

OCTOBER 2020

THE LEADING MAGAZINE FOR ● ENDOCRINOLOGISTS

Endocrine news

Obesity OBSERVATIONS

New research underscores
how obesity impacts
endocrine health.

- Could bariatric surgery for pediatric patients lead to healthier adults?
- New guidelines recommend routine thyroid function testing in patients with obesity.
- Obesity and its impact on the immune system of COVID-19 patients.

A MOMENT'S NOTICE:

Tips to reduce the stress of being on call

HONORING ENDOCRINOLOGY:

The 2020 Warren Alpert Foundation Prize winners

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Hormone Science to Health

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Uniting the Global Endocrine Community

It is more important than ever that the healthcare community worldwide unite and work together in an inclusive environment. The Endocrine Society has always welcomed our international members and strived to offer relevant benefits across the globe. I am happy to report on several new initiatives to increase our international cooperation with the goal of improving patient care.

Collaboration with the European Society of Endocrinology on Clinical Practice Guidelines

The Endocrine Society and the European Society of Endocrinology (ESE) have reached a historic agreement to jointly develop Clinical Practice Guidelines providing

joint Clinical Practice Guideline program also will recognize global differences in access to diagnostic tools and therapies. This collaboration will kick off with the development of two inaugural guidelines: Diabetes in Pregnancy, led by the Endocrine Society, and Management of Corticosteroid Therapy, led by the European Society of Endocrinology.

We hope that this collaboration will be just the first of many opportunities to work collaboratively with the European Society of Endocrinology. This partnership establishes our organizations as international leaders in this effort and will serve as a model for international cooperation throughout the endocrine community. I see this as an opportunity for our organizations to learn and grow with the goal of providing the best care to patients worldwide.

Partnering with International Societies

Since **ENDO Online 2020**, we have partnered with several endocrine-related sister societies from around the world by participating in their own virtual meetings. We have collaborated on educational sessions and/or invited member speakers to virtually partake in the 22nd European Congress of Endocrinology e-ECE 2020 (September 5 – 9, 2020), EndoBridge in Turkey (October 22 – 24, 2020), The 17th Asia-Oceania Congress of Endocrinology and the 8th Seoul International Congress of Endocrinology and Metabolism (October 28 – 31, 2020), ENDORECIFE in Brazil (November 11 – 14, 2020), the 60th International Congress of the Mexican Society for Nutrition and Endocrinology (November 17 – 21, 2020), and the 34th Brazilian Congress of Endocrinology and Metabolism (November 28 – December 5, 2020). We value these opportunities to collaborate with international societies and hope that such partnerships will help us achieve our shared mission to accelerate scientific breakthroughs and improve patient care worldwide.

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evidence-based recommendations for clinical care and practice. Developing globally relevant guidelines will support the delivery of up-to-date care to patients worldwide. The

The participation of international members (and non-members) to our two most recent virtual events is evidence of how the global endocrine community has no barriers. At **ENDO Online 2020**, over 70% of the 27,000 registrants were from outside the U.S., spanning 140 countries. In mid-

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We look forward to growing our global outreach, both virtually and, eventually, in person, to continue pursuing our mission to unite, lead, and grow the global endocrine community.

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September, we held a virtual Clinical Endocrinology Update where 40% of the 1,090 participants were international, representing 49 countries.

We look forward to growing our global outreach, both virtually and, eventually, in person, to continue pursuing our mission to unite, lead, and grow the global endocrine community.

If you have any questions or comments, please contact me at president@endocrine.org.

Gary D. Hammer, MD, PhD
President, Endocrine Society



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FROM THE **EDITOR**

Obesity: An Epidemic Within an Epidemic

This month, *Endocrine News* takes a closer look at the ongoing and unrelenting epidemic of obesity and its effects on human health. Instead of a single cover story on the topic, this month we've devoted three features to this issue based on some of the latest research and recommendations from a couple of medical societies.

In "Primary Care: Pediatricians Urge Greater Access to Surgery for Severely Obese Youth" on page 26, Eric Seaborg addresses the latest set of guidelines from the American Academy of Pediatrics regarding bariatric surgery recommendations in severely obese young people. Referred to as an "epidemic within an epidemic," childhood obesity can not only be brought under control by these procedures but there is also the noted benefit of better overall health well into adulthood. Also the recommendations are in accordance with what the Endocrine Society recommends in its clinical practice guideline, "Pediatric Obesity: Assessment, Treatment, and Prevention" according to that guideline's committee chair, Dennis M. Styne, MD, who adds, "It has the same indications, the same contraindications, and recommends the same high-level, experienced, comprehensive team approach to bariatric surgery. And it confirms that children, even more than adults, are denied bariatric surgery — even when they meet the criteria that have been established."

On page 38, Kelly Horvath writes about a new study from the September issue of *Endocrinology* regarding obesity in COVID-19 patients. In "Undue Influences: Obesity, COVID-19, and Immune System Havoc," she discusses the findings of this study, which show that many disparities in COVID-19 patients' morbidity and mortality appear to be linked to weight, as well as gender and diabetes status. The study's lead author, Kanakadurga Singer, MD, states that given that obesity is a modifier of disease severity in COVID-19, "we think it is important that future clinical studies of COVID-19 treatments will include subjects from across the weight spectrum, especially treatments that modify the immune response." The authors go on to suggest that future trials should take patient weight into account to determine the most effective treatment protocols.

On page 22, Eric Seaborg opens his article, "Cause & Effect: Patients with Obesity and Thyroid Function Testing" with "The endocrine

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system and obesity can have a push-pull relationship,” which really sums up *all* of these features. However, this article looks at another guideline — this time from the European Society of Endocrinology — which states that patients with obesity should be routinely tested for thyroid function. Robert F. Kushner, MD, states that these new guidelines are structured as a logical set of practical and clinically useful recommendations that apply to patients who present with obesity, adding that “They not only identify when an

endocrinological workup and referral is recommended, but also provide specific guidance on commonly encountered medical co-morbid conditions that are seen in the obesity population.”

As always, if you have any questions, comments, or even ideas for future articles, feel free to email me at: mnewman@endocrine.org. 

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



ENDOCRINE NEWS IN THE NEWS

Back before the entire world shut down, we entered a few of our favorite designs and issues into the annual EDDIE and OZZIE Awards sponsored by *Folio*: magazine, and I'm proud to report that we've received five Honorable Mentions in various categories. Congratulations to the writers and designers involved and big congratulations to Catherine “Cat” Neill, who designed the OZZIE winning entries.

EDDIE Award: Best Full Issue – May 2020



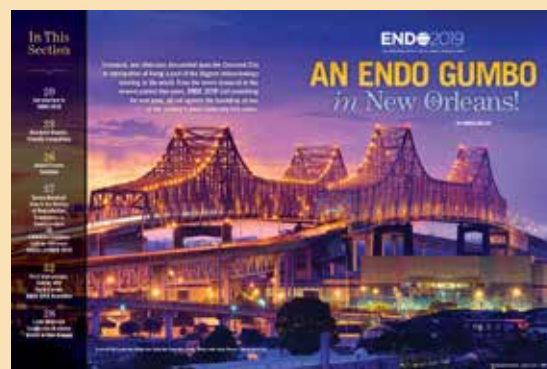
OZZIE Award: Best Feature Design
“Bare Benches” April 2020



OZZIE Award: Best Feature Design
“Untapped Resources” March 2020



OZZIE Award: Best Feature Design
“Beast Node” March 2020



OZZIE Award: Best Section Design
“An ENDO Gumbo” May 2019

ENDO 2021

ENDO 2021 Goes Virtual

The Endocrine Society will switch its annual meeting, **ENDO 2021**, to a fully virtual format.

“After thoughtful deliberation regarding the impact of COVID-19 on the global prospect and inclination for in-person events, we have decided to move forward with **ENDO 2021** in a virtual format,” says Society President Gary D. Hammer, MD, PhD. “We plan to keep intact the principal elements of **ENDO**, which will include top-flight educational programming, opportunities for attendees and industry partners to connect, and robust networking.”

The virtual meeting will be held in a state-of-the-art digital platform from March 20 – 23, 2021, the same dates **ENDO 2021** was originally slated to take place in San Diego, Calif.

ENDO 2021 registration is slated to open in early November. Accepted abstracts will be available for viewing online and published in a supplemental issue of the open access *Journal of the Endocrine Society*. Researchers can submit abstracts for **ENDO 2021** beginning Sept. 28 at: endocrine.org/abstracts.

“While we will miss the ability to network with colleagues in person, endocrine researchers and clinicians have embraced the ability to connect virtually,” Hammer says. “At times more than doubling live attendance, our other virtual events — **ENDO Online 2020**, Clinical Endocrinology Update 2020, and Endocrine Board Review 2020 — have garnered unprecedented, record-breaking participation during the worldwide pandemic. We look forward to coming together to share the latest findings in hormone science and breakthroughs in clinical care at **ENDO 2021**.”

The worldwide pandemic also forced the Society to cancel its annual meeting, **ENDO 2020**, in March. The Society featured select content planned for the meeting during **ENDO Online 2020**, a virtual meeting held in June with record attendance of more than 17,000.



Virtual CEU, EBR 2020 Reach Record Breaking Attendance



The Endocrine Society's first virtual Clinical Endocrinology Update (CEU) and Endocrine Board Review (EBR) meetings collectively attracted more than 1,700 global participants.

CEU 2020 had over 1,100 participants and EBR 2020 had over 600, setting records for both meetings as the largest to date in the Society's history.

CEU 2020, held September 10 – 12, provided an update on the latest diagnosis and treatment recommendations spanning nine endocrine topic areas. The virtual meeting featured both live and on-demand presentations. CEU session recordings are available for purchase. Highlights from this year include:

- ▶ 23 live sessions with the ability to interact directly with faculty;
- ▶ 21 on-demand presentations;
- ▶ 31 expert faculty members;
- ▶ three interactive ancillary symposia;
- ▶ three product theatre presentations; and
- ▶ Virtual exhibit hall.

Endocrine Board Review took place from September 16 to 18 and has long been considered an essential course for endocrinologists preparing to take the boards or practicing physicians seeking an intensive knowledge assessment. Designed as a mock exam, participants were able to engage directly with the experts during live Q&As.

Registrants can access endocrine.org/ceu2020 and endocrine.org/eb2020 content in the corresponding virtual meeting platforms through October 31, 2020.

The Journal of the Endocrine Society Launches Expert Endocrine Consult

The *Journal of the Endocrine Society* (JES) has announced a new type of article to broaden the journal's usefulness and effectiveness among endocrine fellows and practicing clinicians: "Expert Endocrine Consult."

"As a new journal, JES must accumulate data to be assigned an impact factor in Clarivate's Web of Science, but the Endocrine Society's internal calculations would be in the 2.0 – 2.4 range, an impressive result for a journal in only its fourth year of publication, with only three years of citation activity," writes J. Larry Jameson, MD, PhD, dean of the Perelman School of Medicine at the University of Pennsylvania in Philadelphia and editor-in-chief of the *Journal of the Endocrine Society*, in an editorial announcing "Expert Endocrine Consult."

"Expert Endocrine Consult" articles will use common clinical scenarios to spark discussions on things like differential diagnoses and best approaches to management and treatment, referencing all the relevant and recent literature. "We envisage these to resemble typical endocrine attending rounds, case conferences, or discussions at meet-the-professor sessions," Jameson writes.

The JES submission platform is now inviting "Expert Endocrine Consult" manuscripts. "I and my associate editors look forward to receiving your best examples of learning from common or rare patient presentations," Jameson writes.





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As the
consummate
pediatric
endocrinologist,
Howard had
all of the personal
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care of children
with complex
disorders.”**

Remembering Howard E. Kulin, MD

By Richard J. Santen, MD, Professor of Medicine, Division of Endocrinology and Metabolism, University of Virginia, Charlottesville

Howard E. Kulin, MD, passed away peacefully at age 83 on August 17, 2020, after a long illness. He is survived by his wife of 57 years, Hanne, and children Thomas, Eric, and Jacob as well as five grandchildren.

Several aspects of his career provide lessons for all endocrinologists. As the consummate pediatric endocrinologist, Howard had all of the personal qualities and talents necessary for superb care of children with complex disorders. He prided himself on his depth of knowledge regarding the pathophysiologic and clinical aspects of reproductive disorders in children.

Certain characteristics define a superb clinician, most important of which is communication. When talking with patients, Howard intuitively knew how to use language at the level that they could understand. With parents, he could simplify complex concepts and help them to comprehend the key aspects of their child's condition. He presented himself to families in a way that inspired confidence and gained a high degree of respect by both the patients and families. At a completely different level when teaching fellows and other physicians, he could describe the complexity of the conditions in great depth. Although Howard was a productive research investigator, he considered the most important aspect of his career to be a practicing pediatric endocrinologist.

