

NOVEMBER 2013

THE LEADING MAGAZINE FOR ENDOCRINOLOGISTS

# ENDOCRINE **news**

## Forever YOUNG

Has Testosterone  
Replacement Therapy  
Become the Well-Sought  
**FOUNTAIN OF YOUTH?**

**SWEET TOOTH**  
A Closer look  
at Fructose

**UP IN THE AIR**  
Patient Data  
in the Cloud?

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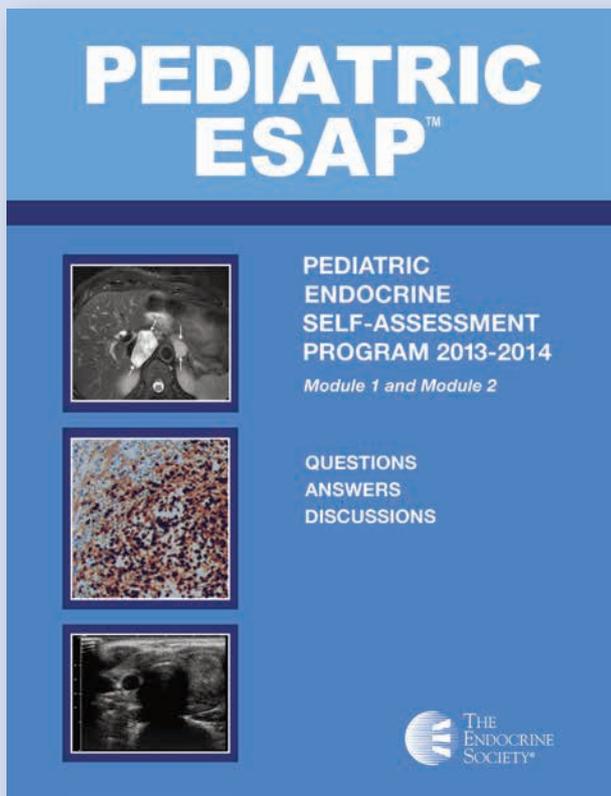
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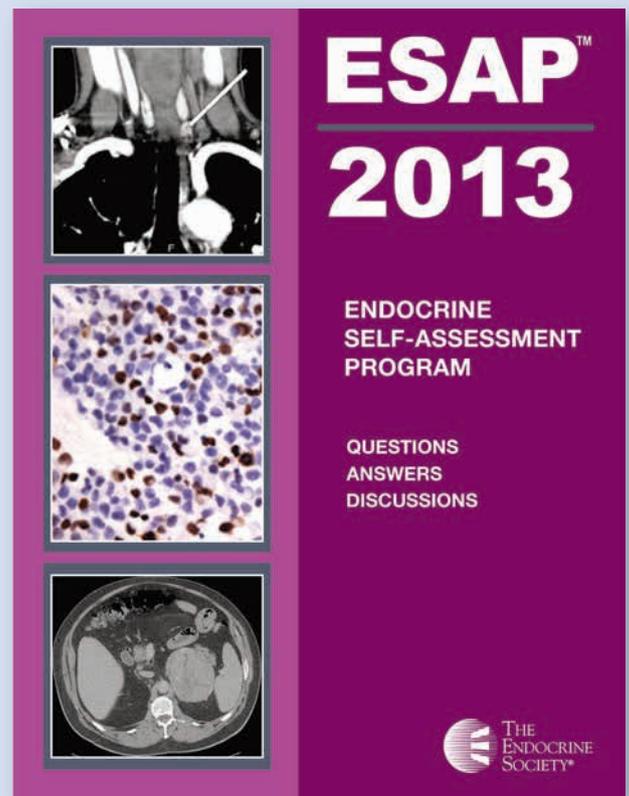


