits similar to liraglutide and approaching those of dulaglutide. "This highlights the value of real-world evidence when trial execution issues may obscure true drug effects and suggests that analysis of RCT effects may benefit from incorporating some of the same causal methods as observational studies. Indeed, RCTs are only randomized on treatment assignment (i.e., what medication the participant is assigned to take) not treatment exposure (i.e., what medication the patient actually takes and is exposed to), and when RCTs exhibit significant post-randomization variation, we need to account for those or at least consider them when interpreting study results," they say.

Another surprising result — that there were no significant differences between semaglutide and liraglutide for any outcome despite prior studies demonstrating semaglutide's superiority — led the researchers to make other important observations about study design. "The finding suggests that liraglutide's cardiovascular benefits may be underappreciated, study populations and contexts matter (in higher-risk patients, differences in efficacy may be more pronounced), and/or that real-world effectiveness may differ from efficacy in selected trial populations," they say.

They likewise found no difference between the GLP-1RA drugs in heart failure (HF) hospitalization risk, despite semaglutide's benefits in the STEP-HFpEF trial for HF symptoms in patients with HFpEF, obesity, and type 2 diabetes (see the Targeting Frailty section of **"Beyond the Scale: What Else Glucagon-like Peptide-1 Receptor Agonists Can Do,"** on page 22 in this issue). "The current study found no differences in these risks between any GLP-1RAs, suggesting that HF benefits may be restricted to patients with significant obesity (as in STEP-HFpEF), HF benefits may emerge primarily in those with existing HF rather than for primary prevention, and/or that the mechanism of semaglutide's benefit may involve weight loss rather than direct cardiac effects," say Sklepinski and McCoy. They conclude that a future study should focus specifically on potential heterogeneous treatment effects as a function of obesity and HF risk.

Speaking of future studies, the team has identified several avenues to explore, including further research on how to best care for people with type 2 diabetes, with obesity, and cardiovascular-kidney-metabolic (CKM) syndrome risk factors more broadly. "First and foremost, it will be important to examine the potential mediating effects of weight loss and glucose-lowering on the effectiveness of different GLP-1RAs to understand both why we are seeing the observed benefits and why differences between drugs exist," they say. "This will also help us better tailor treatment, particularly in patients who may not respond to GLP-1RA therapy with respect to weight loss or glucose-lowering as expected. It is important to understand whether the cardiovascular benefits of GLP-1RAs are limited to those who also experience glycemic and/or weight benefits, or we see benefits in hard outcomes more broadly. Current indirect evidence from the cardiovascular outcomes trials suggests that cardiovascular benefits are at least partly independent of glucose-lowering, but the same analysis was not done for weight loss."

They also want to examine oral semaglutide separately from the subcutaneous formulation, particularly now that an oral version has been approved for weight loss, and to consider dose effects. Tirzepatide was not clinically available for the current study, so they would include it in future comparisons. Future work should also focus on other outcomes important to patients like MASLD/MASH, arthritis, sleep apnea, and others.

"It will also be important to examine use of GLP-1RAs and SGLT2is together," state Sklepinski and McCoy. "Both classes are highly effective in reducing cardiovascular events in patients with type 2 diabetes across the spectrum of CVD risk (notably, our prior work comparing across mediation classes suggests that SGLT2is may be even more favorable than GLP-1RAs for some outcomes and are comparable on others), and we assume that

taking both together is likely to be even more beneficial. But we do not have direct evidence to back this up."

They also want to highlight the importance of implementation research, asking, "how do we improve prescribing, access, affordability, and tolerability? We continue to see many patients who would benefit from these drugs not receive them, and there are many reasons for this: Clinicians do not consistently prescribe them due to lack of awareness or training, high administrative burden, bias, or other reasons; patients cannot fill them due to cost, insurance coverage, or shortages; or patients stop them, again, due to cost, insurance coverage, shortages, or side effects (see the Discontinuation section of **"Beyond the Scale"** in this issue, page 27). Thus, administrative hurdles, worsening insurance coverage, and high costs are major barriers needing to be addressed. "Indeed," say Sklepinski and McCoy, "most patients with type 2 diabetes would benefit from a GLP-1RA (or SGLT2i) for cardiovascular risk reduction, and we should continue to work on multilevel strategies to reduce barriers to prescribing, access, and use." EN

– HORVATH IS A FREELANCE WRITER BASED IN BALTIMORE, MD. IN THE JANUARY ISSUE, SHE WROTE ABOUT A NUMBER OF NEW DIRECTIONS FOR TREATING PATIENTS WITH THYROID CANCER.

AT A GLANCE

- **Among patients with type 2 diabetes and atherosclerotic CVD, the dual agonist tirzepatide was noninferior to dulaglutide with respect to a composite of death from cardiovascular causes, MI, or stroke, and a prespecified secondary analysis suggested a possible lower incidence of death from any cause and of death from non-cardiovascular causes with tirzepatide.**
- **Among GLP-1RAs, semaglutide and liraglutide should be prioritized, if possible, for cardiovascular risk reduction for patients with type 2 diabetes and moderate (not just high) cardiovascular risk.**
- **Future research should evaluate the efficacy of incretin therapy in the setting of various individual cardiometabolic/renal risk factors, compare and contrast the efficacy of various formulations among individual agents, and explore possible complementary effects of combination therapies.**

Endocrine Society journals look at GLP-1RAs and the positive and negative unintended impacts.

side effects

As the use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) expands, so too does our knowledge of just what all these medications can do. GLP-1RAs have now been shown to reduce consumption of alcohol and drugs, even treating addictions to gambling and sex, but these medications can also potentially lead to rare but fatal complications of which endocrinologists should be aware.

A recent paper in the *Journal of the Endocrine Society* reports that GLP-1RAs could potentially be effective treatments for drug and alcohol addiction.

BY DEREK BAGLEY

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are certainly making a lot of headlines these days. They've been around for decades, helping treat patients with type 2 diabetes and short bowel syndrome, but when it was discovered that they could also help patients with obesity, they became several household names — Ozempic, Wegovy, Mounjaro, etc.

Until a couple months ago, these medications were only available as injectables, which discouraged some patients; yet about 12% of U.S. adults reported taking GLP-1RAs for weight loss, diabetes, or another chronic condition, according to a November 2025 KFF Health Track poll. Now that Novo Nordisk's Wegovy has been approved in pill form, a recent Sunlight.com survey suggests that number may jump to 40% in 2026.

As these drugs soar in popularity, researchers and physicians are finding uses for them outside the realm of obesity and diabetes. Clinicians have reported using GLP-1RAs to short-circuit addictions to gambling and sex. A paper recently published in the *Journal of the Endocrine Society* (JES) even describes how GLP-1RAs might be used to treat alcohol and drug addictions.

GLP-1s and Addiction

The authors of **"GLP-1 Therapeutics and Their Emerging Role in Alcohol and Substance Use Disorders: An Endocrinology Primer,"** appearing in October 2025 in JES, point out that the World Health Organization reported 890 million adults and 60 million children and adolescents had obesity in 2022 globally. They go on to connect obesity and addiction. They admit that can be controversial, but they write that obesity may have phenotypic characteristics that resemble addiction, including neurocircuitry mechanisms. "Pathways implicated in addiction also contribute to pathological overeating and obesity," they write.

"Clinical research also shows that some neuroimaging features observed in people with obesity resemble those seen in people with addiction," says Lorenzo Leggio, MD, PhD, clinical director of the National Institute on Drug Abuse and corresponding author of the JES paper. "Finally, in clinical practice, some medications used to treat addiction can also affect appetite and body weight. Taken together, evidence from neuroscience, human research, and clinical practice suggests meaningful overlap between obesity and addiction-related mechanisms."

Leggio says that his lab has long been interested in how gut-brain neuroendocrine pathways may influence alcohol use disorder (AUD). "Our overarching framework is that gut–brain (and other periphery-to-brain) endocrine signaling may play a role in AUD (and potentially other substance use disorders) and could therefore represent novel targets for treatment development. With that in mind, we have studied pathways involving insulin, ghrelin, and GLP-1," he says.

Current treatments for alcohol and other substance use disorders include behavioral therapy and rehabilitation and a few FDA-approved medications, but the irony is that while these disorders can carry a stigma, so can seeking treatment for them. The authors write that there can be self-stigma or internalized stigma, which can lead to reluctance in seeking treatment.