As with most successful individuals, he was influenced by a cadre of internationally recognized mentors and colleagues. Key mentors were the late Melvin Grumbach, chair of pediatrics at the University of California, San Francisco, and past-president of the Endocrine Society, and Mortimer Lipsett and Griff Ross at the NIH. His NIH colleagues included several future leaders in endocrinology including Bert O'Malley, Peter Kohler, Bill McGuire, Lynn Loriaux, Glenn Braunstein, Bruce Nisula, and Wayne Bardin.

Howard had a keen sense of the importance of certain things and the ability to put these in perspective. Whereas most academic physicians put their most prestigious diplomas and awards on their wall, displayed prominently in Howard's office was his diploma from preschool: Diploma — graduate of Mrs. Schwartz Nursery School. He stated that he was very proud of that. This is a man that will be missed by all who came in contact with him over the years. — *Andrea Manni, MD, and Alan Rogol, MD, PhD, provided input to this article.*

For an extended version of this article, go to: www.endocrine.org/howard_kulin.



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BY DEREK BAGLEY
Senior Editor

Clinical Trial Sees Positive Results in Treatment of Prader-Willi Syndrome



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These positive results of the Phase 3 CARE-PWS study strengthen the belief that intranasal carbetocin appears to be an effective treatment for patients living with PWS.
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The Phase 3 CARE-PWS clinical study for the treatment of Prader-Willi Syndrome (PWS) last month returned topline results evaluating LV-101 (intranasal carbetocin). This syndrome is a complex, neurodevelopmental disorder that occurs in approximately one in 16,000 births and is characterized by a false state of starvation and associated hyperphagia to which a deficiency in oxytocin is believed to be contributory. LV-101 is a selective oxytocin-receptor agonist.

CARE-PWS tested two doses of LV-101 versus placebo with an even randomization (1:1:1), specifying the 9.6-mg dose as the primary endpoint and the 3.2-mg dose as the first secondary endpoint. After consultation with the Food and Drug Administration (FDA), enrollment was closed early due to COVID-19 with 119 evaluable patients in the Primary Analysis Set.

While the study did not meet its primary outcome measurements evaluating the 9.6-mg dose of LV-101 (intranasal carbetocin), statistical significance was achieved with the 3.2-mg dose as evaluated by the Hyperphagia Questionnaire for Clinical Trials (HQ-CT) score ($p=0.016$) as the first secondary endpoint. When pooling the two dose arms of LV-101, per a pre-specified analysis, the change in HQ-CT score from baseline to week eight resulted in a p -value of 0.055. Consistency in benefit/response was observed in the 3.2-mg dose arm across other key secondary endpoints, including clinical global impression of change (CGI-C; $p=0.027$) and anxiety and distress behaviors, as evaluated by the PWS Anxiety and Distress Behaviors Questionnaire (PADQ; $p=0.027$). Neither dose demonstrated a statistically significant effect on the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS). LV-101 was generally well-tolerated in the study.

“With no approved therapies to address their most challenging symptoms, patients with PWS continue to suffer from insatiable hunger and anxiety, which are debilitating and can be life-threatening if left untreated,” says Endocrine Society member Jennifer L. Miller, MD, a pediatric endocrinologist at the University of Florida. “These positive results of the Phase 3 CARE-PWS study strengthen the belief that intranasal carbetocin appears to be an effective treatment for patients living with PWS.”

Upon completion of the placebo-controlled period (i.e., after a week), all patients were transitioned into the long-term follow-up period and received intranasal carbetocin. At more than week eight, 98% of patients enrolled in CARE-PWS elected to enter the long-term follow-up period. Of note, further improvements in scores were observed and subsequently maintained after a week in both dose arms.

Safety data show that LV-101 (intranasal carbetocin) was generally well-tolerated. Treatment emergent adverse events (TEAEs) occurring in 5% or more of participants during the placebo-controlled period (TEAEs $\geq 5\%$) at the 3.2-mg dose include headache (16.3% vs. 7.0% for placebo), flushing (14.0% vs. 0.0% for placebo), diarrhea (9.3% vs. 2.3% for placebo), nasal discomfort (7.0% vs. 2.3% for placebo), pyrexia (7.0% vs. 0.0% for placebo), and upper respiratory tract infection (7.0% vs. 4.7% for placebo), all of which were considered mild or moderate. TEAEs $\geq 5\%$ at the 9.6-mg dose include flushing (20.5% vs. 0.0% for placebo), epistaxis (13.6% vs. 2.3% for placebo), and headache (9.1% vs. 7.0% for placebo), all of which were also mild to moderate in severity.

Levo Therapeutics is funding the study and made the announcement.

Positive Results Announced in Type 1 Diabetes Clinical Trial of Microbe-Based Therapy

A clinical trial investigating a possible novel treatment of early-onset type 1 diabetes last month met the primary endpoint assessing the safety and tolerability of a new class of microbe-based therapeutic agents. Precigen ActoBio is evaluating this therapy — AG019 ActoBiotics — as a monotherapy and in combination with teplizumab.

AG019 is formulated as an oral capsule consisting of engineered *Lactococcus lactis* specifically modified to deliver autoantigen human proinsulin (hPINS) and the tolerance-enhancing cytokine human interleukin-10 (hIL-10) to the mucosal lining of the gastrointestinal tissues. Administration of AG019 is designed to induce specific regulatory T cells (Tregs) that could reduce or eliminate the destruction of insulin-producing cells, potentially stabilizing or improving insulin production.

The Phase 1b open-label portion of the study evaluates the safety and tolerability of AG019 administered as a single dose and repeated daily doses as a monotherapy in adult and adolescent patients. The primary endpoint for assessing safety and tolerability is treatment-emerging adverse events (TEAEs) reported up to six months after treatment initiation. Nineteen patients were treated in the Phase 1b monotherapy portion of the study, and 17 patients were evaluated at six months. The Phase 2a portion of the study is currently ongoing and investigates the safety and tolerability of AG019 in combination with teplizumab (PRV-031), which is currently under investigation in the PROTECT Phase 3 study for the treatment of newly diagnosed type 1 diabetes.

Key findings from the Phase 1b AG019 monotherapy portion study for patients six months after treatment initiation include:

- The study met its primary endpoint demonstrating safety and tolerability. No serious or severe TEAEs were reported in any of the patients treated with AG019 monotherapy, and no patient discontinued treatment.
- Eight-week treatment with AG019 monotherapy was safe and well-tolerated in daily dosages up to 6×10^{11} CFU (colony-forming units) in adult and adolescent patients with type 1 diabetes.
- There was no evidence for systemic exposure of bacteria and proteins (hPINS/hIL-10) in the circulation, confirming the safety profile of AG019. The analysis of fecal samples confirmed gastrointestinal exposure of AG019 in most treated patients.
- C-peptide levels, a common biomarker used to measure pancreatic beta cell function, demonstrate slower decline in C-peptide levels in 67% of adult patients (six out of nine) receiving AG019 monotherapy with 44% of these adult patients (four out of nine) showing stabilization of mean four hours C-peptide area under the curve (AUC) levels at six months (within 9.7% of the baseline level). This was based on the comparison of the median percent decline in mean four hours C-peptide AUC from baseline between patients receiving AG019 monotherapy and patients who received placebo from previous studies.

“Though preliminary, C-peptide data for the Phase 1b AG019 monotherapy is encouraging in this limited data set,” says Kevan Herold, MD, professor of immunobiology and of medicine at Yale University and principal investigator for the AG019 Phase 1b/2a clinical study. “The positive topline data from the Phase 1b monotherapy portion of study provides compelling rationale for continued clinical development of this promising investigational therapeutic candidate.”



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When the extracellular vesicles carrying inflammatory molecules interact with breast cancer cells, we see they are able to modify their behavior, so that they become more aggressive with increased capacity to invade other tissues.

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Increased Breast Cancer Risk in Obesity Linked to Fat Cell Chemicals

Obesity increases the release of tumor-promoting molecules from fat tissue and is associated with an increased risk of breast cancer, according to a study published in *Endocrine-Related Cancer*. The study found that fat tissue from people with obesity released increased amounts of extracellular vesicles (EVs) enriched in harmful and inflammatory molecules into the blood stream, which can alter breast cancer cells to become more aggressive and invasive. These findings suggest that substances released from fat tissue may increase tumor malignancy that could lead to new therapeutic targets and improved cancer treatments.

Researchers led by Christina Barja-Fidalgo, PhD, of the State University of Rio de Janeiro, Brazil, point out that obesity is a global, public health problem with rapidly increasing rates that has been linked to increased risk of breast cancer. Breast cancer is the most common cancer among women, and despite the well-known association between obesity and increased breast cancer risk, few studies have evaluated the role of fat tissue. Fat tissue is known to release inflammatory molecules that can increase the risk of diabetes, cardiovascular disease, and cancer. They also produce EVs that carry inflammatory molecules and other substances, including enzymes and molecules that are involved in cell-to-cell communication. More of these vesicles are released from the fat tissue of people with obesity. A better understanding of how the contents of EVs may affect cancer cells could help explain the link between obesity and a poor cancer prognosis.

The researchers analyzed the effects of the fat tissue-derived EVs on breast cancer cells. Fat tissue was obtained from obese patients who

had undergone weight-loss surgery and from lean people undergoing plastic surgery. These tissues were incubated in culture for 24 hours, and the amount and type of substances secreted from both were compared. The analysis showed that the fat tissue from obese patients secreted higher amounts of inflammatory molecules and also produced a greater number of small vesicles, which may increase breast cancer risk.

“When the extracellular vesicles carrying inflammatory molecules interact with breast cancer cells, we see they are able to modify their behavior, so that they become more aggressive with increased capacity to invade other tissues,” Barja-Fidalgo says.

Findings: These findings demonstrate how obesity can induce alterations in fat tissue function, which may explain how obesity contributes to increased breast cancer risk, as well as why obese women are more likely to have a worse prognosis.

Barja-Fidalgo adds: “Identifying these harmful fat tissue secretions in the blood of obese patients could be a new parameter to be monitored, as an indicator of cancer progress. Understanding the content of the vesicles released by fat tissue during obesity may provide new therapeutic targets and improve cancer treatment.”

Barja-Fidalgo now plans to investigate the characteristics and specific contents of extracellular vesicles released by fat tissue, to determine the main molecules associated with obesity-induced alterations in tumor cells and their modes of action.

Anorexia May Stunt Young Women's Growth

Girls with anorexia nervosa can have stunted growth and may not reach their full height potential, according to a new study published in *The Journal of Clinical Endocrinology & Metabolism*.

People with anorexia nervosa (AN) have an intense fear of gaining weight and a disturbed body image (such as thinking they are fat even when they are very underweight). Researchers led by Dalit Modan-Moses, MD, of the Edmond and Lily Safra Children's Hospital, Chaim Sheba Medical Center, in Tel Hashomer, Israel, point out that adequate nutrition is essential for normal growth, and while there have been studies looking into how AN affects growth patterns in adolescents, reports have conflicted over the effect of AN on height and permanence of growth impairment. "Moreover, previous studies have not assessed the association between hormonal changes occurring during weight rehabilitation and catch-up growth or [adult height] of AN patients," the authors write.

"Our findings emphasize the importance of early and intensive intervention aiming at normalization of body weight, which may result in improved growth and allow patients to



reach their full height potential," Modan-Moses says. "We suggest that the height impairment is a marker for other complications of anorexia nervosa affecting the person's overall health in several aspects: bone health, cognitive function, and problems with pregnancy and childbirth later in life. Early diagnosis and treatment could prevent, or at least reduce, the risk of these complications."

The researchers studied 255 girls around 15 years old who were hospitalized for anorexia nervosa. They measured their height at the time of admission, discharge, and at adult height and found it was lower than expected. Adult height was significantly shorter than expected when compared to the genetic potential according to the average of the patient's parents' heights.

"Whereas the premorbid height of female adolescent AN patients is normal, linear growth retardation is a prominent feature of their illness," the authors conclude. "Weight restoration is associated with catch-up growth, but complete catch-up is often not achieved."

The authors go on to write that their findings point to the need for weight gain over an extended period to prevent long-term, irreversible tissue damage, and this study may even have implications for adolescents suffering from inflammatory bowel disease and cystic fibrosis. "This study may have implications for the management of malnutrition in adolescents with other chronic diseases in order to achieve optimal adult height and bone health," Modan-Moses says.



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This study may have implications for the management of malnutrition in adolescents with other chronic diseases in order to achieve optimal adult height and bone health.

