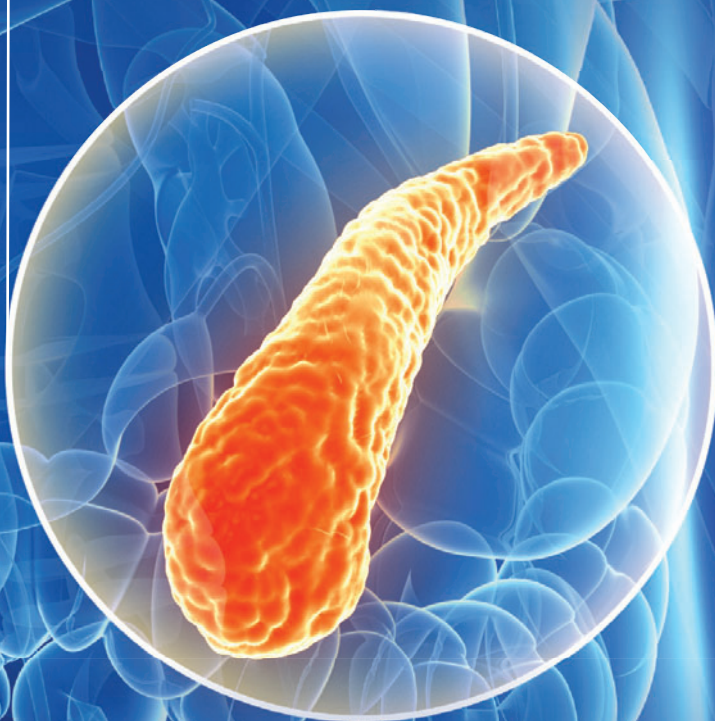


SEPTEMBER 2015

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

Endocrine news

A New Hope?



A new study shows that total pancreatectomy with islet autotransplantation — sooner rather than later — can prevent the onset of diabetes and improve quality of life in patients with chronic pancreatitis.

MIND THE GAP:

Gender Pay Disparities

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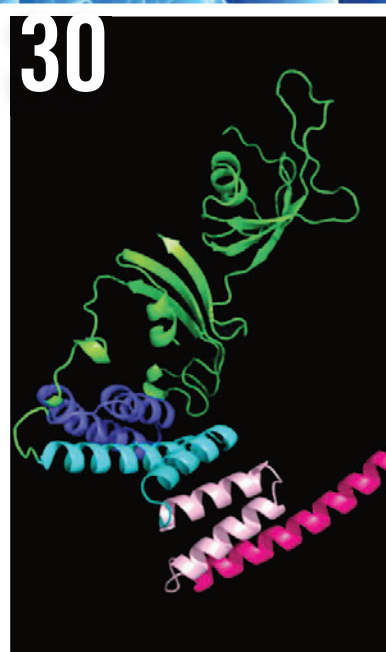
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ENDOCRINE SOCIETY

Hormone Science to Health



Participation: Your Key to Personal and Professional Success

I JOINED THE ENDOCRINE SOCIETY 25 YEARS AGO and have been involved in a variety of roles throughout the years, culminating with my current service as president. This journey has been very rewarding, as I have met many colleagues who are now friends, and I have learned from a wide variety of experiences along the way. This has been possible for me because many years ago when I first joined the Society I volunteered to serve on a committee. There are many opportunities available for members to participate on committees, subcommittees, focus groups, and task forces. I would encourage you to become involved — particularly those of you who are new trainees and early career professionals — as you are the future of our Society.

Committees and Task Forces

Each year the president-elect names nearly 100 members to committees, which is usually a three-year commitment. In addition, there are other ways to engage with the Society on a shorter-term basis, as part of a focused group formed to address a specific issue. A few months ago I convened task forces to address current needs in Leadership Development, Knowledge Integration, and ENDO, and this provided me a great opportunity to invite new members who had volunteered for committee service to participate. Increasingly, the Society will be reaching out to members who have expressed interest to involve them in working groups with short-term assignments, as well as focus groups to give feedback on ideas or existing products from the end-user perspective. I encourage you to volunteer and to take advantage of opportunities to provide your input. By giving your time and expertise to the Endocrine Society you will gain knowledge, learn new skills, and make connections that will be valuable assets for your professional career in the future. If you are interested, please visit: www.endocrine.org/volunteer

Recognizing Colleagues, Mentors, and Mentees

Each year, the Society presents more than \$800,000 in awards to endocrinologists at all stages of their careers to recognize their dedication to excellence in research, education, and clinical

practice in the field of endocrinology. The Awards Call for Nominations will launch this fall, and I encourage all of our members to participate in the nomination process to celebrate the accomplishments of your peers, mentors, and mentees. Please take the time to learn more about our awards at www.endocrine.org/awards and to submit your nominations. The selected awardees will be recognized at ENDO 2016 in Boston.

Election for Officers and Council

The ballot for the 2016 Endocrine Society election was sent on September 1. The Society governance is well balanced, and each year a president-elect, a vice president, and a council-designated seat are elected from one of the three constituencies — basic scientists, clinical scientists, and physicians-in-practice — with the candidates for each of the positions coming from a different constituency. The positions on the ballot for the 2016 election are:

- President-Elect (Clinical Scientist)
- Vice President (Physician-in-Practice)
- Council (one Basic Science seat and two At Large seats)

Our Society has an outstanding group of qualified candidates on the ballot, and I encourage all our voting members to participate in this very important activity. The officers and council members embrace the Society's mission, vision, and strategic plan and provide thoughtful oversight and stewardship of the Society.

Please remember to cast your vote and remind your colleagues as well. This is your Society, and your participation in the election is important! If you have any questions or comments, you can reach me via president@endocrine.org. 

Lisa H. Fish, MD
President, Endocrine Society

SEPTEMBER 2015

Endocrine news

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

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

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

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FROM THE EDITOR



Endocrine News 2.0

WELCOME TO THE DEBUT OF THE REFRESHED *ENDOCRINE NEWS*! As you thumb through this issue, it will be obvious that there has been a significant design overhaul. We felt this “reboot” vital in order to make *Endocrine News* a more viable vehicle for how readers receive information. The goal is to present the content in a contemporary and reader-friendly context because magazines should be dynamic with a need to evolve. That’s what we’re doing with *Endocrine News*. It’s had a very similar look for the last several years, and now it’s time to present a publication that can deliver noteworthy content in a manner that appeals to our audience while also reflecting current design standards. Also, a special thanks to the designer of this new look, Catherine Neill Juchheim of CNJ Creative, LLC. Bravo!

But the change will be gradual. While the refreshed design is officially being unveiled in this issue, the coming months will see a few new surprises peppered in amongst the magazine’s familiar features. One new type of article is the First Person feature, “Long Distance Relationship” on page 18, written by Matthew Bouchonville about his experiences in working with Endo ECHO in rural New Mexico. He details how he’s been able to connect with patients — and other healthcare professionals — via telemedicine. Bouchonville says the experience has made him a better doctor. “By sharing my expertise as an endocrinologist and working as part of a multi-disciplinary team to mentor primary care providers in rural and underserved communities, I’m helping more patients with diabetes and other endocrine conditions get the care they need and live healthier lives,” he writes.

These First Person articles are a new addition to the line-up, and they will require input from you, the members of the *Endocrine Society*. We want to use these articles as a way for you to tell your day-to-day stories of working in the field of endocrinology. Whether you’re a scientist in a lab, a clinician treating patients, or a researcher in the clinic, we want you to share your experiences with our more than 22,000 readers. So if you have a story you’d like to share with your endocrinology brethren, feel free to send me an email at mnewman@endocrine.org.

This month’s cover story, “A New Hope,” by Kelly Horvath (p. 10) concerns treating chronic pancreatitis with a total pancreatectomy with islet autotransplantation, based on a study and editorial published in the May issue of *The Journal of Clinical Endocrinology & Metabolism*. Essentially, it was revealed that if this procedure is performed sooner, rather than later, the the patient could maintain a better quality of life; plus the risk of diabetes onset was significantly reduced.

AGAIN, enjoy the “remodeled” *Endocrine News*, and please let me know your thoughts and comments on the redesign. 

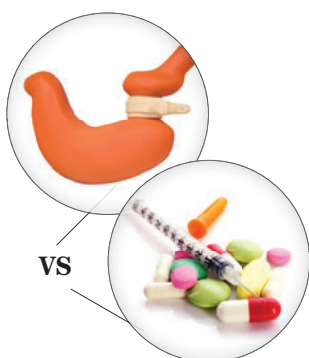
— Mark A. Newman, Editor, *Endocrine News*

ENDOCRINE
SOCIETY

Gastric Band Surgery and Intensive Medical Program Yield Similar Benefits on T2D



BY DEREK BAGLEY



Findings:

Goldfine and her team conclude that these findings point to LAGB and IMWM having similar beneficial outcomes on diabetes control, cardiometabolic risk, and quality of life over one year. “These results may be useful in guiding obese patients with T2D when they explore their options for glycemic and weight management, but it will be important to assess the durability of health benefits from these approaches as differences may emerge over time,” they write.

Laparoscopic adjustable gastric band (LAGB) surgery and an intensive medical diabetes and weight management (IMWM) program have similar one-year benefits on diabetes control, cardiometabolic risk, and patient satisfaction, according to a study recently published in the *Journal of Clinical Endocrinology & Metabolism*.

Researchers led by Allison B. Goldfine, MD, of the Joslin Diabetes Center at Harvard Medical School, noted that surgical recommendations, as opposed to lifestyle changes and pharmacological interventions, for treating type 2 diabetes (T2D) remain controversial. So Goldfine and her team set out to compare the two approaches.

In a 12-month, randomized clinical trial the researchers compared 23 people undergoing LAGB surgery to 22 people participating in an IMWM program. The subjects were “aged 21 – 65 years with body mass index of 30 – 45 kg/m², T2D diagnosed more than 1 year earlier, and glycated hemoglobin (HbA1c) 6.5% on antihyperglycemic medication(s).” After randomization, five participants did not undergo surgery. “Seven of the 18 LAGB and eight of the 22 IMWM participants had BMI below 35 kg/m²,” the authors write. “Of those that initiated intervention, three missed 12-month assessments due to time constraints, and one moved out of state. Twelve-month retention rates were 94% in the LAGB group and 82% in the IMWM group.”

The proportion of patients who met the primary glycemic endpoint (HbA1c 6.5% and fasting glucose 7.0 mmol/L at 12 months, on or off medication) was 33% in the LAGB group and 23% in the IMWM group. HbA1c reduction was similar in both groups and three and 12 months, and weight loss was similar in both groups at three months but greater in the LAGB group at 12 months. “Systolic blood pressure reduction was greater after IMWM than LAGB, whereas changes in diastolic blood pressure, lipids, fitness, and cardiovascular risk scores were similar between groups,” the researchers write. “Patient-reported health status, assessed using the Short Form-36, Impact of Weight on Quality of Life, and Problem Areas in Diabetes, all improved similarly between groups.”

Researchers Identify Genetic Markers Linking Risk for Both Type 2 Diabetes and Alzheimer's



Certain patients with type 2 diabetes (T2D) may have specific genetic risk factors that put them at higher risk for developing Alzheimer's disease (AD), according to a study conducted at and published recently in *Molecular Aspects of Medicine*.

Researchers led by Giulio Maria Pasinetti, MD, PhD, of the Icahn School of Medicine at Mount Sinai in New York City used recent genome-wide association study (GWAS) findings to investigate whether T2D and AD share common genetic etiological factors and the potential impact of these genetic factors on the cellular and molecular mechanisms that may contribute to the development of both these diseases.

GWAS look at differences at many points in the genetic code to see if, across a population, one or more variations in the code are found more often in those with a given trait (for example, high risk for a disease). Even the smallest genetic variations — called single nucleotide polymorphisms (SNPs) — can have a major impact on a trait by swapping just one of the 3.2 billion “letters” that make up the human DNA code.

The researchers retrieved SNPs associated with T2D and AD from large-scale GWAS meta-analysis and tested for any overlap. “We then explored the function of the shared T2D/AD GWAS SNPs by leveraging expressional quantitative trait loci, pathways, gene ontology data, and co-expression networks,” they write. “We found 927 SNPs associated with both AD and T2D with $p\text{-value} \leq 0.01$, an overlap significantly larger than random chance (overlapping $p\text{-value}$ of 6.93×10^{-28}). Among these, 395 of the shared GWAS SNPs have the same risk allele for AD and T2D, suggesting common pathogenic mechanisms underlying the development of both AD and T2D.”

The authors conclude that their study tentatively supports epidemiological observation of disease concordance between T2D and AD. “Moreover,” they write, “the studies provide the much-needed information for the design of future novel therapeutic approaches, for a subpopulation of T2D subjects with genetic disposition to AD, that could benefit T2D and reduce the risk for subsequent development of AD.”

Findings: “We identified multiple genetic differences in terms of SNPs that are associated with higher susceptibility to develop type 2 diabetes as well as Alzheimer's disease,” Pasinetti says. “Many of these SNPs are traced to genes whose anomalies are known to contribute to T2D and AD, suggesting that certain diabetic patients with these genetic differences are at high risk for developing Alzheimer's. Our data highlights the need for further exploration of genetic susceptibility to Alzheimer's disease in patients with T2D.”

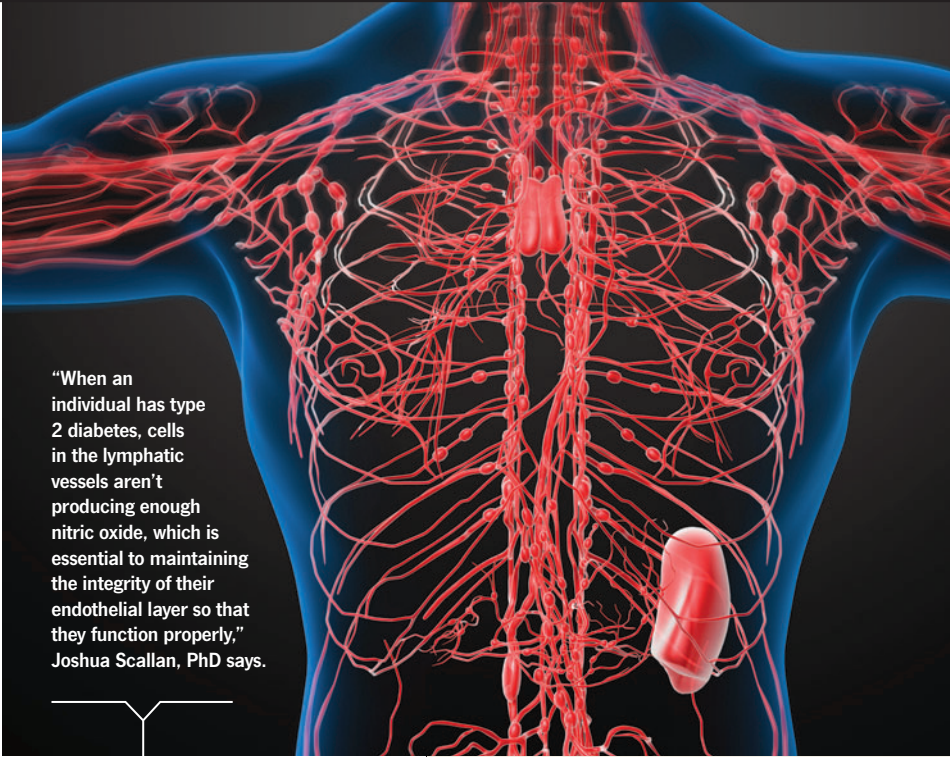
Impact of Type 2 Diabetes on Lymphatic Vessels Identified

For the first time, researchers have identified how type 2 diabetes (T2D) affects lymphatic vessels — a finding that could lay the groundwork for new therapies to improve the lives of people with the condition, according to a study recently published in *Cardiovascular Research*.

The scientists, led by Joshua Scallan, PhD, of the University of Missouri, examined the lymphatic integrity of transgenic mice and developed a new assay that “quantifies the solute permeability of murine collecting lymphatic vessels,” since studying lymphatic vessel function in animals has been a challenge for researchers, because unlike blood vessels, lymph vessels are clear and appear almost invisible. They write, “When compared to age-matched wild-type (WT) controls, the permeability of collecting lymphatics from diabetic, leptin receptor-deficient (*db/db*) mice was elevated >130-fold. Augmenting nitric oxide (NO) production by suffusion of L-arginine rescued this defect. Using pharmacological tools and *eNOS*^{-/-} mice, we found that NO increased WT lymphatic permeability, but reduced *db/db* lymphatic permeability. These conflicting actions of NO were reconciled by the finding that phosphodiesterase 3 (PDE3), normally inhibited by NO signaling, was active in *db/db* lymphatics and inhibition of this enzyme restored barrier function.”

“When an individual has type 2 diabetes, cells in the lymphatic vessels aren’t producing enough nitric oxide, which is essential to maintaining the integrity of their endothelial layer so that they function properly,” Scallan says. “We found that by giving the lymphatic vessels L-arginine, an amino acid commonly found in red meat, poultry, dairy products, and nutritional supplements, we were able to boost their nitric oxide production and restore their ability to act as a barrier.”

Findings: The authors conclude that they have identified the first lymphatic vascular defect in T2D, as the disease causes an enhanced permeability due to low NO bioavailability. “Further,” they continue, “this demonstrates that PDE3 inhibition is required to maintain lymphatic vessel integrity, and represents a viable therapeutic target for lymphatic endothelial dysfunction in metabolic disease.”



“When an individual has type 2 diabetes, cells in the lymphatic vessels aren’t producing enough nitric oxide, which is essential to maintaining the integrity of their endothelial layer so that they function properly,” Joshua Scallan, PhD says.

Study Looks at Telephone Interventions to Improve Diabetes Control

Periodic telephone counseling can be a highly effective, low-cost tool for lowering blood-sugar levels in minority, urban adults with uncontrolled diabetes, according to a study recently published in the *American Journal of Preventive Medicine*.

Researchers led by Elizabeth A. Walker, PhD, RN, of the Albert Einstein College of Medicine in New York, analyzed 941 adults with diabetes living in the South Bronx. Participants were predominantly Latino (68%) or non-Latino black (28%), with 70% foreign born and 55% Spanish speaking, all recruited through the New York City Department of Health and Mental Hygiene (Health Department) A1c Registry.



All 941 adults were mailed printed diabetes self-management materials. Additionally, half (443) were randomized to receive telephone calls from the Health Department health educators about the importance and rationale for adhering to their medication regimens, maintaining good nutrition and exercising. Telephone-group participants who had moderately elevated blood A1c levels (between 7% and 9%) could receive up to four phone counseling sessions over one year; those with extremely elevated A1c levels (above 9%) could receive up to eight calls. After one year, the researchers assessed participants' A1c change through the A1c Registry.

The greatest difference in A1c levels involved people who initially had extremely elevated A1c levels: For those getting telephone intervention (completing an average of 6.3 calls), their A1c levels decreased an average of 2.1% (from 11.3% to 9.2%) versus an average decrease of 1.3% among print-only group individuals with extremely elevated A1c levels (from 11.0% to 9.7%). Phone calls were less helpful for people in the moderately elevated A1c group — possibly because they completed too few phone-counseling sessions (an average of 3.4 calls). On average, their A1c levels didn't change over the course of the year, while A1c levels increased by 0.2% (from 7.8% to 8.0%) among print-only participants with moderately elevated A1c levels. Overall, those in the telephone group decreased their A1c by 0.4% more than those in the print-only group.

Findings: The authors conclude that “a telephone intervention delivered by health educators can be a clinically effective tool to improve diabetes control in diverse populations, specifically for those with worse metabolic control identified using a registry.” They also note that the findings are particularly important as they demonstrate the value of an intervention that is culturally sensitive and individually tailored for a low-income and non-English speaking population. ^{EN}

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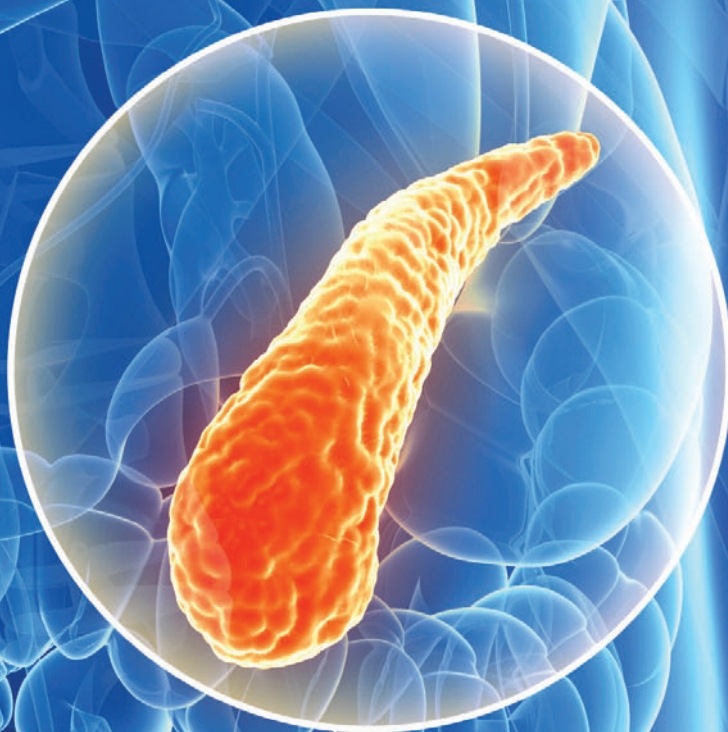
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Even though it has been around for 40 years to treat chronic pancreatitis, a new study shows that a total pancreatectomy with islet autotransplantation, sooner rather than later, can stave off the onset of diabetes and improve quality of life.



A New Hope?

BY KELLY HORVATH

A diagnosis of chronic pancreatitis (CP) once doomed a patient to significantly diminished quality of life (QOL) at best and full-blown diabetes to eventual death at worst.

These dire prognoses are not necessarily the case any longer, due to the enormous success of the nearly 40-year-old procedure known as total pancreatectomy with islet autotransplantation (TP/IAT). The twofold problem is, many clinicians are unaware that the procedure exists, and many of those who do know about it mistakenly believe that they do not have access to a facility that can implement it.

A NEW LEASE ON LIFE

In the May 2015 issue of *The Journal of Clinical Endocrinology & Metabolism (JCEM)*, the manuscript entitled “Factors Associated With Islet Yield and Insulin Independence After Total Pancreatectomy and Islet Cell Autotransplantation in Patients With Chronic Pancreatitis Utilizing Off-site Islet Isolation: Cleveland Clinic Experience,” reveals just how mistaken that latter notion is. “In our study, we show that patients can get this care at a lot of places without too much cost involved,” says the article’s lead author, Betul A. Hatipoglu, MD, in the Department of Endocrinology, Diabetes and Metabolism at the Cleveland Clinic Foundation in Ohio. “We improved both quality of care and patient QOL in the long term, and we are very happy about that.”



“Another reason not to wait to operate is that the ultimate outcome of [chronic pancreatitis] is diabetes in most cases. That is not a great reward at the end of the road. My message is, get [total pancreatectomy with islet autotransplantation] done as soon as you realize that the disease course is chronic and irreversible to relieve pain — that is the main reason — but also to prevent diabetes.”

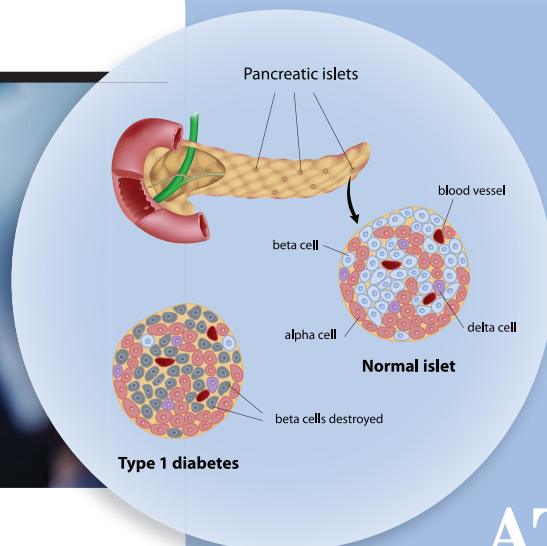
— R. PAUL ROBERTSON, MD,
EDITOR-IN-CHIEF, *THE JOURNAL OF CLINICAL
ENDOCRINOLOGY & METABOLISM*

Without islet transplantation, total pancreatectomy invariably causes diabetes. Although the patient's pain may wax and wane, in a large segment of patients with chronic, relentless pain, overall QOL will continue to deteriorate due to chronic pain, narcotic addiction, weight loss, diarrhea, and general disability. As a result of the inflammatory process in the pancreas, islet destruction ensues and the islet mass diminishes, leading ultimately to diabetes. TP/IAT removes the patient's own islets from the resected pancreas and transplants them into the patient's liver. This effectively gives the patient a new lease on life. But because laboratories that are equipped to isolate the islet cells from the removed pancreas are very expensive to establish and therefore scarce, TP/IAT has been regrettably underutilized.

To reverse this unfortunate and unnecessary trend, Hatipoglu and team sought to determine whether the IAT component of TP/IAT could be conducted off-site — in this case at the University of Pittsburgh's islet isolation lab. In a cohort of 18 male and 18 female patients averaging age 38 years, they achieved rates of islet yields and insulin independence commensurate with those that centers with on-site labs report, about 33%. “The most important point I want to get out there is that it would be impossible and not at all cost effective for every institution performing pancreatectomies to run an islet isolation lab,” Hatipoglu says. “With our study, we were able to show that collaborating with another lab capable of isolating the islets for us yielded very similar outcomes, which means that one lab can serve many hospitals. This kind of networking will allow clinicians to serve their patients the best possible way. Not every patient can afford to go to one of the larger centers, and we showed that it is okay to treat them locally.”

DON'T WAIT TO OPERATE

In “Total Pancreatectomy and Islet Autotransplantation for Chronic Pancreatitis: Breaking Down Barriers,” an accompanying editorial by *JCEM* editor-in-chief, R. Paul Robertson, MD, at the University of Washington in Seattle, the cause of publicizing the success and accessibility of TP/IAT is further heralded. “Transplantation centers should understand that they do not need their own islet isolation facility and can learn how to work with an existing one — like the Cleveland Clinic has done with the University of Pittsburgh. That demonstration opens the door — because now, when healthcare providers make the diagnosis of chronic, irreversible pancreatitis, they can realistically consider taking the entire pancreas out.” In other words, delaying the procedure — which was once considered routine for this disease — is not going to improve anything and could potentially make the patient's condition much worse. The patient will continue to suffer pain and disability



as long as the pancreas stays inside the body. Moreover, many of these patients have been forced to leave their jobs or forfeit care of their families because of the debilitating nature of their disease.

“Another reason not to wait to operate is that the ultimate outcome of CP is diabetes in most cases. That is not a great reward at the end of the road,” Robertson says. “My message is, get [TP/IAT] done as soon as you realize that the disease course is chronic and irreversible to relieve pain — that is the main reason — but also to prevent diabetes.” Although no strict definition of “irreversible course” exists, what Robertson calls “clinical common sense” indicates that the condition of a pancreatitis patient with significantly reduced QOL for the prior couple of years is likely going to worsen, leaving no good reason to try to retain the pancreas. “Some surgeons will take out progressively more of the pancreas over time, but each time they take out a little more, the patient is that much closer to diabetes. Those surgeons are not just removing the inflamed non-islet tissue, they are also taking out functional islets with each piece of the pancreas,” he says.

Hatipoglu agrees that delaying can mean a less favorable outcome for the patient. “If you are too late, then the patient’s pain management might not be as good as if the procedure had been done earlier, and the islet mass will not be in great shape. Timing of the surgery is therefore very important and should be a decision made by a multidisciplinary team,” she says.