"We need to expand addiction medicine education in medical school and residency training," Leggio says. "Alcohol and other substance use disorders are common, and clinicians should be

Eli J. Louwagie, MD, PhD

> Although clinical, empirical data guides medical practice; every patient is unique and deserves individualized considerations. Many patients are on a combination of a SGLT2 inhibitor with a GLP-1 receptor agonist or tirzepatide (a dual agonist) **and have incredible success without adverse reactions, but we are still figuring out the patient characteristics that would put them at higher risk of poor outcomes."**
>
> — ELI J. LOUWAGIE, MD, PHD, DEPARTMENT OF INTERNAL MEDICINE, LEWISGALE HOSPITAL MONTGOMERY, BLACKSBURG, VA.

prepared to recognize them, just like hypertension and diabetes. Education alone isn't the whole solution, but it's an important part of reducing stigma. And reducing stigma is critical if we want current and future medications for substance use disorders to have their full impact."

The authors write that the effects of GLP-1RAs on alcohol use have been studied extensively. Preclinical trials in rodents and nonhuman primates show these medications reduce alcohol intake. Humans have shared anecdotal reports about how taking GLP-1RAs for other indications helped them reduce their alcohol consumption as well. "I have heard that from some patients, typically in calls or emails: They have noticed reduced drinking and/or smoking after starting a GLP-1 receptor agonist," Leggio says. "But these are anecdotal observations, not clinical evidence, and they shouldn't be taken as a basis for changing treatment without medical guidance."

Alcohol and other substance use disorders are common, but they remain substantially underdiagnosed and undertreated. Leggio says that it is important to emphasize that these are not "bad behaviors" or "bad habits" but chronic medical conditions, like diabetes, hypertension, or rheumatoid arthritis. "The possibility that GLP-1 receptor agonists may be effective for some substance use disorders is promising, but we need large randomized controlled trials to confirm benefit and clarify for whom they work best," he says.

Unforeseen Reactions

In February 2025, the paper, **"Euglycemic Ketoacidosis Following Coadministration of an SGLT2 Inhibitor and Tirzepatide,"** appeared in *JCEM Case Reports*, describing a patient who was admitted to the intensive care unit after being placed on both medications. Tirzepatide is a novel dual GLP-1 and glucose-dependent insulinotropic polypeptide receptor agonist recently approved for diabetes and weight loss.

The authors write that they suspect that the two medications had synergistic effects in the patient, leading to adequate control of his blood sugars yet a state of starvation, ketone production, and resultant systemic acidification. "The patient required treatment and monitoring in an ICU to make a full recovery," they write. "As tirzepatide is a relatively new medication whose side-effect profile has yet to be fully characterized, clinicians should be aware of this rare yet potentially fatal complication."

"Although GLP-1 receptor agonists show impressive efficacy and favorable side effect profiles, it is necessary that we determine all risks and side-effects, particularly rare ones, to

minimize chances of poor outcomes," says the paper's first author Eli J. Louwagie, MD, PhD, of the Department of Internal Medicine at LewisGale Hospital Montgomery in Blacksburg, Va. "This is especially important considering the increasing use of these medications."

The authors write that, to their knowledge, this is the first case detailing a patient developing this serious condition after starting tirzepatide for diabetes (in contrast to those treated with tirzepatide for weight loss). Louwagie tells *Endocrine News* that he and his co-authors would want clinicians to keep this potential side effect in mind for all patients presenting with signs of ketoacidosis while on tirzepatide.

"There were several factors varying between our patient and the other cases, particularly our patient also taking an SGLT2 inhibitor, but our case may suggest greater risk of EKA for a patient on synergistic regimens," Louwagie says. "Further studies are needed to investigate this hypothesis, but we suspect recent changes in medication prescribing practices and medication prices will result in large datasets allowing scientists to investigate these potential relationships."

Christine Rode Schwarz, PhD, of the Steno Diabetes Center in Copenhagen, and her co-authors pointed to this case in a commentary titled, **"Mechanism and Context: Making Sense of Adverse Events With GLP-1-based Therapy,"** also published in *JCEM Case Reports* later that year. The authors write that Louwagie's case report (and others') should not detract from the substantial value of GLP-1-based therapies, but they do speak yet again to the importance of individualized therapy.

Schwarz says the commentary is a call for disciplined use, not a warning against the class of medications. "GLP-1–based therapies deliver major benefits for glycemia, weight, and in some settings cardiovascular risk," she says. "Most adverse events reflect expected pharmacology interacting with patient context. When prescribing is supervised and thoughtful, these medicines are effective and safe."

Louwagie agrees that the case report highlights the need for individualized care. "Although clinical, empirical data guides medical practice, every patient is unique and deserves individualized considerations," he says. "Many patients are on a combination of an SGLT2 inhibitor with a GLP-1 receptor agonist or tirzepatide (a dual agonist) and have incredible success without adverse reactions, but we are still figuring out the patient characteristics that would put them at higher risk of poor outcomes." EN

– BAGLEY IS THE SENIOR EDITOR OF ENDOCRINE NEWS. IN THE JANUARY ISSUE HE WROTE ABOUT THE CONNECTION BETWEEN THE THYROID AND CARDIAC HEALTH.

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> — LORENZO LEGGIO, MD, PHD, CLINICAL DIRECTOR, NATIONAL INSTITUTE ON DRUG ABUSE, BETHESDA, MD.

BEYOND *the scale*

What Else Glucagon-like Peptide-1 Receptor Agonists Can Do

In the United States, American Heart Month is observed in February to raise awareness about cardiovascular disease, the leading cause of death worldwide. To a similar end, ***Endocrine News*** focuses on a few recent journal studies that take a closer look at the impacts of incretin-based therapies in the setting of obesity and impaired cardiovascular health as well as how they affect the liver, quality of life, insulin resistance, and much more.

BY KELLY HORVATH

February is heart month at *Endocrine News*, making it an opportune time to examine four recent studies that explore various aspects of glucagon-like peptide-1 receptor agonists (GLP-1RAs) and related incretin-based therapies, given obesity's profound impact on cardiovascular health.

Recent advances in obesity pharmacotherapy have shown unprecedented efficacy in weight reduction and cardiometabolic improvement. GLP-1RAs (and their offshoots that add agonists of other key metabolic regulation substances) have shown particular promise in patients with obesity-related cardiovascular and metabolic complications, offering synergistic benefits that extend beyond weight loss. The picture is not yet perfect, however, and a substantial proportion of patients discontinue treatment within the first year due to barriers related to cost, access, and tolerability. Nevertheless, evidence suggests these therapies may be especially valuable for high-risk patient populations who have been underserved or excluded from aggressive treatment approaches.

Novel Agents

Published in *Endocrinology* in August 2025, **"Novel Dual and Triple Agonists Targeting GLP-1, GIP, Glucagon, and GDF15 for Type 2 Diabetes and Obesity Management"** sets the stage for how remarkably these agents have transformed the treatment landscape and what additional benefits may lie on the horizon. Chao Zheng, PhD, from The Second Affiliated Hospital, School of Medicine, Zhejiang University in Hangzhou, China, and team sought to expand the potential patient populations who can benefit by exploring novel peptide-based therapies, citing GLP-1RAs' lack of effectiveness in a significant proportion of patients. While it is as yet premature to integrate these agents into clinical practice, the researchers undertook a comprehensive overview of what we know so far about dual and triple agonists that target glucose-dependent insulinotropic polypeptide (GIP), another incretin; glucagon; and/or growth differentiation factor 15 (GDF15) in addition to GLP-1.

As the team points out, strong, sustained agonists at the GIP receptor (GIPR) inhibit appetite and stimulate insulin secretion. And, since GIPRs and GLP-1 receptors belong to a related family, the logical next step was to develop a coagonist that targets both — enter tirzepatide. With its demonstrated superior potency and efficacy compared to the single GLP-1RAs such as semaglutide, tirzepatide paved the way for continued experimentation with combined agents.