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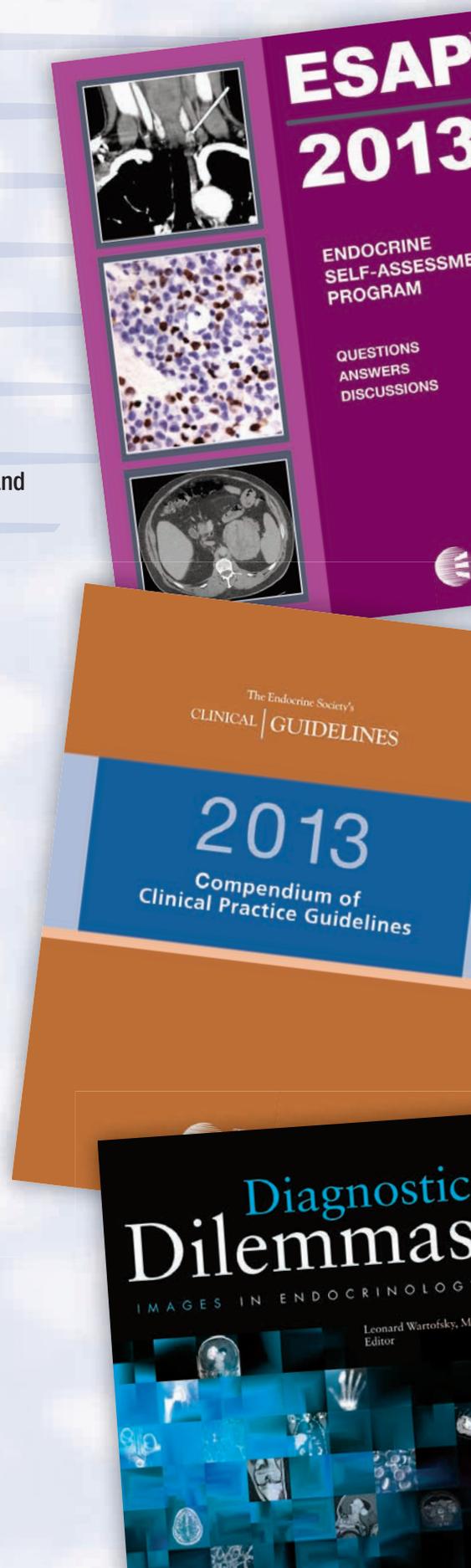
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## Countdown to ICE/ENDO 2014 in Chicago Begins

The world of endocrinology is converging at ICE/ENDO 2014, the 16th International Congress of Endocrinology held jointly with The Endocrine Society's 96th Annual Meeting and Expo.



Teresa K. Woodruff, PhD,  
President  
The Endocrine Society

As president of The Endocrine Society it has been my honor to work with the Annual Meeting Steering Committee (AMSC), including the eight members of the Program Organizing Committee from the International Society of Endocrinology, to plan this exciting meeting. Under the excellent leadership of its chairs, Derek Leroith, Kevin Grove, Matthew Ringel, and our first clinician-in-practice chair, Carol Wysham, the AMSC has created a scientific program that showcases the most cutting-edge

research and clinical practices and features international perspectives on the practice of endocrinology.

Attendees will find much to choose from with more than 80 symposia, 70 Meet-the-Professor sessions, and numerous special clinical, basic, and educational sessions. The excellent scientific program and opportunities to meet attendees from around the world will make ICE/ENDO 2014 a meeting not to be missed.

### A few highlights of this year's meeting include:

- **Diabetes Diagnosis & Management (DDM)** The Friday before ENDO officially begins, the Society offers this full-day program in recognition of the worldwide epidemic of diabetes. DDM provides an in-depth discussion of current practice challenges and a state-of-the-art update for all who treat diabetes.
- **Early Career Forum** Also on Friday, this full-day program (formerly Endocrine Trainee Day) offers opportunities for fellows and students to interact with their peers and be inspired by recognized leaders from our endocrine community.
- **The oral sessions and the poster presentations** are the heart of our annual meeting. Abstracts are due Jan. 29, 2014, so talk with your team to be ready for submission!
- **Featured Poster Presentations** Returning for

the second year, presenters with the highest-scoring poster abstracts will each have just three minutes to review three slides highlighting the significance of their research. These sessions will take place immediately before oral sessions, on the same day as the posters are presented.

- **Endocrine Year In ...** These sessions will recap the most important advances of the year in the areas of type 1 diabetes, pituitary disease, reproduction, germ cells, and stem cells.
- **Master Clinicians Sessions ICE/ENDO 2014** will feature two of these highly popular sessions, in which experienced clinical endocrinologists present their most challenging cases to endocrine experts. This year's sessions cover lipid disorders and thyroid cancer. Come and enjoy these lively and informative exchanges.

The Expo is the hub of activity during the meeting and home to exhibits, posters, cafes, and places to lounge and network with your colleagues. Start each morning with a complimentary cup of coffee, and grab lunch at the Expo while you peruse the posters and exhibits.

Don't forget to sign a team up for the fifth annual ENDO Trivia Cup Challenge, moderated by Brad Anawalt and Jon Levine. This event is entertaining and lighthearted, and will test your endocrine knowledge!

Chicago, my hometown, is a vibrant city and a world-class travel destination. I look forward to welcoming you here for an outstanding ICE/ENDO!