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ENDO 2021

Virtual Event • March 20 – 23, 2021

KEY DATES **ABSTRACT DEADLINE • October 29, 2020**
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The all-virtual **ENDO 2021** will mirror the principal elements of **ENDO**, including top-flight educational programming, an interactive EXPO center, and networking opportunities. **ENDO 2021** is the leading global meeting for endocrinology research and clinical care. Join us for the most well attended and valued translational endocrinology meeting in the world. Bringing together leading experts, researchers, and the most respected clinicians in the field, **ENDO 2021** represents a convergence of science and practice that highlights and facilitates breakthrough discoveries in the field of endocrinology. Spend time connecting with peers and colleagues, exchanging ideas and information, and getting out in front of the latest trends and advancements in hormone health.

Abstract submission will still occur as planned, and abstracts will be presented virtually to all participants. All accepted abstracts will be published in a supplemental issue of the open access *Journal of the Endocrine Society* and will be assigned a DOI and indexed in PubMed and PubMed Central. The submission window opened on September 28 at: endocrine.org/abstracts.

www.endocrine.org/endo2021

CMHC Live Online

October 21 – 24, 2020

For the first time in its 15-year history, the Cardiometabolic Health Conference (CMHC) will deliver a historic cardiometabolic educational event entirely online as the 2020 Annual CMHC Live Online: Evolving Paradigms in Cardiometabolic Care: Disparities & Advancements. Led by leading clinical experts, this conference will present the latest information and updates across the cardiometabolic healthcare industry as well as provide a deep dive into the intersection of social determinants of health and cardiometabolic care. Through an advanced learning structure, this offering will help you build a practical strategy through which to both keep your practice up to date and effectively navigate the challenges of inequity in healthcare.

www.cardiometabolichealth.org

ObesityWeek® 2020

November 3 – 6, 2020

ObesityWeek® is home to the latest developments related to obesity from cutting-edge basic and clinical research to state-of-the-art treatment and prevention to the latest efforts in advocacy and public policy. Present your latest work and stay up to date on the latest advances in the field by attending the interactive, all-virtual ObesityWeek® 2020. The overarching theme for ObesityWeek® 2020 will be Pathways to Precision Obesity Care. A key component in the development of precision care for obesity is recognizing and understanding the inherent heterogeneity in both the patterns of development and expression of obesity, and ObesityWeek® 2020 programming will draw particular attention to these topics.

www.obesityweek.org

Diabetes and Its Complications

Livestream

November 12 – 14, 2020

Anyone who provides care for people with diabetes knows that these patients often have a myriad of comorbidities and complications, and that optimizing their care is frequently complex and challenging. It is with these challenges in mind that Harvard Medical School faculty have developed this CME program, which will provide comprehensive updates, practice recommendations, and the newest evidence-based strategies for the treatment and care of the person with or at risk for diabetes.

<http://hmsdiabetescourse.com/>

Project ECHO

Project ECHO events are live, interactive seminars using virtual platforms that allow participants to connect in real time to provide feedback on cases. Launched at the University of New Mexico in 2003, ECHO stands for Extension of Community Healthcare Outcomes, and it is built on the idea that while not everyone can be a specialist, all patients deserve access to specialty care.

Type 1 Diabetes Care and Management

Open to all clinicians, this virtual program seeks to educate primary care providers, care teams, and non-diabetes specialists in best practices for type 1 diabetes care and management. With many therapeutic and pharmacological options available, clinicians need additional resources to stay up to date. This program features live, interactive seminars and on-demand webinars, and will focus on evidence-based methods for addressing type 1 diabetes with a goal of improving health-related quality-of-life for patients and empowering clinicians to provide the best possible care.

www.endocrine.org/project_echo_type1diabetescare

Using Insulin in Type 1 Diabetes

The second ECHO in this series will feature Diana Isaacs, PharmD, from Cleveland Clinic as she discusses different approaches to using insulin to treat people with type 1 diabetes. By the end of this program, attendees will be able to: Compare and contrast the various insulin options for type 1 diabetes; design an insulin treatment plan for a person newly diagnosed with type 1 diabetes; and modify an insulin regimen based on glucose data and individual factors. This live, interactive ECHO will take place on Thursday, October 15, 2020 at 7pm ET.

www.endocrine.org/project_echo_insulin_type1_diabetes

INTERNATIONAL ITINERARY

EndoBridge 2020

Virtual Event

October 22 – 24, 2020

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

www.endobridge.org

AOCE – SICEM 2020

Virtual Congress

October 28 – 31, 2020

The 17th Asia – Oceania Congress of Endocrinology and the 8th Seoul International Congress of Endocrinology and Metabolism will take place in Seoul, Korea. AOCE – SICEM 2020 will provide a platform to network with colleagues, exchange ideas, discover novel opportunities, and increase professional knowledge. It will be held at the Swiss Grand Hotel in Seoul.

<http://sicem.kr/main.asp>

ICE 2020: 19th International Congress of Endocrinology

Virtual Meeting

February 2021

19th International Congress of Endocrinology (ICE 2020), 4th Latin American Congress of Endocrinology (CONLAEN), and 13th Congress of the Argentine Federation of Endocrinology Societies (FASEN) is organized by MCI Group – Argentina. Topics to be discussed include: big data and its impact in health, human diseases, artificial intelligence, and big-data mining; thyroid cancer diagnosis and treatment; advances in pheochromocytomas and paragangliomas; the tsunami of diabetes in lower- and middle-income countries; preserving reproduction in cancer patients; and so much, much more.

www.ice-2020.com

BY DEREK BAGLEY



Daniel J. Drucker, MD



Joel F. Habener, MA, MD

Gut Instincts:

The Endocrinologists Behind the 2020 Warren Alpert Foundation Prize

Endocrine Society members Daniel J. Drucker, MD, and Joel F. Habener, MA, MD, received the 2020 Warren Alpert Foundation Prize on October 1. They talk to *Endocrine News* about their award-winning research of key intestinal hormones as well as their distinguished careers and what this award means to them.

On October 1, the Warren Alpert Foundation Prize was presented in a virtual symposium to a trio of researchers 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.

Two longstanding Endocrine Society members were recognized: Daniel J. Drucker, MD, professor of medicine, University of Toronto, Toronto, Canada; editor-in-chief, *Endocrine Reviews*; and Joel F. Habener, MA, MD, chief of Laboratory of Molecular Endocrinology, Massachusetts General Hospital; professor of medicine, Harvard Medical School in Boston, Massachusetts; along with 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. The understanding of the complex hormonal symphony underlying the regulation of metabolism and gastrointestinal function flows from the work of many scientists. However, it is the seminal discoveries of Holst, Habener, and Drucker that propelled the field forward and enabled the design of several new classes of disease-altering treatments.

The three award winners identified a family of glucagon-like peptides in the 1970s and 1980s and since then have led the field of metabolism research with studies that went from basic science observations to the clinic and ultimately enabled the development of several new classes of medications for the treatment of metabolic disorders..

Endocrine News caught up with Drucker and Habener to discuss what this prize means for the field of endocrinology, the work that led to this recognition, and where we go from here.

What does this mean to you and your lab to have your work recognized like this?

Joel F. Habener: The Warren Alpert Foundation Prize is a very prestigious award given to workers whose discoveries have made an impact in the treatment of disease. I am honored to receive this award, shared with my colleagues Drs. Drucker and Holst, on behalf of all of my co-workers over the years. My lab members, current and past, are proud to have this award bestowed on me as a spokesman for our accomplishments. Favorable peer recognition is one of the highest awards one can receive as a scientist.

It is important to recognize that the work was done by the lab staff including fellows, post-docs, students, visiting scientists,

technicians, under my guidance, as well as with numerous collaborators.

Daniel J. Drucker: The Warren Alpert Foundation Prize recognizes the importance of this series of discoveries for people with diabetes, obesity, cardiovascular disease, and short bowel syndrome. Importantly, it is also terrific recognition for all the trainees and colleagues who have made so many important contributions to this field along the way.

I should note that hundreds of talented scientists and clinician investigators have done important work over the past few decades to slowly build the body of knowledge enabling the successful translation of this basic science to the clinic. It really does take a village to help make a safe and effective medicine.

What was your reaction when you heard that you would be receiving the 2020 Warren Alpert Prize?

JFH: It was quite a surprise when I received the email from Harvard Medical School and the phone call from Dean George Daley informing me of the award. I was aware of the existence of the Alpert award as the highest award given by Harvard Medical School in recognition of outstanding scientific achievement. However, I did not consider that I would ever be an awardee.





“ It seems perfectly reasonable to include the field of endocrinology and metabolism in the running for the prize as we see the increasing prevalence of obesity and diabetes with associated metabolic and cardiovascular disorders (now including COVID-19). **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.**”

— JOEL HABENER, MA, MD, CHIEF OF LABORATORY OF MOLECULAR ENDOCRINOLOGY, MASSACHUSETTS GENERAL HOSPITAL; PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL IN BOSTON, MASSACHUSETTS

DJD: It is very gratifying to see that basic science work in the area of gut endocrinology can ultimately find an application in human health and provide advances in care not previously attainable with conventional established therapies.

This is the first time in many years that the prize has been awarded for endocrinology. What does this mean for you to have the field recognized like this?

JFH: It seems perfectly reasonable to include the field of endocrinology and metabolism in the running for the prize as we see the increasing prevalence of obesity and diabetes with associated metabolic and cardiovascular disorders (now including COVID-19). 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. 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.

Can you give us a little background and tell us a little about your involvement in this work? What made you want to look at gut hormones as potential therapeutic targets?

JFH: My interests and work in this field evolved stepwise with several discoveries over several decades starting in the middle 1970s. Earlier, I had spent two years (1967 – 1969) at the National Institutes of Health (NIH) conducting research in molecular biology. That was a time when recombinant DNA technology was being developed and my experience at the NIH convinced me to pursue a career in basic discovery research and to exploit the power of recombinant DNA technology. After completing my clinical training in internal medicine at the MGH in 1972, and further basic laboratory research on the biosynthesis of parathyroid hormone under the tutorship of John Potts at the MGH and Alexander Rich at MIT, it was my great fortune to become an investigator with the Howard Hughes Medical Institute (who provided support for 31 years). At the same time the MGH appointed me as the chief of a newly established Laboratory of Molecular Endocrinology.

To begin my independent research career at the MGH, I chose to explore the biosynthetic pathways of glucagon and somatostatin, two of the three major hormones produced by the endocrine

pancreas (islets of Langerhans). Insulin, the third hormone made in the islets, had recently been found by the Donald Steiner laboratory to be synthesized in the form of a large prohormone (proinsulin) serving as a precursor protein from which insulin was formed by the joining of two peptide fragments cleaved from proinsulin by an endopeptidase (prohormone convertase) in the beta cells. We chose to go about pursuing the goal of determining the structures (amino acid sequences) of the initial translation products of glucagon and somatostatin using a recombinant DNA technology approach. As a source of tissue, we used the Brockmann body of the Atlantic anglerfish, in which the endocrine cells of the pancreas are contained apart from the exocrine pancreas, providing a rich source of the mRNAs encoding the hormones.

The recombinant DNA approach succeeded, resulting in the discoveries of the prohormone for somatostatin and two distinct non-allelic prohormones for glucagon in the late 1970s. Each of the individual anglerfish proglucagons encoded the fish versions of glucagon and a second peptide resembling but distinct from glucagon. We 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. GIP had been previously identified and defined by Hans Creutzfeldt as an “incretin,” a factor produced in the intestines in response to meals or an oral glucose load, that augmented glucose-dependent insulin secretion. The seemingly sequence similarities of the anglerfish GRPs to GIP thusly raised the possibility that the anglerfish GRPs might be related to mammalian incretin factors. Thusly, the determination of the structures of the mammalian proglucagon became an important initial goal. This undertaking was achieved in the ensuing two to three years, establishing the amino acid sequences of the rat proglucagon mRNA, and the rat proglucagon gene in my lab (1984), and the guinea pig and human counter parts by Graeme Bell in William Rutter’s lab at UCSF (1983), and Donald Steiner’s lab (1986).

The remarkable findings in the studies of mammalian proglucagons was that they contained the sequence of glucagon, and not one but two additional GRPs, re-named GLP-1 and GLP-2. One of the GLPs (GLP-1) appears to be the homolog of anglerfish GRP. 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.

DJD: One of my projects was to try and uncover a role for GLP-1. I examined many cell lines for GLP-1 responsivity, reasoning that like glucagon, GLP-1 might stimulate cyclic AMP — I finally found a robust cyclic AMP response to GLP-1, together with stimulation of glucose-dependent insulin secretion, using islet beta cell lines.

A decade later, I stumbled upon the first actions of GLP-2, which had also eluded detection till the mid-1990s. We found that GLP-2 was a potent stimulator of bowel growth, recapitulating a subset of actions that had been described in case reports of a few rare patients with glucagon-producing tumors. Having learned a bit about intellectual property in the Habener lab, I also filed a series of patents describing GLP-2 action for the treatment of intestinal disorders but could not have predicted that teduglutide, a GLP-2 analogue originally developed in our lab, would be approved decades later for the treatment of short bowel syndrome. Most gratifyingly, teduglutide enables 10% – 20% of people with SBS to discontinue intravenous feeding, and a much greater proportion of teduglutide-treated subjects reduce the number of nights per week of IV nutrition required to sustain their fluid and energy requirements. Collectively, these results have made a big difference in the quality of life for some people with short bowel syndrome.