Dual and triple incretin-based agonists show remarkable potential to more effectively treat the intertwined metabolic problems of type 2 diabetes and obesity, with all the cardiovascular and other comorbidities they confer. These multitarget drugs are designed to create synergy across pathways that regulate appetite, insulin secretion, hepatic metabolism, and energy expenditure, producing broader metabolic benefits than single-receptor therapies. For example, pairing GLP-1 with glucagon aims to merge GLP-1's strong appetite-suppressing and glucose-lowering effects with glucagon's lipolytic and thermogenic actions (possibly mediated indirectly through factors such as FGF21).

> "Discontinuation of injectable semaglutide and tirzepatide for obesity is common in clinical practice. Although potential causes of this have been speculated about by clinicians and third-party payers, no U.S.-based study to date has quantified the reasons for it. **We believe that a better understanding of the reasons could help address the barriers to continued use of these medications."**
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> — HAMLET GASOYAN, PHD, CENTER FOR VALUE-BASED CARE RESEARCH, CLEVELAND CLINIC; DEPARTMENT OF MEDICINE, CLEVELAND CLINIC LERNER COLLEGE OF MEDICINE OF CASE WESTERN RESERVE UNIVERSITY SCHOOL OF MEDICINE, CLEVELAND, OHIO

GLP-1/glucagon, GLP-1/GIP, GLP-1/GDF15, and GLP-1/GIP/glucagon demonstrate distinct yet complementary and synergistic profiles in glycemic control, weight reduction, and metabolic improvements with added benefits in cardio protection, anti-inflammation, and hepatic health.

Early coagonists showed improved glucose tolerance and lipid metabolism alongside weight loss driven by both reduced food intake and increased energy expenditure, such as cotadutide, a daily injectable, which improves liver metabolism and has reduced HbA1c in clinical trials while also showing kidney-protective effects (e.g., reduced albumin-to-creatinine ratio).

Another, efinopegdutide, produces dose-dependent weight loss and may reduce liver fat more than semaglutide, but has shown more adverse events and less consistent glycemic benefit. Bamadutide improved weight and glycemic measures and sometimes outperformed liraglutide, although its activity appears biased toward the GLP-1R. Other dual agonists include survodutide, mazdutide, and pemvidutide, with evidence of meaningful weight loss and cardiometabolic improvements.

GLP-1R/GIPR dual agonists like the aforementioned tirzepatide enhance glycemic control by increasing insulin secretion, suppressing glucagon, and slowing gastric emptying — while potentially improving satiety via central mechanisms.

Triple GLP-1/GIP/glucagon agonists aim for even more comprehensive metabolic control. Long-acting retatrutide, for example, produced substantial HbA1c and weight reductions and showed promise for reducing hepatic fat and improving metabolic dysfunction–associated steatotic liver disease (MASLD)-related biomarkers. Efocipegtrutide shows potential benefits in obesity, MASLD/fibrosis, dyslipidemia, and even neuroinflammation in preclinical models.

Despite their demonstrated potential in preclinical and clinical studies, challenges persist with these agents. The research team cites mechanistic complexities, long-term safety uncertainties, and the need for optimized dosing regimens, all of which require further investigation. Personalized approaches, guided by patient-specific biomarkers and phenotypes, may maximize therapeutic efficacy. "Future research must prioritize head-to-head trials (e.g., tirzepatide versus retatrutide) and validate predictive biomarkers (e.g., GDF15 for anti-inflammatory responses) to advance precision medicine. Collaborative efforts across research, clinical, and pharmaceutical domains are essential to translate these innovations into transformative therapies, ultimately improving outcomes for the global diabetes population," say the study authors.

Targeting Frailty

In **"Frailty and Effects of Semaglutide in Obesity-Related HFpEF: Findings From the STEP-HFpEF Program,"** published in *JACC: Heart Failure* in September 2025, Ambarish Pandey, MD, MSCS, of the Divisions of Cardiology and Geriatrics in the Department of Internal Medicine at the University of Texas Southwestern Medical Center, in Dallas, and team demonstrated just how effective semaglutide can be in the setting of heart failure with preserved ejection fraction (HFpEF) and accompanying frailty. Based on the results in 1,145 participants from the "Research Study to Investigate How Well Semaglutide Works in People Living with Heart Failure and Obesity (STEP-HFpEF)," Pandey and team sought to answer a nagging question. "This question has been on our

minds since the completion of the STEP-HFpEF trial," says Pandey. "Over 60% of participants fell into the 'most frail' category. That's a striking number. And it raised a concern we kept hearing: If someone is already frail, won't a medication that causes significant weight loss, particularly muscle loss, make things worse? We needed real data to settle that question."

Semaglutide was the logical choice for this specific patient population, he explains: "The STEP-HFpEF trials were built around semaglutide from the start. But there's a broader rationale. GLP-1RAs do more than promote weight loss. They tamp down inflammation, improve cardiac hemodynamics, and offer metabolic benefits we're still learning about. In obesity-related HFpEF, where inflammation and metabolic dysfunction sit at the center of the disease, semaglutide was a natural fit."

So, while weight loss across the board was anticipated (about 8% to 9% of body weight compared to placebo), the results this team found intriguing were semaglutide's stratum-dependent ability to reduce frailty burden (strata = less frail, more frail, most frail). "Symptom improvements were far more pronounced in the frailest patients," says Pandey. "That disconnect tells us something important. The benefit isn't coming from weight loss alone." He further explains that obesity-related HFpEF and frailty share common ground at the biological level: chronic inflammation, skeletal muscle dysfunction, and depleted metabolic reserve. "Semaglutide seems to act on these overlapping pathways. There's also growing evidence that GLP-1RAs improve muscle quality by clearing out the fat that infiltrates muscle tissue. Frail patients start with the most dysfunction, so they have the most to gain." In fact, after one year, patients on semaglutide demonstrated an 11-point improvement on the Kansas City Cardiomyopathy Questionnaire–Clinical Summary Score, which represented a shift into a less-frail stratum for many. "That's enormous," says Pandey. "It's the kind of change patients actually feel in their daily lives. We may not just be managing symptoms here. We may be changing the trajectory of the disease itself."

These results are striking for another important reason — they counter what Pandey dubs "therapeutic nihilism." Returning to the "nagging question" at the heart of this study, he says that the concern makes sense on the surface. "With GLP-1RAs, 25% to 40% of total weight loss can come from muscle rather than fat. Picture a 70-year-old with HFpEF who already has sarcopenia. The natural worry is that you're speeding up their decline. But there's a deeper issue. Frail patients routinely get undertreated because clinicians fear they won't tolerate medications well."

With such promising findings, Pandey says the team's next step is confirming these results with objective physical measures: the Fried frailty phenotype, Short Physical Performance Battery, grip strength, and gait speed. "We also want detailed body composition imaging through MRI to understand whether the muscle patients retain is actually healthier. Longer follow-up will tell us whether improvements in frailty lead to fewer hospitalizations and better survival. That's the ultimate question."

He has some strong advice for clinicians: "Don't hold back semaglutide because a patient with obesity-related HFpEF looks too frail. They're the ones who stand to benefit most. In our analysis, the frailest patients saw the largest symptom gains,

"Don't hold back semaglutide because a patient with obesity-related HFpEF looks too frail. They're the ones who stand to benefit most. In our analysis, the frailest patients saw the largest symptom gains, were far more likely to improve their frailty status, and experienced fewer serious adverse events on semaglutide than on placebo. **If you've been hesitant because a patient seems fragile, reconsider. That's exactly who should be getting this therapy."**

— AMBARISH PANDEY, MD, MSCS, DIVISIONS OF CARDIOLOGY AND GERIATRICS, DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY OF TEXAS SOUTHWESTERN MEDICAL CENTER, DALLAS

High cost or insurance-related issues are the most common reasons patients discontinue semaglutide or tirzepatide for obesity, further highlighting the need for policies to address cost and discussions between healthcare providers and patients concerning cost and side effects.

were far more likely to improve their frailty status, and experienced fewer serious adverse events on semaglutide than on placebo. If you've been hesitant because a patient seems fragile, reconsider. That's exactly who should be getting this therapy."

Targeting Alström Syndrome

In **"Effectiveness of the Dual GIP/GLP1-Agonist Tirzepatide in 2 Cases of Alström Syndrome, a Rare Obesity Syndrome,"** published in *The Journal of Clinical Endocrinology & Metabolism* (JCEM) in April 2025, Thomas Scherer, MD, of the Medical University of Vienna, in Austria, and team showed tirzepatide's efficacy even in the particularly difficult-to-treat Alström syndrome (AS), a rare, genetic, multisystemic disorder characterized by, among other conditions, diabetes with profound insulin resistance due to marked hyperphagia.