Please share your comments, questions, and ideas by writing to me via [president@endo-society.org](mailto:president@endo-society.org) EN

Teresa K. Woodruff, PhD  
President, The Endocrine Society

NOVEMBER 2013  
**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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This month's cover story features the controversial topic of testosterone therapy and how it has been perceived by some — both inside and outside the medical community — as a new path to the legendary “fountain of youth.” In “Testosterone Replacement Therapy ... Is It the New Fountain of Youth?” (page 14), Glenda Fauntleroy uncovers some surprising statistics regarding this treatment, which has seen its numbers triple in the last decade or so. According to the story, at least one in four men prescribed this therapy never even had their testosterone levels tested. Further controversy surrounds the risks versus the benefits, especially in older men.



Mark A. Newman,  
Managing Editor  
Endocrine News

Regular *Endocrine News* contributor Terri D'Arrigo looks at another hot button issue in both the medical and lay media — the debate over the sweetener that's seemingly everywhere: fructose. “The Frenzy Over Fructose” (page 34) delves into the cupboard and reveals how studies have shown that when the liver is overloaded with highly processed fructose, the risk for diabetes and cardiovascular disease is increased. As the prevalence of diabetes continues its climb, this is an issue that will not be resolved any time soon.

For many practicing physicians, the room full of filing cabinets stuffed to overflowing with patient records is — or soon will be — a thing of the past, as electronic health records are becoming the norm. Rather than keep these records on an on-site hard drive, many are opting to send this data to “the cloud,” a remote information bank. While this makes storage and transmission of data easier than ever imagined, as Melissa Mapes writes in “Partly Cloudy” (page 30), some users are wary of this new system, despite assurances from experts on its reliability.

Speaking of data entry, those physicians participating in the Physician Quality Reporting System — mandated as part of the 2006 Tax Relief and Healthcare Act — have until the end of the year to be registered or face penalties when it comes to getting Medicare payments. Kurt Ullman shows us the ins and outs of this new round of paperwork in “PQRS Moves From Carrot to Stick” on page 32.

If you have any story ideas or topics you'd like to see featured in *Endocrine News*, feel free to reach out to me at [mnewman@endocrine.org](mailto:mnewman@endocrine.org). EN

Mark A. Newman  
Managing Editor, Endocrine News

By Derek Bagley

## EFFECT OF CARBONATION ON BRAIN PROCESSING of Sweet Stimuli in Humans

Carbonation has been shown to change the mind's perception of sweetness, eventually making it difficult for the brain to tell the difference between sugar and artificial sweeteners, according to an article recently published in the journal *Gastroenterology*.

The paper's lead author, Rosario Cuomo, MD, of the University of Naples, says that this "study proves that the right combination of carbonation and

artificial sweeteners can leave the sweet taste of diet drinks indistinguishable from normal drinks."

Of course, carbonated beverages have been linked to myriad health problems, from obesity and diabetes to cardiovascular disease, and have been particularly related to an increased calorie intake. The authors wrote that taste "is the main sensory modality influencing food preferences and dietary behavior and affecting body weight, risk of chronic disease, and health." They used functional magnetic resonance imaging to view the effects of carbonation on the brain when it processes

sweet stimuli.

What they found was that the carbonation in soft drinks "tricks" the brain into thinking the body is receiving sweets and, therefore, rewarding the pleasure center. The mechanism could promote the consumption of carbonated drinks with low calorie content.

The study concludes, "CO<sub>2</sub> modulates the perception of sweetness, reducing the global neural processing of sweetness, the processing of sucrose more than of As-Ac, and the processing difference between sweetening agents. This piece of information is of utmost importance for designing carbonated beverages and is relevant to the regulation of caloric intake."



## GLUCOCORTICOIDS Shown to Affect Adiposity

A paper recently published in the journal *Molecular Endocrinology* has demonstrated the essential role of glucocorticoid receptor (GR)-mediated negative feedback regulation in the paraventricular nucleus (PVN) of the hypothalamus, which cannot be compensated for by intact GR function in the pituitary or extra-hypothalamic areas.

While chronic exposure to elevated glucocorticoids is often associated with anxiety and despair-related behavioral changes, elevation resulting from disrupted PVN GR does not. This may reflect adaptive mechanisms in other brain regions that attenuate GR activation, or that the normal circadian rhythm that is maintained in these animals allows compensation to occur, or that loss of GR in the PVN is protective for the high circulating glucocorticoid levels.

The researchers, led by Louis J. Muglia, MD, PhD, at Cincinnati Children's Hospital Medical Center, showed the substantial differences in phenotypes that can emerge with conditional deletion of different floxed versions of the same gene. This can be due to deletion efficiency or structural/functional characteristics of the recombined locus.

The authors concluded that excess glucocorticoids affect adiposity to different degrees in males and females, suggesting an important interaction of glucocorticoids and sex steroids on metabolism/adipocyte physiology.