Dr. Habener, tell us a little about bringing Dr. Drucker on as a fellow.

JFH: The word had gotten out that our lab had discovered some novel glucagon-related peptides that might be important. As a consequence, Dr. Drucker was encouraged to apply for a position in my lab by his Toronto mentor Gerald Burrow to work on GLP-1 and to obtain some basic training in laboratory research. It was obvious from his outstanding references that Daniel was a superb applicant, so I readily accepted him. Soon after his arrival, I became struck by his intense dedication to learning the technology but also applying the technology to address questions concerning how GLP-1 functions in pancreatic beta cells. 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. 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.



“ It is amazing, today, to see that a GLP-1R agonist has also been approved for and is the number one selling prescription medicine for obesity. **Moreover, GLP-1R agonists reduce the rates of heart attacks, stroke, and death in people with diabetes at risk for cardiovascular disease, which we could not have predicted back in the early 1980s.”**

— DANIEL J. DRUCKER, MD, PROFESSOR OF MEDICINE, UNIVERSITY OF TORONTO, TORONTO, CANADA; EDITOR-IN-CHIEF, *ENDOCRINE REVIEWS*

Dr. Drucker, what was it like going to work in Dr. Habener's lab?

DJD: I was very fortunate as a MD with no lab research experience, to be offered an opportunity for postdoctoral research studies in the lab of Dr. Joel Habener in 1983. Joel, himself a MD graduate, was known for providing training opportunities in the new science of molecular biology early in the 1980s. The laboratory, at the Massachusetts General Hospital, was populated by many talented colleagues and was a terrific environment in which to learn science.

Frankly, I was originally supposed to work on thyroid hormone and TSH action in the Habener lab; however, this thyroid work was transitioning to the Brigham and Women's Hospital under the direction of Dr. Bill Chin, so I was reassigned to work on the glucagon gene. I just wanted to learn molecular biology, and the project did not make a big difference at the time. In hindsight, I was so fortunate to be at the right place and time to benefit from the opportunity to work on the glucagon gene.

The lab was well-funded, and they had just cloned the glucagon gene, which encoded glucagon-like peptides with no known biological function.

This was many years of hard work. Can you share some highlights? Any eureka moments or disappointing moments?

JFH: There were several pleasant surprises along the way and remarkably few disappointments, attesting to the validity of the concept that GLP-1 is truly an active metabolic peptide hormone with many diverse actions. I recall our satisfaction when we identified the active GLP-1 peptide was the 9-36a/37 and not the anticipated amino-terminally extended 1-36a/37 peptide (Mojsov, et al. 1987).

Another finding of great satisfaction (and relief) was that in human subjects with and without diabetes, GLP-1 administration lowered blood glucose levels and did so without causing hypoglycemia. This was an important difference compared to insulin, which has the serious side effect of hypoglycemic shock. The therapeutic index for insulin therapy is narrow, whereas with GLP-1 therapy there is complete safety regarding hypoglycemia. There appeared to be a “glucostat” built into the actions of GLP-1 that required a plasma level of glucose of 60 mg/dl or higher

for GLP-1 to effectively stimulate insulin secretion. We referred to this property of GLP-1 as the “glucose competence concept” (Holz, et al. 1993).

Later studies clearly demonstrated that GLP-1 stimulated both the growth and survival of the pancreatic beta cells that produce insulin. Surprisingly, we discovered that injuries to beta cells produce chemokines, such as SDF-1 that stimulate the glucagon-producing pancreatic alpha cells that lie adjacent to the beta cells in the islets to produce GLP-1. The GLP-1 so produced repairs beta cell injury and stimulates their growth. The mechanism for this induction of GLP-1 production in alpha cells involves the induction of the expression of the prohormone convertase PC1/3 that cleaves GLP-1 from proglucagon.

In this regard, we realized that the alpha cells in the islets appear to serve as guardians of the beta cells. The alpha cells are so to speak on standby next to the beta cells, and when the beta cells are injured, such as by glucotoxicity, they secrete factors that switch on the production of GLP-1 in alpha cells that then rescues the injured beta cells and nurtures them back to health. Remarkably, shortly after we made this discovery, it was shown that severe experimentally induced injuries of beta cells induce alpha cells to transdifferentiate into beta cells (Pedro Herrera lab.) This is a final sacrifice of the guardian alpha cells to the health of beta cells and is a testimony to how important insulin made by beta cells is to survival of the organism.

A quite rewarding finding was that the GLP-1-derived nonapeptide, GLP-1(28-36)amide was bioactive in mice and cultured hepatocytes and beta cells. To explain the increasing evidence pointing to receptor independent actions of GLP-1 in a number of tissues, I had postulated that the C-terminal region of GLP-1 formed a cationic amphipathic helical structure and would be cleaved from GLP-1 by the endopeptidase, neprilysin (NEP 24.11) based on a report by Hupe-Sodemann, et al. 1995. When the studies were carried out, they completely supported the prediction that the nonapeptide mimicked the receptor-independent actions of GLP-1. A recent study reported by the Mansoor Husain lab in Toronto showed that the GLP-1 nonapeptide attenuates post-ischemia reperfusion injury in the hearts of mice and does so by inhibiting fatty acid oxidation (Siraj, 2020).

Remarkably, the nonapeptide does not bind to the GLP-1 receptor but rather appears to enter cells via a cell-penetrating


mechanism and then targets to mitochondria where it modulates energy metabolism. The peptide increases basal energy expenditure in diet-induced obese mice resulting in an inhibition of weight gain, reduces oxidative stress in pancreatic beta cells, and reduces hepatic glucose production.

DJD: Although exciting at the time, I don’t think any of us could have fully predicted the translational story that unfolded gradually over several decades. However, based on these early findings in 1980 – 1982, Joel Habener filed the first patent on the actions of GLP-1 to treat diabetes, so he clearly understood the potential of these very early experimental results.

It is amazing, today, to see that a GLP-1R agonist has also been approved for and is the number one selling prescription medicine for obesity. Moreover, GLP-1R agonists reduce the rates of heart attacks, stroke, and death in people with diabetes at risk for cardiovascular disease, which we could not have predicted back in the early 1980s.

What’s next for your lab? How will this award help you with your upcoming work?

DJD: I am optimistic that GLP-1-based drugs may find new applications in the clinic, perhaps in the treatment of non-alcoholic steatosis, or in the therapy of one or more neurodegenerative disorders. So, there is still a great deal of work to do to explore the mechanisms and therapeutic potential of gut hormone action, and I feel very privileged to be able to contribute to this area of science.

JFH: Our current work and future plans are to explore the mechanisms involved in the actions of the two small peptides, a nonapeptide and a pentapeptide, derived from GLP-1 on energy metabolism in mitochondria. Our preliminary studies point to a direct interaction of the peptides with both the fatty acid oxidation and the apoptosis pathways in mitochondria. The recognition obtained from the award should enhance interest in our studies, and the award money itself will be helpful in providing support for the work. 

A close-up photograph of a hand tipping a white domino in a line on a dark wooden surface. The dominoes are arranged in a row, and the hand is positioned to tip the last one. The background is dark and out of focus.

Cause & *Effect*:

Patients with Obesity and Thyroid Function Testing

According to a new guideline from the European Society of Endocrinology, patients with obesity should be routinely tested for thyroid function. However, testing for other endocrine-related conditions should be guided by the presence of symptoms.

BY ERIC SEABORG

The endocrine system and obesity can have a push-pull relationship.

Some endocrine disorders — such as hypothyroidism and Cushing's syndrome — can cause weight gain and push patients toward the metabolic perturbations related to obesity. Obesity can pull patients toward endocrine dysfunction such as gonadal dysfunction, hypothalamic-pituitary-adrenal axis abnormalities, insulin resistance, and more.

This complexity can confuse the assignments of causes and effects and make it hard to ascertain the most effective testing strategies. The European Society of Endocrinology recently weighed in with help. “Endocrine Work-up in Obesity” is a new clinical practice guideline with evidence-based advice on testing in a host of conditions. It was published in the January issue of the *European Journal of Endocrinology*.

“An increased BMI leads to a number of hormonal changes,” the guideline notes. “Concomitant hormonal diseases can be present in obesity and have to be properly diagnosed — which in turn might be more difficult due to alterations caused by body fatness itself.”

But regardless of any testing strategies, the guideline underlines that “weight loss in obesity should be emphasized as key to restoration of hormonal [balances].” Weight loss is likely to be a more effective treatment for obesity-related conditions than attempting to treat the conditions separately and independently.

The guideline's main sections are devoted to thyroid function, hypercortisolism, hypogonadism in males, gonadal dysfunction in females, and “other hormones.”

Thyroid Function's Special Place

Given the high prevalence of hypothyroidism in obesity, the guideline recommends that all patients with obesity should be tested for thyroid function — the only condition for which it recommends testing without the need for signs and symptoms.

The guideline recommends thyroid screening because of the prevalence, but also because hypothyroidism “could potentiate weight gain and worsen comorbidities in obesity, and because assessment is simple, and treatment is inexpensive and safe.”



The guideline notes that it is worth testing for hypothyroidism because the “symptoms of hypothyroidism (such as fatigue, depression, cramps, menstrual disturbance, or weight gain) are nonspecific and can be confused with those of obesity. If ‘true’ hypothyroidism is present, it potentiates the risk of obesity to develop cardiovascular risk factors and features of metabolic syndrome. Hypothyroidism contributes to an unfavorable lipid profile, and thus, potentially increases vascular risk. Finally, untreated hypothyroidism could blight the attempts at losing body weight.”

The testing should be based on thyroid-stimulating hormone, and if TSH is elevated, free T4 and antibodies should be measured.

“The guidelines ... not only identify when an endocrinological workup and referral is recommended, but also provide specific guidance on commonly encountered medical co-morbid conditions that are seen in the obesity population ... **They do not appear to conflict with recommendations and standards used in the U.S.**”

— ROBERT F. KUSHNER, MD, PROFESSOR OF MEDICINE AND MEDICAL EDUCATION; DIRECTOR, CENTER FOR LIFESTYLE MEDICINE AT NORTHWESTERN UNIVERSITY FEINBERG SCHOOL OF MEDICINE, CHICAGO, ILL.; MEMBER, ENDOCRINE SOCIETY'S "THE SCIENCE OF OBESITY MANAGEMENT: AN ENDOCRINE SOCIETY SCIENTIFIC STATEMENT" GUIDELINE COMMITTEE

Hypercortisolism

“With the exception of screening for hypothyroidism, most endocrine testing is not recommended in the absence of clinical features of endocrine syndromes in obesity, and likewise hormone treatment is rarely needed,” writes John P.H. Wilding, MD, in a commentary that accompanied the guideline. Wilding is professor of medicine at the University of Liverpool in the U.K.

Testing for hypercortisolism should not be performed routinely, but only among people in whom there is clinical suspicion. The guideline specifies that patients using corticosteroids should not be tested for hypercortisolism but carves out an exception to this rule for patients planning on bariatric surgery — testing should be considered in these cases.



If hypercortisolism testing is in order, the guideline recommends an overnight dexamethasone suppression test as the first screening tool.

Male Hypogonadism

Although biochemical testing for hypogonadism is not routinely recommended in male patients with obesity, the guideline recommends investigating key clinical signs and symptoms, such as erectile dysfunction, reduced sexual desire, muscle weakness, changes in mood, fatigue, cognitive impairment, and more.

In the patients with clinical features of hypogonadism, the guideline suggests measuring total and free testosterone, sex hormone-binding globulin (SHBG), follicle-stimulating hormone (FSH), and luteinizing hormone (LH).

Gonadal Dysfunction in Women

The guideline recommends against routine testing for gonadal dysfunction in female patients with obesity and notes that symptoms that justify assessing gonadal function include menstrual irregularities, chronic anovulation, and infertility. The approach to testing depends on the suspected condition.

The guideline notes: “For evaluation of menstrual irregularity, we suggest to assess gonadal function by measuring LH, FSH, total testosterone, SHBG, Δ 4androstenedione, estradiol, 17-hydroxyprogesterone, and prolactin. If the menstrual cycle is irregular but somewhat predictable, we suggest that the assessment should take place during the early follicular phase. For evaluation of anovulation, we suggest gonadal function to be assessed by measuring LH, FSH, estradiol, progesterone, and prolactin.”

When clinical features suggest polycystic ovarian syndrome, the guideline recommends assessing androgen excess,

and specifically, “we suggest to measure total testosterone, free testosterone, Δ 4androstenedione, and SHBG. We additionally recommend to assess ovarian morphology and blood glucose.”