Scherer cares for patients living with rare obesity syndromes and recounts a recent particular struggle to treat two male patients ages 20 and 23 years with AS who did not respond to multimodal obesity therapy, including GLP-1RAs. "We tried the mono agonists available on the European market at that time, which were dulaglutide, liraglutide, and semaglutide," he explains, "but hyperphagia was unaffected and body weight only temporarily mildly dipped and eventually stagnated."

Scherer explains that the situation was particularly critical for one of the men who was experiencing obesity-related metabolic complications including MASLD, dyslipidemia, and type 2 diabetes, requiring insulin doses greater than 100 IU/day despite maximal antidiabetic therapy with metformin 1,000 mg bid, dapagliflozin 5 mg bid, pioglitazone 45 mg qd, and semaglutide 1 mg once weekly. "We decided to start the patient on tirzepatide (imported from the United States at that time) as a final option before considering bariatric surgery," he says. "The second patient followed shortly after, since we saw a marked weight response in our first patient (body weight –27%) and massive reductions in insulin doses (–83%) and resolution of insulin resistance upon starting tirzepatide."

Their choice stands to reason. As described in the first study mentioned here, dual (and triple agonists) work in complementary and synergistic ways. In the case of tirzepatide, Scherer believes the mechanism may relate to its GIPR action: "Since tirzepatide is an imbalanced dual agonist with stronger GIPR action and weaker binding to the GLP-1R compared to classic GLP-1 agonists, a GIP-mediated mechanism seems likely. Studies in rodents showed, for example, that GIPR agonism mediates weight-independent insulin sensitization by improving glucose disposal into white adipose tissue (WAT). This suggests that maybe tirzepatide ameliorates WAT function in AS, thereby improving overall metabolism and insulin sensitivity (also demonstrated by the rapid decline in insulin demand). This is particularly interesting since, in contrast to GLP-1Rs, only GIPRs are expressed in WAT. In addition, loss of function of the *ALMS1* gene in adipose tissue or preadipocytes recapitulates the metabolic phenotype of a global *ALMS1* loss of function, suggesting that adipose tissue failure is a major pathophysiologic component of AS. Ultimately, rodent studies in *ALMS1* knockout mice are needed to get at the exact mechanism at work."

For Scherer's two patients, uptitration of tirzepatide to the maximal dose of 15 mg a week was necessary, but in addition to the weight they lost, they also achieved significant improvements in insulin resistance (which can be quite pronounced in the setting of AS) as well as reduced hyperphagia. This success prompts future studies to not only confirm the findings in larger cohorts but also to explore similar avenues. "It would be great to undertake studies with the newer dual agonists and polyagonists also in rare obesity syndromes such as AS, Prader-Willi syndrome, and Bardet-Biedl syndrome (just to name a few), as the clinical need for effective obesity/hyperphagia therapies in these patients is especially high," says Scherer. "This is an effort where industry and academia need to closely collaborate to find the right patient cohorts, which is not an easy task in rare disease."

Meanwhile, he wants clinicians to know that tirzepatide is a good option for treating obesity, hyperphagia, MASLD, and type 2 diabetes in AS, but because of the rapid therapeutic response it produces, patients require careful monitoring. "Care should be taken in patients with insulin therapy, as rapid adjustments in insulin doses should be anticipated," he says. "Therefore, close meshed control intervals during the uptitration phase of tirzepatide with biweekly to monthly visits are merited to avoid hypoglycemia. Furthermore, patients and caregivers should be mindful of below-target fasting and postprandial glucose readings and make adjustments to the insulin doses in close contact with the treatment center. Using a continuous glucose monitor (CGM) device with alarm function and the possibility of remote monitoring of CGM data would also help mitigate hypoglycemic events in this context."

Discontinuation

As mentioned, the news is not all perfectly rosy, as **"Reasons for Discontinuation of Obesity Pharmacotherapy With Semaglutide or Tirzepatide in Clinical Practice"** shows. Even in this study published in *Obesity* in August 2025 and written by Hamlet Gasoyan, PhD, of the Center for Value-Based Care Research at the Cleveland Clinic and the Department of Medicine, at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University School of Medicine, in Ohio, and team researchers have reason to be hopeful.

"Discontinuation of injectable semaglutide and tirzepatide for obesity is common in clinical practice," says Gasoyan. "Although potential causes of this have been speculated about by clinicians and third-party payers, no U.S.-based study to date has quantified the reasons for it. We believe that a better understanding of the reasons could help address the barriers to continued use of these medications."

Their cross-sectional study examined electronic health record (EHR) data of 288 patients with overweight or obesity and without type 2 diabetes who initiated injectable semaglutide or tirzepatide and discontinued treatment within the

AT A GLANCE

- The dual and triple agonists GLP-1/glucagon, GLP-1/GIP, GLP-1/GDF15, and GLP-1/GIP/glucagon demonstrate distinct yet complementary and synergistic profiles in glycemic control, weight reduction, and metabolic improvements with added benefits in cardioprotection, anti-inflammation, and hepatic health.
- Semaglutide is not only an effective, safe therapy in the high-risk group of frail patients with obesity-related HFpEF, it may even significantly reduce their frailty burden and improve their overall quality of life.
- The dual GLP1/GIP agonist tirzepatide markedly improves body weight, MASLD, insulin resistance, and hyperphagia in people living with Alström syndrome, but monitoring for potential resulting hypoglycemia should be vigilant.
- High cost or insurance-related issues are the most common reasons for treatment discontinuation with semaglutide or tirzepatide for obesity, highlighting the need for policies to address cost and informing discussions between healthcare providers and patients concerning cost and side effects.

> “Patients and caregivers should be instructed to be mindful of below-target fasting and postprandial glucose readings and make adjustments to the insulin doses in close contact with the treatment center. **Using a continuous glucose monitor (CGM) device with alarm function and the possibility of remote monitoring of CGM data would also help mitigate hypoglycemic events in this context.”**
>
> — THOMAS SCHERER, MD, DEPUTY CHIEF, DIVISION OF ENDOCRINOLOGY AND METABOLISM, MEDICAL UNIVERSITY OF VIENNA, VIENNA, AUSTRIA

first year, 145 of whom received semaglutide, and 143 tirzepatide. The researchers found that 137 patients (47.6%) discontinued their medication due to cost or insurance-related issues, 42 (14.6%) due to side effects, 34 (11.8%) due to shortages, seven (2.4%) due to switching to a compounded medication, and five (1.7%) due to unsatisfactory weight loss. Another 31 (10.8%) discontinued for other reasons, and the discontinuation reason was not specified in the EHR for 32 (11.1%) patients.