## NEW DRUG TARGET Could Prevent Diabetes and Obesity

New research from Cleveland Clinic's Lerner Research Institute showed that blocking the function of a protein called ABHD6 in animal models protects against all diseases driven by eating a high-fat diet, including obesity, diabetes, and liver disease. This protein is thought to regulate the brain's endocannabinoid system, which is involved in a variety of processes, including metabolism, craving, and hunger.

These studies suggested a new biological pathway for preventing high-fat-diet-induced obesity, according to Cleveland Clinic research published today in the journal *Cell Reports*.

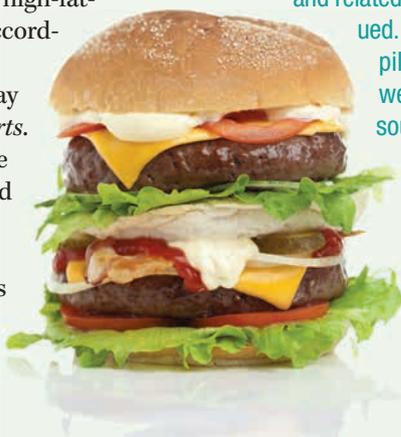
The researchers wrote that they used combined in vivo lipidomic identification and in vitro enzymology approaches to show that ABHD6 can hydrolyze several

lipid substrates, "positioning ABHD6 at the interface of glycerophospholipid metabolism and lipid signal transduction."

"Obesity and diabetes are major threats to global public health and economic vitality, and an urgent need exists for new treatments to offset the health problems associated with these conditions," lead author J. Mark Brown, PhD, said in a Clinic news release.

"We have identified ABHD6 as a new potential drug target for the battle against obesity and related disorders," Brown continued.

"The search for a 'magic pill' to prevent excessive weight gain has long been sought after. These new findings suggest that drugs inhibiting ABHD6 may simultaneously activate fat burning, increase physical activity, and block the formation of new fat in the liver."



## New Therapeutic Potential for **ENDOMETRIAL CANCER**

A study recently published in the journal *Endocrinology* detailed a novel approach to treating endometrial cancer.

The authors wrote that in many human cancers, the tumor suppressor, p27<sup>kip1</sup> (p27), a cyclin-dependent kinase inhibitor critical to cell cycle arrest, undergoes perpetual ubiquitin-mediated proteasomal degradation by the E3 ligase complex SCF-Skp2/Cks1 and/or cytoplasmic mislocalization; lack of nuclear p27 causes aberrant cell cycle progression and cytoplasmic p27 mediates cell migration/metastasis.

Endometrial cancer is the most common cancer of the reproductive organs for women in the U.S., with almost 50,000 new cases diagnosed every year. Risk factors include age, total

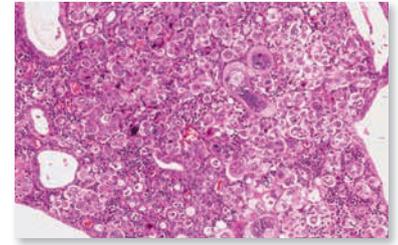
number of menstrual cycles, skin color (white women develop this cancer more often, but black women are more likely to die from it), obesity, and diabetes.

The scientists, led by Leslie I. Gold, PhD, at New York University, injected two-month-old female ovariectomized mice with mitogenic estrogen (E2), a hormone that they had previously shown induces degradation of p27 by the E3 ligase SCFSkp2/Cks1 in primary endometrial epithelial cells (EECs) and endometrial carcinoma (ECA) cell lines, suggesting a pathogenic mechanism for type I ECA, an E2-induced cancer. Treatment of endometrial carcinoma cells-1 (ECC-1) cells with small molecule inhibitors of Skp2/Cks1 E3 ligase activity (Skp2E3LIs;

Timothy Cardozo) stabilizes p27 in the nucleus, decreases p27 in the cytoplasm, and prevents E2-induced proliferation and degradation of p27 in ECC-1 cells and primary ECA cells.

The estrogen-primed mice injected with Skp2E3LIs (Bo Rueda) showed significant increases in nuclear p27 and reduced proliferation of EECs by 42% – 62%. Skp2E3LIs are specific inhibitors of proteolytic degradation that pharmacologically target the binding interaction between the E3 ligase, SCF-Skp2/Cks1, and p27 to stabilize nuclear p27 and prevent cell cycle progression. These targeted inhibitors have the potential to be an important therapeutic advance over general proteasome

inhibitors for cancers characterized by SCF-Skp2/Cks1-mediated destruction of nuclear p27.



The researchers concluded, “These inhibitors might, therefore, be effective in E2-induced endometrial carcinoma in which p27 is both, degraded in the nucleus and/or sequestered in the cytoplasm. Furthermore, their effects should be applicable to other human cancers having similar pathology of low levels of p27 and high levels of Skp2/Cks1 in the nucleus and/or, high cytoplasmic p27.”