Other Hormones

The main points of the section on “other hormones” include:

- ▶ Recommending against routine testing for growth factor or insulin-like growth factor 1, with such testing reserved for patients with suspected hypopituitarism;
- ▶ Suggesting against performing routine tests for vitamin D deficiency;
- ▶ Suggesting not testing for hyperparathyroidism routinely in patients with obesity;
- ▶ Recommending not testing routinely for hormones such as leptin and ghrelin unless there is suspicion of a syndromic obesity; and
- ▶ Suggesting that secondary causes of hypertension be considered in the context of therapy-resistant hypertension in obesity.

“These guidelines should help reduce unnecessary endocrine testing in those referred for assessment of obesity,” Wilding notes in his commentary, “and encourage clinicians to support patients with their attempts at weight loss, which if successful has a good chance of correcting any endocrine dysfunction.”

These new guidelines “will be a welcome addition to the other existing obesity guidelines,” says Robert F. Kushner, MD, professor of medicine and medical education and director of the Center for Lifestyle Medicine at Northwestern University Feinberg School of Medicine. Kushner worked on the committee that wrote “The Science of Obesity Management: An Endocrine Society Scientific Statement.”

“The guidelines are structured as a logical set of practical and clinically useful recommendations that apply to patients who present with obesity. They not only identify when an endocrinological workup and referral is recommended, but also provide specific guidance on commonly encountered medical co-morbid conditions that are seen in the obesity population, such as hypothyroidism, erectile dysfunction, and menstrual irregularity. They do not appear to conflict with recommendations and standards used in the U.S.,” Kushner says. **EN**

RESOURCES

European Society of Endocrinology Clinical Practice Guideline: Endocrine work-up in obesity
<https://eje.bioscientifica.com/view/journals/eje/182/1/EJE-19-0893.xml>

The Science of Obesity Management: An Endocrine Society Scientific Statement and Obesity Pathogenesis: An Endocrine Society Scientific Statement
<https://www.endocrine.org/advancing-research/scientific-statements>



AT A GLANCE

- ▶ **Obesity has a complex relationship with the endocrine system, which complicates testing strategies for endocrine-related conditions.**
- ▶ **A new guideline recommends that all patients with obesity be tested for thyroid function, but that testing for other conditions be based on clinical signs and symptoms that point to a possible underlying endocrine disorder.**
- ▶ **Weight loss remains the key strategy for restoring hormonal imbalances.**

— SEABORG IS A FREELANCE WRITER BASED IN CHARLOTTESVILLE, VA., AND A FREQUENT CONTRIBUTOR TO *ENDOCRINE NEWS*. IN THE SEPTEMBER ISSUE, HE WROTE ABOUT REAL-WORLD EVIDENCE AND THE POSSIBILITY OF VIRTUAL CLINICAL DRUG TRIALS.

A photograph of a person from the chest up, holding a rectangular sign with a wooden frame. The sign has a dark background with the word 'Primary' in white serif font and 'CARE:' in large, bold, orange sans-serif font. The person's face is obscured by the sign, and their torso is visible below. The background is a plain, light-colored wall.

Primary CARE:

BY ERIC SEABORG

Pediatricians Urge Greater Access to Surgery for Severely Obese Youth

As childhood obesity becomes an “epidemic within an epidemic,” new guidance from the American Academy of Pediatrics echoes Endocrine Society recommendations on bariatric surgery for severely obese young people. Aside from reducing their weight, these procedures could benefit young people well into adulthood.



Improved access to bariatric surgery is “urgently needed” for the severely obese pediatric population, according to a new policy statement and technical report from the American Academy of Pediatrics (AAP).

“The overarching message is straightforward,” says Marc P. Michalsky, MD, MBA, professor of clinical surgery and pediatrics at the Ohio State University College of Medicine, who was a primary author of the guideline. “Bariatric surgery for the pediatric population is safe, effective, and should be considered at the primary-care level sooner rather than later.”

The need for aggressive treatment has grown as “severe obesity has outpaced less severe forms of childhood obesity in prevalence, and it disproportionately affects adolescents,” the policy statement says.

Michalsky says that the AAP statement represents an evolution in practice as recognition grows that “robust data” now supports the use of weight-loss surgery among pediatric patients: “Like any clinical treatment strategy, it takes time to become adopted to the point where it is a well-accepted practice model.”



The need for aggressive treatment has grown as “severe obesity has outpaced less severe forms of childhood obesity in prevalence, and it disproportionately affects adolescents,” the policy statement says.

RESOURCES

“Pediatric Metabolic and Bariatric Surgery: Evidence, Barriers, and Best Practices” (Policy Statement)

<https://pediatrics.aappublications.org/content/144/6/e20193223>

“Metabolic and Bariatric Surgery for Pediatric Patients With Severe Obesity” (Technical Report)

<https://pediatrics.aappublications.org/content/144/6/e20193224>

Endocrine Society Pediatric Obesity Guideline Resources

<https://www.endocrine.org/clinical-practice-guidelines/pediatric-obesity>

“What is very compelling about the use of bariatric surgery in the pediatric timeframe is that evidence is beginning to show that certain outcomes related to comorbidity resolution may actually be better when compared to adult patients,” Michalsky says. In addition to the weight loss itself, early improvements in conditions such as diabetes; high blood pressure; and risk of heart disease, liver disease, and kidney disease improve as much as in adults, offering the potential advantage of enlisting the physiological plasticity of youth before the effects of the chronic disease become fixed. “Furthermore, bariatric intervention during the teenage years serves to also eliminate the cumulative impact linked to such conditions, potentially resulting in significant improvement in long-term health for decades to come,” Michalsky says.

Policy Statement and Technical Report

“The guidance is based on a comprehensive review of the literature and consultation with experts in surgical and medical pediatric weight management,” according to Sarah C. Armstrong, MD, professor of pediatrics at Duke University, who chaired the guidance committee. “It includes a policy statement titled *Pediatric Metabolic and Bariatric Surgery: Evidence,*

“ I don’t think there is any time too early to start a conversation about this, especially at the primary care level. Starting a conversation does not automatically assign someone to a bariatric intervention, but often, just having a conversation about this can allow a patient and family to have improved access to multi-disciplinary care designed to treat childhood obesity.”

— MARC P. MICHALSKY, MD, MBA, PROFESSOR OF CLINICAL SURGERY AND PEDIATRICS, OHIO STATE UNIVERSITY COLLEGE OF MEDICINE, COLUMBUS, OHIO



Barriers, and Best Practices to help pediatricians select appropriate patients, guide teens and families through the decision-making process, locate high-quality surgical programs, and advocate for payment. An accompanying technical report titled *Metabolic and Bariatric Surgery for Pediatric Patients With Severe Obesity* details the evidence on procedure types, complications, and outcomes.”

The new guidance “nicely complements” the 2017 Endocrine Society clinical practice guideline on the treatment of pediatric obesity, says Dennis M. Styne, MD, a pediatric endocrinologist at the University of California, Davis, who chaired the Endocrine Society guideline committee.

“It very closely corresponds to what we think,” Styne tells *Endocrine News*. “It has the same indications, the same contraindications, and recommends the same high-level, experienced, comprehensive team approach to bariatric surgery. And it confirms that children, even more than adults, are denied bariatric surgery — even when they meet the criteria that have been established.”



AT A GLANCE

- ▶ Severe obesity among young people is an “epidemic within an epidemic,” says a policy statement from the American Academy of Pediatrics.
- ▶ This severely obese pediatric population urgently needs greater access to bariatric surgery.
- ▶ Young patients can benefit from metabolic and bariatric surgery as much — or even more — than adults, but they have even less access to the procedures than adults do.



“ [The American Academy of Pediatrics recommendation] very closely corresponds to what we think. It has the same indications, the same contraindications, and recommends the same high-level, experienced, comprehensive team approach to bariatric surgery [as the Endocrine Society’s 2017 clinical practice guideline on pediatric obesity]. **And it confirms that children, even more than adults, are denied bariatric surgery — even when they meet the criteria that have been established.**”

— DENNIS M. STYNE, MD, PEDIATRIC ENDOCRINOLOGIST, UNIVERSITY OF CALIFORNIA, DAVIS; CHAIR, THE ENDOCRINE SOCIETY’S “PEDIATRIC OBESITY: ASSESSMENT, TREATMENT, AND PREVENTION” GUIDELINE COMMITTEE

Indications for Surgery

The technical report notes that obesity classifications are not as straightforward among patients younger than age 18 as with adults. In adults, class 2 (severe) obesity is defined as having a BMI of 35 or higher, but the technical report says: “Because BMI values increase over time from age 2 to 18 years, the use of absolute BMI is generally not considered an accurate surrogate for adiposity and may either over- or underestimate associated health risks.” For that reason, the report defines class 2 obesity as having a BMI that is more than 35 or that is greater than 120% of 95th percentile for age and sex. It defines class 3 obesity as a BMI greater than 40 or 140% of the 95th percentile for age and sex.

For patients with class 2 obesity, surgery is indicated if they have clinically significant comorbid conditions, including obstructive sleep apnea, type 2 diabetes, non-alcoholic steatohepatitis, idiopathic intracranial hypertension, or gastroesophageal reflux disease. Surgery is indicated in patients with class 3 obesity regardless of the presence of comorbid conditions.

In addition to the BMI and comorbidity status, the policy statement notes that patients must possess “physiologic, psychological, and developmental maturity; the ability to understand the risks and benefits and adhere to lifestyle modifications; decision-making capacity; and robust family and social supports leading up to and after surgery.”

The contraindications for surgery include a medically correctable cause of obesity; an ongoing substance abuse problem; a medical, psychiatric, psychosocial, or cognitive condition that prevents adherence to postoperative dietary and medication regimens; and current or planned pregnancy within 12 to 18 months of the procedure.

Special Considerations for Youth

Michalsky says that one of the important differences between adult and pediatric patients is the need to assess the young patient’s ability to give informed consent. “We want to make sure that there is a certain level of cognitive maturity and decision-making ability to really comprehend what this type of therapeutic intervention entails, what is involved for their participation, and to fully understand the risks and benefits,” he says.

As with adults, candidates go through a multidisciplinary evaluation. “It is a relatively long process, and usually takes several months to complete,” Michalsky says. “It entails not just a physiologic assessment by physicians, but also requires assessment by a behavioral specialist, as well as a number of other multidisciplinary providers.”

PROBIOTICS' *Potential*



Prodam and her team conclude that probiotic supplementation with *B. breve* BR03 and B632 has determined beneficial effects on weight and insulin metabolism in children and adolescents with obesity who are undergoing dietary training.

“Contrary to prior reports, the evidence does not clearly identify a lower age limit,” committee chair Armstrong says. “Research shows that complications were lowest and outcomes the best when individual and family-level factors drove the decision-making process. There is no evidence to suggest that watchful waiting is effective; in fact, outcomes are improved and complication rates are lower when the surgery is done sooner.”

“I don’t think there is any time too early to start a conversation about this, especially at the primary care level,” Michalsky says. “Starting a conversation does not automatically assign someone to a bariatric intervention, but often, just having a conversation about this can allow a patient and family to have improved access to multidisciplinary care designed to treat childhood obesity.”

The policy statement calls severe obesity among youth an “epidemic within an epidemic” that “portends a shortened life expectancy for today’s children compared with those of their parents’ generation.” Although substantial evidence supports its safety and effectiveness, youth with severe obesity often lack adequate access to surgery, especially those in underserved populations. ^{EN}

Another possible treatment that has made waves recently stems from research presented at the European Congress of Endocrinology’s annual meeting — the all-digital e-ECE 2020 — earlier this month. Researchers found that children with obesity who were put on a calorie-restricted diet and given probiotics lost more weight and saw more improvements in their insulin sensitivity compared with children only on a diet.

The researchers, led by Flavia Prodam, MD, PhD, associate professor in clinical nutrition at the University of Piemonte Orientale in Novara, Italy, point out that microbiota modulation may be an approach to managing obesity, and that previous studies have suggested that probiotic supplementation with *Bifidobacteria* — a group of probiotic bacteria that help prevent infection from other bacteria like *E. Coli*. — could help restore the composition of the gut microbiome and aid in weight loss. Research up to now, however, has only analyzed the effects of mixtures of probiotic strains and not *Bifidobacteria* alone.

Prodam and her team put 100 children and adolescents with obesity on a calorie-controlled diet, and the participants were randomly given either probiotics *Bifidobacterium breve* BR03 and *Bifidobacterium breve* B632, or a placebo for eight weeks. The researchers found that participants who took probiotics saw decreased waist circumference, BMI, insulin resistance, and *E. Coli* concentrations, more so than participants on diet and placebo.