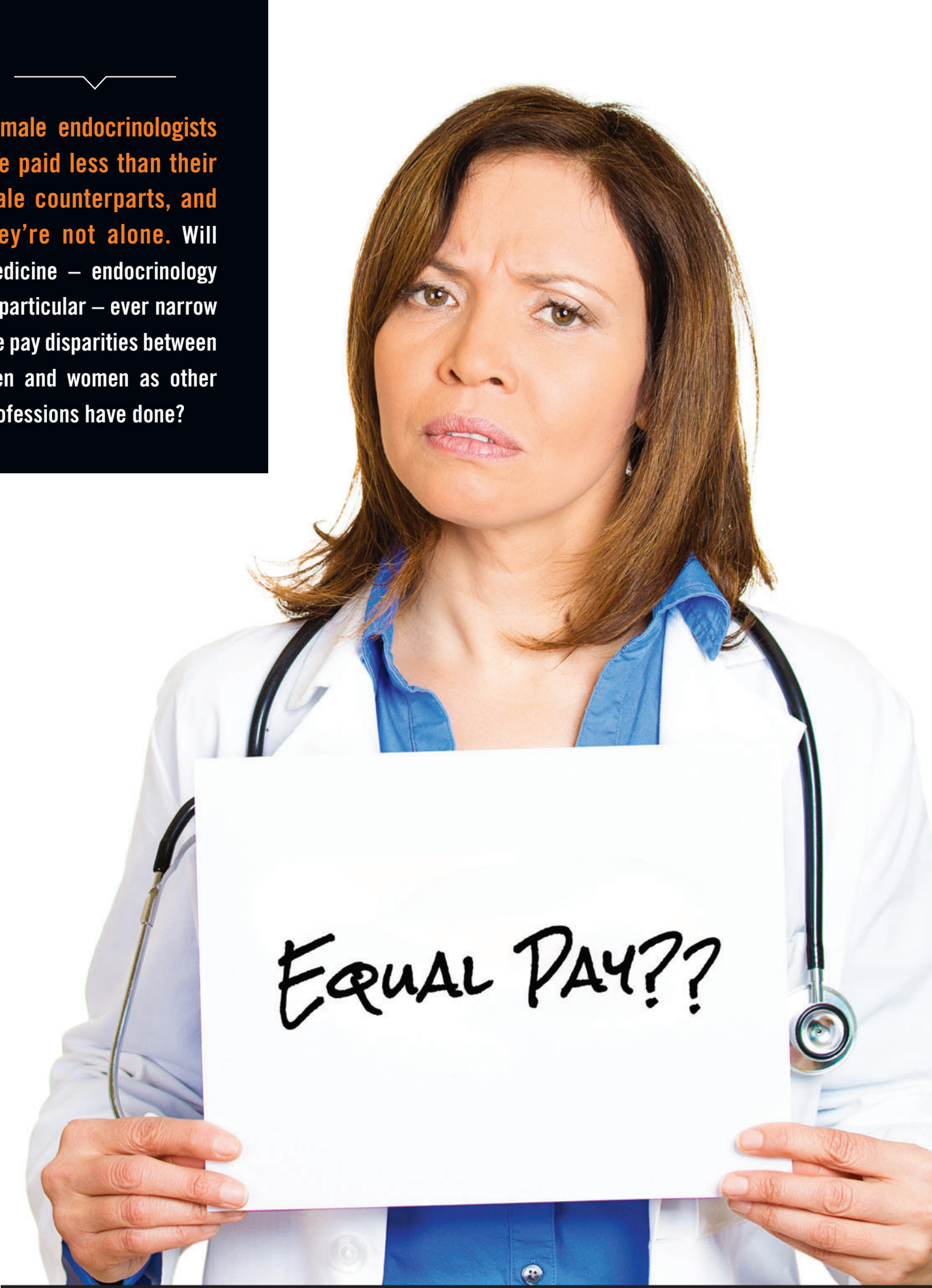
The bottom line is, there appears to be no good reason not to perform TP/IAT with a chronic, irreversible disease course and several important reasons in favor of doing it. It can resolve the pain and reduced QOL associated with CP; it is becoming widely accessible in terms of location and cost, and it prevents the eventual downside to diabetes the patient would otherwise likely face. “[TP/IAT] is gaining momentum, but this snowball needs to roll down the hill a little faster,” Robertson says. Patients should not have to suffer unnecessarily, and the healthcare system could certainly benefit from a lighter diabetes burden. **EN**

HORVATH IS A FREELANCE WRITER BASED IN BALTIMORE, MD. SHE WROTE ABOUT ENDOCRINE-DISRUPTING CHEMICALS’ EFFECTS ON FEMALE REPRODUCTION IN THE JULY ISSUE.

AT A GLANCE

- ▶ **Islet cell autotransplantation provides total pancreatectomy patients with the possibility to remain insulin independent and to prevent diabetes and its complications.**
- ▶ **Lack of an on-site islet isolation lab is not a barrier to performing TP/IAT; the islets can be extracted at an existing offsite lab and shipped back for transplantation into the patient with as successful an outcome as if the islets had been isolated on site.**
- ▶ **Patients have typically had a five- to 10-year history of CP before undergoing TP/IAT; however, waiting only two to three years might even improve on the outcome in terms of preventing diabetes by keeping islet cell function intact. It would also greatly reduce the amount of time the patient needlessly suffers.**

Female endocrinologists are paid less than their male counterparts, and they're not alone. Will medicine — endocrinology in particular — ever narrow the pay disparities between men and women as other professions have done?

A female doctor with brown hair, wearing a white lab coat over a blue shirt, has a stethoscope around her neck. She is holding a white rectangular sign in front of her chest with both hands. The sign has the words "EQUAL PAY??" written on it in a large, black, handwritten-style font. She has a concerned or questioning expression on her face.

EQUAL PAY??

the GENDER Gap

BY GLENDA FAUNTLEROY

It is no secret that women are often paid less than their male counterparts in the same position.

The Equal Pay agenda has made significant news since the White House first revealed that full-time working women earn only about 77 cents for every dollar a man earns.

The gender pay gap spans across almost every profession and doesn't skip the salaries paid to endocrinologists. In 2014, male endocrinologists earned an average salary of \$206,000 compared with the \$168,000 earned by female endocrinologists, according to the "Medscape Endocrinologist Compensation Report 2015."

"There is no doubt that women endocrinologists are paid less than men," says Mary Lee Vance, MD, professor of Medicine, Endocrinology and Metabolism at the University of Virginia School of Medicine in Charlottesville. "I've observed this for over 30 years."

The trend of less pay for female physicians stretches across all specialties. A 2013 study in *JAMA Internal Medicine* reported female physicians earned an average \$56,000 less each year than male physicians — a gap that researchers found hasn't moved since the late 1980s.

Harvard Medical School researchers examined nationwide salaries from 1987 to 2010 and revealed salary earnings of male physicians steadily exceeded female physicians by 25%. Over those same years, however, the salary gap between women and men outside of healthcare shrunk from 28% to 15%.

"There is something that's intrinsically going on within the physician workforce," study author Anupam Jena, PhD, told Reuters.



“ I am not satisfied or accepting of the inequity in salary compared with my male colleagues. This element of inequitable remuneration does impact on the issue of ‘satisfaction,’ including my experience. Why are women paid less than men for the same work? There is no excuse for this.”

— MARY LEE VANCE, MD,
PROFESSOR OF MEDICINE,
ENDOCRINOLOGY AND METABOLISM,
UNIVERSITY OF VIRGINIA SCHOOL
OF MEDICINE, CHARLOTTESVILLE

“ALTERNATIVE FACTORS”

When the White House released the National Equal Pay Task Force report in 2013, several articles were subsequently issued that offered the counter-argument. The consensus was that while there is indeed a gap in salaries between men and women, the gap wasn't nearly as great as 77 cents on a dollar.

Some economists and policy analysts also argued that “alternative factors” should be recognized as the reason for pay differences. Education, choice of occupation, hours worked, experience, and career interruptions all affect the compensation of workers, whether male or female, according to the Equal Pay for Equal Work issue brief released last year by The Heritage Foundation.

Craig Fowler, president of the National Association of Physician Recruiters, agrees and says that in his nearly 20 years of physician recruiting he's never had a search where less money was offered to a woman than a man for the same job. “Base compensation is always the same regardless of gender,” Fowler explains. “Differences may come into play when it comes to productivity pay.”

“It is possible that female physicians earn less in productivity compensation due to outside responsibilities, such as family and children that pull on their time,” he continues. “Females may not work as many hours as men, therefore, see fewer patients and consequently earn less in production dollars.”

The Medscape report backs Fowler's sentiment. It noted that women tend to work shorter hours and fewer weeks than men, revealing that 18% of female endocrinologists work part time compared with 7% of male endocrinologists. Family obligations are the main reasons.

Susan Herzlinger Botein, MD, of Boston's Joslin Diabetes Center, agrees that working women have more challenges and obligations at home but acknowledges there are “plenty of stay-at-home dads who allow female physicians who prefer to work full-time to do so.”

“In the absence of that, because of the time demands of paperwork and documentation, ‘full time’ clinical work invariably is completed in so-called off hours,” says Botein. “Due to the demands and pleasure of having a family, full-time clinical work does not work for many of us. I feel fortunate to be able to spend time with my young children and hope that this also makes me a better and happier physician.”

So, does gender discrimination in healthcare play a role in salary differences or career advancement? Most female physicians say yes. Rock Health, a healthcare venture funding group, surveyed 400 female physicians and found that women feel gender continues to hold them back. In fact, 96% believed gender discrimination still exists. In Rock Health's “The State of Women in Healthcare,” 40% of female respondents also believed their firms do not support women in career development.

WOULD YOU DO IT ALL OVER AGAIN?

The Medscape report revealed other facts about the endocrinology specialty. Endocrinologists are among the lowest-paid physicians, ranking third from the bottom. On average, endocrinologists earned \$196,000 annually — placing the specialty just above family medicine and pediatrics as the lowest wage earners.

Where endocrinologists' work does make a difference is in earning power. Those in office-based single-specialty group practices make the most (\$222,000), with endocrinologists in outpatient clinics ranking second at \$208,000. Those in the specialty earning the least are in academic or government settings (\$186,000) and hospitals (\$162,000). With these numbers in mind and noting the gender pay differences, only 38% of female endocrinologists reported being satisfied with their income — lower than the 45% reported by their male counterparts.

"I am not satisfied or accepting of the inequity in salary compared with my male colleagues," says Vance. "This element of inequitable remuneration does impact on the issue of 'satisfaction,' including my experience. Why are women paid less than men for the same work? There is no excuse for this."

But if they had to do it all over again, 63% of endocrinologists said they would still choose medicine as a career, although less than half (45%) would follow the path of endocrinology once more.

"I think that physicians who would not pursue their specialty are dissatisfied with how their choice fits into their lifestyle, such as the time demands, administrative burden, and income," says Botein. "These factors are, appropriately, not the focus of medical school and residency but can be a surprise. Further, peoples' lives change quite a bit in their 20s and 30s, when these decisions are made," she adds. "It's easier to say 'who needs money?' when you are single without children. I have not second-guessed my career path into endocrinology."

Women in the Medscape survey also differed from men when describing what they find most rewarding about their jobs. Among endocrinologists, 42% of men and 36% of women believe that relationships with patients are a major source of satisfaction. Vance says that she is very satisfied with her career in academic medicine and finds patient care and education of the medicine residents, medical students, and her endocrine fellows most rewarding.

Botein agrees. "I feel fortunate to have chosen a specialty that I find intellectually satisfying and allows close, long-term relationships with my patients. That my job fits into the structure of my family life is not accidental."

Fowler says for female physician job seekers who are looking to leave a current position, the main reason is to be closer to family. "Secondly, I see improved quality of life as another reason, such as hours, call schedule, and volume of patients." **EN**

GLENDIA FAUNTLEROY IS A FREELANCE WRITER BASED IN CARMEL, IND., AND A REGULAR CONTRIBUTOR TO *ENDOCRINE NEWS*. SHE WROTE ABOUT HYPOPHOSPHATASIA IN THE AUGUST ISSUE.

THE GENDER GAP

AT A GLANCE

- ▶ In 2014, male endocrinologists earned an average salary of \$206,000 compared with the \$168,000 earned by female endocrinologists.
- ▶ Some economists and policy analysts argue that "alternative factors" should be recognized as the reason for pay differences.
- ▶ A survey of 400 female physicians found that women feel gender continues to hold them back.



CHANGE TO COME?

Fifty years after the passage of the 1963 Equal Pay Act, the Obama administration's Equal Pay Task Force is working to permanently close the gender pay gap. The very first bill signed into law by the president was the Lilly Ledbetter Fair Pay Act, which extended the time period in which claimants can bring pay discrimination claims.

Since then, a number of other initiatives, including pay data collection and addressing discrimination against mothers and caregivers, have been underway.

- ▶ More information on what's being done can be found at www.whitehouse.gov.



FIRST PERSON

Long Distance Relationship

A new way to deliver care via telemedicine has allowed one endocrinologist the ability to enhance his reach to patients he would otherwise never be able to treat...or even meet.

Matthew Bouchonville, MD, an endocrinologist at the University of New Mexico, shares his experiences with Endo ECHO and its impact in rural New Mexico.

Every Wednesday at noon, my colleagues and I gather around a U-shaped conference table in front of two giant flat-screen TVs. One by one, the faces of our community partners pop up: primary care doctors, nurses, physician assistants, and community health workers from nine federally qualified health centers (FQHCs) across New Mexico.

Here, at our “hub” in Albuquerque at the University of New Mexico, we have at the table an adult endocrinologist (me), a pediatric endocrinologist, a nephrologist, a pharmacist, a psychiatrist, a nurse manager, a community health worker, and a social worker. For the next two hours, we listen and ask questions as the primary care teams at the FQHCs present their cases of patients who have diabetes.

We don’t see these patients directly. Yet, by “telementoring” our FQHC colleagues, we are helping to ensure that they receive excellent, comprehensive care for their conditions from trained providers in their home communities, instead of having to wait for months and drive for hours to see us, the specialists.

A MEANINGFUL SOLUTION

Approximately 30 million people in the U.S. have diabetes, and 40% of those cases are uncontrolled. Although diabetes is a manageable disease, our healthcare system is struggling to meet the demand for care at a time when the number of endocrinologists is shrinking.



Bouchonville listens to a case presentation by Ninad Shet, MD, (on screen) of La Casa Family Health Center in Roswell, N.M. On the left screen are primary care clinicians connecting to the teleclinic from across the state.

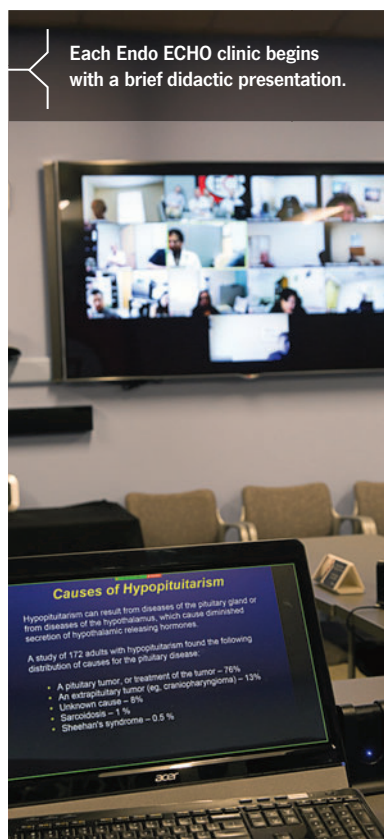


About MATTHEW BOUCHONVILLE

Matthew Bouchonville has been a faculty member of the University of New Mexico School of Medicine Division of Endocrinology, Diabetes, and Metabolism since 2011. As medical director of Endo ECHO, he mentors multiple clinicians in underserved communities around the state in collaboration with a multidisciplinary panel of experts to leverage scarce specialty resources to the front lines of community care. Bouchonville's goal is to improve access to care for all patients with diabetes and other metabolic conditions by sharing the lessons learned from Endo ECHO with academic medical centers around the world. He is a 2006 graduate of the Eastern Virginia Medical School Medical College and is fluent in Spanish and Vietnamese (in addition to English).

“When patients have significant psycho-social barriers — as so many patients with diabetes do — it’s important for doctors to step back and consider their patients’ priorities so that they can guide them toward self-management in ways that fit their lives.”

Each Endo ECHO clinic begins with a brief didactic presentation.



I’m now part of a meaningful solution to that problem. It’s an exciting new approach to care delivery that we’re calling “Endo ECHO,” and it has made me a better doctor. (ECHO stands for Extension for Community Healthcare Outcomes and is a collaborative model of medical education and care management that empowers clinicians to provide better care to more people, right where they live.)

By sharing my expertise as an endocrinologist and working as part of a multi-disciplinary team to mentor primary care providers in rural and underserved communities, I’m helping more patients with diabetes and other endocrine conditions get the care they need and live healthier lives. I’m actually reaching exponentially more patients than I do by seeing patients one on one.

And the care, I believe, is better, because it is informed by specialists across disciplines — in real time. During our Endo ECHO clinics, we discuss not only whether a patient’s blood glucose is under control but also whether he or she has depression, taking prescription medications for comorbid conditions, has adequate home support, and other aspects of his life.

PATIENT GOALS

By bringing the perspectives of a range of professionals together all at once to bear on patient care recommendations, we not only expand access to specialty care, but we also expedite the entire treatment process. For a patient to get referrals and appointments for each of these specialists separately would probably take months.

Most importantly, during the weekly teleclinics, we ask our community partners to tell us about their patients’ goals. What is most important to the patient?

This is a question that too often gets lost in the disease management process. Before I began participating in Endo ECHO, my treatment was oriented around my goals as a doctor. But when patients have significant psycho-social barriers — as so many patients with diabetes do — it’s important for doctors to step back and consider their patients’ priorities so that they can guide them toward self-management in ways that fit their lives. Otherwise you might never achieve your goals as a doctor for your patient. And then the patient is labelled as non-compliant.

For example, in my own practice, I recently saw a patient with type 2 diabetes who wasn’t self-managing. Instead of counseling her about non-compliance, I asked her about her life. And I listened.

It turned out that she’s taking care of a father with Alzheimer’s, as well as a son who has depression. By the time we finished our conversation, she realized that, in order to take care of others, she needed to take better care of herself. Before Endo ECHO, I would not have had that conversation.



Surrounding Bouchonville at the Endo ECHO “hub” in Albuquerque are (l to r, at table) UNM endocrinologist Mark Burge, MD; UNM psychiatrist Brant Hagar, MD; nurse manager, Jessica Kirk; clinic coordinator Leena Matlib; Endo ECHO CHW trainer, Vanessa Acosta; Project ECHO’s Melissa Meier (seated in back are pharmacy students).

SUPPORTING FRONT-LINE PROVIDERS

But the real power of Endo ECHO is at the community level, among front-line providers who previously struggled to keep up with new diabetes technologies, had difficulty accessing specialty expertise in a timely manner, and generally had little support.

Through Endo ECHO, these primary care providers are newly empowered: They belong to an ongoing learning network; they are constantly exposed to best practices; and they have mentoring relationships with a team of specialists who are also available to them outside the weekly teleclinics.

All this is particularly helpful in managing patients with type 1 diabetes, where changing technology plays such an important role.

In addition, each FQHC in Endo ECHO is paired with a community health worker whose job is to help patients navigate their psycho-social issues and act as their advocate. The community health workers are essential members of the Endo ECHO team because of their close relationships with their patients and insights into their patients’ everyday lives and challenges.

Like all doctors, I went into medicine to do good. Through Endo ECHO, I am part of a movement, practicing medicine in a way that I never dreamed of doing, collaboratively, in a community of free and ongoing knowledge-sharing, for the benefit of patients I will never know, or even see. 

ENDO ECHO’S ORIGINS

Although Endo ECHO launched in November 2014, the model on which it is based has operated for more than 10 years — and its effectiveness has been proven. Endo ECHO’s predecessor was Project ECHO, which began as a way to bring desperately needed specialty care to patients in New Mexico with hepatitis C. A 2011 study published in the *New England Journal of Medicine* showed that the quality of hepatitis C care provided by ECHO-trained clinicians was equal to that of care provided by university-based specialists.

Since then, Project ECHO has expanded — across diseases and specialties — across urban and rural locales, across different types of delivery services, and even across the globe. Today, Project ECHO has more than 40 hub partners with teleclinics covering 40-plus diseases and conditions in the U.S. It has programs in 11 countries — and it’s growing.

For more information on the Endo ECHO program, go to <http://echo.unm.edu>.



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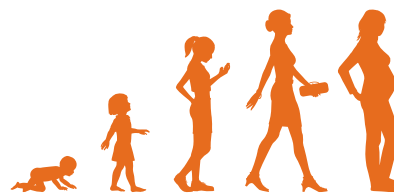
[†] For Research Use Only. Not for use in
diagnostic procedures.



Heir Apparent:

BY NILS KRONE, MD, FRCPCH,
RICHARD J. AUCHUS, MD, PHD,
AND NICOLE REISCH, MD

A Multi-Faceted Look at
One of the Most Common
Inherited Metabolic Disorders,
Congenital Adrenal Hyperplasia



Congenital adrenal hyperplasia (CAH) ranks among the most common inherited metabolic disorders, with the classic form (i.e., 21-hydroxylase deficiency) affecting about one in 15,000 newborns. It is characterized by a complex imbalance of steroid hormones, with reduced cortisol and aldosterone synthesis and excessive adrenal androgen production. Neonatal screening programs in most industrialized countries now enable early diagnosis in classic CAH and timely introduction of hormone substitution treatment. While this reduces life-threatening salt-wasting crises in newborns, hormone substitution over a lifetime poses new challenges in adult patients.

In this Tri-Point article, a **basic researcher** provides insights from model organism for altered adrenal steroid production, a **clinical researcher** discusses medical treatment options and challenges for adult patients with CAH, and a **clinical practitioner** highlights fertility-related challenges in adult CAH patients.





Nils Krone, MD, FRCPCH,
Centre for Endocrinology,
Diabetes and Metabolism,
University of Birmingham,
Birmingham, UK

HIGHLIGHTS

Classic and non-classic presentations of congenital adrenal hyperplasia are caused by a continuum of impairment of steroid enzyme activity.

In vitro expression analysis of genetic variants has greatly contributed to the understanding of the molecular pathogenesis of all forms of CAH.

Murine models have improved the understanding of the pathophysiology of CAH; in particular the discovery of impaired metanephrine synthesis in 21-hydroxylase deficiency.

A Basic Researcher's Perspective

— NILS KRONE, MD, FRCPCH*

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders leading to impaired glucocorticoid biosynthesis. The clinical presentation of different CAH forms depends on the underlying enzymatic defect. Deficiencies of 21-hydroxylase (CYP21A2) and 11 β -hydroxylase (CYP11B1) only affect adrenal steroid hormone biosynthesis, whereas 17 α -hydroxylase (CYP17A1) deficiency and 3 β -hydroxysteroid dehydrogenase type 2 (HSD3B2) deficiency also impair gonadal steroid production. P450 oxidoreductase deficiency (PORD) presents with apparent combined CYP17A1-CYP21A2 deficiency. In addition, PORD also causes skeletal malformations and severe genital ambiguity in both sexes. Traditionally, three further enzymatic deficiencies are classified within the CAH group. Steroidogenic acute regulatory protein (StAR) deficiency leads to a lipid adrenal and gonadal lipid accumulation resulting in Lipoid CAH (CLAH). P450 side-chain cleavage (CYP11A1) deficiency resembles the CLAH clinical presentation; however, patients have normal-sized or absent adrenals. Aldosterone synthase (CYP11B2) deficiency manifests with isolated mineralocorticoid deficiency and normal glucocorticoid synthesis.

Genetics of 21-Hydroxylase Deficiency

In clinical practice, the term CAH is often synonymously used for 21-hydroxylase deficiency (21OHD). 21OHD is caused by mutations in the CYP21A2 gene and accounts for about 95% of CAH cases in the general population. The majority of CYP21A2-inactivating mutations are caused by intergenic recombinations within the RCCX module. CYP21A2 gene deletions and CYP21A1P/CYP21A2 chimeric genes account for approximately 20% to 25% of 21OHD alleles in most Caucasian populations. About 70% to 75% of 21OHD disease-causing alleles originate from gene conversions with the CYP21A1P pseudogene, leading to small genetic transfers and single point mutations. The most common CYP21A1P-derived mutations include seven point mutations, a deletion of eight base pairs in exon 3, and the E6 cluster mutation. In addition to these common mutations, more than

150 pseudogene-independent mutations have been reported. The majority of these mutations occur sporadically and have only been reported in a small number of patients.

Genotype-Phenotype Correlation

Soon after the characterization of the CYP21A2 gene and the detection of disease-causing mutations, *in vitro* expression studies using insect and mammalian cells as well as yeast systems have been employed to assess the residual *in vitro* 21-hydroxylase function of common CYP21A2 mutations. These residual activities have built the framework for establishing the genotype-phenotype correlation in patients with CAH. This has been widely adopted to report population studies on 21-hydroxylase deficiency. Mutations are categorized into different mutation groups resembling: Null (mutations predicting absent *in vitro* activity), A (intron 2 splice site mutation), B (mutations such as the p.I172N mutation and mutations with 1% to 10% *in vitro* residual enzyme activity), C (mutations such as p.P30L, p.V281L, and p.P453S or above 20% to 30% *in vitro* 21-hydroxylase activity).

Overall, about 65% to 75% of patients with 21OHD are compound heterozygote. Commonly, the clinical phenotype is determined by the mildest CYP21A2 mutation, consequently allowing for the highest residual enzyme activity. Patients with Null and A genotypes have a high likelihood to present with salt-wasting (SW) CAH, whereas two-thirds of patients with group B genotypes present with simple-virilising (SV) CAH. Patients with group C genotypes commonly have non-classic (NC) CAH. Overall, genotype-phenotype data have supported genetic counselling; however, the best correlation has been found with the degree of renal salt loss. A limitation of pure *in vitro* enzyme analysis is the fact that pathophysiologic changes such as hyperplasia of the adrenal cortex cannot be modelled. This, in addition to other disease modifiers, might explain some of the observed variability of the expressed phenotype in patients with partially inactivating CYP21A2 mutations.

“ In times of more powerful genetic analysis methodologies such as next generation sequencing, modelling of genetic variants, and disease modifiers, it is becoming increasingly important to understand the clinical consequences.”



The same principle establishing the *in vitro* activity of genetic variants has been applied in rarer deficiencies leading to CAH. Over the last five to 10 years, complete and partial mutations have been also described in all other forms of CAH where classic and non-classic presentations are now well established.

Animal Models of CAH

A naturally occurring *Cyp21a2*-deficient mouse was identified soon after the cloning of the human *CYP21A2* gene. Further molecular characterization demonstrated loss of the active *Cyp21a1* gene by unequal crossing over between the active *Cyp21a1* gene and its pseudogene (*Cyp21a2-p*) leading to a chimeric *Cyp21a1-Cyp21a2-p* gene including a partial deletion of *Cyp21a1*. This chimeric gene carries several pseudogene-derived point mutations, missense mutations, and a nonsense mutation. The *in vitro* expression analysis of these mutations demonstrated lack of function of this chimeric gene. Overall, the *Cyp21a2*-deficient mice have been proven to be difficult to maintain postnatally, limiting their use as translational model. Another limitation modelling CAH is the lack of adrenal 17-hydroxylase expression in mice and consequently the lack of androgen excess in the 21-hydroxylase deficient mouse. However, further analysis of adrenals and metanephrine concentrations in these mice demonstrated severe impairment of adrenomedullary function in 21-hydroxylase deficiency. This led to further exploration of the human pathophysiology of CAH showing similar alterations of the adrenal gland in human patients with CAH. Interestingly, the severity of adrenomedullary function is closely correlated with the severity of the *CYP21A2* genotype in humans.

Murine models of other CAH forms have been developed. The 11-hydroxylase (*cyp11b1*) null mouse showed glucocorticoid deficiency and mineralocorticoid excess, adrenal hyperplasia, and mild hypokalemic hypertension as well as glucose intolerance. Remarkably and contrary to humans, affected female mice were found to be infertile. The murine deletion model of the steroidogenic

acute regulatory protein (StAR) showed a very high similarity to humans affected with the classic form of CLAH due to StAR mutation. Similar to humans suffering from CLAH, these mice also showed a considerable heterogeneity in the presentation and onset of adrenal insufficiency. The exact mechanisms explaining this variability remains to be elucidated. A similar severe phenotype was observed in the murine deletion model of P450 side chain cleavage model (*Cyp11a1*). These mice survived to term and then soon died after birth from adrenal insufficiency. In addition, SRY-positive mice show features of sex reversal.

Conclusion and Outlook

In times of more powerful genetic analysis methodologies such as next generation sequencing, modelling of genetic variants, and disease modifiers, it is becoming increasingly important to understand the clinical consequences. *In vitro* expression analysis of genetic variants has greatly contributed to the understanding of the molecular genetics of all forms of CAH. Mouse models of CAH have the limitation that the murine adrenal cortex does not produce androgens. However, the discovery of adrenomedullary impairment in CAH has been mainly achieved via studying murine models. Overall, it remains important to reflect that models only answer the specific question asked toward the model system. It is likely that the current revolution in genomic engineering techniques such as transcription activator like effector nucleases (TALEN) and CRISPER/ CAS9 systems will help to study the effects of complete and partial mutations inactivating steroidogenic pathways and enhance our understanding of pathophysiologic consequences by employing novel *in vitro* and *in vivo* systems.

**Clinical lead for adrenal disorders and disorders of sex development at Birmingham Children's Hospital. His lab currently focuses on creating novel whole organism models of inborn errors of steroidogenesis by applying genomic engineering methods.*

A Clinical Researcher's Perspective

— RICHARD J. AUCHUS, MD, PHD



Richard J. Auchus,

MD, PhD, Professor and
Endocrinology Fellowship
Program Director
Division of Metabolism,
Endocrinology, and Diabetes;
Department of Internal
Medicine, University of
Michigan, Ann Arbor, Mich.

HIGHLIGHTS

Replacing the cortisol deficiency is straightforward, but **better treatments for the androgen excess** are needed.