## **LOW TESTOSTERONE** May Lead to Heart Problems

Men with low testosterone may have to worry about more than loss of body hair and muscle bulk, decreased sex drive, and depression. A review of literature recently published in the *Journal of Clinical Endocrinology and Metabolism* showed that low levels of the important male sex hormone may be linked to cardiovascular problems as well.

These findings come at a time when more and more men are being prescribed testosterone replacement therapy, even though some experts disagree on the therapy’s efficacy. The reviewers, led by Johannes Ruige, MD, PhD, of Ghent University Hospital in Belgium, says that in their research, they were able to make a “modest connection” between testosterone and cardiovascular disease, based on a “growing body of evidence.”

The researchers reviewed studies on testosterone and cardiovascular disease published between 1970 and

2013, and found studies on low T and increased blood pressure, dyslipidemia, atherosclerosis, arrhythmia, thrombosis, endothelial dysfunction, and impaired left ventricular function.

“A specific pathogenesis did not come forward,” Ruige said in an Endocrine Society press release, “but perhaps less frequently investigated events may play a role, such as thrombosis where a blood clot develops in the circulatory system or arrhythmia, where there is a problem with the heart beat or rate. Based on current findings, though, we cannot rule out that low testosterone and heart disease both result from poor overall health.”

However, the

authors noted, testosterone therapy has not been proven to either specifically benefit or harm cardiovascular health. “The cardiovascular risk-benefit profile of T therapy remains largely evasive in view of a lack of well-designed and adequately powered randomized clinical trials,” they wrote.

The reviewers concluded that even though treatment with T to restore T concentrations to this optimal window have not been proven to be beneficial with respect to cardiovascular disease, males with low T and specific cardiovascular conditions such as heart failure or coronary artery disease may benefit from substitution therapy. However, a cautious, restrained approach to T therapy in aging men is advisable, pending clarification of benefits.



## BARIATRIC SURGERY Shows Promise in “Curing” T2D in Obese Patients

Patients with type 2 diabetes mellitus (T2DM) who underwent bariatric surgery showed positive outcomes in controlling T2DM, with a significant amount achieving long-term remission, according to a study recently published in the journal *Annals of Surgery*.

Scientists, led by Stacy Brethauer, MD, at the Cleveland Clinic, evaluated clinical outcomes of 217 patients with T2DM who had bariatric surgery between 2004 — 2007 and then had at least a five-year follow up. Of those participants, 162 had Roux-en-Y gastric bypass surgery, 32 had gastric banding, and 23 had sleeve gastrectomy. The researchers observed that 24% of total patients achieved long-term remission of T2DM, while 26% achieved partial remission — no longer “diabetic,” but they retained blood glucose levels higher than normal. A little more than a third of all

participants showed some improvement in A1C from baseline, while 16% showed no change.

Brethauer said in a clinic news release that 80% of the diabetic patients still control their blood glucose levels (A1c < 7%) five years after surgery, while nearly 30% of the gastric bypass patients had normal blood glucose levels for five years after surgery without taking medications. “This study confirms that the procedure can offer durable remission of diabetes in some patients and should be considered as an earlier treatment option for patients with uncontrolled diabetes,” he added.

The study defined complete remission as, “A1C less than 6% and fasting blood glucose (FBG) less than 100 mg/dL off diabetic medications.” They noted that a shorter duration of T2DM before surgery and keeping the weight off after bariatric surgery “predicted



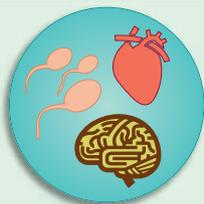
long-term remission.” Conversely, patients who had T2DM for a longer duration and had gained weight again after the surgery experienced a recurrence of T2DM after initial remission (about 19% of participants).

The authors concluded, “Bariatric surgery can induce a significant and sustainable remission and improvement of T2DM and other metabolic risk factors in severely obese patients. Surgical intervention within five years of diagnosis is associated with a high rate of long-term remission.”

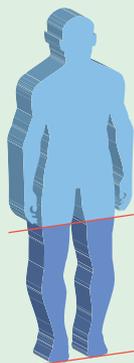
## Fast FACTS About Testosterone



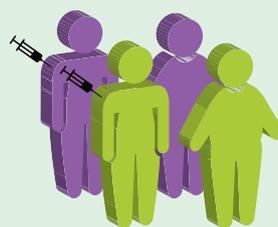
Men with the lowest levels of testosterone have been shown to be up to 560% more generous than men with the highest levels of testosterone.