Prodam and her team conclude that probiotic supplementation with *B. breve* BR03 and B632 has determined beneficial effects on weight and insulin metabolism in children and adolescents with obesity who are undergoing dietary training. Furthermore, the authors write, the microbiome-host configuration could be a predictor of the obesity phenotype and the efficacy of treatment with *B. Breve* strains, but that will require further investigation. — *Derek Bagley*

— SEABORG IS A FREELANCE WRITER BASED IN CHARLOTTESVILLE, VA. AND A FREQUENT CONTRIBUTOR TO *ENDOCRINE NEWS*. IN THE SEPTEMBER ISSUE, HE WROTE ABOUT REAL-WORLD EVIDENCE AND THE POSSIBILITY OF VIRTUAL CLINICAL DRUG TRIALS.



BY ERIC SEABORG

Steroids in the Age of COVID

As corticosteroids gain traction for treating COVID-19, guidelines from the Centers for Disease Control and Prevention call for giving dexamethasone to some COVID-19 patients. However, there are still unanswered questions on the optimal timing and approach.

As researchers and clinicians search desperately for effective treatments for COVID-19, the drugs that appear to be the most effective so far are the glucocorticoids endocrinologists know well.

Dexamethasone came to the forefront in mid-June with the announcement of results from the RECOVERY trial in the U.K., which evaluated six interventions. Dexamethasone reduced deaths by 35% in patients on mechanical ventilation and 20% among non-ventilated patients on oxygen therapy.

Based on these results, the Centers for Disease Control and Prevention (CDC) updated its treatment guidelines to recommend using 6 mg per day of dexamethasone for up to 10 days in hospitalized patients who are mechanically ventilated or on supplemental oxygen. The guidelines recommend against its use in patients not on supplemental oxygen. If dexamethasone is not available, the CDC recommends using alternative glucocorticoids such as prednisone, methylprednisolone, or hydrocortisone (as of an August 27 update).

A Flurry of Studies

The evidence for the effectiveness of glucocorticoids was greatly strengthened at the start of September when *JAMA* published several studies confirming the RECOVERY results. The studies included three randomized trials that tested corticosteroids — two of hydrocortisone and one of dexamethasone — in treating critically ill COVID-19 patients as well as a meta-analysis of trials among critically ill patients who had received either dexamethasone, hydrocortisone, or methylprednisolone. The studies confirmed that corticosteroids reduced mortality compared with placebo or usual care.

Randomized clinical trial results of these drugs in COVID-19 are so important because, as the CDC guideline notes: “Corticosteroids have been studied in critically ill patients with acute respiratory distress syndrome with conflicting results.” For example, prednisone reduced the risk of death in patients with *Pneumocystis jirovecii* pneumonia and hypoxia, but corticosteroids were associated with delayed virus clearance in outbreaks of other coronaviruses, including Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS).

Not all studies of corticosteroids in COVID-19 have found a benefit, and their effectiveness may relate to the point in disease progression when they are given, according to Richard Auchus, MD, PhD, a professor of internal medicine and of pharmacology at the University of Michigan.





Cytokine Storm Warning

Although the exact reason the drugs are effective remains a question for further research, the most likely avenue is that they counter the “profound overactivity of the immune system” induced by COVID-19 infection, according to Paul M. Stewart, MD, a professor at the University of Leeds in the U.K. and editor-in-chief of *The Journal of Clinical Endocrinology & Metabolism*. “It is not a viral load issue, but more that the immune system kicks in with a cytokine storm that causes tissue damage, activates macrophages and the coagulation system, leading to multi-organ failure and death from COVID. The general belief is that dexamethasone is suppressing many of the pathways that are involved in that response.”

But if that is the case, it raises the question of the best timing for giving the drugs. Most patients’ own immune systems fight off COVID-19 infection, so providers need to be very careful about giving a drug like a corticosteroid at an immunosuppressive dose.

Auchus notes that patients not getting any kind of oxygen or mechanical ventilation have not been shown to “benefit because they hadn’t gotten to the inflammatory stage of the infection. Yet there is a lot of thrombosis that occurs with COVID infection of the lungs. If it has gotten to that stage, dexamethasone is probably not going to help, because the microthromboses are going to prevent oxygenation. At that point, just quelling the

inflammation isn’t going to help. It is going to be a narrowly defined window of when the drug is effective.”

C-Reactive Protein

An observational study by Keller, et al. in the August *Journal of Hospital Medicine* might shed some light on how to identify the patients who might benefit. The study examined the use of glucocorticoids within 48 hours of admission among COVID-19 patients at four hospitals in New York City. Because there were differing guidances early in the pandemic, some clinicians prescribed systemic glucocorticoids to patients with COVID-19 while others did not.

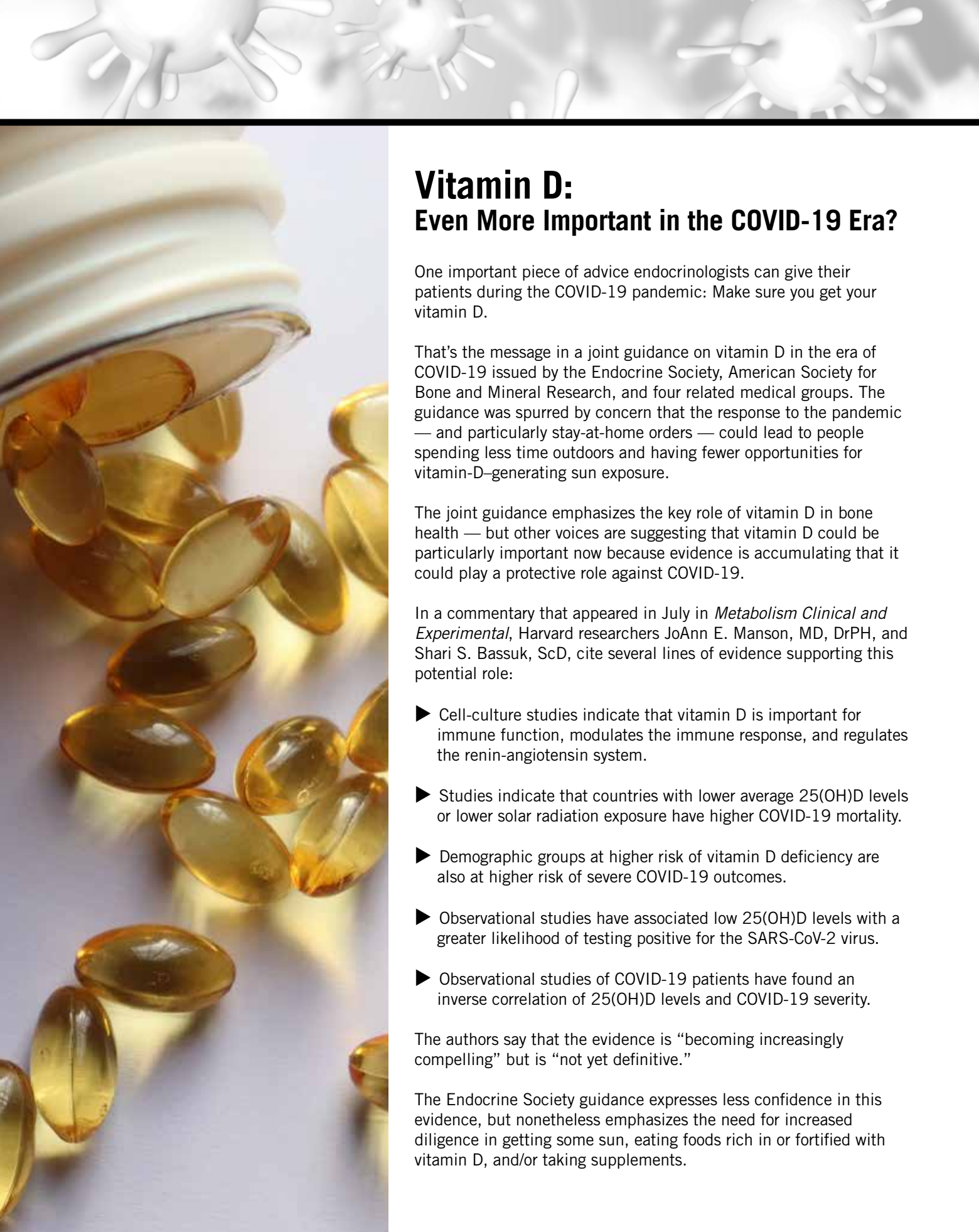
The study found that glucocorticoid treatment was associated with significantly reduced risk of mortality or need for mechanical ventilation among patients whose initial C-reactive protein (CRP) concentrations were greater than 20 mg/dL, but that the treatment was associated with significantly increased risk of these poor outcomes among patients whose initial CRP results were less than 10 mg/dL.

“Cytokine storm syndrome (CSS) is a hyperinflammatory condition that occurs in a subset of COVID-19 patients, often resulting in multiorgan dysfunction. CRP is markedly elevated in CSS, and improved outcomes with glucocorticoid therapy in this subgroup may indicate benefit in this inflammatory

“

It is not a viral load issue, but more that the immune system kicks in with a cytokine storm that causes tissue damage, activates macrophages and the coagulation system, leading to multi-organ failure and death from COVID. **The general belief is that dexamethasone is suppressing many of the pathways that are involved in that response.”**

— PAUL M. STEWART, MD, PROFESSOR, UNIVERSITY OF LEEDS, LEEDS, U.K.; EDITOR-IN-CHIEF, *THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM*



Vitamin D: Even More Important in the COVID-19 Era?

One important piece of advice endocrinologists can give their patients during the COVID-19 pandemic: Make sure you get your vitamin D.

That's the message in a joint guidance on vitamin D in the era of COVID-19 issued by the Endocrine Society, American Society for Bone and Mineral Research, and four related medical groups. The guidance was spurred by concern that the response to the pandemic — and particularly stay-at-home orders — could lead to people spending less time outdoors and having fewer opportunities for vitamin-D-generating sun exposure.

The joint guidance emphasizes the key role of vitamin D in bone health — but other voices are suggesting that vitamin D could be particularly important now because evidence is accumulating that it could play a protective role against COVID-19.

In a commentary that appeared in July in *Metabolism Clinical and Experimental*, Harvard researchers JoAnn E. Manson, MD, DrPH, and Shari S. Bassuk, ScD, cite several lines of evidence supporting this potential role:

- ▶ Cell-culture studies indicate that vitamin D is important for immune function, modulates the immune response, and regulates the renin-angiotensin system.
- ▶ Studies indicate that countries with lower average 25(OH)D levels or lower solar radiation exposure have higher COVID-19 mortality.
- ▶ Demographic groups at higher risk of vitamin D deficiency are also at higher risk of severe COVID-19 outcomes.
- ▶ Observational studies have associated low 25(OH)D levels with a greater likelihood of testing positive for the SARS-CoV-2 virus.
- ▶ Observational studies of COVID-19 patients have found an inverse correlation of 25(OH)D levels and COVID-19 severity.

The authors say that the evidence is “becoming increasingly compelling” but is “not yet definitive.”

The Endocrine Society guidance expresses less confidence in this evidence, but nonetheless emphasizes the need for increased diligence in getting some sun, eating foods rich in or fortified with vitamin D, and/or taking supplements.



AT A GLANCE

- ▶ Randomized clinical trials have confirmed that glucocorticoids can reduce mortality among critically ill COVID-19 patients, so CDC guidelines now recommend the use of dexamethasone in hospitalized COVID-19 patients on ventilators or supplemental oxygen.
- ▶ Though the exact mechanism is not known, corticosteroids are believed to reduce mortality by calming the cytokine storm and immune overreaction that can be fatal in COVID-19.
- ▶ Key questions remain about identifying which patients will benefit, the best timing of use, and how to avoid disrupting the body's immune response.

“There is a lot of thrombosis that occurs with COVID infection of the lungs. If it has gotten to that stage, dexamethasone is probably not going to help, because the microthromboses are going to prevent oxygenation. **At that point, just quelling the inflammation isn't going to help. It is going to be a narrowly defined window of when the drug is effective.**”

— RICHARD AUCHUS, MD, PHD, PROFESSOR, INTERNAL MEDICINE, PHARMACOLOGY, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICHIGAN

phenotype. Patients with lower CRP are less likely to have CSS and may experience more harm than benefit associated with glucocorticoid treatment,” the authors conclude.

Further complicating the use of corticosteroids is that although they have anti-inflammatory, antifibrotic, and vasoconstrictive effects, they are also associated with hyperglycemia, which is well-established as a risk factor for severe COVID-19 infections.

But they are also attractive because they are inexpensive and widely available. Stewart notes that dexamethasone is also very easy to use compared with other glucocorticoids, such as hydrocortisone, which has a shorter half-life.