CAH patients develop **characteristic intra-adrenal and ectopic adrenal tumors** by unknown mechanisms.

Obtaining **long-term outcomes data** for all aspects of CAH will be challenging.

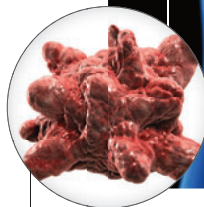
Classic 21-hydroxylase deficiency (21OHD): Not One Simple Defect

The physiology of 21OHD fundamentally reflects a block in cortisol synthesis and diversion of cortisol precursors to androgens under ACTH stimulation. Patients with 21OHD also are prone to develop adrenal adenomas, myelolipomas, and adrenal rest tumors, most commonly in the testes. For women with classic 21OHD, genital virilization, interference with gonadal function, and low rates of fecundity add to the challenges. While some consequences might be predictable, simple models do not explain the variable disease manifestations, and current therapies do not mitigate all complications.

Traditionally, 21OHD treatment has been limited to glucocorticoids, mineralocorticoids, salt, and surgery. Replacing the adrenal insufficiency is not difficult, but normalizing the androgen excess usually requires higher and/or more frequent glucocorticoid doses, particularly to blunt the early-morning rise in ACTH and adrenal steroids. These extra doses create compliance challenges and long-term consequences from life-long over-replacement. Genital reconstruction surgery improves many aspects of appearance and function, but the androgen effects on the brain persist, and chronic urogenital difficulties are common.

Outcomes from large 21OHD cohorts have begun to appear. The National Institutes of Health (NIH) report of 183 patients with classic and 61 patients with non-classic 21OHD found no standard treatment regimen, androgens mostly above or below the normal range, short stature, low bone mineral density in 37% of adults, and high rates of obesity and the metabolic syndrome. The British Congenital adrenal hyperplasia Adult Study Executive (CaHASE) study of 203 adults also found mostly abnormal steroid values with a tendency for over-treatment, a high prevalence of cushingoid features, low bone mineral density in 40%, obesity in 40%, markedly compromised fertility, and reduced quality of life. Similar studies from several other groups confirm these findings. Can we do better than these unflattering statistics?

Adrenal Rest Tumor



Taking a step back and setting a clinical research agenda

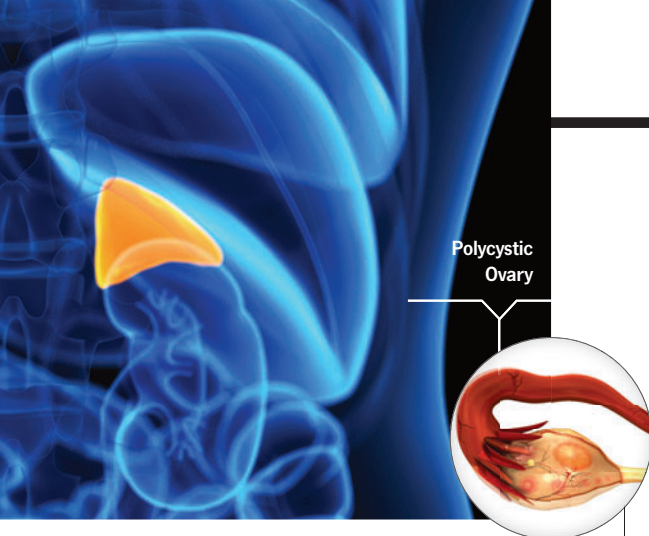
What are the steroids and pathways that lead to virilization in the fetus, bone age advancement in the child, and impaired fertility in the adult?

Ordinarily, the major 19-carbon product of the adrenal is dehydroepiandrosterone sulfate (DHEAS). Androstenedione (AD), testosterone (T), and dihydrotestosterone (DHT) are minor adrenal products; however, T and DHT arise from extra-adrenal metabolism of DHEA. DHEAS is paradoxically low-normal and easily suppressed in classic 21OHD, and recent evidence suggests that DHT in the newborn derives from the 5 α -reduced “backdoor” pathway without the intermediacy of AD and T.

How should we monitor therapy at different stages of life, and what are our goals?

Because 17-hydroxyprogesterone (17OHP) accumulates proximal to the block in 21OHD, 17OHP is the gold standard for diagnosis of 21OHD and is widely used to monitor treatment. Yet androgens and estrogens — not 17OHP — cause the problems. Although AD and T are used to monitor therapy, estrogen concentrations below the limits of the best commercial assays will advance bone age. Serum 17OHP is a very sensitive measure of control, but values fluctuate wildly during the day in relation to dosing, and 17OHP correlates poorly with downstream metabolites. The onset of adrenarche and puberty complicate management. In adolescents and adults, sex steroids and 17OHP also derive from the gonads, so one must estimate the contribution from the adrenal. Other steroids such as 21-deoxycortisol are more specific for 21OHD than 17OHP, and this analyte has been used to eliminate false-positive results of newborn screening and to improve diagnostic testing for non-classic 21OHD.

Why do some patients fare so well and others struggle? With the crisp enzymatic defect and the



A Clinical Practitioner's Perspective

— NICOLE REISCH, MD



Nicole Reisch, MD, Head of CAH outpatient clinic and research group, clinical and translational research team leader at the Medizinische Klinik und Poliklinik IV, Klinikum der Ludwig-Maximilians-Universität, Ziemssenstr, München, Germany

Fertility-Related Challenges in Females with Classic CAH

Multiple studies have demonstrated reduced fertility in females with classic CAH because of 21-hydroxylase deficiency. The birth rate in females with CAH is substantially reduced compared to the general population. It is estimated that only 25% of women with CAH ever attempt pregnancy and only 10% of those with the severe salt-wasting form. The reasons for this observation are manifold: vaginal insufficiency with dyspareunia, anovulatory menstrual cycles because of adrenal androgen excess, reduced endometrium growth during follicular phase because of adrenal progesterone production, additional ovarian hyperandrogenism (secondary polycystic ovary) because of adrenal-derived androgens in many patients, multiple psychosexual factors, or masculinization of the central nervous system due to prenatal androgen excess. One study, investigating 35 adult females with classic CAH, showed that seven were homosexual, eight were married, 13 never have had sexual intercourse, and three patients were without any sexual activity. In this cohort 18 out of 22 patients who actually had sexual intercourse reported painful penetration. The sexual function, as measured by the Female Sexual Function Index, was lower compared to controls and substantially lower in those patients with higher Prader stadium. This finding has been confirmed by a Swedish study showing that sexual life and function is perceived as less satisfactory in genotype "null."

Most studies on fertility in female patients with CAH, however, do not take into consideration the percentage of patients indeed having attempted to conceive. Thereby, these studies do not represent the actual pregnancy rate. Having a closer look on the actual pregnancy rate in women attempting to conceive, there was no difference in women with CAH and the general population (pregnancy rate in classic CAH 91.3% versus 95.0%) and no difference in women with the salt-wasting (88.9%)

limited number of pseudogene-derived mutations in most patients, genotype-phenotype correlations in 21OHD are strong but not perfect, even among siblings bearing the same mutations. Response to therapy is highly variable as well. Polymorphism in the genes encoding steroid and drug metabolism enzymes and changes in their expression from environmental exposures might be responsible.

Why do tumors develop? Some studies have shown absence of ACTH receptors in myelolipomas and no correlation of adrenal rest tumors with biochemical measures of control.

What are the preferred timings and procedures for reconstruction surgeries? New techniques and trends develop as soon as cohorts from the older procedures reach the stage of "long-term" follow-up.

How can we gather evidence to guide parents and patients for a rare disease with so many confounding variables? Collaborations and prospective protocols are essential.

Treatments on the horizon

Sustained-release hydrocortisone preparations are being studied. Greater convenience should improve compliance — but will control be better and complications lower? Continuous subcutaneous hydrocortisone infusion makes sense physiologically and has been shown to improve control with lower total dose in a few patients, but is this approach practical? We showed that abiraterone acetate added to replacement hydrocortisone doses normalized androgens in adult women with classic 21OHD, but the study was short. Will androgen biosynthesis inhibitors benefit children with 21OHD? With innovation and broad collaboration among clinical researchers, we can begin to answer these questions and to improve outcomes.

HIGHLIGHTS

Fertility is reduced in both males and females with classic congenital adrenal hyperplasia caused by 21-hydroxylase deficiency.

In males with classic CAH, there are two main reasons for reduced fertility and fecundity: First, testicular adrenal rest tumors — adrenal suppressive therapy with dexamethasone can effectively restore fertility, whereas surgery can neither restore fertility nor HPA axis integrity. Second, adrenal-derived androgens lead to a suppression of gonadotropins causing testicular atrophy and impaired spermatogenesis.

In females with classic CAH, optimal gluco- and mineralocorticoid substitution therapy has been shown to normalize fecundity.

In non-classic CAH, an increased rate of miscarriages (25%) can be normalized by low dose hydrocortisone therapy.

“ Having a closer look on the actual pregnancy rate in women attempting to conceive, there was no difference in women with CAH and the general population and no difference in women with the salt-wasting and the simple virilizing forms of classic CAH.”



and the simple virilizing forms (92.9%) of classic CAH. In fact, in the majority of women, a spontaneous conception (76.2%) was achieved. Prednisolone administered once every eight hours has been shown to effectively suppress progesterone in the follicular phase and to improve receptibility of the endometrium. The treatment target for women attempting to conceive is a follicular-phase serum progesterone <2 nmol/l (<0.6 ng/ml). Prednisolone might possibly be superior to hydrocortisone in this respect, however, evidence-based data are missing. As dexamethasone passes the placenta, it should be substituted by hydrocortisone or prednisolone to avoid adrenal suppression and possible negative metabolic effects on the fetus. Dexamethasone should only be given if prenatal therapy of the fetus is wanted and warranted. It should only be implemented within the setting of a clinical trial approved by an ethics committee. During pregnancy, renin concentration physiologically increases about five-fold. In classic CAH with and without mineralocorticoid deficiency substantially elevated renin concentrations compared to healthy controls have been described. An increase of fludrocortisone in salt-wasting CAH or the addition of fludrocortisone in simple virilizing CAH may therefore be necessary and reasonable. Hoepffner, et al. described a normalization and improved conception after the addition of fludrocortisone.

Fertility-Related Challenges in Males with Classic CAH

For a long time, fertility issues in CAH have focused on females whereas males have received much less attention. In recent years, however, it has become obvious that maintaining fertility in males appears to be even more of a problem than in females. There are no data on sexuality in males with CAH. However, fertility in males is substantially reduced compared to the general population. There are two main reasons for subfertility in males: first, suppression of gonadotropins by either adrenal-derived androgens (and

their conversion to estrogens) in case of under-replacement of glucocorticoids or by external glucocorticoids in case of over-replacement. Both mechanisms lead to impaired spermatogenesis and testicular atrophy.

The second major reason is testicular adrenal rest tumors. The pathogenesis of these tumors is not yet completely understood. They are thought to arise from adrenocortical remnants that have descended with the testes during fetal life or from postnatally reprogrammed Leydig cell precursors. Testicular adrenal rest tumors (TARTs) are usually bilateral and always benign. The tumors have been found to express adrenal-specific markers such as MC2-receptor, ATII-receptor, and CYP11B1. They also have been shown to be ACTH-dependent to a certain degree and thus are potentially reversible with the adrenal-suppressive therapy, dexamethasone. They are located in the rete testis and impair spermatogenesis by either mechanical obstruction of the tubuli seminiferi, or they may interfere with the local and/or systemic hormone milieu by their own hormone production. So far, no correlation of TART development and common measures of disease control in CAH has been shown. Still it is very likely that disease control plays a major role in TART growth. As surgical removal of TART has been shown to restore neither fertility nor HPA axis, surgical treatment of TART is only recommended for discomfort and pain relief and always should be testis sparing.

Fertility-Related Challenges in Females with Non-Classic CAH

The miscarriage rate in women with non-classic CAH has been shown to be substantially increased (25% versus 6% in the general population). However, it can be normalized with low to moderate doses of hydrocortisone prior to and during pregnancy, therefore, it is recommended at these times. ^{EN}

ACKNOWLEDGEMENT: THIS ARTICLE WAS REVIEWED BY FELIX BEUSCHLEIN, MD, UNIVERSITY OF MUNICH; AND RUTH KERI, PHD, CASE WESTERN RESERVE UNIVERSITY.

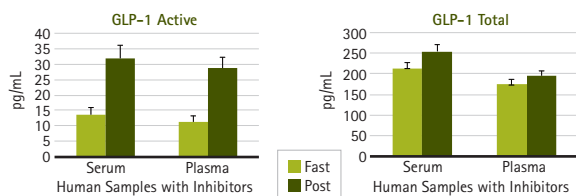
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A Peculiar Trait

ENDOCRINE NEWS TALKS TO MÁRTA KORBONITS, MD, PHD, AT THE QUEEN MARY UNIVERSITY OF LONDON ABOUT HER RESEARCH IN SEEKING THE MUTATIONS BEHIND A FAMILIAL ADENOMA.

BY MELISSA MAPES



MÁRTA KORBONITS, MD, PHD

Three-dimensional structure of human AIP with the characteristic C terminal tetra-trico-peptide domain (three pairs of alpha helices and a final 7th alpha helix), crucial in the protein-protein interactions of AIP.



About one in every thousand individuals will develop a pituitary adenoma, a noncancerous but disruptive tumor on the pituitary gland that can induce a variety of negative side effects. But, among these patients, approximately 5% suffer from a very particular inherited form of the disease: familial isolated pituitary adenoma (FIPA).

Márta Korbonits, MD, PhD, professor of endocrinology at the Queen Mary University of London, is searching for the origins of this genetic disorder in hopes of helping physicians diagnose it faster and provide better care for patients. Among families with FIPA, one in five cases can be traced back to the gene called aryl hydrocarbon receptor interacting protein (AIP), but for the other 80 percent of families facing the disease, the cause is still unknown.

Korbonits spoke with *Endocrine News* about her research and the importance of finding FIPA before its effects become irreversible.

Endocrine News: What drew you to research in the field of endocrinology, and how did you choose your specific specialty?

Márta Korbonits: I have wanted to be an endocrinologist since medical school. I've always been excited about the complexity of the pathways and the phenotypes patients are showing. I found the logic in endocrinology fascinating, and I never looked back.

I've been working in translational endocrine science for 20-plus years and have always been interested in the way a problem may start with a singular patient and end up informing you about the pathophysiology of a disease as well as the basic physiology of the body. When seeing patients, you discover novel aspects or functions that may be relevant not just for that disease,

but for the regulation of that hormone. Informing clinical practice and physiology with this two-way kind of work is really exciting.

EN: What are you currently working on?

MK: My main project at this point is working on familial pituitary adenomas. These involve patients who have a pituitary adenoma and also have a family history of this disease, although in some cases there is no known family history despite having genetic origin of the disease. One of the interesting aspects is why some people develop the disease while other family members having the same mutation are spared. We are also interested in the exact mechanism of how the mutations cause the disease.

There have been some really interesting findings regarding the phenotypes and their correlation to the exact gene mutation, or the genotype. Our study includes one of the largest groups of patients with this disease. We are combining clinical data with experimental results — identifying DNA mutation in patient samples and recreating these mutations in the lab to be able to do functional experiments.

EN: Among your projects, what accomplishments are you most proud of?

MK: I am proud that we were able to help put this disease on the table in the United Kingdom and elsewhere by identifying quite a lot of patients with pituitary adenomas and screening their families for the disease as well. We were able to provide genetic advisement for patients and, via screening, sometimes discovered patients who did not even realize that they had the disease. If we can interfere earlier, we hopefully have a better chance to cure or successfully treat the pituitary adenoma. So I am glad we were able to help in this regard.

My most publicized work was a project involving a patient born 250 years ago in Northern Ireland. We identified the mutation in him and also identified families living with the same disease, and then turned to his relatives who are alive today. After that, we did a whole population screening

“

If we can interfere earlier, we hopefully have a better chance to **cure or successfully treat the pituitary adenoma.**

”

of the community he was from and identified some additional cases. Hopefully, this made [the community] aware of the disease so that it can be recognized sooner.

EN: If you had unlimited funding, how would you use it to enhance your laboratory and research?

MK: I would screen patients whose clinical picture suggests that they have this particular disease and use the resources to analyze all of our existing samples. We have many additional samples that we would like to analyze.

EN: Where do you see your scientific work heading in the future? How do you hope to affect change with your projects?

MK: I see identifying these new genes as the next step in this work. The other important step is to identify the mechanism of how the genes work and eventually develop new types of treatments and methods for diagnosing the disease sooner.

EN: Any final thoughts you would like to share with our readers?

MK: If you have a patient or multiple patients with familial pituitary adenomas, please do not hesitate to contact me. FIPA is a relatively rare disease, and lots of patients have been told in the past that it is not familial but, in some cases, it actually is. *(Those working with patients that have been diagnosed with familial pituitary adenoma can get in touch with Korbonits at m.korbonits@qmul.ac.uk.)* 

POSSIBLE FAMILIAL PITUITARY ADENOMA SYMPTOMS

Depending on the type of tumor that develops (somatotrophinoma, prolactinoma, non-functioning, corticotrophinoma, or TSH-producing), patients with FIPA may experience a wide range of symptoms, including:

- ▶ Difficulty sleeping
- ▶ Erectile dysfunction
- ▶ Fast or irregular heartbeat
- ▶ Fatigue
- ▶ Gigantism
- ▶ Headaches
- ▶ Infertility
- ▶ Lack of pituitary gland function
- ▶ Irritability
- ▶ Lack of menstruation
- ▶ Low testosterone in men
- ▶ Overactive thyroid
- ▶ Poor libido
- ▶ Production of breast milk (not related to pregnancy)
- ▶ Visual disturbances
- ▶ Weight change

More information on FIPA can be found at www.fipapatient.org.

Endocrine news

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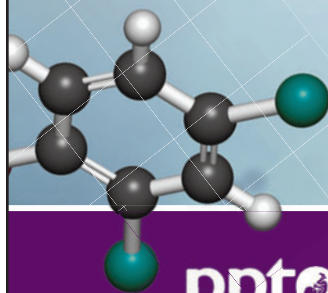


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Senate Majority Leader
Mitch McConnell (R-KY)

Threat of Government Shutdown Looms; NIH Funding in Jeopardy

A key issue that the U.S. Congress must resolve by September 30 (the end of the fiscal year) is how to fund the government and all federal programs, including the National Institutes of Health (NIH). Although appropriations bills were able to be passed by committees in both the House and the Senate, neither body has been able to bring this legislation to a full vote. Prior to leaving Washington for the August congressional recess, Senate Majority Leader Mitch McConnell (R-KY) reported that legislators “haven’t even begun to plan how to cover the government’s funding after the fiscal year ends on September 30.” The House will be in session for only 10 days in September (the Senate has 15 days scheduled).

Democrats in the Senate have effectively shut down the process by blocking consideration of any bills that fund programs at the reduced sequester levels. At the same time, a debate over the Confederate Flag on federal grounds has deterred House leadership from bringing up the remaining bills on their side. Then, of course, there is the blanket veto threat from President Obama, which has all but guaranteed that these bills would never be enacted under current levels. Adding to the gridlock, a number of Republican leaders have “threatened to reject” a spending bill “needed to keep the government open” unless funding for Planned Parenthood is removed.

Therefore, the Congress has the following options: Lawmakers could negotiate a deal that provides sequestration relief, if only on a partial and/or temporary basis. They could do a continuing resolution (a mechanism that would fund programs at current levels/no increases) that is either short term or year long, and/or they could risk a government shutdown.

TAKE ACTION:
Now is a critical time to contact your members of Congress and urge support for a deal on the budget that will give some relief to research funding. Please visit the Society’s online advocacy campaign at www.endocrine.org/advocacy to contact Congress.

Endocrine Society Endorses Bill to Improve Safety of Personal Care Products



Sen. Dianne Feinstein (D-CA)



Sen. Susan Collins (R-ME)

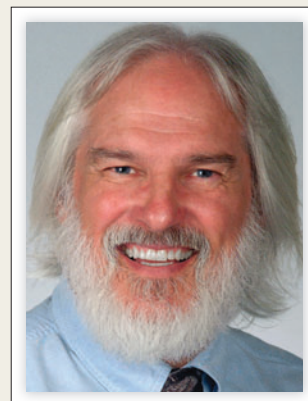


The bill prioritizes several chemicals commonly used in personal care products for immediate review by the U.S. Food and Drug Administration (FDA).

In recent months, Endocrine Society members and staff have worked with the office of Sen. Dianne Feinstein (D-CA) on legislative efforts to improve the regulatory oversight of personal care products, such as cosmetics, shampoos, and lotions. On April 20, Sen. Feinstein and Sen. Susan Collins (R-ME) introduced S.1014, the Personal Care Products Safety Act (PCPSA). The bill prioritizes several chemicals commonly used in personal care products for immediate review by the FDA. One of the priority chemicals, propyl paraben, is highlighted as an endocrine-disrupting chemical (EDC) that can mimic estrogen and is “linked to a wide range of health effects, including reproductive system disorders.”

The Endocrine Society was encouraged that the PCPSA sets a rigorous safety standard for FDA review of chemicals and includes provisions to allow public access to product statements. The Society joined the Environmental Working Group, Society for Women’s Health Research, and other consumer health organizations in endorsing the Personal Care Products Safety Act. The Society believes that this bill will help ensure a safe marketplace for personal care products and reduce harms from exposure to toxic chemicals such as EDCs, and we will continue to work with Sen. Feinstein to advance the legislation and other efforts to support public health. In September, the Endocrine Society will participate in a congressional briefing to raise awareness of the PCPSA and encourage committee consideration of the legislation.

Remembering EDC Research Pioneer Louis J. Guillette, Jr.



The world of endocrine-disrupting chemical research recently lost a giant in the field with the passing of Louis J. “Lou” Guillette, 60.

Director of the Marine Biomedicine & Environmental Sciences Center and professor of Ob/Gyn at the Medical University of South Carolina, Lou was a HHMI professor, Heinz Award Winner, and former “Professor of the Year” at the University of Florida. He had a profound influence on the field of endocrine disruption research, and on all those who knew him, not only because of his knowledge of vertebrate reproductive biology and comparative endocrinology, but also because of his ability to communicate to broad audiences.

Lou’s doctoral work was on the evolution of viviparity in a *Sceloporus* lizard, and this led to the initiation of a work program on the reproductive biology of alligators when he took a position in the Zoology Department at the University of Florida. His discoveries revealing the effects of chemical pollution on male reproductive biology of alligators in Lake Apopka were landmark and led to a prolific career that later expanded to embrace the study and public communication of the connections between wildlife health and human health, and the use of wildlife as human environmental health sentinels.

An index of the breadth of Lou’s work was the diversity of funding agencies from which he attracted support, including NIH, NSF, EPA, DOE, NASA, U.S. Fish & Wildlife Service, and many state and private foundations. Who else but Lou could hold a chair in marine genomics as well as in obstetrics and gynecology all at the same time? Lou’s greatest commitment was to his students and their development; he mentored dozens of students and postdocs and succeeded in developing one-to-one relationships with all his students that have lasted far beyond the students’ tenure.

He was warm and outgoing and has shaped the thinking and careers of a great number of scientists around the world.

— R. THOMAS ZOELLER, UNIVERSITY OF MASSACHUSETTS, AMHERST, MASS., AND SUSAN JOBLING, BRUNEL UNIVERSITY, LONDON, UK

Endocrine Society Comments on NIH Initiatives

As part of the Endocrine Society’s comprehensive advocacy program, the Society submits comments on Requests for Information (RFIs) from the National Institutes of Health (NIH) and other research funding agencies. This summer, the NIH issued RFIs on biomedical technology development and health disparities research, two topics of great interest to endocrinologists.

Technology Development

On June 10, the National Institute of General Medical Sciences (NIGMS) issued a RFI on “innovative approaches to technology development for the biomedical research community.” NIGMS is considering efforts to both support the development of new technologies and how best to ensure broad access to newly developed technologies. In response to the RFI, the Endocrine Society identified several challenges that researchers face in the generation, development, and application of new technologies. For example, researchers are forced to continuously update equipment and expertise in response to new technological developments, evaluate multiple expensive and time-consuming approaches to experiments, and navigate numerous new resources, databases, and biobanks.

The Endocrine Society recommended that the NIH continue to develop and encourage the use of centralized resources that help researchers quickly access databases and analyze data. The Society also encouraged the NIH to seek new ways to foster connections between basic and clinical researchers, and explore the use of public-private partnerships to create user-friendly data mining tools and support applied biomedical research.

Health Disparities Research

The National Institute on Minority Health and Health Disparities (NIMHD) is embarking on a scientific planning process in collaboration with other NIH institutes and centers to define a vision that will guide the development of the science of health disparities research for the next decade. On April 17, the NIMHD issued a RFI “Soliciting Input into the NIH Science Vision for Health Disparities Research.” In response to the RFI, the Endocrine Society highlighted infrastructure and resource needs for teams that study health disparities, scientific advances that should be prioritized in the vision, and policy considerations to reduce barriers to effective care.

The Society’s response also highlighted the *Endocrine Society’s Scientific Statement on Health Disparities in Endocrine Disorders* as an important resource the NIH should reference to identify key questions that should be addressed by additional research. We anticipate that the Science Vision for Health Disparities Research will be an important tool to reduce health disparities in the coming decade and staff will continue to seek opportunities to engage with the NIH and the NIMHD as the Science Vision develops. 

Society Participates in NICHD Advisory Council Meeting

As part of a comprehensive approach to enhance the visibility of endocrinology among research funding agencies, the Society participated in the June 4 meeting of the National Advisory Child Health and Human Development (NACHHD) Council. The Council advises the director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) on research, support activities, and functions of the institute.

During the director's report, NICHD director Alan Guttmacher, MD, provided updates on several projects of interest to the extramural research community. Guttmacher highlighted a new online system, the NICHD Data and Specimen Hub (N-DASH), which will allow the storage and access of de-identified data from NICHD-supported studies. The N-DASH platform launched in late June with data from 14 initial studies. The director then noted that they are closer to delivering an interactive mobile app to develop crowd-sourced data to detail the natural history and variations of human pregnancy. The app will also allow women to receive accurate information about pregnancy from trusted sources and let pregnant women know about opportunities to participate in research. Additionally, Guttmacher announced the launch of a new Spanish-language website to broaden community outreach.

The Council was joined by the director of the National Institute for General Medical Studies (NIGMS), Jon Lorsch, PhD, to discuss NIGMS' efforts to refocus its portfolio on

investigator-initiated research. Lorsch described the institute's rationale for increasing the funding of "programs" rather than "projects" through the institute's Maximizing Investigator's Research Award (MIRA) program. Specifically, the institute's data suggest that research funding is skewed toward a top tier of researchers, and that additional efficiencies might be enabled through a more equitable distribution of funds, for example, by reducing investigator time spent writing grant applications. The MIRA program proposes to award grants of up to \$750,000 per year for up to five years.

However, the awards will be open to established investigators with at least two existing R01 grants who make the MIRA award their primary source of funding. This implies that researchers will be comfortable trading a greater overall dollar amount for additional efficiency and funding security. The NICHD has established a working group to consider whether to implement a similar program through the R35 mechanism. The working group is weighing many options, including identifying a target career stage and evaluating how many awards NICHD should support through this mechanism.

In a separate concept clearance and review session, the three proposals shown in the table below were discussed by the Council and passed with no objection. Concept clearance represents an early step in the process of developing Requests for Application and Program Announcements, and the final details and eventual publication are subject to additional approval. — *Joe Laakso, PhD, associate director, science policy*

PROGRAM NAME	FUNDING MECHANISM	PROGRAM CONTACT
Population Dynamics Centers Research Infrastructure FY 2016–2020	P2C	Rebecca L. Clark, PhD, Population Branch Dynamics
Specialized Centers for Research in Pediatric Developmental Pharmacology	U54	Ekaterini Tisliou, MD, Obstetric and Pediatric Pharmacology and Therapeutics Branch
Omics Approaches to Assess Human Placental Development and Function in Real Time	R01/R21	David Weinberg, PhD, Office of the Director



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- ▶ **Abstract submission:**
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November 10, 2015
- ▶ **Early registration:**
October 6, 2015 –
January 13, 2016
- ▶ **Advance registration:**
January 14, 2016 –
February 25, 2016
- ▶ **Late-breaking
abstract submission:**
January 19, 2016 –
February 17, 2016
- ▶ **Housing reservation
deadline:**
March 8, 2016

The most important innovations and latest insights in endocrinology will hit the East Coast Friday, April 1 – Monday, April 4, as **ENDO 2016** lands in Boston. Join leading practitioners and researchers from around the world for four exhilarating days of education and networking.

Celebrate the Society's Centennial

The Society has come a long way from June 1916 when a group gathered at the American Medical Association's meeting to explore creating a professional society for those working in the fledgling field of endocrinology. That discussion resulted in the founding of the Association for the Study of Internal Secretions with 300 charter members. Do you know what year the name was changed to the Endocrine Society? Learn the answer to this and more as we celebrate the legacy of the Society through special historical perspectives in the key areas of scientific discovery that encompass endocrinology.