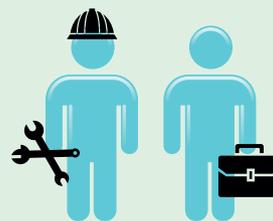
Too little testosterone can be a bad thing, but too much can have unwanted effects as well. Excess testosterone can shrink testicles and lead to infertility, cause cardiovascular problems, and may kill brain cells.



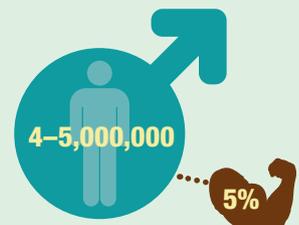
Low testosterone affects about 40% of men over 45.



40% Around 50% of men with diabetes and half of obese men have low testosterone.



Testosterone levels have been shown to influence career choices.



Low testosterone affects roughly 4 – 5 million men, but only about 5% of those receive testosterone replacement therapy.



70% The most common form of therapy for low testosterone is the gel, taken by about 70% of patients.



Men with type 2 diabetes are twice as likely to have low testosterone as men without diabetes.

# INTERESTED IN INVESTIGATOR-SPONSORED RESEARCH

**TO BE A LEADER** in worldwide operations and scientific excellence, the Collaborative Science Center of Excellence of Bristol-Myers Squibb (BMS) continuously looks for new and innovative approaches to facilitate the ongoing development of research with the objective of helping to address the unmet needs of patients with serious diseases.

Bristol-Myers Squibb has updated its process for receiving Web applications for Investigator-Sponsored Research (ISR) to expedite the review process and to provide increased transparency in specific areas of ongoing research interest to BMS. Specific time periods for submissions are now offered. Bristol-Myers Squibb will have two open cycles—the first commencing in April and the second commencing in October. Each cycle will be open for approximately 12 weeks. BMS anticipates receiving and reviewing the majority of ISR applications during these two cycles.

The submissions for non-interventional research, non-clinical research, and from cooperative groups and networks are received and reviewed on an ongoing basis. Submissions for the fellows research program will have one open cycle, commencing in December.

BMS evaluates all requests received and gives priority to proposals that support its mission related to research in the following therapeutic areas: cardiovascular, metabolics, neuroscience, oncology, immunology, and virology.



*For more information, please visit [www.bms.com/israpplications](http://www.bms.com/israpplications).*



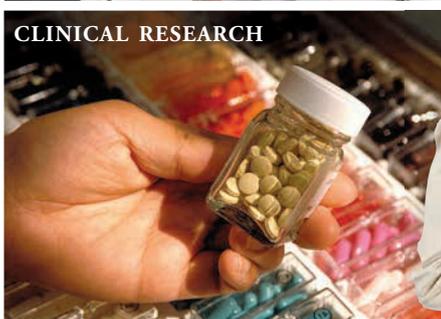
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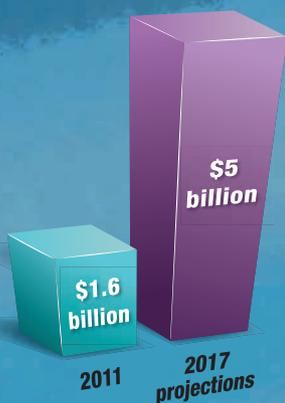


**CLINICAL RESEARCH**

**COOPERATIVE GROUPS AND NETWORKS**



# Testosterone Replacement Therapy



Annual spending on prescription testosterone.  
Source: Bloomberg

## AT-A-GLANCE

- The number of men using testosterone replacement therapy has tripled over the past 10 years.
- A recent study found that 25% of the men prescribed the drug never had their testosterone levels measured.
- Controversy remains over the benefits vs. risks, particularly in older men.

# ... is it the new FOUNTAIN OF YOUTH?

By Glenda Fautleroy

**D**rug commercials promise men with low testosterone relief from decreased sex drive, loss of energy, and moodiness. It appears the message has hit home as use of testosterone replacement therapy has skyrocketed over the last 10 years.

The number of men over age 40 prescribed treatment for “low T” has tripled since 2001, according to a study published this June in *JAMA Internal Medicine* that tracked prescriptions of more than 10 million men from one of the nation’s largest health insurers. Use of testosterone therapy has increased from 0.81% of men in 2001 to 2.9% in 2011.

The increase in prescriptions was seen in men of all age groups. And of the four forms examined — topical gel, skin patch, oral forms, and injectables — the use of testosterone gel had the highest boost in prescriptions with more than a five-fold jump.

“We believe this trend has been driven, in large part, by direct-to-consumer marketing campaigns targeting middle-aged men, the rapid expansion of clinics specializing in the treatment of low testosterone, and the development of new drugs and improved delivery mechanisms, particularly transdermal gels,” explains Jacques Baillargeon, PhD, of the University of Texas Medical Branch at Galveston, who was the study’s lead author.