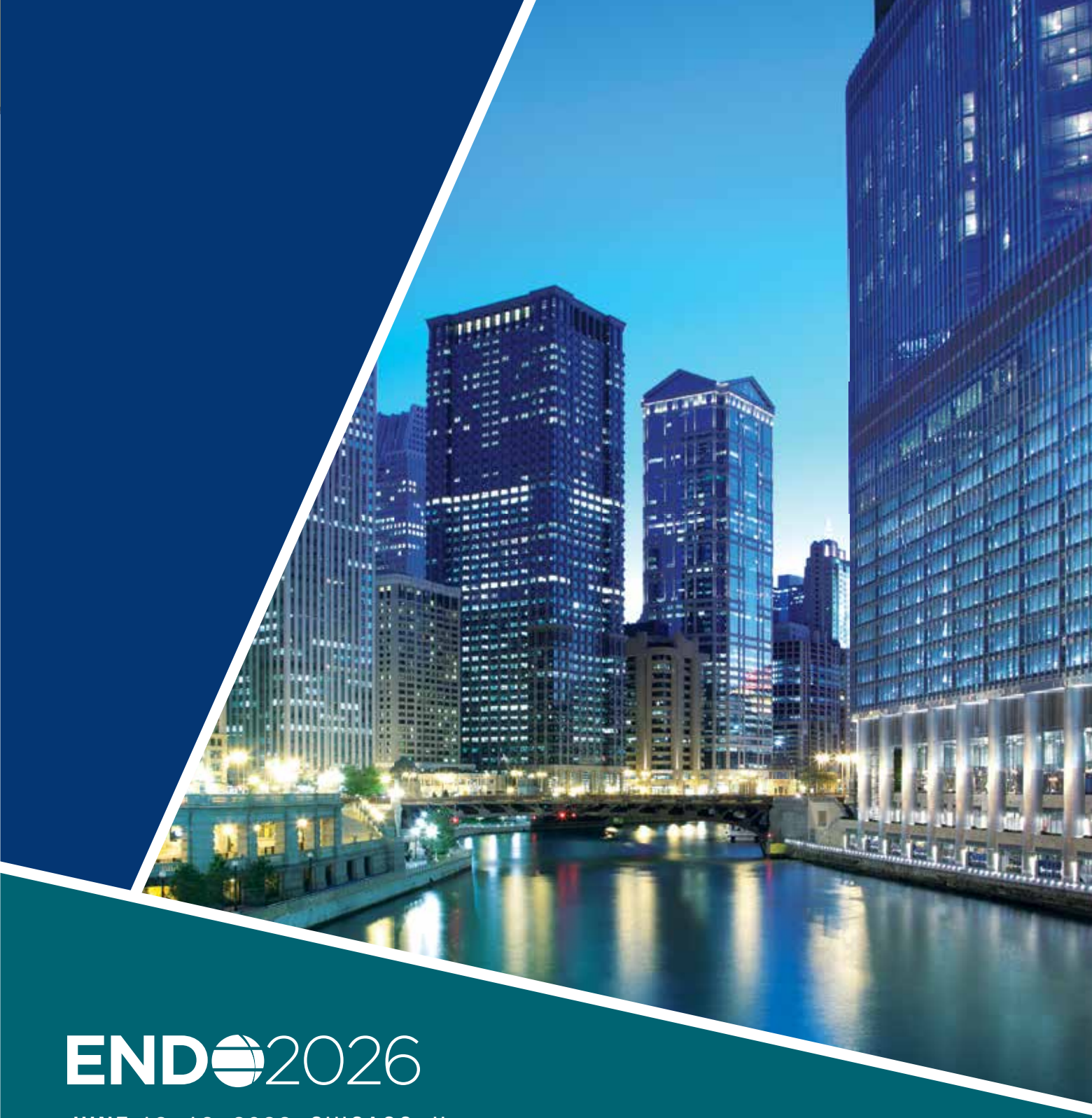
“Our findings are in line with studies that examined the association of insurance type, copayment amount, and socioeconomic factors with the initiation and persistence with novel obesity medications,” says Gasoyan. “Discontinuation due to factors typically irrelevant in clinical trial settings (i.e., cost or insurance-related issues and medication shortages) could contribute to the substantial discrepancy between discontinuation rates in pivotal Phase 3 trials and those reported in real-world studies.”

Regarding discontinuation due to side effects, Gasoyan says we do not currently know of patient-level predictors that would help identify who might experience side effects and why. “The most helpful recommendation for patients would be to work closely with their clinician on gradual dosing and making specific dietary and lifestyle adjustments,” he says.

Indeed, the team’s next steps involve individualizing therapy. “In our future work, we will be generating evidence on what alternative obesity treatment works best for whom, to help patients and providers make evidence-based decisions when continuing with a specific novel obesity medication is not possible,” says Gasoyan. Helpfully, recent policy changes regarding cost may make having a variety of options to readily choose from more possible from an affordability perspective. “These are positive developments that will improve access and treatment persistence among patients needing obesity medications, particularly those covered by Medicare, state Medicaid programs in states that will choose to participate, and those who can afford the cash pay option.”

Meanwhile, Gasoyan says, “recognizing the primary reasons for discontinuation may facilitate more informed discussions between clinicians and their patients, helping to address challenges in long-term persistence with these highly effective medications.” EN

– HORVATH IS A FREELANCE WRITER BASED IN BALTIMORE, MD. IN THE JANUARY ISSUE, SHE WROTE ABOUT A NUMBER OF NEW DIRECTIONS FOR TREATING PATIENTS WITH THYROID CANCER.



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BY DEREK BAGLEY

Joel Habener, MD

When **Joel Habener, MD,** passed away at the age of 88 in December, the scientific community around the world mourned a titan. *Endocrine News* pays tribute to Habener, his accomplishments, and how he helped change metabolic medicine.

Remembering **Joel Habener, MD**

The world of endocrinology — and indeed the world — lost a titan at the end of 2025 in Joel Habener, MD, who passed away December 28 at the age of 88. Habener, a professor of medicine at Harvard Medical School and director of the Laboratory of Molecular Endocrinology at Massachusetts General Hospital in Boston, was instrumental in the development of GLP-1-based drugs that have revolutionized the treatment of type 2 diabetes, obesity, and beyond.

In the 1970s, Habener became interested in how the hormone glucagon fits into the puzzle of how the body regulates blood sugar levels. When Habener cloned the gene for glucagon, he discovered that it encodes not only glucagon itself, but also another molecule that resembles glucagon-like peptide-1.

"Joel Habener was a pioneer in molecular endocrinology who utilized the power of molecular biology to gain unique insights into the structure and processing of prohormones," says Daniel J. Drucker, MD, senior investigator at the Lunenfeld-Tanenbaum Research Institute, Sinai Health, and a university professor in the Department of Medicine at the University of Toronto's Temerty Faculty of Medicine in Ontario. "Habener was widely recognized for welcoming clinical trained fellows who often gained their first real exposure to basic science in his lab. His foundational science was fundamental to the birth of the nascent field of GLP-1 biology and changed the fields of endocrinology and clinical medicine."

Awards Season

Habener, along with colleagues Drucker; Lotte Bjerre Knudsen, DMSc, chief scientific advisor and head of the GLP-1 Centre of Excellence at Novo Nordisk; and Svetlana Mojsov, PhD, research associate professor at Rockefeller University in New York, have received many awards and accolades in recent years for their discovery of these GLP-1 therapies that led to blockbuster drugs like Ozempic and Wegovy, which the FDA in December 2025 approved as a once-daily pill for weight loss (20 years after the FDA approved the first GLP-1 drug for type 2 diabetes).

"That two-decade progression cleanly captures how Joel's career has sent ripples through healthcare," George Q. Daley, MD, PhD, dean of the Faculty of Medicine at Harvard, wrote in a statement honoring Habener.

In 2020, Habener, along with Drucker and Jens Juul Holst, MD, DMSc, professor, Department of Biomedical Sciences; Group Leader, Translational Metabolic Physiology, Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Denmark,

took home the Warren Alpert Foundation Prize for their discoveries about the function of key intestinal hormones, their effects on metabolism, and the subsequent design of treatments for type 2 diabetes, obesity, and short bowel syndrome — the first time in many years this prestigious award has gone to investigators in the field of endocrinology.

"These are diseases with a high morbidity and mortality and are attracting greater research efforts to understand the pathophysiology and to develop effective therapies to combat them," Habener told *Endocrine News* at the time. "Obesity and its ensuing constellation of ensuing disorders known as the metabolic syndrome include diabetes, steatohepatitis, hypertension, and even dementia and certain types of cancer."

The next year, Habener, Drucker, and Holst were recognized with the 2021 Canada Gairdner International Award for their research on glucagon-like peptides that led to major advances in the treatment of type 2 diabetes, obesity, and intestinal disorders. The independent and collaborative work of Habener, Drucker, and Holst enhanced the understanding of how gastrointestinal organs function and created new classes of drugs for the treatment of metabolic disorders, specifically type 2 diabetes, obesity, and short bowel syndrome.

The three discovered glucagon-like peptides (GLP-1 and -2) and elucidated their biology and physiological function and played critical roles in the design and testing of therapies informed by their initial and subsequent discoveries. These three scientists were awarded for a combined body of work with significant impact on the field of diabetes and short bowel syndrome but were also recognized for their individual discoveries that underpin the translational results.

Habener, Knudsen, and Mojsov won the 2024 Lasker–DeBakey Clinical Medical Research Award again for their work on GLP-1RAs. Habener, Mojsov, and Knudsen also received the Friends of the National Library of Medicine's (FNLM's) 2025 Distinguished Medical Science Award for their groundbreaking contributions to the development of GLP-1 therapies.