A Mecca for Endocrinologists

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ENDO 2016 will present thought-provoking speakers in insightful sessions, and the opportunity for you to explore all of the key areas of endocrinology from basic discoveries to clinical applications. The networking at **ENDO** makes the meeting a can't-miss event every year.

In addition to the outstanding presentations, there will be pre-conference events starting on Thursday, March 30, and **ENDOExpo** will provide information on the latest advances in products and services for **ENDO** attendees.

ENDOCRINE CASES: Timely Advice from Experts in the Field



The Endocrine Society offers members an exclusive benefit — Endocrine Cases. Envisioned and developed by immediate past president Richard J. Santen, MD, this online tool allows members to submit their most challenging clinical cases and have Society experts weigh in. Present real or hypothetical situations, and test your hypothesis against what the experts recommend. Visit endocrine.org/Cases to learn more about this valuable and informative member benefit.

EVENT CALENDAR

SEPTEMBER 8 – 12

MIAMI

Clinical Endocrinology
Update

www.endocrine.org/ceu

OCTOBER 9 – 12

SEATTLE

American Society for Bone
and Mineral Research
Annual Meeting

www.asbmr.org

OCTOBER 17 – 21

CHICAGO

Neuroscience 2015

www.sfn.org

OCTOBER 18 – 23

ORLANDO

Thyroid ITC 2015

www.thyroid.org

NOVEMBER 1 – 7

LOS ANGELES

Obesity Week 2015

www.obesity.org

New Diabetes Management Program from HHN



In November, the Hormone Health Network (HHN) will launch a new collaborative diabetes management program called Diabetes

Awareness Information for Loved Ones and You (D.A.I.L.Y.) aimed at patients as well as clinicians who treat diabetes.

D.A.I.L.Y. will provide resources that are tailored to an individual patient's needs and can be shared with healthcare professionals to encourage a collaborative approach to diabetes management. Users enroll as a person with diabetes, family member or friend of a person with diabetes, or as a healthcare professional. The goal is to provide access to useful educational resources that are tools not rules for diabetes self-management. As the leading experts in diabetes treatment, endocrinologists helped to develop program content to ensure patients and their loved ones receive the most trusted information.

Ahead of the launch, HHN has released the new logo for D.A.I.L.Y., which was created with input from diabetes experts, Endocrine Society membership and staff, and, more importantly, using patients' input and uses the sun itself as a centerpiece, according to HHN director, Cheretta Clerkley. "The sun is a symbol of warmth, light, hope, knowledge, and awareness," she says. "The logo conveys what we hope patients and healthcare professionals will gain from enrollment in this program, which we hope will be a more humanistic, positive, and approachable feel toward taking control of diabetes management."

For more information about D.A.I.L.Y. or to pre-enroll, visit, www.hormone.org/about-us/volunteer/diabetes-you.

Society Publishes Clinical Practice Guideline on Cushing's Syndrome

In July, the Society issued a Clinical Practice Guideline (CPG) on strategies for treating Cushing's syndrome entitled *Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline*, which was published online and appeared in the August issue of *The Journal of Clinical Endocrinology & Metabolism (JCEM)*.

Cushing's syndrome occurs when a person has excess cortisol in the blood for an extended period, according to the Hormone Health Network. When it is present in normal amounts, cortisol is involved in the body's response to stress, maintains blood pressure and cardiovascular function, keeps the immune system in check, and converts fat, carbohydrates, and proteins into energy. Chronic overexposure to the hormone can contribute to the development of cardiovascular disease, infections, and blood clots in veins.

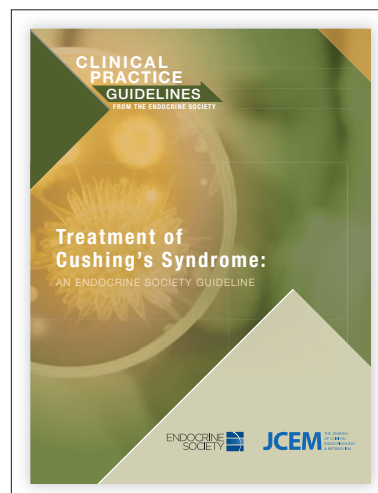
In some cases, tumors found on the adrenal or pituitary glands or elsewhere in the body cause the overproduction of cortisol and lead to the development of Cushing's syndrome. The CPG focus on this form of the condition, known as endogenous Cushing's syndrome.

"People who have active Cushing's syndrome face a greater risk of death — anywhere from nearly twice as high to nearly five times higher — than the general population," says Lynnette K. Nieman, MD, of the National Institutes of Health's Eunice Kennedy Shriver National Institute of Child Health and Human Development in Bethesda, MD, and chair of the task force that authored the guideline. "To reduce the risk of fatal cardiovascular disease, infections, or blood clots, it is critical to identify the cause of the Cushing's syndrome and restore cortisol levels to the normal range."

In the CPG, the Endocrine Society recommends that the first-line treatment for endogenous Cushing's syndrome be the removal of the tumor unless surgery is not possible or unlikely to address the excess cortisol. Surgical removal of the tumor is optimal because it leaves intact the hypothalamic-pituitary-adrenal axis, which is integral to the body's central stress response.

Other members of the Endocrine Society task force who developed this CPG include: Beverly M.K. Biller of Massachusetts General Hospital, in Boston, Mass.; James W. Findling of the Medical College of Wisconsin, in Milwaukee, Wisc.; M. Hassan Murad of the Mayo Clinic, in Rochester, Minn.; John Newell-Price of the University of Sheffield, in Sheffield, U.K.; Martin O. Savage of the William Harvey Research Institute at Barts and the London School of Medicine and Dentistry, in London, U.K.; and Antoine Tabarin of CHU de Bordeaux and INSERM at the University of Bordeaux, in Bordeaux, France.

The CPG was co-sponsored by the European Society of Endocrinology. 



In the CPG, the Endocrine Society recommends that the first-line treatment for endogenous Cushing's syndrome be the removal of the tumor unless surgery is not possible or unlikely to address the excess cortisol.



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Questions should be directed to Elizabeth Kan at 202.971.3621 or ekan@endocrine.org.

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What You Should Know About

SHARED DECISION MAKING (SDM)

Shared Decision Making gets patients involved in their healthcare treatment plan. SDM takes into account the best scientific evidence and the values and preferences of the patient to provide the most effective therapy possible. For better patient outcomes, consider implementing an SDM plan in your practice.



WHY SDM?

- Improve patient satisfaction and involvement with their care
- Help patients assume greater responsibility for health care decisions
- Promote compliance and adherence to treatment regimens
- Empower patients to be more knowledgeable and active in managing their care

EVIDENCE FOR SDM

- Reduction in use of tests
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- Better health outcomes
- Lower litigation rates

BEST PRACTICES FOR IMPLEMENTING SDM



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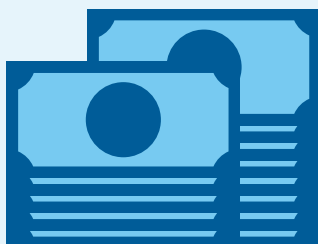
- Strong desire to engage in SDM about treatment options
- Multiple barriers inhibit conversation with physicians about health decisions
- Feel compelled to confirm to socially sanctioned roles and defer to physicians
- Physicians can be authoritarian
- Fear of being categorized “difficult” prevents patients from participating more fully in their own health care

(Frosch, et al. Health Affairs, 2012)

IMPACT ON COSTS

- Lewin Group estimated
SDM for 11 procedures saved

\$9 BILLION
nationally over 10 years



- Group Health used SDM for
hip or knee replacement: 38%
fewer knee and 26% fewer hip
surgeries, **COST LOWERED BY**

12–21% OVER 6 MONTHS.

SHARED DECISION MAKING STAGES

- 1 Establish ongoing partnership (trust, mutual respect)
- 2 Foster two-way information exchange between the physician and the patient
- 3 Support a process of deliberation; patients encouraged to express preferences
- 4 Make a decision that honors provider's expert knowledge and respects patient's individual needs

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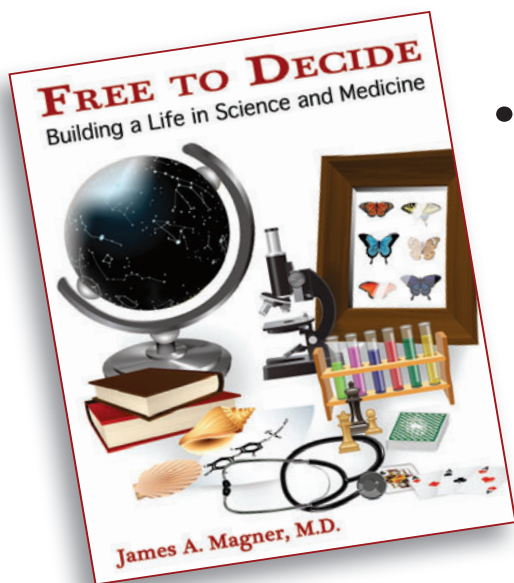
Shared Decision Making tools specific to diabetes can be accessed at accurateinsulin.org.

The Hormone Health Network is the nation's endocrine patient education resource. We are committed to helping patients have more informed discussions with their health care providers about hormone health, disease, and treatment. All of our educational resources are free and based on the clinical and scientific expertise of the Endocrine Society.



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100 YEARS
OF HORMONE SCIENCE TO HEALTH

Type 2 Diabetes:

- The recommended starting dose of TOUJEO in insulin naïve patients with type 2 diabetes is 0.2 units per kilogram of body weight once daily. The dosage of other anti-diabetic drugs may need to be adjusted when starting TOUJEO to minimize the risk of hypoglycemia [See **Warnings and Precautions** (5.3)].

2.3 Starting Dose in Patients with either Type 1 or Type 2 Diabetes Already on Insulin Therapy

- To minimize the risk of hypoglycemia when changing patients from a once daily long-acting or intermediate acting insulin product to TOUJEO, the starting dose of TOUJEO can be the same as the once daily long-acting dose. For patients controlled on LANTUS (insulin glargine, 100 units/mL) expect that a higher daily dose of TOUJEO will be needed to maintain the same level of glycemic control [see *Clinical Pharmacology* (12.2) in the full prescribing information and *Clinical Studies* (14.1) in the full prescribing information].
- To minimize the risk of hypoglycemia when changing patients from twice-daily NPH insulin to once-daily TOUJEO, the recommended starting TOUJEO dose is 80% of the total daily NPH dosage.
- To minimize the risk of hyperglycemia when changing patients to TOUJEO, monitor glucose frequently in the first weeks of therapy titrate the dose of TOUJEO per instructions and the dose of other glucose lowering therapies per standard of care. [See **Warning and Precautions** (5.2) and *Clinical Pharmacology* Section (12.2) in the full prescribing information].

2.4 Important Administration Instructions

- Prior to initiation of TOUJEO, patients should be trained by their healthcare professional on proper use and injection technique. Training reduces the risk of administration errors such as needle sticks and incomplete dosing.
- Patient should follow the *Instructions for Use* to correctly use the pen device and administer TOUJEO.
- Patients should be informed that the dose counter of the TOUJEO SoloStar disposable prefilled pen shows the number of units of TOUJEO to be injected. The TOUJEO SoloStar prefilled pen has been specifically designed for TOUJEO, therefore no dose conversion is required [Patient counseling information (17) in the full prescribing information].
- Patients should be instructed to visually inspect the TOUJEO solution for particulate matter and discoloration prior to administration and only use if the solution is clear and colorless with no visible particles.
- For single patient use only [see **Warnings and Precautions** (5.1)].
- Refrigerate unused (unopened) TOUJEO SoloStar prefilled pens.

4. CONTRAINDICATIONS

TOUJEO is contraindicated:

- During episodes of hypoglycemia [See **Warnings and Precautions** (5.3)].
- In patients with hypersensitivity to insulin glargine or one of its excipients [See **Warnings and Precautions** (5.5)].

5. WARNINGS AND PRECAUTIONS**5.1 Never Share a TOUJEO SoloStar pen Between Patients**

TOUJEO SoloStar disposable prefilled pens must never be shared between patients, even if the needle is changed. Pen sharing poses a risk for transmission of blood-borne pathogens.

5.2 Hyperglycemia or Hypoglycemia with Changes in Insulin Regimen

Changes in insulin strength, manufacturer, type, or method of administration may affect glycemic control and predispose to hypoglycemia [see **Warnings and Precautions** (5.3)] or hyperglycemia. These changes should be made cautiously and only under close medical supervision, and the frequency of blood glucose monitoring should be increased. For patients with type 2 diabetes, dosage adjustments of concomitant oral anti-diabetic products may be needed.

On a unit to unit basis, TOUJEO has a lower glucose lowering effect than LANTUS [See *Clinical Pharmacology* (12.2) in the full prescribing information]. In clinical trials, patients who changed to TOUJEO from other basal insulins experienced higher average fasting plasma glucose levels in the first weeks of therapy compared to patients who were changed to LANTUS. To minimize the risk of hyperglycemia when initiating TOUJEO monitor glucose daily, titrate TOUJEO according to labeling instructions, and adjust co-administered glucose lowering therapies per standard of care [See *Dosage and Administration* (2.2, 2.3)]. Higher doses of TOUJEO were required to achieve similar levels of glucose control compared to LANTUS in clinical trials [see *Clinical Studies* (14.1) in the full prescribing information].

The onset of action of TOUJEO develops over 6 hours following an injection. In type 1 diabetes patients treated with IV insulin, consider the longer onset of action of TOUJEO before stopping IV insulin. The full glucose lowering effect may not be apparent for at least 5 days [See *Dosage and Administration* (2.2) and *Clinical Pharmacology* (12.2) in the full prescribing information].

5.3 Hypoglycemia

Hypoglycemia is the most common adverse reaction associated with insulin, including TOUJEO. Severe hypoglycemia can cause seizures, may be life-threatening or cause death. Hypoglycemia can impair concentration ability and reaction time; this may place an individual and others at risk in situations where these abilities are important (e.g., driving, or operating other machinery). Hypoglycemia can happen suddenly and symptoms may differ in each individual and change over time in the same individual. Symptomatic awareness of hypoglycemia may be less pronounced in patients with longstanding diabetes, in patients with diabetic nerve disease, in patients using medications that block the sympathetic nervous system (e.g., beta-blockers) [See *Drug Interactions* (7)], or in patients who experience recurrent hypoglycemia.

Risk Factors for Hypoglycemia

The timing of hypoglycemia usually reflects the time-action profile of the administered insulin formulation.

As with all insulin preparations, the glucose lowering effect time course of TOUJEO may vary in different individuals or at different times in the same individual and depends on many conditions, including the area of injection as well as the injection site blood supply and temperature [see *Clinical Pharmacology* (12.2) in the full prescribing information]. Other factors which may increase the risk of hypoglycemia include changes in meal pattern (e.g., macro-nutrient content or timing of meals), changes in level of physical activity, or changes to co-administered medication [see *Drug Interactions* (7)]. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia [see *Use in Specific Populations* (8.5, 8.6)].

Risk Mitigation Strategies for Hypoglycemia

Patients and caregivers must be educated to recognize and manage hypoglycemia. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia. In patients at higher risk for hypoglycemia and patients who have reduced symptomatic awareness of hypoglycemia, increased frequency of blood glucose monitoring is recommended. To minimize the risk of hypoglycemia do not administer TOUJEO intravenously, intramuscularly or in an insulin pump or dilute or mix TOUJEO with any other insulin products or solutions.

5.4 Medication Errors

Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors between TOUJEO and other insulins, instruct patients to always check the insulin label before each injection.

5.5 Hypersensitivity and Allergic Reactions

Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products, including TOUJEO. If hypersensitivity reactions occur, discontinue TOUJEO; treat per standard of care and monitor until symptoms and signs resolve [See **Adverse Reactions** (6)]. TOUJEO is contraindicated in patients who have had hypersensitivity reactions to insulin glargine or other of the excipients [See **Contraindications** (4)].

5.6 Hypokalemia

All insulin products, including TOUJEO, cause a shift in potassium from the extracellular to intracellular space, possibly leading to hypokalemia. Untreated hypokalemia may cause respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia if indicated (e.g., patients using potassium-lowering medications, patients taking medications sensitive to serum potassium concentrations).

5.7 Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists

Thiazolidinediones (TZDs), which are peroxisome proliferator-activated receptor (PPAR)-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin. Fluid retention may lead to or exacerbate heart failure. Patients treated with insulin, including TOUJEO, and a PPAR-gamma agonist should be observed for signs and symptoms of heart failure. If heart failure develops, it should be managed according to current standards of care, and discontinuation or dose reduction of the PPAR-gamma agonist must be considered.

6. ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere:

- Hypoglycemia [See **Warnings and Precautions** (5.3)]
- Hypersensitivity and allergic reactions [See **Warnings and Precautions** (5.5)]
- Hypokalemia [See **Warnings and Precautions** (5.6)]

6.1 Clinical trial experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug, and may not reflect the rates actually observed in clinical practice.

The data in Table 1 reflect the exposure of 304 patients with type 1 diabetes to TOUJEO with mean exposure duration of 23 weeks. The type 1 diabetes population had the following characteristics: Mean age was 46 years and mean duration of diabetes was 21 years. Fifty five percent were male, 86% were Caucasian, 5 % were Black or African American and 5 % were Hispanic. At baseline, the mean eGFR was 82 mL/min/1.73m² and 35% of patients had eGFR ≥ 90 mL/min/1.73m². The mean BMI was 28 kg/m². HbA1c at baseline was greater or equal to 8% in 58% of patients.

The data in Table 2 reflect the exposure of 1242 patients with type 2 diabetes to TOUJEO with mean exposure duration of 25 weeks. The type 2 diabetes population had the following characteristics: Mean age was 59 years and mean duration of diabetes was 13 years. Fifty three percent were male, 88% were Caucasian, 7% were Black or African American and 17% were Hispanic. At baseline, mean eGFR was 79 mL/min/1.73m² and 27% of patients had an eGFR ≥ 90 mL/min/1.73m². The mean BMI was 35 kg/m². HbA1c at baseline was greater or equal to 8% in 66% of patients.

Common adverse reactions were defined as reactions occurring in ≥ 5% of the population studied.

Common adverse reactions occurring for TOUJEO-treated subjects during clinical trials in patients with type 1 diabetes mellitus and type 2 diabetes mellitus are listed in Table 1 and Table 2, respectively. Hypoglycemia is discussed in a dedicated subsection below.

Table 1: Adverse reactions in two pooled clinical trials of 26 weeks and 16 weeks duration in adults with type 1 diabetes (with incidence ≥ 5%)

	TOUJEO + mealtime insulin*, % (n=304)
Nasopharyngitis	12.8
Upper respiratory tract infection	9.5

*"mealtime insulin" refers to insulin glulisine, insulin lispro, or insulin aspart

Table 2: Adverse reactions in three pooled clinical trials of 26 weeks duration in adults with type 2 diabetes (with incidence ≥ 5%)

	TOUJEO*, % (n=1,242)
Nasopharyngitis	7.1
Upper respiratory tract infection	5.7

*one of the trials in type 2 diabetes included mealtime insulin

Hypoglycemia

Hypoglycemia is the most commonly observed adverse reaction in patients using insulin, including TOUJEO [See **Warnings and Precautions** (5.3)]. In the TOUJEO program, severe hypoglycemia was defined as an event requiring assistance of another person to administer a resuscitative action and documented symptomatic hypoglycemia was defined as an event with typical symptoms of hypoglycemia accompanied by a self-monitored or plasma glucose value equal to or less than 54 mg/dL.

The incidence of severe hypoglycemia in patients with type 1 diabetes receiving TOUJEO as part of a multiple daily injection regimen was 6.6% at 26 weeks. The incidence of documented symptomatic hypoglycemia was 69% at 26 weeks. There were no clinically important differences in hypoglycemia between TOUJEO and LANTUS among type 1 diabetes patients.

The incidence of severe hypoglycemia in patients with type 2 diabetes was 5% at 26 weeks in patients receiving TOUJEO as part of a multiple daily injection regimen, and 1.0% and 0.9% respectively at 26 weeks in the two studies where patients received TOUJEO as part of a basal-insulin only regimen. The incidence of documented symptomatic hypoglycemia in patients with type 2 diabetes receiving TOUJEO ranged from 8% to 37% at 26 weeks and the highest risk was again seen in patients receiving TOUJEO as part of a multiple daily injection regimen. Insulin initiation and intensification of glucose control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

Peripheral Edema

Insulin, including TOUJEO, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Lipodystrophy

Long-term use of insulin, including TOUJEO, can cause lipodystrophy (depression in the skin) or lipohypertrophy (enlargement or thickening of tissue) in some patients and may affect insulin absorption [see **Dosage and Administration** (2.1)].

Weight gain

Weight gain has occurred with some insulin therapies including TOUJEO and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

Allergic Reactions

Some patients taking insulin therapy, including TOUJEO have experienced erythema, local edema, and pruritus at the site of injection. These conditions were usually self-limiting. Severe cases of generalized allergy (anaphylaxis) have been reported [See **Warnings and Precautions** (5.5)].

Cardiovascular Safety

No clinical studies to establish the cardiovascular safety of TOUJEO have been conducted. A cardiovascular outcomes trial, ORIGIN, has been conducted with LANTUS. It is unknown whether the results of ORIGIN can be applied to TOUJEO.

The Outcome Reduction with Initial Glargine Intervention trial (i.e., ORIGIN) was an open-label, randomized, 12,537 patient study that compared LANTUS to standard care on the time to first occurrence of a major adverse cardiovascular event (MACE). MACE was defined as the composite of CV death, nonfatal myocardial infarction and nonfatal stroke. The incidence of MACE was similar between LANTUS and standard care in ORIGIN [Hazard Ratio (95% CI) for MACE; 1.02 (0.94, 1.11)].

In the ORIGIN trial, the overall incidence of cancer (all types combined) [Hazard Ratio (95% CI); 0.99 (0.88, 1.11)] or death from cancer [Hazard Ratio (95% CI); 0.94 (0.77, 1.15)] was also similar between treatment groups.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity.

In a 6-month study of type 1 diabetes patients, 79% of patients who received TOUJEO once daily were positive for anti-insulin antibodies (AIA) at least once during the study, including 62% that were positive at baseline and 44% of patients who developed anti-drug antibody [i.e., anti-insulin glargine antibody (ADA)] during the study. Eighty percent of the AIA positive patients on TOUJEO with antibody test at baseline, remained AIA positive at month 6.

In two 6-month studies in type 2 diabetes patients, 25% of patients who received TOUJEO once daily were positive for AIA at least once during the study, including 42% who were positive at baseline and 20% of patients who developed ADA during the study. Ninety percent of the AIA positive patients on TOUJEO with antibody test at baseline, remained AIA positive at month 6.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors such as: assay methodology, sample handling, timing of sample collection, concomitant medication, and underlying disease. For these reasons, comparison of the incidence of antibodies to TOUJEO with the incidence of antibodies in other studies or to other products, may be misleading.

7. DRUG INTERACTIONS

7.1 Drugs That May Increase the Risk of Hypoglycemia

The risk of hypoglycemia associated with TOUJEO use may be increased with antidiabetic agents, (ACE) inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics. Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is co-administered with these drugs.

7.2 Drugs That May Decrease the Blood Glucose Lowering Effect of TOUJEO

The glucose lowering effect of TOUJEO may be decreased when co-administered with atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isonazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline) and thyroid hormones. Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is co-administered with these drugs.

7.3 Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TOUJEO

The glucose lowering effect of TOUJEO may be increased or decreased when co-administered with alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia. Dose adjustment and increased frequency of glucose monitoring may be required when TOUJEO is co-administered with these drugs.

TOUJEO®

(insulin glargine injection) U-300, for subcutaneous use

7.4 Drugs That May Affect Signs and Symptoms of Hypoglycemia

The signs and symptoms of hypoglycemia [see **Warnings and Precautions** (5.3)] may be blunted when beta-blockers, clonidine, guanethidine, and reserpine are co-administered with TOUJEO.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or a history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes, insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking TOUJEO.

Human data

There are no clinical studies of the use of TOUJEO in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal data

Subcutaneous reproduction and teratology studies have been performed with insulin glargine and regular human insulin in rats and Himalayan rabbits. Insulin glargine was given to female rats before mating, during mating, and throughout pregnancy at doses up to 0.36 mg/kg/day, which is approximately 50 times the recommended human subcutaneous starting dose of 0.2 Units/kg/day (0.007 mg/kg/day). In rabbits, doses of 0.072 mg/kg/day, which is approximately 10 times the recommended human subcutaneous starting dose of 0.2 Units/kg/day (0.007 mg/kg/day), were administered during organogenesis. The effects of insulin glargine did not generally differ from those observed with regular human insulin in rats or rabbits. However, in rabbits, five fetuses from two litters of the high-dose group exhibited dilation of the cerebral ventricles. Fertility and early embryonic development appeared normal.

8.3 Nursing Mothers

Endogenous insulin is present in human milk; it is unknown whether insulin glargine is excreted in human milk. Because many drugs, including human insulin, are excreted in human milk, caution should be exercised when TOUJEO is administered to a nursing woman. Use of TOUJEO is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

8.4 Pediatric Use

The safety and effectiveness of TOUJEO have not been established in pediatric patients.

8.5 Geriatric Use

In controlled clinical studies, 30 of 304 (9.8%) TOUJEO treated patients with type 1 diabetes and 327 of 1242 (26.3%) TOUJEO treated patients with type 2 diabetes were ≥65 years of age, among them 2.0 % of the patients with type 1 and 3.0% of the patients with type 2 diabetes were ≥75 years of age. No overall differences in effectiveness and safety were observed in the subgroup analyses across the age groups.

Nevertheless, caution should be exercised when TOUJEO is administered to geriatric patients. In elderly patients with diabetes, the initial dosing, dose increments, and maintenance dosage should be conservative to avoid hypoglycemia [See **Warnings and Precautions** (5.3), **Adverse reactions** (6) and **Clinical Studies** (14) in the full prescribing information].

8.6 Hepatic Impairment

The effect of hepatic impairment on the pharmacokinetics of TOUJEO has not been studied. Frequent glucose monitoring and dose adjustment may be necessary for TOUJEO in patients with hepatic impairment [See **Warnings and Precautions** (5.3)].

8.7 Renal Impairment

The effect of renal impairment on the pharmacokinetics of TOUJEO has not been studied. Some studies with human insulin have shown increased circulating levels of insulin in patients with renal failure. Frequent glucose monitoring and dose adjustment may be necessary for TOUJEO in patients with renal impairment [See **Warnings and Precautions** (5.3)].

8.8 Obesity

No overall differences in effectiveness and safety were observed in subgroup analyses based on BMI.

10. OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia [see **Warnings and Precautions** (5.3, 5.6)]. Mild episodes of hypoglycemia can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or physical activity level may be needed. More severe episodes of hypoglycemia with coma, seizure, or neurologic impairment may be treated with intramuscular/subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

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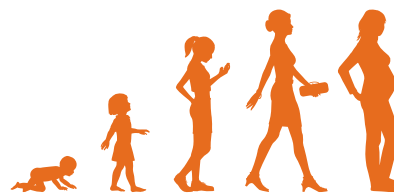
Revised: February 2015



Heir Apparent:

BY NILS KRONE, MD, FRCPCH,
RICHARD J. AUCHUS, MD, PHD,
AND NICOLE REISCH, MD

A Multi-Faceted Look at
One of the Most Common
Inherited Metabolic Disorders,
Congenital Adrenal Hyperplasia



Congenital adrenal hyperplasia (CAH) ranks among the most common inherited metabolic disorders, with the classic form (i.e., 21-hydroxylase deficiency) affecting about one in 15,000 newborns. It is characterized by a complex imbalance of steroid hormones, with reduced cortisol and aldosterone synthesis and excessive adrenal androgen production. Neonatal screening programs in most industrialized countries now enable early diagnosis in classic CAH and timely introduction of hormone substitution treatment. While this reduces life-threatening salt-wasting crises in newborns, hormone substitution over a lifetime poses new challenges in adult patients.

In this Tri-Point article, a **basic researcher** provides insights from model organism for altered adrenal steroid production, a **clinical researcher** discusses medical treatment options and challenges for adult patients with CAH, and a **clinical practitioner** highlights fertility-related challenges in adult CAH patients.





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Diabetes and Metabolism,
University of Birmingham,
Birmingham, UK

HIGHLIGHTS

Classic and non-classic presentations of congenital adrenal hyperplasia are caused by a continuum of impairment of steroid enzyme activity.

In vitro expression analysis of genetic variants has greatly contributed to the understanding of the molecular pathogenesis of all forms of CAH.

Murine models have improved the understanding of the pathophysiology of CAH; in particular the discovery of impaired metanephrine synthesis in 21-hydroxylase deficiency.