He adds that the attention that dexamethasone is getting is exciting from an endocrinology point of view because “any advance in this kind of field immediately attracts the pharmaceutical companies to do more exciting things.” He notes that a “Comment” article by Lammers, et al. in the August *Nature Nanotechnology* already speculates that nano-formulations of dexamethasone administered by inhalation might more effectively target the drugs to sites of inflammation to improve anti-COVID-19 efficacy. The article says that novel techniques such as “pulmonary delivery of dexamethasone liposomes may outperform free dexamethasone when targeting alveolar macrophages as a strategy” to target the drug's effects.

Stewart concludes that “companies looking at how they might use liposomes for dexamethasone delivery and other novel approaches will ultimately be for the benefit of our endocrine patients. These advances always have a silver lining for some of the more fundamental uses of this drug.” ^{EN}

— SEABORG IS A FREELANCE WRITER BASED IN CHARLOTTESVILLE, VA., AND A FREQUENT CONTRIBUTOR TO *ENDOCRINE NEWS*. IN THE SEPTEMBER ISSUE, HE WROTE ABOUT REAL-WORLD EVIDENCE AND THE POSSIBILITY OF VIRTUAL CLINICAL DRUG TRIALS.

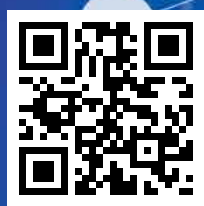
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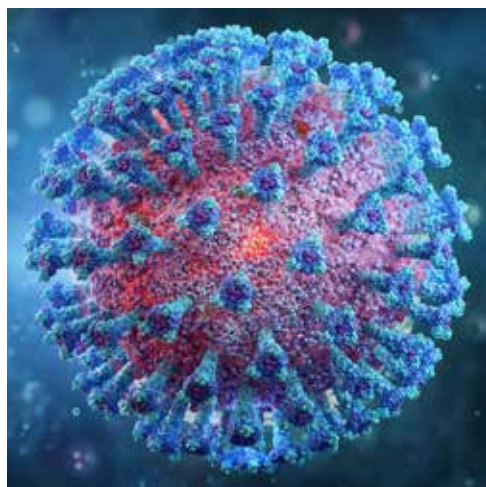


Undue Influences:

A study published last month in *Endocrinology* shows that many disparities in COVID-19 patients' morbidity and mortality appear to be linked to weight, as well as gender and diabetes status. The authors suggest that future trials should take patient weight into account to determine the most effective treatment protocols.

BY KELLY HORVATH

Obesity, COVID-19, and Immune System Havoc



As the state of affairs created by the COVID-19 pandemic continues to evolve, the medical community is becoming increasingly concerned about how comorbid conditions are affected by and how they in turn might affect the course of this mercurial virus.

In a review published in the September issue of *Endocrinology*, a trio of researchers including corresponding author Kanakadurga Singer, MD, of the Department of Pediatrics, Division of Endocrinology, University of Michigan (UM) Medical School, in Ann Arbor, took on COVID-19 and obesity. In “The Collision of Meta-Inflammation and SARS-CoV-2 Pandemic Infection,” Singer and her co-senior author and husband Benjamin H. Singer, MD, PhD, from the UM Division of Pulmonary Critical Care Medicine, and immunology graduate student Gabrielle P. Huizinga, report that, not surprisingly, obesity disrupts the immune system’s ability to respond to the virus. Notably, in the U.S., approximately 35% of men and 40% of women have a body mass index (BMI) >30 kg/m², the threshold for obesity.

Obesity-Driven Inflammation

For Singer and team, this investigation was not only critical, given the U.S.’s obesity epidemic, but it was also the logical next step in their research. “We have a longstanding interest in how obesity influences the immune system and more recently have been studying how obesity interacts with the response to infection,” she explains. From early studies of the role of the immune system in the response to SARS-CoV-2 infection, they gleaned that the parts of the immune system that generate severe COVID-19 are also those that are affected by obesity. “This led us to review what is already known about how obesity and sex influence the immune responses to infection. There has been a robust literature about obesity and its effects on the immune system, and we are hoping to spur greater investigation of the effects of obesity on the immune response in COVID-19,” she continues.

As is well known to endocrinologists, obesity causes a chronic, low-grade inflammatory state in the body. This immune response is possibly amplified in

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The relationship between obesity and COVID-19 outcomes is complex and likely influenced not only by biologic factors but also clinical practice patterns and the organization of health care systems.”

— BENJAMIN H. SINGER, MD, PHD, DIVISION OF PULMONARY CRITICAL CARE MEDICINE, UNIVERSITY OF MICHIGAN MEDICAL SCHOOL, ANN ARBOR, MICHIGAN

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Given that obesity is a modifier of disease severity in COVID-19, we think it is important that future clinical studies of COVID-19 treatments will include subjects from across the weight spectrum, especially treatments that modify the immune response. **Clinicians should consider the possibility that BMI, adiposity, or diabetes status are risk factors for higher morbidity and mortality in COVID-19.**”

— KANAKADURGA SINGER, MD, DEPARTMENT OF PEDIATRICS, DIVISION OF ENDOCRINOLOGY, UNIVERSITY OF MICHIGAN MEDICAL SCHOOL, ANN ARBOR, MICHIGAN

the setting of COVID-19 infection but in a dysregulated way that causes more damage rather than actually fighting off the infection. The association with obesity (along with diabetes and hypertension) and severe manifestations of SARS-CoV-2 infection as well as other viral and even bacterial infections is well-documented.

To get to the bottom of why and how, the researchers set out to extrapolate from the existing literature to connect knowledge of how obesity affects systemic inflammatory syndromes to

COVID-19. “The relationship between obesity and COVID-19 outcomes is complex and likely influenced not only by biologic factors but also clinical practice patterns and the organization of healthcare systems,” says Benjamin Singer. Indeed, to the latter point, obesity (and diabetes) are notorious for making supportive care particularly challenging, for example, requiring closer monitoring. As for the biologic factors, which are probably the bigger culprits, he elaborates, saying, “in this review, we suggest that expansion of inflammatory monocytes that occurs chronically in obesity may poise the immune system to generate



more severe COVID-19 disease.” Importantly, male sex, especially in the setting of obesity, confers a higher risk of severe illness and death, possibly because due to higher androgen and pro-inflammatory cytokine and chemokine levels in males. “There are multiple mechanisms at work in the intersection of obesity, sex, and infection,” he says, “and we are only just beginning to see the preclinical and translational studies that will suggest treatments that might benefit specific groups of patients.”

Role of Angiotensin-Converting Enzyme 2

Angiotensin-converting enzyme 2 (ACE-2) is known to be the functional receptor for the spike glycoprotein of SARS-CoV-2 virus — it’s the gateway to the human lung. Because ACE-2 is also expressed in many other human tissues, including kidney, brain, small intestine, and adipose, the researchers also wanted to explore the question of which symptoms of COVID-19 are due to direct viral effects versus systemic immune responses and whether higher amounts of adipose tissue set the stage for higher viral load.

“In all infections, there is a balance between injury to tissues that are caused by the invading pathogen, the immune response needed to eliminate that infection, and the damage to the body caused by the immune response,” says Benjamin Singer. “Injury to many organ systems, especially the kidneys, brain, and lungs, is a characteristic of the most severe cases of COVID-19. The receptor for the SARS-CoV-2 virus is found in many of those tissues, which means it is possible that direct infection of those tissues is responsible for injury. On the other hand, immune responses have the potential to injure any tissue in the body.” So far, these questions remain unanswered. “The balance between these two processes will become more apparent as more studies examine the relationship between immune phenotype and clinical outcomes,” he says.

Meta-Inflammation and Response to Pathogens

If obesity induces a state of low-grade, chronic inflammation, and patients with obesity are at higher risk for worse illness from COVID-19 infection, the likely conclusion is that the obesity-driven meta-inflammation is influencing the body’s response to pathogenic invasion, ultimately resulting in poorer outcomes.

For Singer and her co-authors, the implication is clear: “Given that obesity is a modifier of disease severity in COVID-19, we think it is important that future clinical studies of COVID-19 treatments will include subjects from across the weight spectrum, especially treatments that modify the immune response. Clinicians should consider the possibility that BMI, adiposity, or diabetes status are risk factors for higher morbidity and mortality in COVID-19.” ^{EN}

— HORVATH IS A FREELANCE WRITER BASED IN BALTIMORE, MD., AND A FREQUENT CONTRIBUTOR TO *ENDOCRINE NEWS*. IN THE SEPTEMBER ISSUE, SHE WROTE ABOUT SUBACUTE THYROIDITIS POST-INFECTION IN COVID-19 PATIENTS.



AT A GLANCE

- ▶ Significant disparities exist in COVID-19 patients' morbidity and mortality based on weight (as well as sex and diabetes status).
- ▶ Obesity-driven hyperactivation of the immune system in COVID-19 infection and consequent cytokine storm may increase both organ damage and illness severity, resulting in impaired viral clearance.
- ▶ Trials for developing COVID-19 treatments should include patients with obesity, and future treatments may need to be stratified across the weight spectrum to avoid further immune system dysregulation in these patients.

A Moment's Notice: GOOD HABITS FOR BEING ON CALL

Sleep disruptions, poor eating habits, lack of exercise, and general malaise can all be a part of those on call hours for every clinician. *Endocrine News* spoke to a few experts for their advice on simple ways to combat the ill effects of being on call.

BY CHERYL ALKON



Being on call — working after hours to provide patient care, either at your medical facility or from home while being available for patient phone inquiries — is a reality for many physicians, especially during residency. With such long hours, what are the best ways to stay sharp while working on call? Maintaining healthy habits, asking for help when needed, being nice, and taking call seriously will all help, say experts.

Mary L. Brandt, MD, professor of surgery at Tulane University School of Medicine, in New Orleans, La., runs the blog WellnessRounds.org. The site gives advice on how to “really succeed in medical school and residency, not just academically, but personally as well,” she writes. Brandt launched the blog in 2010 to share information with medical students and residents about how to live healthier while working in medicine.

“The faculty, residents, and students I work with struggle with how to find time to take care of themselves, as do I,” she says. “The blog serves as a toolkit of how to incorporate exercise, better nutrition, stress reduction, and other wellness habits into busy schedules — all of which benefit a physician working on call.”

Targeted Training

Mihail “Misha” Zilbermint, MD, FACE, is the chairman of the Department of Medicine and the chief and director of Endocrinology, Diabetes, and Metabolism at Suburban Hospital in Bethesda, Md., and an assistant professor at the Division of Endocrinology, Diabetes, and Metabolism at Johns Hopkins School of Medicine, Baltimore, Md. For a better on call experience, he suggests endocrinologists educate themselves, reach out to their senior colleagues as needed, and ultimately, train other healthcare professionals to be able to handle common endocrine issues.

For on-the-job education, the website UpToDate.com is a great resource, he says. “It offers you quick access, but if you’re not satisfied with the answer there, take the time to look up the long answer to see what others have done,” he says.

If fellows or junior endocrinologists take a call and don’t know the answer, “it’s OK to say, ‘Give me some time to think about it and let me call you back,’” Zilbermint says, who has taught fellows at the School of Medicine since 2015. In most cases in endocrinology, there are very few emergencies, he notes.

“It’s OK to sit down and review the patient’s chart to see if they have been admitted for a similar issue before. We all know rushed decisions may not be the best decisions. If you don’t know the answer, pick up the phone and call the attending. We all expect to get a call, and it’s OK to bother someone,” Zilbermint explains. “We have all been in a situation where we don’t know what to do. You utilize your own network of people you work or train with or train under to come up with the right answer for the patient.”

Zilbermint, who has organized more than 100 in-service trainings, said that on-the-job education for nurses, hospitalists, physician’s assistants, and nurse practitioners helps them recognize and handle hypoglycemia, hyperglycemia, insulin pump, and continuous glucose monitor management. “If you invest your time educating them, you will get fewer calls,” he says. This includes letting patients who use insulin pumps and continuous glucose monitors to handle their own technology. “Odds are, those patients know what they are doing,” he says. “Please allow them to use their insulin pumps until they are seen by an endocrinologist. Because people are not familiar, their instinct is to take it off without realizing the insulin pump is the lifeline for that person.”

Above all, a good attitude about being on call goes a long way. “When people call you, no matter what time it is, be very nice to them,” Zilbermint says. “The reason people call you late in the evening is not just to bother you, but they really need help. Be kind, and not grumpy and don’t blame them. People will appreciate it.”

Implementing Healthy Habits During Call

Besides endocrinology-specific advice, general wellness recommendations can help all physicians. “Being on call can

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It's OK to sit down and review the patient's chart to see if they have been admitted for a similar issue before. **We all know rushed decisions may not be the best decisions. If you don't know the answer, pick up the phone and call the attending.**”

— MIHAIL “MISHA” ZILBERMINT, MD, FACE, CHAIRMAN, DEPARTMENT OF MEDICINE, CHIEF AND DIRECTOR, ENDOCRINOLOGY, DIABETES, AND METABOLISM, SUBURBAN HOSPITAL IN BETHESDA, MD.; ASSISTANT PROFESSOR, DIVISION OF ENDOCRINOLOGY, DIABETES, AND METABOLISM, JOHNS HOPKINS SCHOOL OF MEDICINE, BALTIMORE, MD.

fundamentally disturb the things that keep us grounded and well during a ‘normal’ workday,” Brandt says. “The four things that are most disrupted by a call day are meals, sleep, social time, and exercise. Each of these requires a slightly different strategy.”