The 2025 Breakthrough Prize for Life Science was awarded to Habener, Drucker, Knudsen, Mosjov, and Holst. Nicknamed "the Oscars of Science," the Breakthrough Prize for Life Science recognizes the world's top scientists. Each prize is $3 million and is presented in the fields of Life Sciences, Fundamental Physics, and Mathematics. "Joel's receipt (along with his co-awardees) of the 2025 Breakthrough Prize in Life Sciences and the 2024 Lasker–DeBakey Clinical Medical Research Award has made him a likely contender for the Nobel Prize," Daley wrote in a statement. "Although he did not live to see that recognition, the value of Joel's discoveries will continue to accrue with time, as millions of lives are improved and saved. That extraordinary impact is its own enduring honor."

Discovery Channel

According to Habener, his interest and work in the field of gut hormones as therapeutic targets evolved stepwise with several discoveries over several decades starting in the 1970s. "That was a time when recombinant DNA technology was being developed and

> *Habener was widely recognized for welcoming clinical trained fellows who often gained their first real exposure to basic science in his lab.* ***His foundational science was fundamental to the birth of the nascent field of GLP-1 biology and changed the fields of endocrinology and clinical medicine."***
>
> — DANIEL J. DRUCKER, MD, SENIOR INVESTIGATOR, LUNENFELD-TANENBAUM RESEARCH INSTITUTE, SINAI HEALTH; PROFESSOR, DEPARTMENT OF MEDICINE, UNIVERSITY OF TORONTO'S TEMERTY FACULTY OF MEDICINE, ONTARIO, CANADA

my experience at the NIH convinced me to pursue a career in basic discovery research and to exploit the power of recombinant DNA technology," Habener said.

Habener completed his training in internal medicine at Massachusetts General Hospital (MGH) in1972 and became an investigator at Howard Hughes Medical Institute, while at the same time being named chief of the newly established Laboratory of Molecular Endocrinology at MGH.

Habener used pancreatic cells from anglerfish to demonstrate that glucagon and somatostatin were encoded in the pancreatic cells as larger, precursor hormones. During additional mammal studies, he discovered two new hormones related to glucagon that are known as GLP-1 and GLP-2.

Habener explained that each of the individual anglerfish proglucagons encoded the fish versions of glucagon and a second peptide resembling but distinct from glucagon. Habener and his colleagues named these distinct second peptides GRPs — glucagon-related peptides. Comparisons of the amino acid sequences of the GRPs, suggested sequence similarities with mammalian GIP, termed gastric inhibitory peptide, later re-named glucose-dependent insulinotropic polypeptide.

"The remarkable findings in the studies of mammalian proglucagons was that they contained the sequence of glucagon, and not one but two additional GRPs, renamed GLP-1 and GLP-2. One of the GLPs (GLP-1) appears to be the homolog of anglerfish GRP," Habener explained at the time. "In addition, at the level of the gene structure and organization, each of the three peptides, glucagon, GLP-1, and GLP-2 are encoded in separate exons."

Drucker served as a fellow in Habener's lab in the 1980s and outlined the processing of proglucagon and the biology of GLP-1 action on insulin-producing cells, which led to the development of multiple types of treatments for type 2 diabetes.

"During the three years that he spent in my lab before returning to Toronto, he first-authored, or co-authored, 12 publications describing his work, a clearly impressive accomplishment for someone who had little prior background in basic research," Habener said of Drucker. "This high level of research productivity focused on the GLP-1s continued in Toronto. Notable early accomplishments were the creation and characterization of the GLP-1 receptor knock-out mouse and the demonstration that GLP-2 promoted the growth of the intestinal epithelium."

Together, Habener, Drucker, and their colleagues made major contributions to endocrinology and changed the treatment of metabolic and gastrointestinal diseases. Their work is both basic and translational, a true example of bench to bedside research.

"Habener will be remembered as a visionary scientist whose discoveries transformed the field of metabolic medicine and as a highly sought after mentor who trained generations of independent investigators," Drucker says. EN

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— DANIEL J. DRUCKER, MD, SENIOR INVESTIGATOR, LUNENFELD-TANENBAUM RESEARCH INSTITUTE, SINAI HEALTH; PROFESSOR, DEPARTMENT OF MEDICINE, UNIVERSITY OF TORONTO'S TEMERTY FACULTY OF MEDICINE, ONTARIO, CANADA

– BAGLEY IS THE SENIOR EDITOR OF *ENDOCRINE NEWS*. IN THE JANUARY ISSUE, HE WROTE ABOUT JCEM CR STUDIES THAT LINKED THYROID DYSFUNCTION TO CARDIOVASCULAR ISSUES.

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BY MARIA ANDREA CAMILLETTI, PHD

On behalf of the Endocrine Society's Early Career Special Interest Group, Maria Andrea Camilletti, PhD, takes us on a guided journey from family influences to how she developed such a keen interest in the pituitary, and explains why it brings her so much joy.

From pituitary tumors to iPSCs-based models for congenital hypopituitarism

A Personal Pituitary journey

Maria Andrea Camilletti, PhD

As a child, I knew I wanted to be a scientist without really knowing what a scientist actually did. Perhaps it was due to my family's influence; my mother was a biochemist and my grandfather and uncle were both agronomists and engineers, and they all taught me to be curious about the world. These influential family members were who first introduced me to the marvelous world of the life sciences when I was very young.

In 2007, I began my studies in biological sciences at the Faculty of Natural and Exact Sciences at the University of Buenos Aires (UBA), a very prestigious public university in Argentina. The university was a bustling environment, and I felt lucky to be there where I could learn from excellent professors who were also active scientists. Their commitment and motivation were inspiring.

In 2011, I met Graciela Diaz, PhD, a recognized researcher in pituitary tumors, and joined her lab at the Institute of Biology and Experimental Medicine (IBYME) for a student fellowship. She was initiating her independent career at the time. Graciela showed me all the aspects of becoming a neuroendocrinology researcher, including the obstacles of doing science in a country with various economic challenges. Most importantly, she got me profoundly engaged with the pituitary gland.

This tiny gland, located in the base of the brain, controls many essential body functions, including reproduction, growth, behavior, metabolism, and overall homeostasis.

After completing my PhD, I was convinced I wanted to stay on the pituitary research path, so I joined the laboratory of María Inés Pérez Millán, PhD, a brilliant, young researcher who had just set up her lab in Buenos Aires after a six-year postdoc at the University of Michigan. My postdoc project was part of María Inés's ambitious idea to create a multigene panel for congenital hypopituitarism (CH), a complex genetic disease characterized by a deficiency of one or more pituitary hormones. The goal was to improve the molecular diagnosis of CH by detecting gene-specific candidate variants.

Immersing myself in bioinformatics and clinical genomics was both a challenging and rewarding experience. Working with patient data allowed me to exchange research results with renowned experts and physicians managing pituitary disorders from different hospitals across Argentina. We screened more than 170 pediatric patients for genetic alterations using our own custom-based sequencing panel, ultimately solving 15.3% of the sporadic cases. However, most of the variants we found were classified as variants of uncertain significance (VUS). This meant that additional functional assays were necessary to dissect the pathogenic mechanism, if one was present definitively.

New Questions Demand New Approaches

To find a reliable tool for exploring the role of novel genes and genetic variants for CH, we turned to induced pluripotent stem cell (iPSC) technologies as an excellent cellular model for our studies.

> “I hope our research contributes to the community by offering better diagnosis, genetic counseling, and future treatments for patients and their families. **[Induced pluripotent stem cell]–based technologies have shown potential for modeling hormonal deficiencies and hold promise for cell transplantation to treat hypopituitarism in the future, offering new opportunities for personalized therapies.”**
>
> — MARIA ANDREA CAMILLETTI, PHD, ASSISTANT RESEARCHER, LABORATORIO DE INVESTIGACIONES APLICADAS EN NEUROCIENCIAS (LIAN), INSTITUTO DE NEUROCIENCIAS (INEU-CONICET), FUNDACION PARA LA LUCHA CONTRA LAS ENFERMEDADES NEUROLOGICAS DE LA INFANCIA (FLENI), BUENOS AIRES, ARGENTINA

With this shift in focus, I joined the Institute of Neuroscience at FLENI, one of the leading neurological institutes in Argentina and Latin America, with a new position as an independent researcher in the Laboratory of Applied Research to Neurosciences.

iPSCs were first generated through groundbreaking technology developed by Shinya Yamanaka and Kazutoshi Takahashi in Kyoto, Japan, in 2006, and since then, they have revolutionized medicine. They possess two unique features that make them attractive for health research: their capacity for self-renewal and the ability to differentiate into virtually any specialized cell type, including endocrine cells. Because iPSCs can be generated directly from a patient’s own mature somatic cells (like skin or blood), they circumvent many of the ethical issues associated with embryonic stem cells.