A Basic Researcher's Perspective

— NILS KRONE, MD, FRCPCH*

Congenital adrenal hyperplasia (CAH) is a group of autosomal recessive disorders leading to impaired glucocorticoid biosynthesis. The clinical presentation of different CAH forms depends on the underlying enzymatic defect. Deficiencies of 21-hydroxylase (CYP21A2) and 11 β -hydroxylase (CYP11B1) only affect adrenal steroid hormone biosynthesis, whereas 17 α -hydroxylase (CYP17A1) deficiency and 3 β -hydroxysteroid dehydrogenase type 2 (HSD3B2) deficiency also impair gonadal steroid production. P450 oxidoreductase deficiency (PORD) presents with apparent combined CYP17A1-CYP21A2 deficiency. In addition, PORD also causes skeletal malformations and severe genital ambiguity in both sexes. Traditionally, three further enzymatic deficiencies are classified within the CAH group. Steroidogenic acute regulatory protein (StAR) deficiency leads to a lipid adrenal and gonadal lipid accumulation resulting in Lipoid CAH (CLAH). P450 side-chain cleavage (CYP11A1) deficiency resembles the CLAH clinical presentation; however, patients have normal-sized or absent adrenals. Aldosterone synthase (CYP11B2) deficiency manifests with isolated mineralocorticoid deficiency and normal glucocorticoid synthesis.

Genetics of 21-Hydroxylase Deficiency

In clinical practice, the term CAH is often synonymously used for 21-hydroxylase deficiency (21OHD). 21OHD is caused by mutations in the *CYP21A2* gene and accounts for about 95% of CAH cases in the general population. The majority of *CYP21A2*-inactivating mutations are caused by intergenic recombinations within the RCCX module. *CYP21A2* gene deletions and *CYP21A1P/CYP21A2* chimeric genes account for approximately 20% to 25% of 21OHD alleles in most Caucasian populations. About 70% to 75% of 21OHD disease-causing alleles originate from gene conversions with the *CYP21A1P* pseudogene, leading to small genetic transfers and single point mutations. The most common *CYP21A1P*-derived mutations include seven point mutations, a deletion of eight base pairs in exon 3, and the E6 cluster mutation. In addition to these common mutations, more than

150 pseudogene-independent mutations have been reported. The majority of these mutations occur sporadically and have only been reported in a small number of patients.

Genotype-Phenotype Correlation

Soon after the characterization of the *CYP21A2* gene and the detection of disease-causing mutations, *in vitro* expression studies using insect and mammalian cells as well as yeast systems have been employed to assess the residual *in vitro* 21-hydroxylase function of common *CYP21A2* mutations. These residual activities have built the framework for establishing the genotype-phenotype correlation in patients with CAH. This has been widely adopted to report population studies on 21-hydroxylase deficiency. Mutations are categorized into different mutation groups resembling: Null (mutations predicting absent *in vitro* activity), A (intron 2 splice site mutation), B (mutations such as the p.I172N mutation and mutations with 1% to 10% *in vitro* residual enzyme activity), C (mutations such as p.P30L, p.V281L, and p.P453S or above 20% to 30% *in vitro* 21-hydroxylase activity).

Overall, about 65% to 75% of patients with 21OHD are compound heterozygote. Commonly, the clinical phenotype is determined by the mildest *CYP21A2* mutation, consequently allowing for the highest residual enzyme activity. Patients with Null and A genotypes have a high likelihood to present with salt-wasting (SW) CAH, whereas two-thirds of patients with group B genotypes present with simple-virilising (SV) CAH. Patients with group C genotypes commonly have non-classic (NC) CAH. Overall, genotype-phenotype data have supported genetic counselling; however, the best correlation has been found with the degree of renal salt loss. A limitation of pure *in vitro* enzyme analysis is the fact that pathophysiologic changes such as hyperplasia of the adrenal cortex cannot be modelled. This, in addition to other disease modifiers, might explain some of the observed variability of the expressed phenotype in patients with partially inactivating *CYP21A2* mutations.

“ In times of more powerful genetic analysis methodologies such as next generation sequencing, modelling of genetic variants, and disease modifiers, it is becoming increasingly important to understand the clinical consequences.”



The same principle establishing the *in vitro* activity of genetic variants has been applied in rarer deficiencies leading to CAH. Over the last five to 10 years, complete and partial mutations have been also described in all other forms of CAH where classic and non-classic presentations are now well established.

Animal Models of CAH

A naturally occurring *Cyp21a2*-deficient mouse was identified soon after the cloning of the human *CYP21A2* gene. Further molecular characterization demonstrated loss of the active *Cyp21a1* gene by unequal crossing over between the active *Cyp21a1* gene and its pseudogene (*Cyp21a2-p*) leading to a chimeric *Cyp21a1-Cyp21a2-p* gene including a partial deletion of *Cyp21a1*. This chimeric gene carries several pseudogene-derived point mutations, missense mutations, and a nonsense mutation. The *in vitro* expression analysis of these mutations demonstrated lack of function of this chimeric gene. Overall, the *Cyp21a2*-deficient mice have been proven to be difficult to maintain postnatally, limiting their use as translational model. Another limitation modelling CAH is the lack of adrenal 17-hydroxylase expression in mice and consequently the lack of androgen excess in the 21-hydroxylase deficient mouse. However, further analysis of adrenals and metanephrine concentrations in these mice demonstrated severe impairment of adrenomedullary function in 21-hydroxylase deficiency. This led to further exploration of the human pathophysiology of CAH showing similar alterations of the adrenal gland in human patients with CAH. Interestingly, the severity of adrenomedullary function is closely correlated with the severity of the *CYP21A2* genotype in humans.

Murine models of other CAH forms have been developed. The 11-hydroxylase (*cyp11b1*) null mouse showed glucocorticoid deficiency and mineralocorticoid excess, adrenal hyperplasia, and mild hypokalemic hypertension as well as glucose intolerance. Remarkably and contrary to humans, affected female mice were found to be infertile. The murine deletion model of the steroidogenic

acute regulatory protein (StAR) showed a very high similarity to humans affected with the classic form of CLAH due to StAR mutation. Similar to humans suffering from CLAH, these mice also showed a considerable heterogeneity in the presentation and onset of adrenal insufficiency. The exact mechanisms explaining this variability remains to be elucidated. A similar severe phenotype was observed in the murine deletion model of P450 side chain cleavage model (*Cyp11a1*). These mice survived to term and then soon died after birth from adrenal insufficiency. In addition, SRY-positive mice show features of sex reversal.

Conclusion and Outlook

In times of more powerful genetic analysis methodologies such as next generation sequencing, modelling of genetic variants, and disease modifiers, it is becoming increasingly important to understand the clinical consequences. *In vitro* expression analysis of genetic variants has greatly contributed to the understanding of the molecular genetics of all forms of CAH. Mouse models of CAH have the limitation that the murine adrenal cortex does not produce androgens. However, the discovery of adrenomedullary impairment in CAH has been mainly achieved via studying murine models. Overall, it remains important to reflect that models only answer the specific question asked toward the model system. It is likely that the current revolution in genomic engineering techniques such as transcription activator like effector nucleases (TALEN) and CRISPER/ CAS9 systems will help to study the effects of complete and partial mutations inactivating steroidogenic pathways and enhance our understanding of pathophysiologic consequences by employing novel *in vitro* and *in vivo* systems.

**Clinical lead for adrenal disorders and disorders of sex development at Birmingham Children's Hospital. His lab currently focuses on creating novel whole organism models of inborn errors of steroidogenesis by applying genomic engineering methods.*

A Clinical Researcher's Perspective

— RICHARD J. AUCHUS, MD, PHD



Richard J. Auchus,
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HIGHLIGHTS

Replacing the cortisol deficiency is straightforward, but **better treatments for the androgen excess** are needed.

CAH patients develop **characteristic intra-adrenal and ectopic adrenal tumors** by unknown mechanisms.

Obtaining **long-term outcomes data** for all aspects of CAH will be challenging.

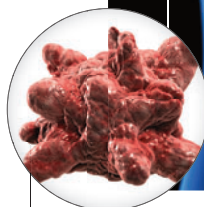
Classic 21-hydroxylase deficiency (21OHD): Not One Simple Defect

The physiology of 21OHD fundamentally reflects a block in cortisol synthesis and diversion of cortisol precursors to androgens under ACTH stimulation. Patients with 21OHD also are prone to develop adrenal adenomas, myelolipomas, and adrenal rest tumors, most commonly in the testes. For women with classic 21OHD, genital virilization, interference with gonadal function, and low rates of fecundity add to the challenges. While some consequences might be predictable, simple models do not explain the variable disease manifestations, and current therapies do not mitigate all complications.

Traditionally, 21OHD treatment has been limited to glucocorticoids, mineralocorticoids, salt, and surgery. Replacing the adrenal insufficiency is not difficult, but normalizing the androgen excess usually requires higher and/or more frequent glucocorticoid doses, particularly to blunt the early-morning rise in ACTH and adrenal steroids. These extra doses create compliance challenges and long-term consequences from life-long over-replacement. Genital reconstruction surgery improves many aspects of appearance and function, but the androgen effects on the brain persist, and chronic urogenital difficulties are common.

Outcomes from large 21OHD cohorts have begun to appear. The National Institutes of Health (NIH) report of 183 patients with classic and 61 patients with non-classic 21OHD found no standard treatment regimen, androgens mostly above or below the normal range, short stature, low bone mineral density in 37% of adults, and high rates of obesity and the metabolic syndrome. The British Congenital adrenal hyperplasia Adult Study Executive (CaHASE) study of 203 adults also found mostly abnormal steroid values with a tendency for over-treatment, a high prevalence of cushingoid features, low bone mineral density in 40%, obesity in 40%, markedly compromised fertility, and reduced quality of life. Similar studies from several other groups confirm these findings. Can we do better than these unflattering statistics?

Adrenal
Rest Tumor



Taking a step back and setting a clinical research agenda

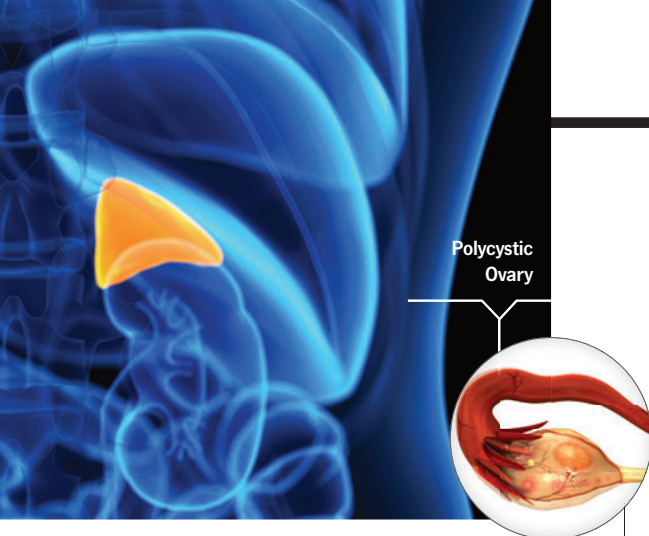
What are the steroids and pathways that lead to virilization in the fetus, bone age advancement in the child, and impaired fertility in the adult?

Ordinarily, the major 19-carbon product of the adrenal is dehydroepiandrosterone sulfate (DHEAS). Androstenedione (AD), testosterone (T), and dihydrotestosterone (DHT) are minor adrenal products; however, T and DHT arise from extra-adrenal metabolism of DHEA. DHEAS is paradoxically low-normal and easily suppressed in classic 21OHD, and recent evidence suggests that DHT in the newborn derives from the 5 α -reduced “backdoor” pathway without the intermediacy of AD and T.

How should we monitor therapy at different stages of life, and what are our goals?

Because 17-hydroxyprogesterone (17OHP) accumulates proximal to the block in 21OHD, 17OHP is the gold standard for diagnosis of 21OHD and is widely used to monitor treatment. Yet androgens and estrogens — not 17OHP — cause the problems. Although AD and T are used to monitor therapy, estrogen concentrations below the limits of the best commercial assays will advance bone age. Serum 17OHP is a very sensitive measure of control, but values fluctuate wildly during the day in relation to dosing, and 17OHP correlates poorly with downstream metabolites. The onset of adrenarche and puberty complicate management. In adolescents and adults, sex steroids and 17OHP also derive from the gonads, so one must estimate the contribution from the adrenal. Other steroids such as 21-deoxycortisol are more specific for 21OHD than 17OHP, and this analyte has been used to eliminate false-positive results of newborn screening and to improve diagnostic testing for non-classic 21OHD.

Why do some patients fare so well and others struggle? With the crisp enzymatic defect and the



A Clinical Practitioner's Perspective

— NICOLE REISCH, MD



Nicole Reisch, MD, Head of CAH outpatient clinic and research group, clinical and translational research team leader at the Medizinische Klinik und Poliklinik IV, Klinikum der Ludwig-Maximilians-Universität, Ziemssenstr, München, Germany

Fertility-Related Challenges in Females with Classic CAH

Multiple studies have demonstrated reduced fertility in females with classic CAH because of 21-hydroxylase deficiency. The birth rate in females with CAH is substantially reduced compared to the general population. It is estimated that only 25% of women with CAH ever attempt pregnancy and only 10% of those with the severe salt-wasting form. The reasons for this observation are manifold: vaginal insufficiency with dyspareunia, anovulatory menstrual cycles because of adrenal androgen excess, reduced endometrium growth during follicular phase because of adrenal progesterone production, additional ovarian hyperandrogenism (secondary polycystic ovary) because of adrenal-derived androgens in many patients, multiple psychosexual factors, or masculinization of the central nervous system due to prenatal androgen excess. One study, investigating 35 adult females with classic CAH, showed that seven were homosexual, eight were married, 13 never have had sexual intercourse, and three patients were without any sexual activity. In this cohort 18 out of 22 patients who actually had sexual intercourse reported painful penetration. The sexual function, as measured by the Female Sexual Function Index, was lower compared to controls and substantially lower in those patients with higher Prader stadium. This finding has been confirmed by a Swedish study showing that sexual life and function is perceived as less satisfactory in genotype "null."

Most studies on fertility in female patients with CAH, however, do not take into consideration the percentage of patients indeed having attempted to conceive. Thereby, these studies do not represent the actual pregnancy rate. Having a closer look on the actual pregnancy rate in women attempting to conceive, there was no difference in women with CAH and the general population (pregnancy rate in classic CAH 91.3% versus 95.0%) and no difference in women with the salt-wasting (88.9%)

limited number of pseudogene-derived mutations in most patients, genotype-phenotype correlations in 21OHD are strong but not perfect, even among siblings bearing the same mutations. Response to therapy is highly variable as well. Polymorphism in the genes encoding steroid and drug metabolism enzymes and changes in their expression from environmental exposures might be responsible.

Why do tumors develop? Some studies have shown absence of ACTH receptors in myelolipomas and no correlation of adrenal rest tumors with biochemical measures of control.

What are the preferred timings and procedures for reconstruction surgeries? New techniques and trends develop as soon as cohorts from the older procedures reach the stage of "long-term" follow-up.

How can we gather evidence to guide parents and patients for a rare disease with so many confounding variables? Collaborations and prospective protocols are essential.

Treatments on the horizon

Sustained-release hydrocortisone preparations are being studied. Greater convenience should improve compliance — but will control be better and complications lower? Continuous subcutaneous hydrocortisone infusion makes sense physiologically and has been shown to improve control with lower total dose in a few patients, but is this approach practical? We showed that abiraterone acetate added to replacement hydrocortisone doses normalized androgens in adult women with classic 21OHD, but the study was short. Will androgen biosynthesis inhibitors benefit children with 21OHD? With innovation and broad collaboration among clinical researchers, we can begin to answer these questions and to improve outcomes.

HIGHLIGHTS

Fertility is reduced in both males and females with classic congenital adrenal hyperplasia caused by 21-hydroxylase deficiency.

In males with classic CAH, there are two main reasons for reduced fertility and fecundity: First, testicular adrenal rest tumors — adrenal suppressive therapy with dexamethasone can effectively restore fertility, whereas surgery can neither restore fertility nor HPA axis integrity. Second, adrenal-derived androgens lead to a suppression of gonadotropins causing testicular atrophy and impaired spermatogenesis.

In females with classic CAH, optimal gluco- and mineralocorticoid substitution therapy has been shown to normalize fecundity.

In non-classic CAH, an increased rate of miscarriages (25%) can be normalized by low dose hydrocortisone therapy.

“ Having a closer look on the actual pregnancy rate in women attempting to conceive, there was no difference in women with CAH and the general population and no difference in women with the salt-wasting and the simple virilizing forms of classic CAH. ”



and the simple virilizing forms (92.9%) of classic CAH. In fact, in the majority of women, a spontaneous conception (76.2%) was achieved. Prednisolone administered once every eight hours has been shown to effectively suppress progesterone in the follicular phase and to improve receptibility of the endometrium. The treatment target for women attempting to conceive is a follicular-phase serum progesterone <2 nmol/l (<0.6 ng/ml). Prednisolone might possibly be superior to hydrocortisone in this respect, however, evidence-based data are missing. As dexamethasone passes the placenta, it should be substituted by hydrocortisone or prednisolone to avoid adrenal suppression and possible negative metabolic effects on the fetus. Dexamethasone should only be given if prenatal therapy of the fetus is wanted and warranted. It should only be implemented within the setting of a clinical trial approved by an ethics committee. During pregnancy, renin concentration physiologically increases about five-fold. In classic CAH with and without mineralocorticoid deficiency substantially elevated renin concentrations compared to healthy controls have been described. An increase of fludrocortisone in salt-wasting CAH or the addition of fludrocortisone in simple virilizing CAH may therefore be necessary and reasonable. Hoepffner, et al. described a normalization and improved conception after the addition of fludrocortisone.

Fertility-Related Challenges in Males with Classic CAH

For a long time, fertility issues in CAH have focused on females whereas males have received much less attention. In recent years, however, it has become obvious that maintaining fertility in males appears to be even more of a problem than in females. There are no data on sexuality in males with CAH. However, fertility in males is substantially reduced compared to the general population. There are two main reasons for subfertility in males: first, suppression of gonadotropins by either adrenal-derived androgens (and

their conversion to estrogens) in case of under-replacement of glucocorticoids or by external glucocorticoids in case of over-replacement. Both mechanisms lead to impaired spermatogenesis and testicular atrophy.

The second major reason is testicular adrenal rest tumors. The pathogenesis of these tumors is not yet completely understood. They are thought to arise from adrenocortical remnants that have descended with the testes during fetal life or from postnatally reprogrammed Leydig cell precursors. Testicular adrenal rest tumors (TARTs) are usually bilateral and always benign. The tumors have been found to express adrenal-specific markers such as MC2-receptor, ATII-receptor, and CYP11B1. They also have been shown to be ACTH-dependent to a certain degree and thus are potentially reversible with the adrenal-suppressive therapy, dexamethasone. They are located in the rete testis and impair spermatogenesis by either mechanical obstruction of the tubuli seminiferi, or they may interfere with the local and/or systemic hormone milieu by their own hormone production. So far, no correlation of TART development and common measures of disease control in CAH has been shown. Still it is very likely that disease control plays a major role in TART growth. As surgical removal of TART has been shown to restore neither fertility nor HPA axis, surgical treatment of TART is only recommended for discomfort and pain relief and always should be testis sparing.

Fertility-Related Challenges in Females with Non-Classic CAH

The miscarriage rate in women with non-classic CAH has been shown to be substantially increased (25% versus 6% in the general population). However, it can be normalized with low to moderate doses of hydrocortisone prior to and during pregnancy, therefore, it is recommended at these times. ^{EN}

ACKNOWLEDGEMENT: THIS ARTICLE WAS REVIEWED BY FELIX BEUSCHLEIN, MD, UNIVERSITY OF MUNICH; AND RUTH KERI, PHD, CASE WESTERN RESERVE UNIVERSITY.

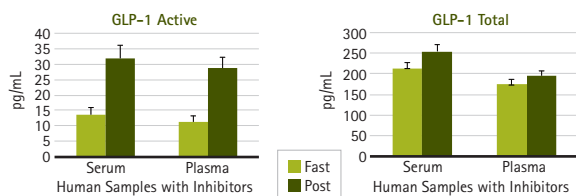
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A Peculiar Trait

ENDOCRINE NEWS TALKS TO MÁRTA KORBONITS, MD, PHD, AT THE QUEEN MARY UNIVERSITY OF LONDON ABOUT HER RESEARCH IN SEEKING THE MUTATIONS BEHIND A FAMILIAL ADENOMA.

BY MELISSA MAPES



MÁRTA KORBONITS, MD, PHD

Three-dimensional structure of human AIP with the characteristic C terminal tetratricopeptide domain (three pairs of alpha helices and a final 7th alpha helix), crucial in the protein-protein interactions of AIP.



About one in every thousand individuals will develop a pituitary adenoma, a noncancerous but disruptive tumor on the pituitary gland that can induce a variety of negative side effects. But, among these patients, approximately 5% suffer from a very particular inherited form of the disease: familial isolated pituitary adenoma (FIPA).

Márta Korbonits, MD, PhD, professor of endocrinology at the Queen Mary University of London, is searching for the origins of this genetic disorder in hopes of helping physicians diagnose it faster and provide better care for patients. Among families with FIPA, one in five cases can be traced back to the gene called aryl hydrocarbon receptor interacting protein (AIP), but for the other 80 percent of families facing the disease, the cause is still unknown.

Korbonits spoke with *Endocrine News* about her research and the importance of finding FIPA before its effects become irreversible.

Endocrine News: What drew you to research in the field of endocrinology, and how did you choose your specific specialty?

Márta Korbonits: I have wanted to be an endocrinologist since medical school. I've always been excited about the complexity of the pathways and the phenotypes patients are showing. I found the logic in endocrinology fascinating, and I never looked back.

I've been working in translational endocrine science for 20-plus years and have always been interested in the way a problem may start with a singular patient and end up informing you about the pathophysiology of a disease as well as the basic physiology of the body. When seeing patients, you discover novel aspects or functions that may be relevant not just for that disease,

but for the regulation of that hormone. Informing clinical practice and physiology with this two-way kind of work is really exciting.

EN: What are you currently working on?

MK: My main project at this point is working on familial pituitary adenomas. These involve patients who have a pituitary adenoma and also have a family history of this disease, although in some cases there is no known family history despite having genetic origin of the disease. One of the interesting aspects is why some people develop the disease while other family members having the same mutation are spared. We are also interested in the exact mechanism of how the mutations cause the disease.

There have been some really interesting findings regarding the phenotypes and their correlation to the exact gene mutation, or the genotype. Our study includes one of the largest groups of patients with this disease. We are combining clinical data with experimental results — identifying DNA mutation in patient samples and recreating these mutations in the lab to be able to do functional experiments.

EN: Among your projects, what accomplishments are you most proud of?

MK: I am proud that we were able to help put this disease on the table in the United Kingdom and elsewhere by identifying quite a lot of patients with pituitary adenomas and screening their families for the disease as well. We were able to provide genetic advisement for patients and, via screening, sometimes discovered patients who did not even realize that they had the disease. If we can interfere earlier, we hopefully have a better chance to cure or successfully treat the pituitary adenoma. So I am glad we were able to help in this regard.

My most publicized work was a project involving a patient born 250 years ago in Northern Ireland. We identified the mutation in him and also identified families living with the same disease, and then turned to his relatives who are alive today. After that, we did a whole population screening

“

If we can interfere earlier, we hopefully have a better chance to **cure or successfully treat the pituitary adenoma.**

”

of the community he was from and identified some additional cases. Hopefully, this made [the community] aware of the disease so that it can be recognized sooner.

EN: If you had unlimited funding, how would you use it to enhance your laboratory and research?

MK: I would screen patients whose clinical picture suggests that they have this particular disease and use the resources to analyze all of our existing samples. We have many additional samples that we would like to analyze.

EN: Where do you see your scientific work heading in the future? How do you hope to affect change with your projects?

MK: I see identifying these new genes as the next step in this work. The other important step is to identify the mechanism of how the genes work and eventually develop new types of treatments and methods for diagnosing the disease sooner.

EN: Any final thoughts you would like to share with our readers?

MK: If you have a patient or multiple patients with familial pituitary adenomas, please do not hesitate to contact me. FIPA is a relatively rare disease, and lots of patients have been told in the past that it is not familial but, in some cases, it actually is. *(Those working with patients that have been diagnosed with familial pituitary adenoma can get in touch with Korbonits at m.korbonits@qmul.ac.uk.)* 

POSSIBLE FAMILIAL PITUITARY ADENOMA SYMPTOMS

Depending on the type of tumor that develops (somatotrophinoma, prolactinoma, non-functioning, corticotrophinoma, or TSH-producing), patients with FIPA may experience a wide range of symptoms, including:

- ▶ Difficulty sleeping
- ▶ Erectile dysfunction
- ▶ Fast or irregular heartbeat
- ▶ Fatigue
- ▶ Gigantism
- ▶ Headaches
- ▶ Infertility
- ▶ Lack of pituitary gland function
- ▶ Irritability
- ▶ Lack of menstruation
- ▶ Low testosterone in men
- ▶ Overactive thyroid
- ▶ Poor libido
- ▶ Production of breast milk (not related to pregnancy)
- ▶ Visual disturbances
- ▶ Weight change

More information on FIPA can be found at www.fipapatient.org.



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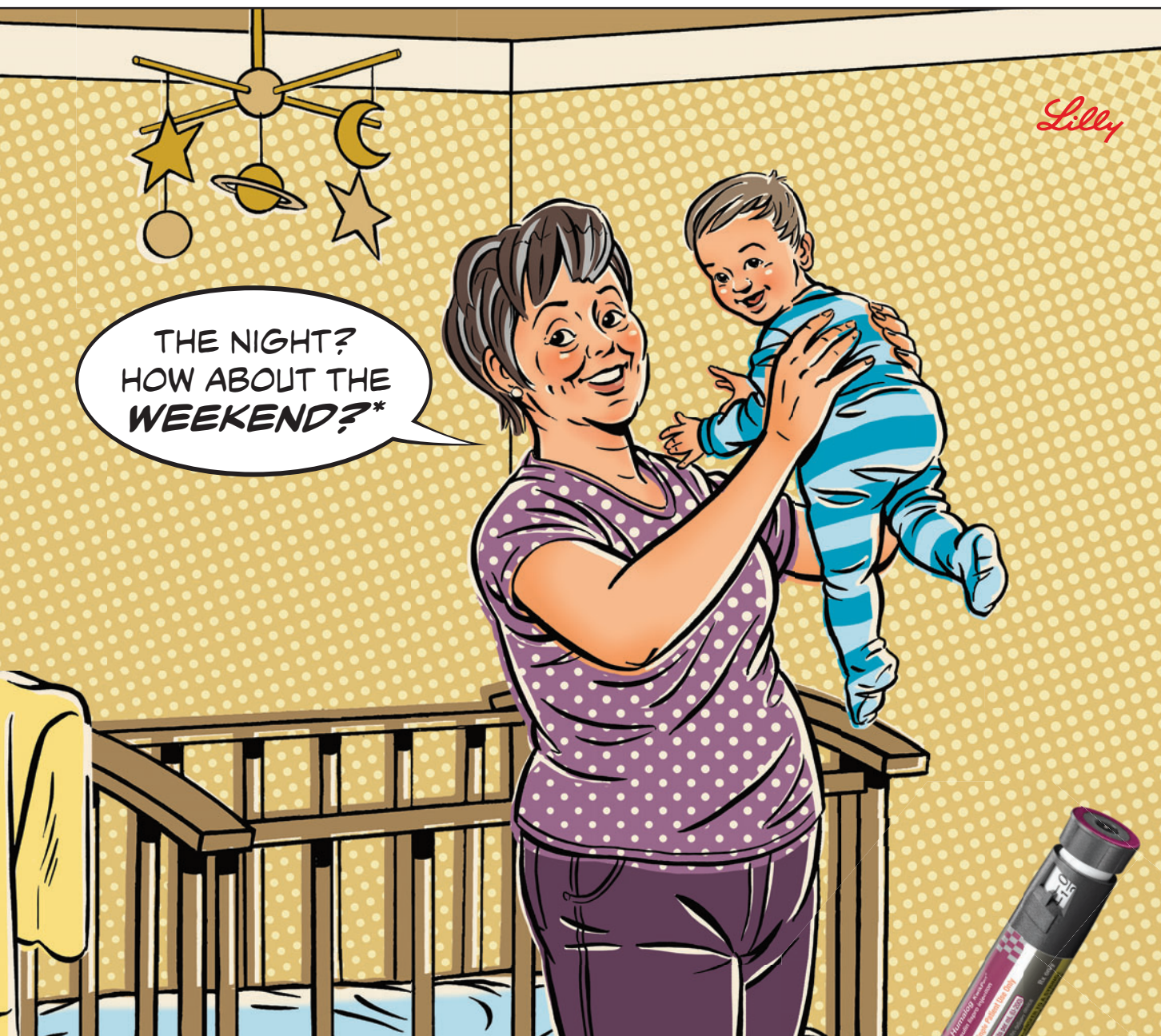
[‡]Once opened, Humalog prefilled pens should be thrown away after 28 days, even if insulin remains.