Martin Miner, MD, clinical associate professor of Family



Men who used testosterone therapy over the last decade.  
Source: “Trends in Androgen Prescribing in the U.S., 2001 to 2011”,  
*JAMA Internal Medicine*

Medicine and Urology at the Warren Alpert School of Medicine at Brown University, agrees there has been a huge spike in testosterone use but adds that one issue highly resonant with clinicians who prescribe the therapy is that today’s baby boomers want to remain more active as they age.

“They are replacing joints, stenting arteries, and enjoying arduous exercise,” Miner says. “Testosterone replacement therapy improves mobility in aging men, improves lean body mass, muscle mass, and bone strength.” Miner led another recent study appearing in *Postgraduate Medicine* that observed men who took 1% testosterone gel for 12 months.

Testosterone therapy is specifically approved to treat abnormally low testosterone levels associated with symptoms and signs caused by low testosterone, a condition known as male hypogonadism. Blood tests determine whether testosterone levels

## OnPOINT from The Endocrine Society

The Endocrine Society has a Clinical Practice Guideline that deals with testosterone therapy, specifically in men with androgen deficiencies: *Testosterone Therapy in Men with Androgen Deficiency Syndromes* (2006; revised, 2010) at [www.endocrine.org](http://www.endocrine.org). Among the revised recommendations were prostate-specific antigen (PSA) exclusion criteria, PSA follow-up guidelines, and guidance on treating older men with testosterone therapy. Information on new testosterone formulations and on emerging causes of androgen deficiency is also included in the revised guideline.

The Hormone Health Network ([www.hormone.org](http://www.hormone.org)) also has a fact sheet on testosterone therapy.

are in the normal range, generally 300 to 1,000 ng/dL, but what's "normal" may differ depending on the laboratory that conducts the test, according to The Endocrine Society's Clinical Guidelines. Testosterone levels decline about 1% – 2% each year as men age, the guidelines report. And some studies estimate that almost 14 million men in the U.S. over the age of 45 have below normal testosterone levels.

### A Rush to Prescribe?

The recent spike in prescriptions has some questioning whether physicians are becoming too eager to give men the replacement therapy. Are male patients just looking for the fountain of youth? Is testosterone becoming the latest sex-enhancing drug?

In the *JAMA Internal Medicine* study, researchers found that hypogonadism, in fact, was not the only diagnosis driving the prescription of replacement therapy.

Only half of the men were diagnosed with hypogonadism. Diagnosis of fatigue made up 34%, erectile dysfunction 31%, and psycho-sexual dysfunction was nearly 12%. What's more, the study reported that a quarter of the men did not have their levels tested before they were prescribed the hormone.

These facts contradict The Endocrine Society's Clinical Practice Guidelines that recommend testosterone treatment only in men with "consistent symptoms and signs and unequivocally low serum testosterone levels."

Karen Herbst, PhD, MD, associate professor at the University of Arizona, says that because testosterone testing is not a routine test done during an annual exam, men need either to have some signs or symptoms that would prompt the provider to measure the testosterone level or they have to ask to be measured themselves.

"I think if a man came in and said 'I'm more fatigued now than I was before, my libido is a little bit down, and my erections aren't as hard,' those three things would definitely prompt a provider to measure it," says Herbst.

### Weighing the Risks

Safety information on the popular topical gel warns users about the potential risk to their female partners and children who may come into contact with testosterone remaining on the skin surface of the application site of the gel. It's a danger that worries many of its users.

The risk to family members is a definite concern, says Herbst. "If my patients choose the gel, the next thing I do is explain how to avoid transferring," she explains.

Herbst says that although prescribing information cautions users to avoid contact for at least an hour, she tells patients to boost the wait time up to four hours and gives strict instructions on wearing t-shirts and washing hands after applying.

Transferring is not the only concern. For men who choose testosterone skin patches, irritation is a common complaint, as is pain at the injection site for those who take testosterone injections.