Modeling Disease for Personalized Medicine

My current research is specifically centered on expanding our knowledge of congenital hormonal deficiencies by generating iPSC-based in vitro models.

To achieve this, we generated an iPSC line from a patient diagnosed with GH deficiency and craniofacial malformations who carries a novel, heterozygous nonsense variant in FOXA2 (c.686C>A; p.S229*). This gene is poorly characterized in hormonal diseases, and its role in pituitary development is largely unknown. This study, a collaboration with specialists from the Garrahan Hospital and the Faculty of Natural and Exact Sciences, represents the crucial first step for disease modeling. The next steps are aimed at obtaining pituitary cells from the generated patient iPSCs (and comparing them with control-iPSCs) to examine the effect of the FOXA2 variant on the clinical phenotype.

This is particularly relevant for providing better diagnoses of pituitary hormonal deficiencies locally and for helping to

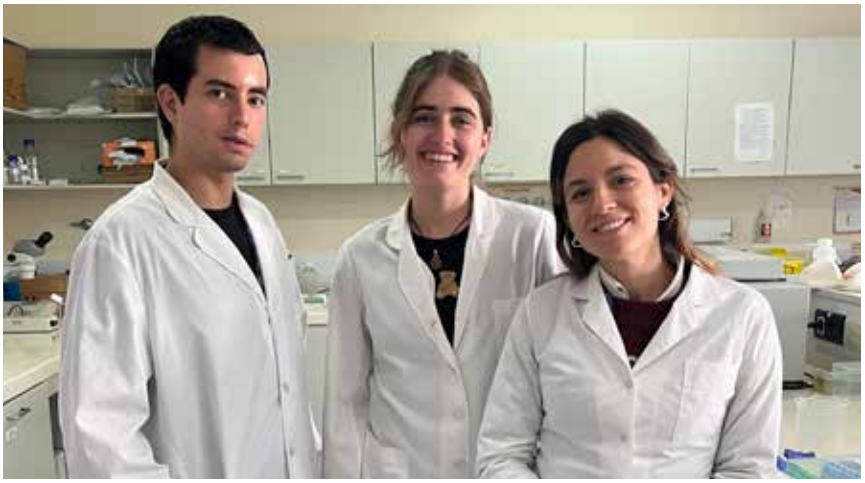
fill the gap of why FOXA2 heterozygous variants can cause CH in children. Additionally, my lab is currently working on generating a FOXA2 knockout iPSC line using gene-editing tools. We will use genomics and proteomics approaches to investigate the role of this gene in pituitary differentiation and to reveal the transcriptional regulatory landscape of this novel gene during this process.

The Thrill of the Lab and Mentorship

I personally have a lot of fun in the laboratory. Culturing iPSCs is complicated, but it's incredibly satisfying when you finalize protocols without contamination or technical problems. Working with iPSCs can be challenging because they stress easily, and antibiotics are not allowed to maintain the cultures! As a lab mate often says, you have to become a kind of "ninja-culture technician" when working with this cell type.

Additionally, teaching new PhD students is very motivating, especially when we discuss scientific data or get the chance to exchange results with a broader audience at national or international conferences. The feeling of mentoring the next generation of scientists is deeply rewarding.

At the end of the day, I hope our research contributes to the community by offering better diagnosis, genetic counseling, and future treatments for patients and their families. iPSC-based technologies have shown potential for modeling hormonal deficiencies and hold promise for cell transplantation to treat hypopituitarism in the future, offering new opportunities for personalized therapies. EN



Top: Camilletti (right) in the lab with two of her students, Gonzalo Tomás Chirino Felker, PhD fellow (left), and Chiara Grosso, undergraduate student (center).
Bottom: The entire team stepped away from the laboratory on a sunny day in Buenos Aires to take a group photo. The team is composed of undergraduate students, PhD fellows, postdocs, and researchers who all work in the Laboratorio de Investigaciones Aplicadas en Neurociencias (LIAN), Instituto de Neurociencias (INEU-CONICET), Fundación para la Lucha contra las Enfermedades Neurológicas de la Infancia (FLENI).

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– CAMILLETTI IS AN ASSISTANT RESEARCHER AT THE LABORATORIO DE INVESTIGACIONES APLICADAS EN NEUROCIENCIAS (LIAN), INSTITUTO DE NEUROCIENCIAS (INEU-CONICET), FUNDACION PARA LA LUCHA CONTRA LAS ENFERMEDADES NEUROLOGICAS DE LA INFANCIA (FLENI), BUENOS AIRES, ARGENTINA

The Endocrine Society's 2026 recipient of the Outstanding Clinical Investigator Laureate Award, **Samuel Klein, MD,** has spent the better part of the past 30 years researching why obesity affects people differently. He talks to ***Endocrine News*** about this perplexing dilemma and how he hopes his research could one day help solve this puzzle.

Both Ends of the SPECTRUM

Talking Obesity Science with Samuel Klein, MD

BY GLENDA FAUNTLEROY SHAW

Samuel Klein, MD

For more than three decades, Samuel Klein, MD, has pondered a seemingly simple question: Why do some people with obesity develop serious metabolic disease while others remain remarkably healthy? The answers — grounded in meticulous human studies and translational science — have transformed how clinicians and researchers understand fat biology and metabolic risk. In recognition of these contributions, the Endocrine Society has named Klein one of its 2026 laureates, awarding him the Outstanding Clinical Investigator Award.

Klein is the William H. Danforth Professor of Medicine and Nutritional Science at Washington University School of Medicine in St. Louis, Mo. He is also the director of the Center for Human Nutrition and the Division of Nutritional Science & Obesity Medicine. He earned his medical degree at Temple University and master's degree in nutritional biochemistry and metabolism from the Massachusetts Institute of Technology. Klein completed a subsequent fellowship in gastroenterology at Mount Sinai Hospital in New York and has been a member of the Washington University School of Medicine faculty since 1994.

Throughout his career, Klein's research efforts have also help unlock the mystery of how weight loss improves the metabolic problems caused by obesity.

"He is a unique physician-scientist who conducts studies in human subjects that are directed at understanding the pathogenesis and pathophysiology of obesity and diabetes in an effort to ultimately improve health and clinical care," wrote Rexford S. Ahima, MD, PhD, director of Division of Endocrinology, Diabetes and Metabolism at Johns Hopkins University School of Medicine, in his nomination of Klein for the Laureate Award.

Endocrine News asked Klein more about the short- and long-term impact of his research and the advice he gives to today's aspiring investigators.

Endocrine News: **What did the news of receiving the Laureate recognition mean to you, and how do you hope it might influence your future work or opportunities?**

Samuel Klein: Receiving the Endocrine Society's Outstanding Clinical Investigator Award is obviously a great honor. I want to acknowledge that this award recognizes the many contributions from research staff, trainees, and colleagues that made the work happen. The Laureate recognition of our work supports the importance of combining clinical and basic science techniques in studying multi-organ system biology in people to enhance our understanding of the pathogenesis of obesity-related metabolic diseases.

> It is important to follow the data and not become personally invested in a particular hypothesis. Research is an exploration to find the truth. **There is nothing wrong in being wrong, but it's a mistake to remain locked into a position that is not supported by new data."**
>
> — SAMUEL KLEIN, MD, WILLIAM H. DANFORTH PROFESSOR OF MEDICINE AND NUTRITIONAL SCIENCE, WASHINGTON UNIVERSITY SCHOOL OF MEDICINE, ST. LOUIS, MO.

EN: What impact do you envision your work will have in the short and long term?

Klein: Obesity is typically associated with a constellation of metabolic abnormalities and diseases, including insulin resistance, prediabetes, type 2 diabetes, atherogenic dyslipidemia, and metabolic dysfunction associated steatotic liver disease, which are important risk factors for cardiovascular disease. However, there is considerable heterogeneity in these metabolic complications and some people with obesity are protected from many of the adverse metabolic effects of excess body fat and can be considered "metabolically healthy."