Reference:

1. Humalog [Prescribing Information]. Indianapolis, IN: Lilly USA, LLC; 2015.

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THE NIGHT?
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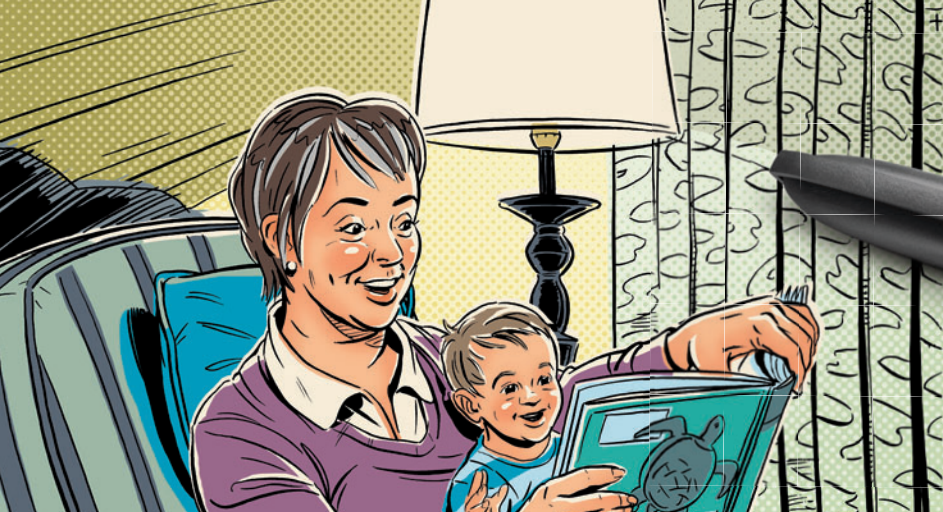
- Humalog is contraindicated during episodes of hypoglycemia and in patients who are hypersensitive to Humalog or any of its excipients.
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- Changes in Insulin Regimen:** Changes may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously under close medical supervision and the frequency of blood glucose monitoring should be increased.

- Hypoglycemia:** Severe hypoglycemia may be life threatening and can cause seizures or death. Hypoglycemia is the most common adverse reaction of Humalog. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. Hypoglycemia can happen suddenly and symptoms may vary for each person and may change over time. Early warning symptoms of hypoglycemia may be different or less pronounced under conditions such as long-standing diabetes, diabetic nerve disease, use of medications such as beta-blockers, or in patients who experience recurrent hypoglycemia. These situations may result in severe hypoglycemia and possibly loss of consciousness prior to the patient's awareness of hypoglycemia.

Timing of hypoglycemia usually reflects the time-action profile of administered insulins which may vary in different individuals or at different times in the same individual. Other factors such as changes in food intake, injection site, exercise, and concomitant medications may increase the risk of hypoglycemia.

Educate patients to recognize and manage hypoglycemia. In patients at higher risk for hypoglycemia and patients with reduced symptomatic awareness, increased frequency of blood glucose monitoring is recommended. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia.

- Hypoglycemia Due to Medication Errors:** Instruct patients to always check the insulin label before each injection to avoid medication errors. Humalog U-200 should not be transferred from the Humalog KwikPen to a syringe as overdose and severe hypoglycemia can occur.

- Hypersensitivity Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with Humalog. If hypersensitivity reactions occur, discontinue Humalog and treat per standard of care until signs and symptoms resolve.

- Hypokalemia:** Hypokalemia may be life threatening. Insulins, including Humalog, cause a shift in potassium from the extracellular to intracellular space possibly leading to hypokalemia, which, if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia (eg, patients using potassium-lowering medications or medications sensitive to serum potassium concentrations).

- Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists:** Thiazolidinediones (TZDs), which are PPAR-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin, including Humalog. This may lead to or exacerbate heart failure. Observe patients for signs and symptoms of heart failure and consider discontinuation or dose reduction of the PPAR-gamma agonist.

Important Safety Information for Humalog 100 units/mL and Humalog 200 units/mL KwikPen, continued

Warnings and Precautions, continued

- Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction:** Malfunction of the insulin pump device, infusion set, or insulin degradation can rapidly lead to hyperglycemia and ketoacidosis. Patients using subcutaneous insulin infusion pumps must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure.

Drug Interactions

- Some medications may alter glucose metabolism, insulin requirements, and the risk for hypoglycemia or hyperglycemia. Signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs. Particularly close monitoring may be required.

Adverse Reactions

- Adverse reactions associated with Humalog include hypoglycemia, hypokalemia, allergic reactions, injection-site reactions, lipodystrophy, pruritus, rash, weight gain, and peripheral edema.

Use in Specific Populations

- Humalog has not been studied in children with type 1 diabetes less than 3 years of age or in children with type 2 diabetes.

Dosage and Administration

- Humalog should be given within 15 minutes before or immediately after a meal.
- Humalog U-100 can be administered intravenously under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia. Do NOT administer Humalog U-200 intravenously.
- Humalog U-100 for subcutaneous injection should only be mixed with NPH insulin. If Humalog U-100 is mixed with NPH insulin, Humalog should be drawn into the syringe first. Injection should occur immediately after mixing. Do NOT mix Humalog U-200 in a syringe with any other insulin.
- Humalog U-100 should not be diluted or mixed when used in an external insulin pump. Change Humalog U-100 in the reservoir at least every 7 days. Change the infusion set and insertion site at least every 3 days. Do NOT use Humalog U-200 in a subcutaneous insulin infusion pump.
- Do NOT perform dose conversion when using either the Humalog U-100 or Humalog U-200 KwikPens. The dose window shows the number of insulin units to be delivered and no conversion is needed.

Please see Brief Summary of Prescribing Information on adjacent pages.

Please see Instructions for Use included with the pen.

HI U200 HCP ISI 26MAY2015

Humalog® and Humalog® KwikPen® are registered trademarks of Eli Lilly and Company and are available by prescription only.

Humalog 200^{U/mL}
KwikPen®

insulin lispro injection (rDNA origin)
200 units/mL

Humalog® (insulin lispro injection) Brief Summary: Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE

Humalog is an insulin analog indicated to improve glycemic control in adults and children with diabetes mellitus.

ADMINISTRATION

Humalog has a rapid onset of action and should be given within 15 minutes before a meal or immediately after a meal.

CONTRAINDICATIONS

Humalog is contraindicated:

- During episodes of hypoglycemia.
- In patients who are hypersensitive to Humalog or to any of its excipients.

WARNINGS AND PRECAUTIONS

- **Never Share a Humalog KwikPen, Cartridge, Reusable Pen Compatible with Lilly 3 mL Cartridges, or Syringe Between Patients:** Humalog KwikPens, cartridges, and reusable pens compatible with Lilly 3 mL cartridges must never be shared between patients, even if the needle is changed. Patients using Humalog vials must never share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.

- **Changes in Insulin Regimen:** Changes may affect glycemic control and predispose to hypoglycemia or hyperglycemia. These changes should be made cautiously under close medical supervision and the frequency of blood glucose monitoring should be increased.

- **Hypoglycemia:** Severe hypoglycemia may be life threatening and can cause seizures or death. Hypoglycemia is the most common adverse reaction of Humalog. The patient's ability to concentrate and react may be impaired as a result of hypoglycemia. Hypoglycemia can happen suddenly and symptoms may vary for each person and may change over time. Early warning symptoms of hypoglycemia may be different or less pronounced under conditions such as long-standing diabetes, diabetic nerve disease, use of medications such as beta-blockers, or in patients who experience recurrent hypoglycemia. These situations may result in severe hypoglycemia and possibly loss of consciousness prior to the patient's awareness of hypoglycemia.

Timing of hypoglycemia usually reflects the time-action profile of administered insulins which may vary in different individuals or at different times in the same individual. Other factors such as changes in food intake, injection site, exercise, and concomitant medications may increase the risk of hypoglycemia.

Educate patients to recognize and manage hypoglycemia. In patients at higher risk for hypoglycemia and patients with reduced symptomatic awareness, increased frequency of blood glucose monitoring is recommended. Patients with renal or hepatic impairment may be at higher risk of hypoglycemia.

- **Hypoglycemia Due to Medication Errors:** Instruct patients to always check the insulin label before each injection to avoid medication errors. Humalog U-200 should not be transferred from the Humalog KwikPen to a syringe as overdose and severe hypoglycemia can occur.
- **Hypersensitivity Reactions:** Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with Humalog. If hypersensitivity reactions occur, discontinue Humalog and treat per standard of care until signs and symptoms resolve.
- **Hypokalemia:** Hypokalemia may be life threatening. Insulins, including Humalog, cause a shift in potassium from the extracellular to intracellular space possibly leading to hypokalemia, which, if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death. Monitor potassium levels in patients at risk for hypokalemia (eg, patients using potassium-lowering medications or medications sensitive to serum potassium concentrations).
- **Fluid Retention and Heart Failure with Concomitant Use of PPAR-gamma Agonists:** Thiazolidinediones (TZDs), which are PPAR-gamma agonists, can cause dose-related fluid retention, particularly when used in combination with insulin, including Humalog. This may lead to or exacerbate heart failure. Observe patients for signs and symptoms of heart failure and consider discontinuation or dose reduction of the PPAR-gamma agonist.

- **Hyperglycemia and Ketoacidosis Due to Insulin Pump Device Malfunction:** Malfunction of the insulin pump device, infusion set, or insulin degradation can rapidly lead to hyperglycemia and ketoacidosis. Patients using subcutaneous insulin infusion pumps must be trained to administer insulin by injection and have alternate insulin therapy available in case of pump failure.

DRUG INTERACTIONS

Some medications may alter glucose metabolism, insulin requirements, and the risk for hypoglycemia or hyperglycemia. Signs of hypoglycemia may be reduced or absent in patients taking anti-adrenergic drugs. Particularly close monitoring may be required

ADVERSE REACTIONS

Adverse reactions associated with Humalog include hypoglycemia, hypokalemia, allergic reactions, injection-site reactions, lipodystrophy, pruritus, rash, weight gain, and peripheral edema.

Lipodystrophy

Long-term use of insulin, including Humalog, can cause lipodystrophy at the site of repeated insulin injections or infusion. Lipodystrophy includes lipohypertrophy (thickening of adipose tissue) and lipoatrophy (thinning of adipose tissue), and may affect insulin absorption. Rotate insulin injection or infusion sites within the same region to reduce the risk of lipodystrophy (see Dosage and Administration).

Weight Gain

Weight gain can occur with insulin therapy, including Humalog, and has been attributed to the anabolic effects of insulin and the decrease in glucosuria.

Peripheral Edema

Insulin, including Humalog, may cause sodium retention and edema, particularly if previously poor metabolic control is improved by intensified insulin therapy.

Allergic Reactions

Local Allergy—As with any insulin therapy, patients taking Humalog may experience redness, swelling, or itching at the site of the injection. These minor reactions usually resolve in a few days to a few weeks, but in some occasions, may require discontinuation of Humalog. In some instances, these reactions may be related to factors other than insulin, such as irritants in a skin cleansing agent or poor injection technique.

Systemic Allergy—Severe, life-threatening, generalized allergy, including anaphylaxis, may occur with any insulin, including Humalog. Generalized allergy to insulin may cause whole body rash (including pruritus), dyspnea, wheezing, hypotension, tachycardia, or diaphoresis.

In controlled clinical trials, pruritus (with or without rash) was seen in 17 patients receiving regular human insulin (n=2969) and 30 patients receiving Humalog (n=2944).

Localized reactions and generalized myalgias have been reported with injected metacresol, which is an excipient in Humalog (see Contraindications).

DOSE ADJUSTMENT AND MONITORING

Glucose monitoring is essential for patients receiving insulin therapy. Changes to an insulin regimen should be made cautiously and only under medical supervision. Changes in insulin strength, manufacturer, type, or method of administration may result in the need for a change in insulin dose. Concomitant oral antidiabetic treatment may need to be adjusted.

As with all insulin preparations, the time course of action for Humalog may vary in different individuals or at different times in the same individual and is dependent on many conditions, including the site of injection, local blood supply, or local temperature. Patients who change their level of physical activity or meal plan may require adjustment of insulin dosages.

Insulin Initiation and Intensification of Glucose Control

Intensification or rapid improvement in glucose control has been associated with a transitory, reversible ophthalmologic refraction disorder, worsening of diabetic retinopathy, and acute painful peripheral neuropathy. However, long-term glycemic control decreases the risk of diabetic retinopathy and neuropathy.

DOSAGE AND ADMINISTRATION

- Humalog should be given within 15 minutes before or immediately after a meal.
- Humalog U-100 can be administered intravenously under medical supervision with close monitoring of blood glucose and potassium levels to avoid hypoglycemia and hypokalemia. Do NOT administer Humalog U-200 intravenously.

- Humalog U-100 for subcutaneous injection should only be mixed with NPH insulin. If Humalog U-100 is mixed with NPH insulin, Humalog should be drawn into the syringe first. Injection should occur immediately after mixing. Do NOT mix Humalog U-200 with any other insulin.
- Do NOT administer Humalog U-200 intravenously.
- Do NOT mix Humalog U-200 with any other insulin.
- Do NOT use Humalog U-200 in a subcutaneous insulin infusion pump.
- Do NOT perform dose conversion when using either the Humalog U-100 or Humalog U-200 KwikPens. The dose window shows the number of insulin units to be delivered and no conversion is needed.

USE IN SPECIFIC POPULATIONS

Pregnancy—Pregnancy Category B. All pregnancies have a background risk of birth defects, loss, or other adverse outcome regardless of drug exposure. This background risk is increased in pregnancies complicated by hyperglycemia and may be decreased with good metabolic control. It is essential for patients with diabetes or history of gestational diabetes to maintain good metabolic control before conception and throughout pregnancy. In patients with diabetes or gestational diabetes insulin requirements may decrease during the first trimester, generally increase during the second and third trimesters, and rapidly decline after delivery. Careful monitoring of glucose control is essential in these patients. Therefore, female patients should be advised to tell their physicians if they intend to become, or if they become pregnant while taking Humalog.

Although there are limited clinical studies of the use of Humalog in pregnancy, published studies with human insulins suggest that optimizing overall glycemic control, including postprandial control, before conception and during pregnancy improves fetal outcome.

Nursing Mothers—It is unknown whether insulin lispro is excreted in human milk. Use of Humalog is compatible with breastfeeding, but women with diabetes who are lactating may require adjustments of their insulin doses.

Pediatric Use—Humalog is approved for use in children for subcutaneous daily injections and for subcutaneous continuous infusion by external insulin pump. Humalog has not been studied in pediatric patients younger than 3 years of age. Humalog has not been studied in pediatric patients with type 2 diabetes.

Renal Impairment—Patients with renal impairment may be at increased risk of hypoglycemia and may require more frequent HUMALOG dose adjustment and more frequent blood glucose monitoring.

Hepatic Impairment—Patients with hepatic impairment may be at increased risk of hypoglycemia and may require more frequent HUMALOG dose adjustment and more frequent blood glucose monitoring.

OVERDOSAGE

Excess insulin administration may cause hypoglycemia and hypokalemia. Mild episodes of hypoglycemia usually can be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery. Hypokalemia must be corrected appropriately.

PATIENT COUNSELING INFORMATION: See FDA-approved patient labeling and Patient Counseling Information section of the Full Prescribing Information.

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Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

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Additional information can be found at www.humalog.com.

Available by prescription only.

HI U200 HCP BS 26MAY2015

Humalog® (insulin lispro injection)

HI U200 HCP BS 26MAY2015



Senate Majority Leader
Mitch McConnell (R-KY)

Threat of Government Shutdown Looms; NIH Funding in Jeopardy

A key issue that the U.S. Congress must resolve by September 30 (the end of the fiscal year) is how to fund the government and all federal programs, including the National Institutes of Health (NIH). Although appropriations bills were able to be passed by committees in both the House and the Senate, neither body has been able to bring this legislation to a full vote. Prior to leaving Washington for the August congressional recess, Senate Majority Leader Mitch McConnell (R-KY) reported that legislators “haven’t even begun to plan how to cover the government’s funding after the fiscal year ends on September 30.” The House will be in session for only 10 days in September (the Senate has 15 days scheduled).

Democrats in the Senate have effectively shut down the process by blocking consideration of any bills that fund programs at the reduced sequester levels. At the same time, a debate over the Confederate Flag on federal grounds has deterred House leadership from bringing up the remaining bills on their side. Then, of course, there is the blanket veto threat from President Obama, which has all but guaranteed that these bills would never be enacted under current levels. Adding to the gridlock, a number of Republican leaders have “threatened to reject” a spending bill “needed to keep the government open” unless funding for Planned Parenthood is removed.

Therefore, the Congress has the following options: Lawmakers could negotiate a deal that provides sequestration relief, if only on a partial and/or temporary basis. They could do a continuing resolution (a mechanism that would fund programs at current levels/no increases) that is either short term or year long, and/or they could risk a government shutdown.

TAKE ACTION:
Now is a critical time to contact your members of Congress and urge support for a deal on the budget that will give some relief to research funding. Please visit the Society’s online advocacy campaign at www.endocrine.org/advocacy to contact Congress.

Endocrine Society Endorses Bill to Improve Safety of Personal Care Products



Sen. Dianne Feinstein (D-CA)



Sen. Susan Collins (R-ME)

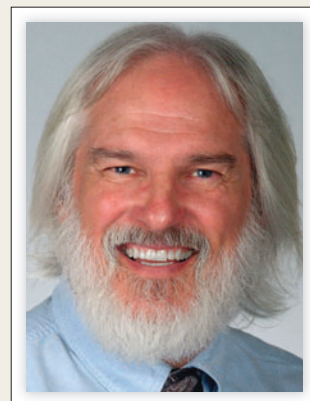


The bill prioritizes several chemicals commonly used in personal care products for immediate review by the U.S. Food and Drug Administration (FDA).

In recent months, Endocrine Society members and staff have worked with the office of Sen. Dianne Feinstein (D-CA) on legislative efforts to improve the regulatory oversight of personal care products, such as cosmetics, shampoos, and lotions. On April 20, Sen. Feinstein and Sen. Susan Collins (R-ME) introduced S.1014, the Personal Care Products Safety Act (PCPSA). The bill prioritizes several chemicals commonly used in personal care products for immediate review by the FDA. One of the priority chemicals, propyl paraben, is highlighted as an endocrine-disrupting chemical (EDC) that can mimic estrogen and is “linked to a wide range of health effects, including reproductive system disorders.”

The Endocrine Society was encouraged that the PCPSA sets a rigorous safety standard for FDA review of chemicals and includes provisions to allow public access to product statements. The Society joined the Environmental Working Group, Society for Women’s Health Research, and other consumer health organizations in endorsing the Personal Care Products Safety Act. The Society believes that this bill will help ensure a safe marketplace for personal care products and reduce harms from exposure to toxic chemicals such as EDCs, and we will continue to work with Sen. Feinstein to advance the legislation and other efforts to support public health. In September, the Endocrine Society will participate in a congressional briefing to raise awareness of the PCPSA and encourage committee consideration of the legislation.

Remembering EDC Research Pioneer Louis J. Guillette, Jr.



The world of endocrine-disrupting chemical research recently lost a giant in the field with the passing of Louis J. “Lou” Guillette, 60.

Director of the Marine Biomedicine & Environmental Sciences Center and professor of Ob/Gyn at the Medical University of South Carolina, Lou was a HHMI professor, Heinz Award Winner, and former “Professor of the Year” at the University of Florida. He had a profound influence on the field of endocrine disruption research, and on all those who knew him, not only because of his knowledge of vertebrate reproductive biology and comparative endocrinology, but also because of his ability to communicate to broad audiences.

Lou’s doctoral work was on the evolution of viviparity in a *Sceloporus* lizard, and this led to the initiation of a work program on the reproductive biology of alligators when he took a position in the Zoology Department at the University of Florida. His discoveries revealing the effects of chemical pollution on male reproductive biology of alligators in Lake Apopka were landmark and led to a prolific career that later expanded to embrace the study and public communication of the connections between wildlife health and human health, and the use of wildlife as human environmental health sentinels.

An index of the breadth of Lou’s work was the diversity of funding agencies from which he attracted support, including NIH, NSF, EPA, DOE, NASA, U.S. Fish & Wildlife Service, and many state and private foundations. Who else but Lou could hold a chair in marine genomics as well as in obstetrics and gynecology all at the same time? Lou’s greatest commitment was to his students and their development; he mentored dozens of students and postdocs and succeeded in developing one-to-one relationships with all his students that have lasted far beyond the students’ tenure.

He was warm and outgoing and has shaped the thinking and careers of a great number of scientists around the world.

— R. THOMAS ZOELLER, UNIVERSITY OF MASSACHUSETTS, AMHERST, MASS., AND SUSAN JOBLING, BRUNEL UNIVERSITY, LONDON, UK

Endocrine Society Comments on NIH Initiatives

As part of the Endocrine Society’s comprehensive advocacy program, the Society submits comments on Requests for Information (RFIs) from the National Institutes of Health (NIH) and other research funding agencies. This summer, the NIH issued RFIs on biomedical technology development and health disparities research, two topics of great interest to endocrinologists.

Technology Development

On June 10, the National Institute of General Medical Sciences (NIGMS) issued a RFI on “innovative approaches to technology development for the biomedical research community.” NIGMS is considering efforts to both support the development of new technologies and how best to ensure broad access to newly developed technologies. In response to the RFI, the Endocrine Society identified several challenges that researchers face in the generation, development, and application of new technologies. For example, researchers are forced to continuously update equipment and expertise in response to new technological developments, evaluate multiple expensive and time-consuming approaches to experiments, and navigate numerous new resources, databases, and biobanks.

The Endocrine Society recommended that the NIH continue to develop and encourage the use of centralized resources that help researchers quickly access databases and analyze data. The Society also encouraged the NIH to seek new ways to foster connections between basic and clinical researchers, and explore the use of public-private partnerships to create user-friendly data mining tools and support applied biomedical research.

Health Disparities Research

The National Institute on Minority Health and Health Disparities (NIMHD) is embarking on a scientific planning process in collaboration with other NIH institutes and centers to define a vision that will guide the development of the science of health disparities research for the next decade. On April 17, the NIMHD issued a RFI “Soliciting Input into the NIH Science Vision for Health Disparities Research.” In response to the RFI, the Endocrine Society highlighted infrastructure and resource needs for teams that study health disparities, scientific advances that should be prioritized in the vision, and policy considerations to reduce barriers to effective care.

The Society’s response also highlighted the *Endocrine Society’s Scientific Statement on Health Disparities in Endocrine Disorders* as an important resource the NIH should reference to identify key questions that should be addressed by additional research. We anticipate that the Science Vision for Health Disparities Research will be an important tool to reduce health disparities in the coming decade and staff will continue to seek opportunities to engage with the NIH and the NIMHD as the Science Vision develops. 



Say hello to once-weekly TANZEUM



Indications and Usage for TANZEUM

TANZEUM is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Limitations of Use:

- TANZEUM is not recommended as first-line therapy for patients inadequately controlled on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans. Prescribe TANZEUM only to patients for whom the potential benefits are considered to outweigh the potential risk.
- TANZEUM has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.
- TANZEUM is not indicated in the treatment of patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis. TANZEUM is not a substitute for insulin in these patients.
- TANZEUM has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis. The use of TANZEUM is not recommended in patients with pre-existing severe gastrointestinal disease.
- TANZEUM has not been studied in combination with prandial insulin.

Important Safety Information for TANZEUM

WARNING: RISK OF THYROID C-CELL TUMORS

Carcinogenicity of albiglutide could not be assessed in rodents, but other glucagon-like peptide-1 (GLP-1) receptor agonists have caused thyroid C-cell tumors in rodents at clinically relevant exposures. Human relevance of GLP-1 receptor agonist induced C-cell tumors in rodents has not been determined. It is unknown whether TANZEUM® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. TANZEUM is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC with the use of TANZEUM and inform them of the symptoms of thyroid tumors (e.g., mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound monitoring is of uncertain value for early detection of MTC in patients treated with TANZEUM.

CONTRAINDICATIONS

Hypersensitivity: TANZEUM is contraindicated in patients with a prior serious hypersensitivity reaction to albiglutide or to any of the product components.

WARNINGS AND PRECAUTIONS

Risk of Thyroid C-cell Tumors: Counsel patients regarding the potential risk for MTC with the use of TANZEUM and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, or persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with TANZEUM. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

For your adult patients with type 2 diabetes currently on basal insulin and/or oral antidiabetic medicine and in need of additional glycemic control

- The only once-weekly GLP-1 receptor agonist studied in a head-to-head, Phase III trial versus prandial insulin in patients taking basal insulin (HARMONY 6)¹
- FREE for 12 months to patients. Subject to eligibility, restrictions apply

Available by prescription only.



Make every week a TANZEUM week

Important Safety Information for TANZEUM (cont'd)

WARNINGS AND PRECAUTIONS (cont'd)

Acute Pancreatitis: In clinical trials, acute pancreatitis has been reported in association with TANZEUM. After initiation of TANZEUM, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, promptly discontinue TANZEUM. If pancreatitis is confirmed, TANZEUM should not be restarted. TANZEUM has not been studied in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: The risk of hypoglycemia is increased when TANZEUM is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. Therefore, patients may require a lower dose of sulfonylurea or insulin to reduce the risk of hypoglycemia in this setting.

Hypersensitivity Reactions: Across 8 Phase III clinical trials, a serious hypersensitivity reaction with pruritus, rash, and dyspnea occurred in a patient treated with TANZEUM. If hypersensitivity reactions occur, discontinue use of TANZEUM; treat promptly per standard of care and monitor until signs and symptoms resolve.

Renal Impairment: In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. In a trial of TANZEUM in patients with renal impairment, the frequency of such gastrointestinal reactions increased as renal function declined. Because these reactions may worsen renal function, use caution when initiating or escalating doses of TANZEUM in patients with renal impairment. Monitor renal function in patients with renal impairment reporting severe adverse gastrointestinal reactions.

Macrovascular Outcomes: There have been no clinical trials establishing conclusive evidence of macrovascular risk reduction with TANZEUM or any other antidiabetic drug.

ADVERSE REACTIONS

The most common adverse reactions, excluding hypoglycemia, reported in $\geq 5\%$ of patients treated with TANZEUM and more commonly than in patients treated with placebo, are: upper respiratory tract infection (14.2 vs 13.0); diarrhea (13.1 vs 10.5); nausea (11.1 vs 9.6); injection site reaction (10.5 vs 2.1); cough (6.9 vs 6.2); back pain (6.7 vs 5.8); arthralgia (6.6 vs 6.4); sinusitis (6.2 vs 5.8); influenza (5.2 vs 3.2).

DRUG INTERACTIONS

TANZEUM delays gastric emptying and may impact absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with TANZEUM.

USE IN SPECIFIC PATIENT POPULATIONS

Pediatric Use: Safety and effectiveness of TANZEUM have not been established in pediatric patients (younger than 18 years).

Please see Brief Summary of Prescribing Information, including Boxed Warning, for TANZEUM on the following pages.

GLP-1 = glucagon-like peptide-1.

Reference: 1. Prescribing Information for TANZEUM.

www.GSKSource.com

TANZEUM is a registered trademark of GSK.

Once-weekly
Tanzeum[®]
albiglutide
30mg, 50mg for injection

TANZEUM® (albiglutide) for injection, for subcutaneous use

BRIEF SUMMARY

The following is a brief summary only; see full prescribing information for complete product information.

WARNING: RISK OF THYROID C-CELL TUMORS

- **Carcinogenicity of albiglutide could not be assessed in rodents, but other glucagon-like peptide-1 (GLP-1) receptor agonists have caused thyroid C-cell tumors in rodents at clinically relevant exposures. Human relevance of GLP-1 receptor agonist induced C-cell tumors in rodents has not been determined. It is unknown whether TANZEUM® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans [see Warnings and Precautions (5.1), Nonclinical Toxicology (13.1)].**
- **TANZEUM is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC with the use of TANZEUM and inform them of the symptoms of thyroid tumors (e.g., mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound monitoring is of uncertain value for early detection of MTC in patients treated with TANZEUM [see Contraindications (4.1), Warnings and Precautions (5.1)].**

1 INDICATIONS AND USAGE

TANZEUM is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus [see Clinical Studies (14) of full prescribing information]. **Limitations of Use:** TANZEUM is not recommended as first-line therapy for patients inadequately controlled on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans. Prescribe TANZEUM only to patients for whom the potential benefits are considered to outweigh the potential risk [see Warnings and Precautions (5.1)]. TANZEUM has not been studied in patients with a history of pancreatitis [see Warnings and Precautions (5.2)]. Consider other antidiabetic therapies in patients with a history of pancreatitis. TANZEUM is not indicated in the treatment of patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis. TANZEUM is not a substitute for insulin in these patients. TANZEUM has not been studied in patients with severe gastrointestinal (GI) disease, including severe gastroparesis. The use of TANZEUM is not recommended in patients with pre-existing severe gastrointestinal disease [see Adverse Reactions (6.1)]. TANZEUM has not been studied in combination with prandial insulin.