For eating, Brandt suggests stocking your work bag with nutritious snacks and meals to ensure there are healthy choices for when hunger strikes. “It’s important to eat, and to eat well, when you are on call,” she says. “That means it’s best to plan ahead and take nourishing and delicious food with you to work. In addition, put a couple of balanced snacks in your pocket (like a small bag of raisins and almonds) in case it is an overpowering call that keeps you from sitting down to eat.”



For sleeping, even small amounts help. “Don’t ever pass up an opportunity to sleep while you can,” Brandt says. “If it’s a sleepless call, make up those hours by going to bed early the next night, and if possible, take a nap.”

When trying to maintain social time with friends and family, virtual connections can help when in-person visits aren’t possible, due to long call hours (or pandemic-related social distancing). “Stay connected with occasional texts, funny memes, or just sending an appropriate emoji,” she says.

To get enough exercise, think about how to fit fitness into your schedule. “If your call is like most people’s, you’ll be able to squeeze in two or three sessions of weight training and three to five sessions of aerobic exercise in a week,” Brandt says. “Make it a priority, even if it has to be part of your call day. For example, taking the stairs counts as aerobic training, and pushups and squats are ways to do strength training without any equipment.”

Overall, working such healthy habits into the call schedule helps to maintain your body and mind so that you’ll perform better despite the long hours and potentially stressful situations that call can bring. Don’t ignore or minimize call’s effects, either.

“Think of a hard call night as the same thing as jet lag (minus the change in time zone),” Brandt says. “It is a real stress on your physiology, and you need to plan to recover from it — both for your health and to be able to care for your patients.” ^{EN}

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Endocrine Society Members Rally (Online) for Medical Research



On September 17, members of the Endocrine Society joined over 400 advocates to call on the Congress to provide increased funding for biomedical research as part of the 8th Annual Rally for Medical Research.

Although the COVID-19 pandemic prevented participants from gathering in person, Rally organizers were able to arrange tele- and videoconference meetings for research advocates around the country and congressional offices and staff. During the meetings, our members helped to raise the profile of endocrine research and reinforce the urgent need for additional funding for the National Institutes of Health (NIH).

The Rally is consistently a high-profile event on the Hill, and the Endocrine Society once again provided a large contingent of members for the meetings. Prior to the Rally, organizers hosted an online reception featuring NIH Director Francis Collins, MD, PhD, along with several congressional champions for NIH research. The invited speakers celebrated the important work that NIH-funded scientists contribute to and thanked advocates for their commitment to supporting biomedical research.

During the meetings with congressional offices, Rally participants reinforced the following important messages:

- We expressed appreciation to Congress for providing five straight years of robust funding increases for the NIH, including an increase of \$2.6 billion in FY 2020 and for recognizing how the NIH is playing a vital role in the COVID-19 response.



This screen grab of a tweet from Endocrine Society member Joy Wu, MD, PhD, shows one of the virtual rallies in progress with other Society members and the staff from the office of Sen. Kamala Harris, D-CA.

- ▶ We asked Congress to provide the NIH with at least \$44.7 billion (a \$3 billion increase) to the base budget in FY 2021 to support the opportunities for life-saving medical research.
- ▶ We urged Congress to provide at least \$15.5 billion in emergency supplemental funding for the NIH in the next COVID-19 relief package to support the wide range of medical research that has been stalled or lost due to the pandemic, as well as ongoing research on COVID-19 itself.

While our member researchers and clinicians were meeting with members of Congress, the Society's staff also got in on the action by posting on social media and tweeting at their elected representatives using the Rally hashtag (#RallyMedRes) about why they support federally funded research.

Given the ongoing pandemic, advocacy for the NIH is even more important this year. In addition to passing an annual appropriations bill to fund the NIH and the rest of the government, Congress is also struggling to agree on the path forward for the next emergency supplemental funding bill to respond to the COVID-19 pandemic.

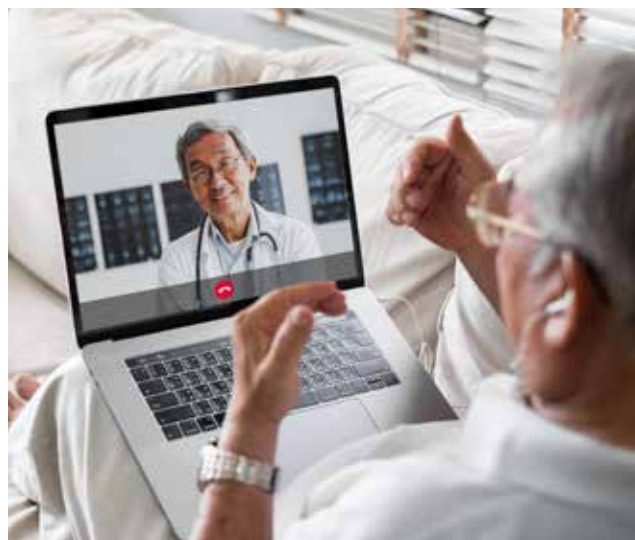
To ensure that biomedical researchers can address endocrine research priorities, help labs and institutions safely reopen, and also respond to new research needs related to COVID-19, the NIH urgently needs a strong base appropriation in addition to emergency supplemental funds. To learn more and find out how you can be an advocate for the NIH, please visit the Endocrine Society's advocacy website at: www.endocrine.org/advocacy.

Advocate Now for Endocrinology

Congress is expected to address several priority issues for the Endocrine Society this fall – either before it recesses for the elections or as part of a “lame duck” session after the elections. Please visit www.endocrine.org/takeaction to see how you can lend your voice to:

- ▶ Support additional funding for the National Institutes of Health;
- ▶ Support continuation of the Special Diabetes Program (SDP);
- ▶ Support various COVID-19 relief policies, including expanded coverage of telehealth, access to PPE, provider relief.

Society Weighs in on Proposed Changes to Physician Payment and Telehealth



In August, the Centers for Medicare and Medicaid Services (CMS) released proposed changes to the Medicare Physician Fee Schedule (MPFS).

The proposed rule updates payment policies and payment rates for Part B services furnished under the MPFS. The Endocrine Society, under the leadership of the Clinical Affairs Core Committee, developed comments focused on the proposed changes related to physician payment for evaluation and management services and the need to extend current telehealth waivers beyond the Public Health Emergency. The proposed rule would add eight services to the Medicare telehealth list permanently and would also add a new category of services to the temporary telehealth list for the duration of the COVID-19 public health emergency.

The Medicare Physician Fee Schedule affects members of the Society and the important work they do for patients. For more information about the proposed rule, the Society's analysis, and the Society's comments, please visit: www.endocrine.org/improving-practice/macra.

House Science, Space, and Technology Committee Discusses Research Relief Legislation

On September 9, the House Science, Space, and Technology Committee conducted a hearing about “The Impact of the COVID-19 Crisis on University Research.” While delivering their opening remarks, Haley Stevens (D-MI), chairwoman of the Subcommittee on Research and Technology, and Eddie Bernice Johnson (D-TX), chairwoman of the full Committee, spoke about the financial pressures facing researchers and institutions as they begin to emerge from lockdowns and address other disruptions due to the COVID-19 pandemic. Witnesses at the hearing, including Ryan Muzzio, a graduate student at Carnegie Mellon University, described challenges and delays that they and their colleagues are facing, including the disproportionate impact that women and underrepresented minority scientists experience during the crisis.

The Endocrine Society joined with other scientific societies before and during the hearing on social media to draw attention to and express support for the Research Investment to Spark the Economy (RISE) Act. The RISE Act would authorize approximately \$26 billion in emergency relief for federal science agencies, including the NIH, NSF, and others, to allow researchers to safely

continue working on federally funded research during this challenging time.

We welcome the Science, Space, and Technology Committee’s efforts to advance the RISE Act, and we will continue to advocate for necessary research relief so that we can continue to support researchers during this challenging time and not lose progress on critical endocrine research priorities due to the COVID-19 pandemic. **EN**






Drug Pricing Becomes Campaign Issue and an Issue for Open Enrollment Season

Last month, the Trump administration issued a new executive order (EO) aimed at lowering the cost of prescription drugs including insulin.

The new order, which expands on a previous order released earlier this year, directs the Secretary of Health and Human Services (HHS) to set up a process to require Medicare to pay the same price for prescription drugs, including insulin, as other developed nations, which often have lower prices. The new EO expands upon the previous order by including all drugs covered under Medicare. However, it is unlikely that this order will take effect anytime soon because rulemaking will need to be established to implement the order. Also, because the EO does not carry the force of law, it is likely to be challenged in court. Meanwhile, Congress is also eyeing drug pricing as an issue it may tackle during the “lame duck” session after the elections. Although several legislative proposals have been offered, it is not clear what direction the leadership may go. However, the continuing increases for insulin are likely to draw attention.

Meanwhile, fall is the time when Medicare and other private insurers also allow individuals to select their health plan for the coming year. Medicare beneficiaries who rely on insulin should pay attention to whether a plan offers insulin at a

discount and if it participates in a pilot program offering a \$35 a month insulin co-pay card. With that in mind, Eli Lilly & Company is kicking off a nationwide campaign, “Insulin Affordability: Learn. Act. Share,” to educate people about the actions they must take to receive most Lilly insulins for \$35 per month through the Lilly Insulin Value Program. The next several months will be important for those who use insulin that have commercial plans to find ways to save during the high-deductible period in early 2021. One important resource for people with diabetes is www.insulinaffordability.com.

The Society continues to advocate for lowering the cost of insulin and other prescription drugs. We recently updated our Insulin Affordability Position Statement, which details our work on this issue and provides recommendations for policy makers to lower the cost of this lifesaving drug. You can view the statement by visiting www.endocrine.org/advocacy/position-statements/increasing-insulin-affordability. 

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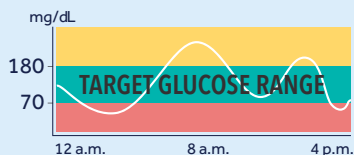
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KEEPING YOU IN THE KNOW ABOUT TIME-IN-RANGE

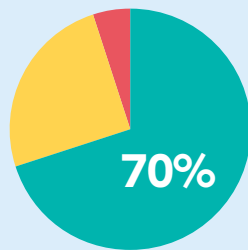
What Is Time-in-Range?

Time-in-Range or TIR is the amount of time those with diabetes spend with their blood glucose levels in a recommended target range and is represented as a percentage. Finding this happy medium can be difficult. So, more and more people with diabetes use continuous glucose monitoring (CGM) to help achieve more TIR. CGM generates a great deal of data showing where your current glucose levels are, where they've been, and what direction they are going. The hours per day spent "in-range" and "out-of-range" can vary but here are a few things to keep in mind:

Goals can vary in each person, but a typical target glucose range is 70 to 180 mg/dL.



For most people with type 1 or type 2 diabetes, a **TIR above 70%** is recommended. That's just under **17 hours** of a 24-hour day.



You should aim to spend:

- at least 70% (17 hours) in range 70–180 mg/dL
- less than 25% (6 hours) above 180 mg/dL with less than 5% (1 hour) above 250 mg/dL
- less than 4% (58 minutes) below 70 mg/dL with less than 1% (14 minutes) below 54 mg/dL

TIR targets can be lower for older or high-risk individuals and for those under age 25.

Talk with your healthcare provider about the TIR that's best for you.



Understanding Time-in-Range Improves Diabetes Management

Today's CGM systems allow you to track your blood glucose moment by moment and in real time. This helps you find times, such as before or after eating, or before or after physical activity, when your blood glucose is out-of-range. Identifying these times allows you to take steps, such as adjusting medication, to smooth out the highs and lows. Staying in-range helps maintain your energy level, mood, and overall quality of life.

Measuring hemoglobin A1c levels has been a common way to track success managing diabetes. But it only represents the average blood glucose (sugar) value over the past 2 to 3 months as a single snapshot and does not capture the fast and frequent blood glucose (sugar) changes you can experience. There can be parts of the day, such as during sleep, when you are spending time with blood glucose levels dangerously low (hypoglycemia) or high (hyperglycemia).

CGM can provide a daily glucose profile that displays a graph of the glucose readings from midnight-to-midnight. It's easy to spot which hours of each day you are in-range, above range, and below range. This information can help you adjust what you eat and drink, get the right amount of exercise, and modify your insulin dosing.



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