We hope that our work encourages the study of groups of people at the two ends of the metabolic heterogeneity spectrum (i.e., those with metabolically healthy and metabolically unhealthy obesity) because a better understanding of the mechanisms responsible for the ends of the spectrum will provide insights into the mechanisms that can cause or prevent obesity-related metabolic diseases and identify novel pathways for therapeutic intervention.

EN: What advice would you give to aspiring scientists just beginning their careers in research?

Klein: It is important to follow the data and not become personally invested in a particular hypothesis. Research is an exploration to find the truth. There is nothing wrong in being wrong, but it's a mistake to remain locked into a position that is not supported by new data.

EN: If you could turn the calendar back to the start of your research career, what would you do differently?

Klein: I would have spent less time at work and more time developing hobbies that I could pursue in retirement.

EN: Science can be all-consuming. What's your favorite way to unplug when you step away from the bench?

Klein: I like to escape with exercise and by reading true crime novels. EN

About the Award:
Since 1944, the Endocrine Society has recognized the achievements of its members with the annual Laurate Awards. The Outstanding Clinical Investigator Award honors an accomplished scientist who has made substantial contributions to the understanding of the progression and treatment of endocrine and metabolic diseases. The 2026 Laureates will be recognized at **ENDO 2026** in Chicago, Ill., June 13 – 16.

– SHAW IS A FREELANCE WRITER BASED IN CARMEL, IND. SHE'S A REGULAR CONTRIBUTOR TO *ENDOCRINE NEWS* AND AUTHOR OF LABORATORY NOTES.

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ENDOCRINE SOCIETY

Society Advocates for NIH Funding as Next Year's Budget Process Kicks Off

As this article went to press, Congress had yet to complete a full-year spending bill for the current fiscal year (FY 2026) to fund the National Institutes of Health (NIH).

This ongoing uncertainty has impacted NIH's ability to award grants, with consequences for our member scientists and their work. Meanwhile, the Trump administration aims to release their budget for FY 2027 in the coming weeks, kicking off next year's budget negotiations.

With so much at stake for this fiscal year and next, we have elevated our efforts to advocate for medical research, engaging members to explain to policymakers why robust NIH funding matters for scientists, patients, and the nation's health. Two high-impact actions in particular aim to influence both FY 2026 and FY 2027 negotiations.

Engaging the Medical Research Community

In January, the Endocrine Society spearheaded an organizational sign-on letter to congressional leadership urging them to complete work on a full-year appropriations bill for FY 2026 that increases funding for the NIH.

The letter also calls for Congress to protect the NIH from interference in grantmaking. Specifically, we asked Congress to prevent the administration from imposing arbitrary caps on negotiated facilities and administrative cost rates and minimize near-term impacts on grant success rates by limiting the number of forward-funded grants to levels consistent with previous years.

> "With so much at stake for this fiscal year and next, we have elevated our efforts to advocate for medical research, engaging members to explain to policymakers why robust NIH funding matters for scientists, patients, and the nation's health."

More than 100 research, medical professional, and patient advocacy organizations endorsed the letter, reflecting the breadth of support for the NIH and the Endocrine Society's leadership in convening the community.

Meeting with Members of Congress

On March 13, the Endocrine Society will conduct a virtual Hill Day for our member scientists with their elected officials as the process for FY 2027 funding gets underway and congressional offices identify their priority areas for funding next year.

While the Endocrine Society has conducted a March Hill Day focused on research funding every year by bringing our members to Washington, this year we are scaling up our engagement with Congress by organizing a virtual Researcher Hill Day so that we can engage more members and conduct more congressional meetings via Zoom. During these meetings, we will urge representatives to increase funding for the NIH and share stories of how endocrine research impacts their districts and states.

For those who volunteer to participate, the Society will conduct a training call, provide materials, and schedule meetings.

Everyone Should Get Involved!

As we look back on 2025, it is clear that if we are going to be successful, we will need everyone to take action and make their voices heard.

If you are interested in participating in our March 13 Researcher Hill Day, we encourage you to send an e-mail to: advocacy@endocrine.org, and a member of our team will follow up with more information. We also urge all Endocrine Society members to take action by sending a letter to your representatives through our online campaign at: www.endocrine.org/advocacy/take-action.

These visits and letters have real impact, and now is the time to influence Congress to support the NIH!

A New Era in Endocrinology

Innovations on the horizon position 2026 as a pivotal year for endocrinology with advanced products, devices, and digital platforms reshaping how care is delivered and experienced.

BY COURTNEY CARSON

For decades, endocrine treatment centered largely on replacing what the body could no longer produce or adjusting therapies within narrow clinical guidelines. Today, a new generation of connected sensors, automated delivery systems, and integrated technology platforms are reshaping that model. These tools are designed to reduce the day-to-day burden of managing endocrine disorders, improve the user experience, and better integrate care into everyday life. Below, we highlight several notable technologies that have recently launched or are expected to emerge in the year ahead.

Medtronic Simplera Sync and Instinct Sensors

Medtronic is expanding the continuous glucose monitor options compatible with its MiniMed 780G. In addition to the Guardian 4 sensor, users can now choose between two new options. The Simplera Sync is a six-day disposable sensor designed for ease of use and reduced insertion complexity, while the Instinct is a 15-day sensor built on Abbott's FreeStyle Libre technology that offers extended wear time and fewer sensor changes. This added flexibility allows patients and providers to better balance accuracy, comfort, and wear duration based on individual needs and lifestyle preferences. As automated insulin delivery reaches a broader and more diverse population, Medtronic's multi-sensor strategy reflects a shift toward adaptable systems rather than a one-size-fits-all approach.

www.medtronicdiabetes.com

Biolinq Shine The Biolinq Shine represents a first-of-its-kind approach to glucose monitoring, eliminating the need for a hypodermic needle entirely. Designed for people with diabetes who do not use insulin, the quarter-sized adhesive sensor integrates glucose range monitoring with automatic tracking of physical activity and sleep. Instead of displaying numerical values, Shine uses a simple, color-coded LED system to communicate glucose status in real time — blue indicating glucose is in target range, with other colors prompting users to take action. The sensor functions independently of a smartphone, while a companion app provides personalized insights and trend analysis over time.

www.biolinq.com

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Twin Health Twin Health represents a different kind of innovation by blending hardware, software, and human support into a single, coordinated system. The platform combines continuous glucose monitoring, a smart scale, blood pressure monitoring, a smartwatch, and AI-driven coaching to create a personalized "digital twin" for each participant. By modeling how an individual responds to food, activity, sleep, and stress, Twin Health delivers tailored, real-time guidance supported by remote health coaches, with all data and recommendations unified within a single digital platform. **usa.twinhealth.com**

Dexcom G7 15-Day Continuous Glucose Monitor The Dexcom G7 15-Day extends sensor wear while preserving the look, feel, and functionality of the current G7 system. Requiring fewer sensor changes each month, the 15-day G7 is designed to minimize interruptions to daily routines and remains compatible with leading automated insulin delivery systems. The longer wear time supports more consistent glucose monitoring with less hands-on management, improving continuity and convenience for everyday use. **www.dexcom.com**

Omnipod 6 Insulet is set to launch the Omnipod 6 by 2027, advancing automated insulin delivery with an adaptive learning algorithm that continuously improves insulin dosing over time. Designed to pair with multiple continuous glucose monitors and supported by upgraded apps and controllers, Omnipod 6 aims to reduce the need for frequent manual adjustments by users and clinicians. Looking ahead, Insulet looks to further simplify this process with plans to introduce a fully automated system that eliminates meal announcements altogether. **www.omnipod.com**

Together, these products reflect a shift toward more adaptive, user-centered endocrine technology — from needle-free sensors and extended-wear CGMs to automated insulin delivery and AI-enabled care platforms. As these tools continue to evolve in 2026 and beyond, the emphasis is increasingly on flexibility, simplicity, and integration, allowing care to adjust to patients rather than the other way around. EN

–CARSON IS A FREELANCE WRITER BASED IN BIRMINGHAM, ALA., SHE FREQUENTLY COVERS NEW TECHNOLOGY FOR *ENDOCRINE NEWS*.