4 CONTRAINDICATIONS

4.1 Medullary Thyroid Carcinoma: TANZEUM is contraindicated in patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) [see Warnings and Precautions (5.1)]. **4.2 Hypersensitivity:** TANZEUM is contraindicated in patients with a prior serious hypersensitivity reaction to albiglutide or to any of the product components [see Warnings and Precautions (5.4)].

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-cell Tumors: Carcinogenicity of albiglutide could not be assessed in rodents due to the rapid development of drug-clearing, anti-drug antibodies [see Nonclinical Toxicology (13.1)]. Other GLP-1 receptor agonists have caused dose-related and treatment-duration-dependent thyroid C-cell tumors (adenomas or carcinomas) in rodents. Human relevance of GLP-1 receptor agonist induced C-cell tumors in rodents has not been determined. It is unknown whether TANZEUM causes thyroid C-cell tumors, including MTC, in humans [see Boxed Warning, Contraindications (4.1)]. Across 8 Phase III clinical trials [see Clinical Studies (14) of full prescribing information], MTC was diagnosed in 1 patient receiving TANZEUM and 1 patient receiving placebo. Both patients had markedly elevated serum calcitonin levels at baseline. Cases of MTC in patients treated with liraglutide, another GLP-1 receptor agonist, have been reported in the postmarketing period; the data in these reports are insufficient to establish or exclude a causal relationship between MTC and GLP-1 receptor agonist use in humans. TANZEUM is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of TANZEUM and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, or persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with TANZEUM. Such monitoring may increase the risk of unnecessary procedures, due to the low specificity of serum calcitonin testing for MTC and a high background incidence of thyroid disease. Significantly elevated serum calcitonin may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Acute Pancreatitis: In clinical trials, acute pancreatitis has been reported in association with TANZEUM. Across 8 Phase III clinical trials [see Clinical Studies (14) of full prescribing information], pancreatitis adjudicated as likely related to therapy occurred more frequently in patients receiving TANZEUM (6 of 2,365 [0.3%]) than in patients receiving placebo (0 of 468 [0%]) or active comparators (2 of 2,065 [0.1%]). After initiation of TANZEUM, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe

abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, promptly discontinue TANZEUM. If pancreatitis is confirmed, TANZEUM should not be restarted. TANZEUM has not been studied in patients with a history of pancreatitis to determine whether these patients are at increased risk for pancreatitis. Consider other antidiabetic therapies in patients with a history of pancreatitis.

5.3 Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: The risk of hypoglycemia is increased when TANZEUM is used in combination with insulin secretagogues (e.g., sulfonylureas) or insulin. Therefore, patients may require a lower dose of sulfonylurea or insulin to reduce the risk of hypoglycemia in this setting [see Dosage and Administration (2.2) of full Prescribing Information, Adverse Reactions (6.1)]. **5.4 Hypersensitivity Reactions:** Across 8 Phase III clinical trials [see Clinical Studies (14) of full prescribing information], a serious hypersensitivity reaction with pruritus, rash, and dyspnea occurred in a patient treated with TANZEUM. If hypersensitivity reactions occur, discontinue use of TANZEUM; treat promptly per standard of care and monitor until signs and symptoms resolve [see Contraindications (4.2)]. **5.5 Renal Impairment:** In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration. In a trial of TANZEUM in patients with renal impairment [see Clinical Studies (14.3) of full prescribing information], the frequency of such gastrointestinal reactions increased as renal function declined [see Use in Specific Populations (8.6)]. Because these reactions may worsen renal function, use caution when initiating or escalating doses of TANZEUM in patients with renal impairment [see Dosage and Administration (2.3) of full prescribing information, Use in Specific Populations (8.6)]. **5.6 Macrovascular Outcomes:** There have been no clinical trials establishing conclusive evidence of macrovascular risk reduction with TANZEUM or any other antidiabetic drug.

6 ADVERSE REACTIONS

The following serious reactions are described below or elsewhere in the prescribing information: Risk of Thyroid C-cell Tumors [see Warnings and Precautions (5.1)], Acute Pancreatitis [see Warnings and Precautions (5.2)], Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin [see Warnings and Precautions (5.3)], Hypersensitivity Reactions [see Warnings and Precautions (5.4)], Renal Impairment [see Warnings and Precautions (5.5)]. **6.1 Clinical Trials Experience:** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. **Pool of Placebo-Controlled Trials:** The data in Table 1 are derived from 4 placebo-controlled trials. TANZEUM was used as monotherapy in 1 trial and as add-on therapy in 3 trials [see Clinical Studies (14) of full prescribing information]. These data reflect exposure of 923 patients to TANZEUM and a mean duration of exposure to TANZEUM of 93 weeks. The mean age of participants was 55 years, 1% of participants were 75 years or older and 53% of participants were male. The population in these studies was 48% white, 13% African/African American, 7% Asian, and 29% Hispanic/Latino. At baseline, the population had type 2 diabetes for an average of 7 years and had a mean HbA1c of 8.1%. At baseline, 17% of the population in these studies reported peripheral neuropathy and 4% reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR >60 mL/min/1.73 m²) in 91% of the study population and moderately impaired (eGFR 30 to 60 mL/min/1.73 m²) in 9%. Table 1 shows common adverse reactions excluding hypoglycemia associated with the use of TANZEUM in the pool of placebo-controlled trials. These adverse reactions were not present at baseline, occurred more commonly on TANZEUM than on placebo, and occurred in at least 5% of patients treated with TANZEUM.

Table 1. Adverse Reactions in Placebo-controlled Trials Reported in ≥5% of Patients Treated with TANZEUM^a

Adverse Reaction	Placebo (N=468) %	TANZEUM (N=923) %
Upper respiratory tract infection	13.0	14.2
Diarrhea	10.5	13.1
Nausea	9.6	11.1
Injection site reaction ^b	2.1	10.5
Cough	6.2	6.9
Back pain	5.8	6.7
Arthralgia	6.4	6.6
Sinusitis	5.8	6.2
Influenza	3.2	5.2

^aAdverse reactions reported includes adverse reactions occurring with the use of glycemic rescue medications which included metformin (17% for placebo and 10% for TANZEUM) and insulin (24% for placebo and 14% for TANZEUM).

^bSee below for other events of injection site reactions reported.

Continued on next page

Adverse Reactions (cont'd)

Gastrointestinal Adverse Reactions: In the pool of placebo-controlled trials, gastrointestinal complaints occurred more frequently among patients receiving TANZEUM (39%) than patients receiving placebo (33%). In addition to diarrhea and nausea (see Table 1), the following gastrointestinal adverse reactions also occurred more frequently in patients receiving TANZEUM: vomiting (2.6% versus 4.2% for placebo versus TANZEUM), gastroesophageal reflux disease (1.9% versus 3.5% for placebo versus TANZEUM), and dyspepsia (2.8% versus 3.4% for placebo versus TANZEUM). Constipation also contributed to the frequently reported reactions. In the group treated with TANZEUM, investigators graded the severity of GI reactions as "mild" in 56% of cases, "moderate" in 37% of cases, and "severe" in 7% of cases. Discontinuation due to GI adverse reactions occurred in 2% of individuals on TANZEUM or placebo.

Injection Site Reactions: In the pool of placebo-controlled trials, injection site reactions occurred more frequently on TANZEUM (18%) than on placebo (8%). In addition to the term injection site reaction (see Table 1), the following other types of injection site reactions also occurred more frequently on TANZEUM: injection site hematoma (1.9% versus 2.1% for placebo versus TANZEUM), injection site erythema (0.4% versus 1.7% for placebo versus TANZEUM), injection site rash (0% versus 1.4% for placebo versus TANZEUM), injection site hypersensitivity (0% versus 0.8% versus for placebo versus TANZEUM), and injection site hemorrhage (0.6% versus 0.7% for placebo versus TANZEUM). Injection site pruritus also contributed to the frequently reported reactions. The majority of injection site reactions were judged as "mild" by investigators in both groups (73% for TANZEUM versus 94% for placebo). More patients on TANZEUM than on placebo: discontinued due to an injection site reaction (2% versus 0.2%), experienced more than 2 reactions (38% versus 20%), had a reaction judged by investigators to be "moderate" or "severe" (27% versus 6%) and required local or systemic treatment for the reactions (36% versus 11%).

Pool of Placebo- and Active-controlled Trials: The occurrence of adverse reactions was also evaluated in a larger pool of patients with type 2 diabetes participating in 7 placebo- and active-controlled trials. These trials evaluated the use of TANZEUM as monotherapy, and as add-on therapy to oral antidiabetic agents, and as add-on therapy to basal insulin [see *Clinical Studies* (14) of full prescribing information]. In this pool, a total of 2,116 patients with type 2 diabetes were treated with TANZEUM for a mean duration of 75 weeks. The mean age of patients treated with TANZEUM was 55 years, 1.5% of the population in these studies was 75 years or older and 51% of participants were male. Forty-eight percent of patients were white, 15% African/African American, 9% Asian, and 26% were Hispanic/Latino. At baseline, the population had diabetes for an average of 8 years and had a mean HbA1c of 8.2%. At baseline, 21% of the population reported peripheral neuropathy and 5% reported retinopathy. Baseline estimated renal function was normal or mildly impaired (eGFR >60 mL/min/1.73 m²) in 92% of the population and moderately impaired (eGFR 30 to 60 mL/min/1.73 m²) in 8% of the population. In the pool of placebo- and active-controlled trials, the types and frequency of common adverse reactions excluding hypoglycemia were similar to those listed in Table 1.

Other Adverse Reactions: Hypoglycemia: The proportion of patients experiencing at least one documented symptomatic hypoglycemic episode on TANZEUM and the proportion of patients experiencing at least one severe hypoglycemic episode on TANZEUM in clinical trials [see *Clinical Studies* (14) of full prescribing information] is shown in Table 2. Hypoglycemia was more frequent when TANZEUM was added to sulfonylurea or insulin [see *Warnings and Precautions* (5.3)].

Table 2. Incidence (%) of Hypoglycemia in Clinical Trials of TANZEUM ^a		
Monotherapy ^b (52 Weeks)	Placebo N = 101	TANZEUM 30 mg Weekly N = 101
Documented symptomatic ^c	2%	2%
Severe ^d	-	-
In Combination with Metformin Trial (104 Weeks) ^e	Placebo N = 101	TANZEUM N = 302
Documented symptomatic	4%	3%
Severe	-	-
In Combination with Pioglitazone ± Metformin (52 Weeks)	Placebo N = 151	TANZEUM N = 150
Documented symptomatic	1%	3%
Severe	-	1%
In Combination with Metformin and Sulfonylurea (52 Weeks)	Placebo N = 115	TANZEUM N = 271
Documented symptomatic	7%	13%
Severe	-	0.4%
In Combination with Insulin Glargine (26 Weeks)	Insulin Lispro N = 281	TANZEUM N = 285
Documented symptomatic	30%	16%
Severe	0.7%	-

Table 2. Incidence (%) of Hypoglycemia in Clinical Trials of TANZEUM^a (cont'd)

In Combination with Metformin ± Sulfonylurea (52 Weeks)	Insulin Glargine N = 241	TANZEUM N = 504
Documented symptomatic	27%	17%
Severe	0.4%	0.4%
In Combination with OADs in Renal Impairment (26 Weeks)	Sitagliptin N = 246	TANZEUM N = 249
Documented symptomatic	6%	10%
Severe	0.8%	-

OAD = Oral antidiabetic agents.

^aData presented are to the primary endpoint and include only events occurring on-therapy with randomized medications and excludes events occurring after use of glycemic rescue medications (i.e., primarily metformin or insulin). ^bIn this trial, no documented symptomatic or severe hypoglycemia were reported for TANZEUM 50 mg and these data are omitted from the table. ^cPlasma glucose concentration ≤70 mg/dL and presence of hypoglycemic symptoms. ^dEvent requiring another person to administer a resuscitative action. ^eRate of documented symptomatic hypoglycemia for active controls 18% (glimepiride) and 2% (sitagliptin).

Pneumonia: In the pool of 7 placebo- and active-controlled trials, the adverse reaction of pneumonia was reported more frequently in patients receiving TANZEUM (1.8%) than in patients in the all-comparators group (0.8%). More cases of pneumonia in the group receiving TANZEUM were serious (0.4% for TANZEUM versus 0.1% for all comparators).

Atrial Fibrillation/Flutter: In the pool of 7 placebo- and active-controlled trials, adverse reactions of atrial fibrillation (1.0%) and atrial flutter (0.2%) were reported more frequently for TANZEUM than for all comparators (0.5% and 0%, respectively). In both groups, patients with events were generally male, older, and had underlying renal impairment or cardiac disease (e.g., history of arrhythmia, palpitations, congestive heart failure, cardiomyopathy, etc.).

Appendicitis: In the pool of placebo- and active-controlled trials, serious events of appendicitis occurred in 0.3% of patients treated with TANZEUM compared with 0% among all comparators.

Immunogenicity: In the pool of 7 placebo- and active-controlled trials, 116 (5.5%) of 2,098 patients exposed to TANZEUM tested positive for anti-albiglutide antibodies at any time during the trials. None of these antibodies were shown to neutralize the activity of albiglutide in an in vitro bioassay. Presence of antibody did not correlate with reduced efficacy as measured by HbA1c and fasting plasma glucose or specific adverse reactions. Consistent with the high homology of albiglutide with human GLP-1, the majority of patients (approximately 79%) with anti-albiglutide antibodies also tested positive for anti-GLP-1 antibodies; none were neutralizing. A minority of patients (approximately 17%) who tested positive for anti-albiglutide antibodies also transiently tested positive for antibodies to human albumin. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, the incidence of antibodies to albiglutide cannot be directly compared with the incidence of antibodies of other products.

Liver Enzyme Abnormalities: In the pool of placebo- and active-controlled trials, a similar proportion of patients experienced at least one event of alanine aminotransferase (ALT) increase of 3-fold or greater above the upper limit of normal (0.9% and 0.9% for all comparators versus TANZEUM). Three subjects on TANZEUM and one subject in the all-comparator group experienced at least one event of ALT increase of 10-fold or greater above the upper limit of normal. In one of the 3 cases an alternate etiology was identified to explain the rise in liver enzyme (acute viral hepatitis). In one case, insufficient information was obtained to establish or refute a drug-related causality. In the third case, elevation in ALT (10 times the upper limit of normal) was accompanied by an increase in total bilirubin (4 times the upper limit of normal) and occurred 8 days after the first dose of TANZEUM. The etiology of hepatocellular injury was possibly related to TANZEUM but direct attribution to TANZEUM was confounded by the presence of gallstone disease diagnosed on ultrasound 3 weeks after the event.

Gamma Glutamyltransferase (GGT) Increase: In the pool of placebo-controlled trials, the adverse event of increased GGT occurred more frequently in the group treated with TANZEUM (0.9% and 1.5% for placebo versus TANZEUM).

Heart Rate Increase: In the pool of placebo-controlled trials, mean heart rate in patients treated with TANZEUM was higher by an average of 1 to 2 bpm compared with mean heart rate in patients treated with placebo across study visits. The long-term clinical effects of the increase in heart rate have not been established [see *Warnings and Precautions* (5.6)].

Continued on next page

7 DRUG INTERACTIONS

TANZEUM did not affect the absorption of orally administered medications tested in clinical pharmacology studies to any clinically relevant degree [see *Clinical Pharmacology* (12.3) of full prescribing information]. However, TANZEUM causes a delay of gastric emptying, and thereby has the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with TANZEUM.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: *Pregnancy Category C:* There are no adequate and well-controlled studies of TANZEUM in pregnant women. Nonclinical studies have shown reproductive toxicity, but not teratogenicity, in mice treated with albiglutide at up to 39 times human exposure resulting from the maximum recommended dose of 50 mg/week, based on area under the time-concentration curve (AUC) [see *Nonclinical Toxicology* (13.1, 13.3)]. TANZEUM should not be used during pregnancy unless the expected benefit outweighs the potential risks. Due to the long washout period for TANZEUM, consider stopping TANZEUM at least 1 month before a planned pregnancy. There are no data on the effects of TANZEUM on human fertility. Studies in mice showed no effects on fertility [see *Nonclinical Toxicology* (13.1)]. The potential risk to human fertility is unknown. **8.3 Nursing Mothers:** There are no adequate data to support the use of TANZEUM during lactation in humans. It is not known if TANZEUM is excreted into human milk during lactation. Given that TANZEUM is an albumin-based protein therapeutic, it is likely to be present in human milk. Decreased body weight in offspring was observed in mice treated with TANZEUM during gestation and lactation [see *Nonclinical Toxicology* (13.3)]. A decision should be made whether to discontinue nursing or to discontinue TANZEUM, taking into account the importance of the drug to the mother and the potential risks to the infant. **8.4 Pediatric Use:** Safety and effectiveness of TANZEUM have not been established in pediatric patients (younger than 18 years). **8.5 Geriatric Use:** Of the total number of patients (N = 2,365) in 8 Phase III clinical trials who received TANZEUM, 19% (N = 444) were 65 years and older, and <3% (N = 52) were 75 years and older. No overall differences in safety or effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. **8.6 Renal Impairment:** Of the total number of patients (N = 2,365) in 8 Phase III clinical trials who received TANZEUM, 54% (N = 1,267) had mild renal impairment (eGFR 60 to 89 mL/min/1.73 m²), 12% (N = 275) had moderate renal impairment (eGFR 30 to 59 mL/min/1.73 m²) and 1% (N = 19) had severe renal impairment (eGFR 15 to <30 mL/min/1.73 m²). No dosage adjustment is required in patients with mild (eGFR 60 to 89 mL/min/1.73 m²), moderate (eGFR 30 to 59 mL/min/1.73 m²), or severe (eGFR 15 to <30 mL/min/1.73 m²) renal impairment. Efficacy of TANZEUM in patients with type 2 diabetes and renal impairment is described elsewhere [see *Clinical Studies* (14.3) of full prescribing information]. There is limited clinical experience in patients with severe renal impairment (19 subjects). The frequency of GI events increased as renal function declined. For patients with mild, moderate, or severe impairment, the respective event rates were: diarrhea (6%, 13%, 21%), nausea (3%, 5%, 16%), and vomiting (1%, 2%, 5%). Therefore, caution is recommended when initiating or escalating doses of TANZEUM in patients with renal impairment [see *Dosage and Administration* (2.3) of full prescribing information, *Warnings and Precautions* (5.5), *Clinical Pharmacology* (12.3) of full prescribing information].

10 OVERDOSAGE

No data are available with regard to overdosage in humans. Anticipated symptoms of an overdose may be severe nausea, vomiting, and headache. In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the half-life of TANZEUM (5 days).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: As albiglutide is a recombinant protein, no genotoxicity studies have been conducted. Carcinogenicity of albiglutide could not be assessed in rodents due to the rapid development of drug-clearing, anti-drug antibodies. Other GLP-1 receptor agonists have caused thyroid C-cell tumors in rodent carcinogenicity studies. Human relevance of GLP-1 receptor agonist induced rodent thyroid C-cell tumors has not been determined. In a mouse fertility study, males were treated with subcutaneous (SC) doses of 5, 15, or 50 mg/kg/day for 7 days prior to cohabitation with females, and continuing through mating. In a separate fertility study, females were treated with SC doses of 1, 5, or 50 mg/kg/day for 7 days prior to cohabitation with males, and continuing through mating. Reductions in estrous cycles were observed at 50 mg/kg/day, a dose associated with maternal toxicity (body weight loss and reduced food consumption). There were no effects on mating or fertility in either sex at doses up to 50 mg/kg/day (up to 39 times clinical exposure based on AUC). **13.3 Reproductive and Developmental Toxicity:** In order to minimize the impact of the drug-clearing, anti-drug antibody response, reproductive and developmental toxicity assessments in the mouse were partitioned to limit the dosing period to no more than approximately 15 days in each study. In pregnant mice given SC doses of 1, 5, or 50 mg/kg/day from gestation Day 1 to 6, there were no adverse effects on early embryonic development through implantation at 50 mg/kg/day (39 times clinical exposure based on AUC). In pregnant mice

given SC doses of 1, 5, or 50 mg/kg/day from gestation Day 6 through 15 (organogenesis), embryo-fetal lethality (post-implantation loss) and bent (wavy) ribs were observed at 50 mg/kg/day (39 times clinical exposure based on AUC), a dose associated with maternal toxicity (body weight loss and reduced food consumption). Pregnant mice were given SC doses of 1, 5, or 50 mg/kg/day from gestation Day 6 to 17. Offspring of pregnant mice given 50 mg/kg/day (39 times clinical exposure based on AUC), a dose associated with maternal toxicity, had reduced body weight pre-weaning, dehydration and coldness, and a delay in balanopreputial separation. Pregnant mice were given SC doses of 1, 5, or 50 mg/kg/day from gestation Day 15 to lactation Day 10. Increased mortality and morbidity were seen at all doses (≥ 1 mg/kg/day) in lactating females in mouse pre- and postnatal development studies. Mortalities have not been observed in previous toxicology studies in non-lactating or non-pregnant mice, nor in pregnant mice. These findings are consistent with lactational ileus syndrome which has been previously reported in mice. Since the relative stress of lactation energy demands is lower in humans than mice and humans have large energy reserves, the mortalities observed in lactating mice are of questionable relevance to humans. The offspring had decreased pre-weaning body weight which reversed post-weaning in males but not females at ≥ 5 mg/kg/day (2.2 times clinical exposure based on AUC) with no other effects on development. Low levels of albiglutide were detected in plasma of offspring. Lactating mice were given SC doses of 1, 5, or 50 mg/kg/day from lactation Day 7 to 21 (weaning) under conditions that limit the impact of lactational ileus (increased caloric intake and culling of litters). Doses ≥ 1 mg/kg/day (exposures below clinical AUC) caused reduced weight gain in the pups during the treatment period.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use). The Medication Guide is contained in a separate leaflet that accompanies the product. Inform patients about self-management practices, including the importance of proper storage of TANZEUM, injection technique, timing of dosage of TANZEUM and concomitant oral drugs, and recognition and management of hypoglycemia. Inform patients that thyroid C-cell tumors have been observed in rodents treated with some GLP-1 receptor agonists, and the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, dysphagia, dyspnea, or persistent hoarseness) to their physician [see *Boxed Warning, Warnings and Precautions* (5.1)]. Advise patients that persistent, severe abdominal pain that may radiate to the back and which may (or may not) be accompanied by vomiting is the hallmark symptom of acute pancreatitis. Instruct patients to discontinue TANZEUM promptly and to contact their physician if persistent, severe abdominal pain occurs [see *Warnings and Precautions* (5.2)]. The risk of hypoglycemia is increased when TANZEUM is used in combination with an agent that induces hypoglycemia, such as sulfonylurea or insulin. Instructions for hypoglycemia should be reviewed with patients and reinforced when initiating therapy with TANZEUM, particularly when concomitantly administered with a sulfonylurea or insulin [see *Warnings and Precautions* (5.3)]. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking TANZEUM and seek medical advice promptly if such symptoms occur [see *Warnings and Precautions* (5.4)]. Instruct patients to read the Instructions for Use before starting therapy. Instruct patients on proper use, storage, and disposal of the pen [see *How Supplied/Storage and Handling* (16.2) of full prescribing information, *Patient Instructions for Use* of full prescribing information]. Instruct patients to read the Medication Guide before starting TANZEUM and to read again each time the prescription is renewed. Instruct patients to inform their doctor or pharmacist if they develop any unusual symptom, or if any known symptom persists or worsens. Inform patients not to take an extra dose of TANZEUM to make up for a missed dose. If a dose is missed, instruct patients to take a dose as soon as possible within 3 days after the missed dose. Instruct patients to then take their next dose at their usual weekly time. If it has been longer than 3 days after the missed dose, instruct patients to wait and take TANZEUM at the next usual weekly time.

TANZEUM is a registered trademark of the GSK group of companies.



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Wilmington, DE 19808

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ENDO 2016

Bigger, Better, in Boston in April

SAVE THE DATES

April 1 – 4, 2016
(Friday – Monday)

Boston Convention
and Exhibition Center,
Boston, Mass.

- ▶ **Abstract submission:**
September 9, 2015 –
November 10, 2015
- ▶ **Early registration:**
October 6, 2015 –
January 13, 2016
- ▶ **Advance registration:**
January 14, 2016 –
February 25, 2016
- ▶ **Late-breaking
abstract submission:**
January 19, 2016 –
February 17, 2016
- ▶ **Housing reservation
deadline:**
March 8, 2016

The most important innovations and latest insights in endocrinology will hit the East Coast Friday, April 1 – Monday, April 4, as **ENDO 2016** lands in Boston. Join leading practitioners and researchers from around the world for four exhilarating days of education and networking.

Celebrate the Society's Centennial

The Society has come a long way from June 1916 when a group gathered at the American Medical Association's meeting to explore creating a professional society for those working in the fledgling field of endocrinology. That discussion resulted in the founding of the Association for the Study of Internal Secretions with 300 charter members. Do you know what year the name was changed to the Endocrine Society? Learn the answer to this and more as we celebrate the legacy of the Society through special historical perspectives in the key areas of scientific discovery that encompass endocrinology.

A Mecca for Endocrinologists

Boston is a training hub for endocrinology and many members have trained or worked in this charming historical area. **ENDO 2016** takes place at the Boston Convention & Exhibition Center – the largest convention center in the Northeastern U.S. and a technological marvel. Come and enjoy all Boston has to offer while you reconnect with colleagues from around the world.

Submit Your Abstract for ENDO 2016

Abstract submissions are now being accepted. Submit your work and reserve your place in beautiful Boston. Visit endo2016.org for complete details on abstract submission. See you in April!

A Wealth of Opportunities

ENDO 2016 will present thought-provoking speakers in insightful sessions, and the opportunity for you to explore all of the key areas of endocrinology from basic discoveries to clinical applications. The networking at **ENDO** makes the meeting a can't-miss event every year.

In addition to the outstanding presentations, there will be pre-conference events starting on Thursday, March 30, and **ENDOExpo** will provide information on the latest advances in products and services for **ENDO** attendees.

Society Participates in NICHD Advisory Council Meeting



As part of a comprehensive approach to enhance the visibility of endocrinology among research funding agencies, the Society participated in the June 4 meeting of the National Advisory Child Health and Human Development (NACHHD) Council. The Council advises the director of the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) on research, support activities, and functions of the institute.

During the director's report, NICHD director Alan Guttmacher, MD, provided updates on several projects of interest to the extramural research community. Guttmacher highlighted a new online system, the NICHD Data and Specimen Hub (N-DASH), which will allow the storage and access of de-identified data from NICHD-supported studies. The N-DASH platform launched in late June with data from 14 initial studies. The director then noted that they are closer to delivering an interactive mobile app to develop crowd-sourced data to detail the natural history and variations of human pregnancy. The app will also allow women to receive accurate information about pregnancy from trusted sources and let pregnant women know about opportunities to participate in research. Additionally, Guttmacher announced the launch of a new Spanish-language website to broaden community outreach.

The Council was joined by the director of the National Institute for General Medical Studies (NIGMS), Jon Lorsch, PhD, to discuss NIGMS' efforts to refocus its portfolio on

investigator-initiated research. Lorsch described the institute's rationale for increasing the funding of "programs" rather than "projects" through the institute's Maximizing Investigator's Research Award (MIRA) program. Specifically, the institute's data suggest that research funding is skewed toward a top tier of researchers, and that additional efficiencies might be enabled through a more equitable distribution of funds, for example, by reducing investigator time spent writing grant applications. The MIRA program proposes to award grants of up to \$750,000 per year for up to five years.

However, the awards will be open to established investigators with at least two existing R01 grants who make the MIRA award their primary source of funding. This implies that researchers will be comfortable trading a greater overall dollar amount for additional efficiency and funding security. The NICHD has established a working group to consider whether to implement a similar program through the R35 mechanism. The working group is weighing many options, including identifying a target career stage and evaluating how many awards NICHD should support through this mechanism.

In a separate concept clearance and review session, the three proposals shown in the table below were discussed by the Council and passed with no objection. Concept clearance represents an early step in the process of developing Requests for Application and Program Announcements, and the final details and eventual publication are subject to additional approval. — *Joe Laakso, PhD, associate director, science policy*

PROGRAM NAME	FUNDING MECHANISM	PROGRAM CONTACT
Population Dynamics Centers Research Infrastructure FY 2016–2020	P2C	Rebecca L. Clark, PhD, Population Branch Dynamics
Specialized Centers for Research in Pediatric Developmental Pharmacology	U54	Ekaterini Tislou, MD, Obstetric and Pediatric Pharmacology and Therapeutics Branch
Omics Approaches to Assess Human Placental Development and Function in Real Time	R01/R21	David Weinberg, PhD, Office of the Director

Society Publishes Clinical Practice Guideline on Cushing's Syndrome

In July, the Society issued a Clinical Practice Guideline (CPG) on strategies for treating Cushing's syndrome entitled *Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline*, which was published online and appeared in the August issue of *The Journal of Clinical Endocrinology & Metabolism (JCEM)*.

Cushing's syndrome occurs when a person has excess cortisol in the blood for an extended period, according to the Hormone Health Network. When it is present in normal amounts, cortisol is involved in the body's response to stress, maintains blood pressure and cardiovascular function, keeps the immune system in check, and converts fat, carbohydrates, and proteins into energy. Chronic overexposure to the hormone can contribute to the development of cardiovascular disease, infections, and blood clots in veins.

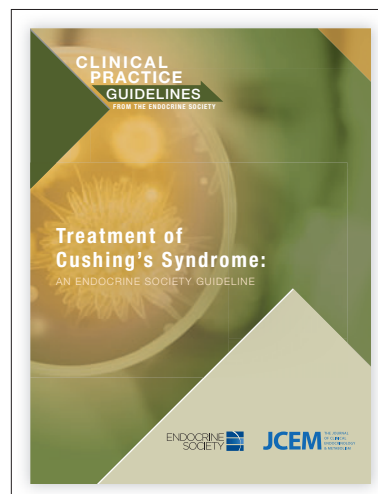
In some cases, tumors found on the adrenal or pituitary glands or elsewhere in the body cause the overproduction of cortisol and lead to the development of Cushing's syndrome. The CPG focus on this form of the condition, known as endogenous Cushing's syndrome.

"People who have active Cushing's syndrome face a greater risk of death — anywhere from nearly twice as high to nearly five times higher — than the general population," says Lynnette K. Nieman, MD, of the National Institutes of Health's Eunice Kennedy Shriver National Institute of Child Health and Human Development in Bethesda, MD, and chair of the task force that authored the guideline. "To reduce the risk of fatal cardiovascular disease, infections, or blood clots, it is critical to identify the cause of the Cushing's syndrome and restore cortisol levels to the normal range."

In the CPG, the Endocrine Society recommends that the first-line treatment for endogenous Cushing's syndrome be the removal of the tumor unless surgery is not possible or unlikely to address the excess cortisol. Surgical removal of the tumor is optimal because it leaves intact the hypothalamic-pituitary-adrenal axis, which is integral to the body's central stress response.

Other members of the Endocrine Society task force who developed this CPG include: Beverly M.K. Biller of Massachusetts General Hospital, in Boston, Mass.; James W. Findling of the Medical College of Wisconsin, in Milwaukee, Wisc.; M. Hassan Murad of the Mayo Clinic, in Rochester, Minn.; John Newell-Price of the University of Sheffield, in Sheffield, U.K.; Martin O. Savage of the William Harvey Research Institute at Barts and the London School of Medicine and Dentistry, in London, U.K.; and Antoine Tabarin of CHU de Bordeaux and INSERM at the University of Bordeaux, in Bordeaux, France.

The CPG was co-sponsored by the European Society of Endocrinology.



In the CPG, the Endocrine Society recommends that the first-line treatment for endogenous Cushing's syndrome be the removal of the tumor unless surgery is not possible or unlikely to address the excess cortisol.



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The Endocrine Society offers members an exclusive benefit — Endocrine Cases. Envisioned and developed by immediate past president Richard J. Santen, MD, this online tool allows members to submit their most challenging clinical cases and have Society experts weigh in. Present real or hypothetical situations, and test your hypothesis against what the experts recommend. Visit endocrine.org/Cases to learn more about this valuable and informative member benefit.

EVENT CALENDAR

SEPTEMBER 8 – 12

MIAMI

Clinical Endocrinology
Update

www.endocrine.org/ceu

OCTOBER 9 – 12

SEATTLE

American Society for Bone
and Mineral Research
Annual Meeting

www.asbmr.org

OCTOBER 17 – 21

CHICAGO

Neuroscience 2015

www.sfn.org

OCTOBER 18 – 23

ORLANDO

Thyroid ITC 2015

www.thyroid.org

NOVEMBER 1 – 7

LOS ANGELES

Obesity Week 2015

www.obesity.org

New Diabetes Management Program from HHN



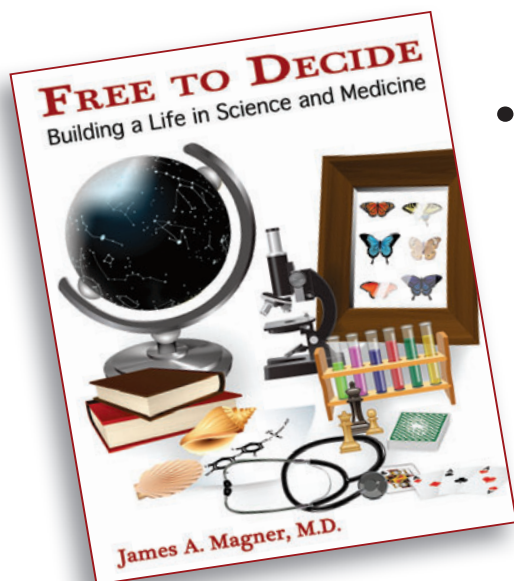
In November, the Hormone Health Network (HHN) will launch a new collaborative diabetes management program called Diabetes

Awareness Information for Loved Ones and You (D.A.I.L.Y.) aimed at patients as well as clinicians who treat diabetes.

D.A.I.L.Y. will provide resources that are tailored to an individual patient's needs and can be shared with healthcare professionals to encourage a collaborative approach to diabetes management. Users enroll as a person with diabetes, family member or friend of a person with diabetes, or as a healthcare professional. The goal is to provide access to useful educational resources that are tools not rules for diabetes self-management. As the leading experts in diabetes treatment, endocrinologists helped to develop program content to ensure patients and their loved ones receive the most trusted information.

Ahead of the launch, HHN has released the new logo for D.A.I.L.Y., which was created with input from diabetes experts, Endocrine Society membership and staff, and, more importantly, using patients' input and uses the sun itself as a centerpiece, according to HHN director, Cheretta Clerkley. "The sun is a symbol of warmth, light, hope, knowledge, and awareness," she says. "The logo conveys what we hope patients and healthcare professionals will gain from enrollment in this program, which we hope will be a more humanistic, positive, and approachable feel toward taking control of diabetes management."

For more information about D.A.I.L.Y. or to pre-enroll, visit, www.hormone.org/about-us/volunteer/diabetes-you. 



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For adults with type 2 diabetes
in addition to diet and exercise

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INDICATION AND LIMITATIONS OF USE

GLYXAMBI tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate.

GLYXAMBI is not recommended in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. GLYXAMBI has not been studied in patients with a history of pancreatitis, and it is unknown if using GLYXAMBI increases the risk of developing pancreatitis in these patients.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

GLYXAMBI is contraindicated in patients with severe renal impairment, end-stage renal disease, or dialysis, a history of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity, or a history of serious hypersensitivity reaction to empagliflozin.

WARNINGS AND PRECAUTIONS

Pancreatitis

There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking linagliptin, a component of GLYXAMBI. Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue GLYXAMBI and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using GLYXAMBI.

Hypotension

Empagliflozin, a component of GLYXAMBI, causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating GLYXAMBI, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy.

Impairment in Renal Function

Empagliflozin, a component of GLYXAMBI, increases serum creatinine and decreases eGFR. Renal function should be evaluated prior to initiating GLYXAMBI and periodically thereafter. More frequent monitoring is recommended with eGFR <60 mL/min/1.73 m².

The risk of impaired renal function with empagliflozin is increased in elderly patients and patients with moderate renal impairment. GLYXAMBI should be discontinued in patients with a persistent eGFR <45 mL/min/1.73 m².

Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues

Insulin and insulin secretagogues are known to cause hypoglycemia. The use of empagliflozin or linagliptin in combination with these agents was associated with a higher rate of hypoglycemia compared with placebo. A lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycemia when used in combination with GLYXAMBI.

Genital Mycotic Infections

Empagliflozin, a component of GLYXAMBI, increases the risk for genital mycotic infections. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop these infections. Monitor and treat as appropriate.

Urinary Tract Infections

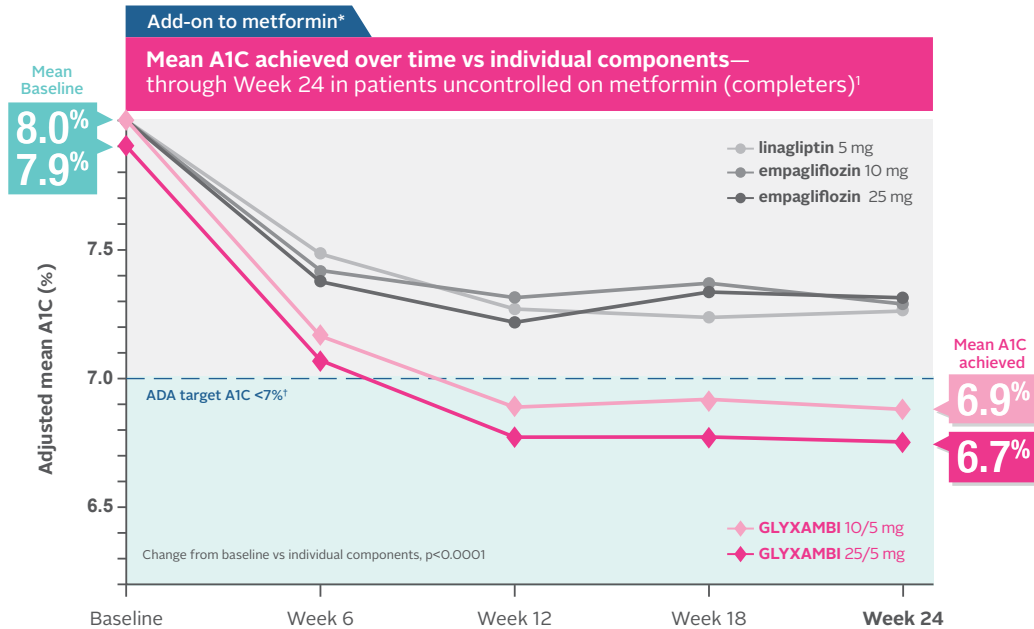
Empagliflozin, a component of GLYXAMBI, increases the risk for urinary tract infections. Monitor and treat as appropriate.

Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin, a component of GLYXAMBI. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue GLYXAMBI, assess for other potential causes for the event, and institute alternative treatment for diabetes.

For adults with type 2 diabetes

GLYXAMBI: Superior A1C reductions vs individual components



Individual component mean A1C achieved from the completer analysis: 7.3% for linagliptin 5 mg, 7.3% for empagliflozin 10 mg, 7.3% for empagliflozin 25 mg.¹

In the modified intent-to-treat analysis of the primary endpoint, the adjusted mean A1C change from baseline for GLYXAMBI 10/5 mg was -1.1% (n=135); GLYXAMBI 25/5 mg, -1.2% (n=133); linagliptin 5 mg, -0.7% (n=128); empagliflozin 10 mg, -0.7% (n=137); empagliflozin 25 mg, -0.6% (n=139). GLYXAMBI vs individual components, p<0.0001.

Study Design: A Phase 3, randomized, double-blind efficacy and safety study of fixed-dose combination GLYXAMBI administered orally vs the individual components of empagliflozin and linagliptin over 52 weeks in adult patients (N=686) with type 2 diabetes mellitus with insufficient glycemic control despite treatment with metformin ≥1500 mg alone. The primary endpoint was A1C change from baseline at 24 weeks. Achievement of A1C target <7.0%, FPG change from baseline, and weight change from baseline vs linagliptin at 24 weeks were key secondary endpoints.²

*1889 mg/day mean dose.¹

¹ADA recommends an A1C target of <7%. Individual goal of patients should be determined by their physician.

For the majority of commercial lives across the nation[§] GLYXAMBI is covered without prior authorization

*Terms & Conditions:

Eligible patients 18 years or older may pay as little as \$0/month with a maximum savings up to \$538/monthly prescription. Card valid for 12 consecutive months from activation date. Eligible patients may re-enroll for additional 12 consecutive-month periods by reactivating expired card; benefits not to exceed program expiration on March 1, 2018. If you live in Massachusetts, card expires on the earlier of June 30, 2017, or date AB-rated generic equivalent is available. One card per patient, not transferable, and cannot be combined with any other offer. Program not health insurance. Only valid for commercially insured patients in the 50 United States, DC, and Puerto Rico. **Not eligible if prescriptions are paid for in part/full by state or federally funded program(s),** like Medicare Part D, Medicaid, Vet. Aff., Dept. of Def., or TRICARE and where prohibited by law. Offer may change at any time, without notice.

[§]Source: Fingertip Formulary, health plan or state listed above, and/or data on file, Boehringer Ingelheim Pharmaceuticals, Inc. as of 05/15/2015.

IMPORTANT SAFETY INFORMATION (continued) WARNINGS AND PRECAUTIONS (continued)

Increased Low-Density Lipoprotein Cholesterol (LDL-C)

Increases in LDL-C can occur with empagliflozin, a component of GLYXAMBI. Monitor and treat as appropriate.

Macrovascular Outcomes

There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with GLYXAMBI or any other antidiabetic drug.

ADVERSE REACTIONS

The most common adverse reactions (≥5%) associated with GLYXAMBI (10/5 mg, 25/5 mg) were urinary tract infections (12.5% and 11.4%, respectively), nasopharyngitis (5.9%, 6.6% respectively), and upper respiratory tract infections (7.0% in both doses).

DRUG INTERACTIONS

Coadministration of empagliflozin, a component of GLYXAMBI, with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.

The efficacy of linagliptin, a component of GLYXAMBI, may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. Therefore, use of alternative treatments to GLYXAMBI is strongly recommended.

USE IN SPECIAL POPULATIONS

Pregnancy

There are no adequate and well-controlled studies of GLYXAMBI or its individual components in pregnant women. GLYXAMBI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known if GLYXAMBI or its individual components is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, discontinue nursing or discontinue GLYXAMBI.

Geriatric Use

Empagliflozin, a component of GLYXAMBI, is expected to have diminished efficacy in elderly patients with renal impairment. The incidence of volume depletion-related adverse reactions and urinary tract infections increased in patients ≥ 75 years treated with empagliflozin.

GLX PROF ISI 1.31.15

References: 1. Data on file. Boehringer Ingelheim Pharmaceuticals, Inc. 2013.

2. DeFronzo RA, Lewin A, Patel S, et al. Combination of empagliflozin and linagliptin as second-line therapy in subjects with type 2 diabetes inadequately controlled on metformin. *Diabetes Care*. 2015;38(3):384-393.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on adjacent pages.



GLYXAMBI® (empagliflozin and linagliptin) tablets, for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

Please see package insert for full Prescribing Information.

INDICATIONS AND USAGE: GLYXAMBI tablets are indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when treatment with both empagliflozin and linagliptin is appropriate. **Limitations of Use:** GLYXAMBI is not recommended for patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. GLYXAMBI has not been studied in patients with a history of pancreatitis. It is unknown whether patients with a history of pancreatitis are at an increased risk for the development of pancreatitis while using GLYXAMBI [see Warnings and Precautions].

CONTRAINDICATIONS: GLYXAMBI is contraindicated in patients with: Severe renal impairment, end-stage renal disease, or dialysis [see Use in Specific Populations]; a history of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity [see Warnings and Precautions and Adverse Reactions]; history of serious hypersensitivity reaction to empagliflozin.

WARNINGS AND PRECAUTIONS: Pancreatitis: There have been postmarketing reports of acute pancreatitis, including fatal pancreatitis, in patients taking linagliptin. Take careful notice of potential signs and symptoms of pancreatitis. If pancreatitis is suspected, promptly discontinue GLYXAMBI and initiate appropriate management. It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using GLYXAMBI. **Hypotension:** Empagliflozin causes intravascular volume contraction. Symptomatic hypotension may occur after initiating empagliflozin [see Adverse Reactions] particularly in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics. Before initiating GLYXAMBI, assess for volume contraction and correct volume status if indicated. Monitor for signs and symptoms of hypotension after initiating therapy and increase monitoring in clinical situations where volume contraction is expected [see Use in Specific Populations]. **Impairment in Renal Function:** Empagliflozin increases serum creatinine and decreases eGFR. The risk of impaired renal function with empagliflozin is increased in elderly patients and patients with moderate renal impairment. More frequent monitoring of renal function is recommended in these patients [see Use in Specific Populations]. Renal function should be evaluated prior to initiating GLYXAMBI and periodically thereafter. **Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues:** Insulin and insulin secretagogues are known to cause hypoglycemia. The use of empagliflozin or linagliptin in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin was associated with a higher rate of hypoglycemia compared with placebo in a clinical trial. Therefore, a lower dose of the insulin secretagogue or insulin may be required to reduce the risk of hypoglycemia when used in combination with GLYXAMBI. **Genital Mycotic Infections:** Empagliflozin increases the risk for genital mycotic infections [see Adverse Reactions]. Patients with a history of chronic or recurrent genital mycotic infections were more likely to develop mycotic genital infections. Monitor and treat as appropriate. **Urinary Tract Infections:** Empagliflozin increases the risk for urinary tract infections [see Adverse Reactions]. Monitor and treat as appropriate. **Hypersensitivity Reactions:** There have been postmarketing reports of serious hypersensitivity reactions in patients treated with linagliptin (one of the components of GLYXAMBI). These reactions include anaphylaxis, angioedema, and exfoliative skin conditions. Onset of these reactions occurred within the first 3 months after initiation of treatment with linagliptin, with some reports occurring after the first dose. If a serious hypersensitivity reaction is suspected, discontinue GLYXAMBI, assess for other potential causes for the event, and institute alternative treatment for diabetes. Angioedema has also been reported with other dipeptidyl peptidase-4 (DPP-4) inhibitors. Use caution in a patient with a history of angioedema to another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with GLYXAMBI. **Increased Low-Density Lipoprotein Cholesterol (LDL-C):** Increases in LDL-C can occur with empagliflozin [see Adverse Reactions]. Monitor and treat as appropriate. **Macrovascular Outcomes:** There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with GLYXAMBI or any other antidiabetic drug.

ADVERSE REACTIONS: Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. **GLYXAMBI:** The safety of concomitantly administered empagliflozin (daily dose 10 mg or 25 mg) and linagliptin (daily dose 5 mg) has been evaluated in a total of 1363 patients with type 2 diabetes treated for up to 52 weeks in active-controlled clinical trials. The most common adverse reactions with concomitant administration of empagliflozin and linagliptin based on a pooled analyses of these studies are shown in Table 1.

Table 1 Adverse Reactions Reported in ≥5% of Patients Treated with GLYXAMBI

	GLYXAMBI 10 mg/5 mg (n=272)	GLYXAMBI 25 mg/5 mg (n=273)
	n (%)	n (%)
Urinary tract infection*	34 (12.5)	31 (11.4)
Nasopharyngitis	16 (5.9)	18 (6.6)
Upper respiratory tract infection	19 (7.0)	19 (7.0)

*Predefined adverse event grouping, including, but not limited to, urinary tract infection, asymptomatic bacteriuria, cystitis

Empagliflozin: Adverse reactions that occurred in ≥2% of patients receiving empagliflozin and more commonly than in patients given placebo included (10 mg, 25 mg, and placebo): urinary tract infection (9.3%, 7.6%, and 7.6%), female genital mycotic infections (5.4%, 6.4%, and 1.5%), upper respiratory tract infection (3.1%, 4.0%, and 3.8%), increased urination (3.4%, 3.2%, and 1.0%), dyslipidemia (3.9%, 2.9%, and 3.4%), arthralgia (2.4%, 2.3%, and 2.2%), male genital mycotic infections (3.1%, 1.6%, and 0.4%), and nausea (2.3%, 1.1%, and 1.4%). Empagliflozin causes an osmotic diuresis, which may lead to intravascular volume contraction and adverse reactions related to volume depletion. **Linagliptin:** Adverse reactions reported in ≥2% of patients treated with linagliptin 5 mg and more commonly than in patients treated with placebo included: nasopharyngitis (7.0% and 6.1%), diarrhea (3.3% and 3.0%), and cough (2.1% and 1.4%). Other adverse reactions reported in clinical studies with treatment of linagliptin monotherapy were hypersensitivity (e.g., urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity) and myalgia. In the clinical trial program, pancreatitis was reported in 15.2 cases per 10,000 patient year exposure while being treated with linagliptin compared with 3.7 cases per 10,000 patient year exposure while being treated with comparator (placebo and active comparator, sulfonylurea). Three additional cases of pancreatitis were reported following the last administered dose of linagliptin. **Hypoglycemia:** Table 2 summarizes the reports of hypoglycemia with empagliflozin and linagliptin over a treatment period of 52 weeks.

Table 2 Incidence of Overall^a and Severe^b Hypoglycemic Adverse Reactions

Add-on to Metformin (52 weeks)	GLYXAMBI 10 mg/5 mg (n=136)	GLYXAMBI 25 mg/5 mg (n=137)
Overall (%)	2.2%	3.6%
Severe (%)	0%	0%

^aOverall hypoglycemic events: plasma or capillary glucose of less than or equal to 70 mg/dL or requiring assistance

^bSevere hypoglycemic events: requiring assistance regardless of blood glucose

Laboratory Tests: GLYXAMBI: Changes in laboratory findings in patients treated with the combination of empagliflozin and linagliptin included increases in cholesterol and hematocrit compared to baseline. **Empagliflozin:** Increase in Low-Density Lipoprotein Cholesterol (LDL-C): Dose-related increases in low-density lipoprotein cholesterol (LDL-C) were observed in patients treated with empagliflozin. LDL-C increased by 2.3%, 4.6%, and 6.5% in patients treated with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively [see Warnings and Precautions]. The range of mean baseline LDL-C levels was 90.3 to 90.6 mg/dL across treatment groups. Increase in Hematocrit: Median hematocrit decreased by 1.3% in placebo and increased by 2.8% in empagliflozin 10 mg and 2.8% in empagliflozin 25 mg treated patients. At the end of treatment, 0.6%, 2.7%, and 3.5% of patients with hematocrits initially within the reference range had values above the upper limit of the reference range with placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively. **Linagliptin:** Changes in laboratory values that occurred more frequently in the linagliptin group and ≥1% more than in the placebo group were increases in uric acid (1.3% in the placebo group, 2.7% in the linagliptin group). **Postmarketing Experience:** Additional adverse reactions have been identified during postapproval use of linagliptin. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Acute pancreatitis, including fatal pancreatitis [see Indications and Usage and Warnings and Precautions]; Hypersensitivity reactions including anaphylaxis, angioedema, and exfoliative skin conditions [see Warnings and Precautions]; Rash.

DRUG INTERACTIONS: Drug Interactions with Empagliflozin: **Diuretics:** Coadministration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion [see Warnings and Precautions]. **Insulin or Insulin Secretagogues:** Coadministration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia [see Warnings and Precautions]. **Positive Urine Glucose Test:** Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control. **Interference with 1,5-anhydroglucitol (1,5-AG)**

Assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control. **Drug Interactions with Linagliptin:** Inducers of P-glycoprotein or CYP3A4 Enzymes: Rifampin decreased linagliptin exposure, suggesting that the efficacy of linagliptin may be reduced when administered in combination with a strong P-gp or CYP3A4 inducer. Therefore, use of alternative treatments is strongly recommended when linagliptin is to be administered with a strong P-gp or CYP3A4 inducer.

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category C: GLYXAMBI: There are no adequate and well-controlled studies in pregnant women with GLYXAMBI or its individual components. GLYXAMBI should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Animal Data: Empagliflozin:** Based on results from animal studies, empagliflozin may affect renal development and maturation. In studies conducted in rats, empagliflozin crosses the placenta and reaches fetal tissues. During pregnancy, consider appropriate alternative therapies, especially during the second and third trimesters. **Linagliptin:** Linagliptin crosses the placenta into the fetus following oral dosing in pregnant rats and rabbits. **Nursing Mothers:** It is not known whether empagliflozin and linagliptin are excreted in human milk. No studies in lactating animals have been conducted with the combined components of GLYXAMBI. Available animal data have shown excretion of empagliflozin and linagliptin in milk. Empagliflozin is secreted in the milk of lactating rats reaching levels up to 5 times higher than that in maternal plasma. Since human kidney maturation occurs *in utero* and during the first 2 years of life when lactational exposure may occur, there may be risk to the developing human kidney. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from empagliflozin, a decision should be made whether to discontinue nursing or to discontinue GLYXAMBI, taking into account the importance of the drug to the mother. **Pediatric Use:** Safety and effectiveness of GLYXAMBI in pediatric patients under 18 years of age have not been established. **Geriatric Use: Empagliflozin:** Empagliflozin is associated with osmotic diuresis, which could affect hydration status of patients age 75 years and older. No empagliflozin dosage change is recommended based on age. A total of 2721 (32%) patients treated with empagliflozin were 65 years of age and older, and 491 (6%) were 75 years of age and older. Empagliflozin is expected to have diminished efficacy in elderly patients with renal impairment [see Use in Specific Populations]. The risk of volume depletion-related adverse reactions increased in patients who were 75 years of age and older to 2.1%, 2.3%, and 4.4% for placebo, empagliflozin 10 mg, and empagliflozin 25 mg. The risk of urinary tract infections increased in patients who were 75 years of age and older to 10.5%, 15.7%, and 15.1% in patients randomized to placebo, empagliflozin 10 mg, and empagliflozin 25 mg, respectively [see Warnings and Precautions and Adverse Reactions]. **Linagliptin:** There were 4040 type 2 diabetes patients treated with linagliptin 5 mg from 15 clinical trials of linagliptin; 1085 (27%) were 65 years and over, while 131 (3%) were 75 years and over. Of these patients, 2566 were enrolled in 12 double-blind placebo-controlled studies; 591 (23%) were 65 years and over, while 82 (3%) were 75 years and over. No overall differences in safety or effectiveness were observed between patients 65 years and over and younger patients. Therefore, no dose adjustment is recommended in the elderly population. While clinical studies of linagliptin have not identified differences in response between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out. **Renal Impairment: Empagliflozin:** The efficacy and safety of empagliflozin have not been established in patients with severe renal impairment, with ESRD, or receiving dialysis. Empagliflozin is not expected to be effective in these patient populations [see Contraindications and Warnings and Precautions]. The glucose lowering benefit of empagliflozin 25 mg decreased in patients with worsening renal function. The risks of renal impairment [see Warnings and Precautions], volume depletion adverse reactions and urinary tract infection-related adverse reactions increased with worsening renal function. **Hepatic Impairment:** GLYXAMBI may be used in patients with hepatic impairment.

OVERDOSAGE: In the event of an overdose with GLYXAMBI, contact the Poison Control Center. Employ the usual supportive measures (e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive treatment) as dictated by the patient's clinical status. Removal of empagliflozin by hemodialysis has not been studied, and removal of linagliptin by hemodialysis or peritoneal dialysis is unlikely.

Additional information can be found at www.hcp.glyxambi.com.

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GLX/BS/5-15

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What You Should Know About

SHARED DECISION MAKING (SDM)

Shared Decision Making gets patients involved in their healthcare treatment plan. SDM takes into account the best scientific evidence and the values and preferences of the patient to provide the most effective therapy possible. For better patient outcomes, consider implementing an SDM plan in your practice.



WHY SDM?

- Improve patient satisfaction and involvement with their care
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PAMPHLETS, VIDEOS, AND WEB

WHAT DO PATIENTS THINK?

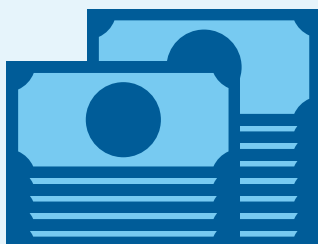
- Strong desire to engage in SDM about treatment options
- Multiple barriers inhibit conversation with physicians about health decisions
- Feel compelled to confirm to socially sanctioned roles and defer to physicians
- Physicians can be authoritarian
- Fear of being categorized “difficult” prevents patients from participating more fully in their own health care

(Frosch, et al. Health Affairs, 2012)

IMPACT ON COSTS

- Lewin Group estimated
SDM for 11 procedures saved

\$9 BILLION
nationally over 10 years



- Group Health used SDM for
hip or knee replacement: 38%
fewer knee and 26% fewer hip
surgeries, **COST LOWERED BY**

12–21% OVER 6 MONTHS.

SHARED DECISION MAKING STAGES

- 1 Establish ongoing partnership (trust, mutual respect)
- 2 Foster two-way information exchange between the physician and the patient
- 3 Support a process of deliberation; patients encouraged to express preferences
- 4 Make a decision that honors provider's expert knowledge and respects patient's individual needs

*Visit hormone.org today to access aides to empower and educate your patients.

Shared Decision Making tools specific to diabetes can be accessed at accurateinsulin.org.

The Hormone Health Network is the nation's endocrine patient education resource. We are committed to helping patients have more informed discussions with their health care providers about hormone health, disease, and treatment. All of our educational resources are free and based on the clinical and scientific expertise of the Endocrine Society.



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*Data on file. Based on TRx data sourced from IMS NPA Database, weekly data through 6/1/15.

Reference: 1. Data on file. Janssen Pharmaceuticals, Inc., Titusville, NJ.

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