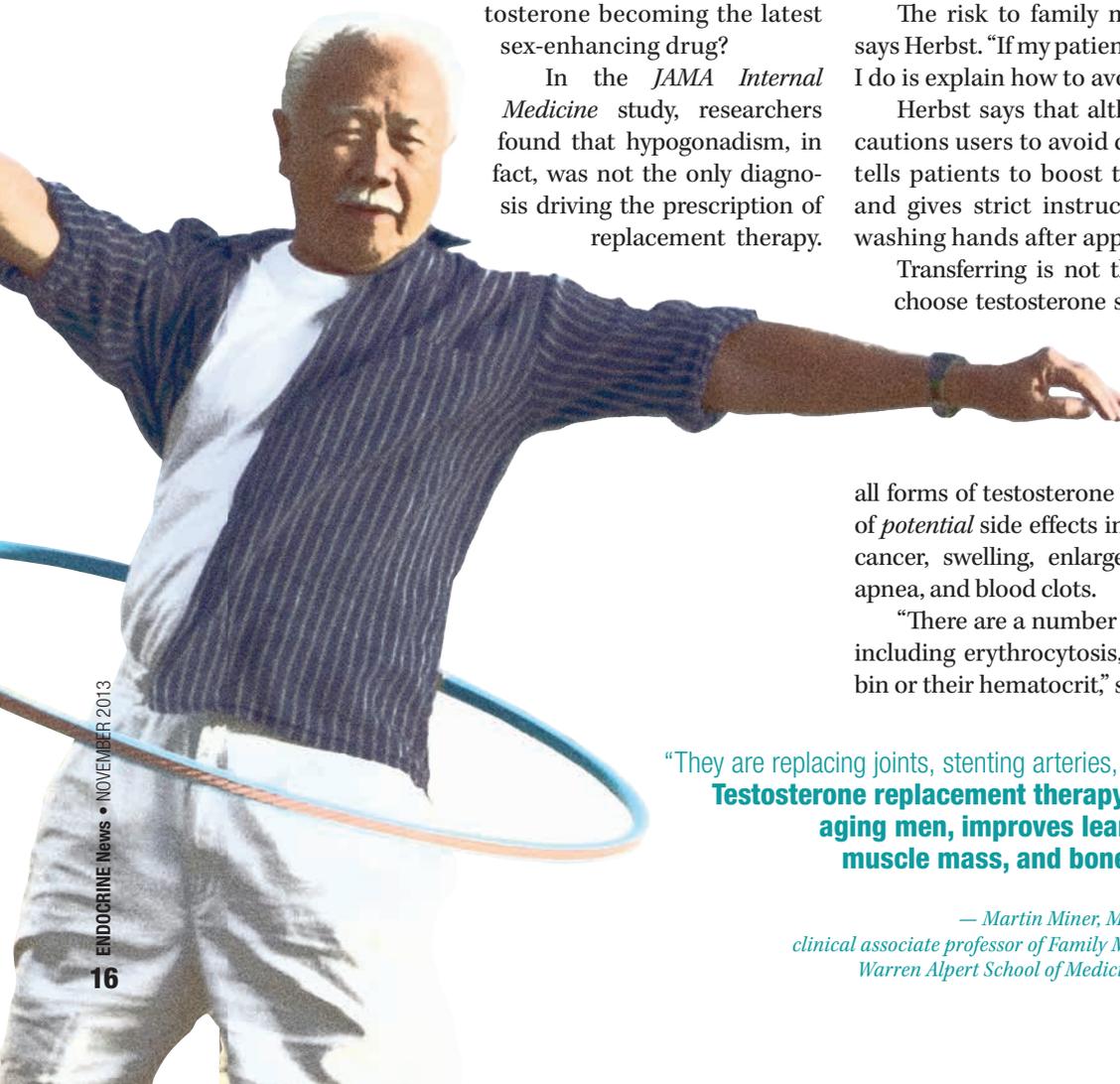
Research studies have investigated the risks using all forms of testosterone therapy and the well-known list of *potential* side effects include increased risk of prostate cancer, swelling, enlarged breasts, worsening of sleep apnea, and blood clots.

"There are a number of side effects with testosterone including erythrocytosis, so we monitor their hemoglobin or their hematocrit," says Herbst.

"They are replacing joints, stenting arteries, and enjoying arduous exercise. **Testosterone replacement therapy improves mobility in aging men, improves lean body mass, muscle mass, and bone strength.**"

— Martin Miner, MD

clinical associate professor of Family Medicine and Urology,  
Warren Alpert School of Medicine, Brown University





### CLOMIPHENE: A Testosterone Alternative?

Clomiphene citrate — used to treat infertility in women for years — is also being given to men to raise testosterone levels and boost sperm counts. While research studies give the pill mixed reviews, some doctors swear by its success.

**Fertility booster.** “It is our drug of choice in young men with hypogonadism who wish to remain fertile, rather than giving them testosterone replacement that would decrease their chances of ever becoming fertile,” says Karen Herbst, PhD, MD, of the University of Arizona. “We’ve actually prescribed clomiphene to young men and their partners have had babies.”

Current data is insufficient to recommend this off-FDA label use of the drug, remarked Glenn Braunstein, Cedars-Sinai’s vice president of Clinical Innovation.

“Nevertheless, I am aware that some physicians in our community do use clomiphene...and are convinced by their anecdotal experience that it has value in improving sperm number and quality,” he added.

**Cheaper choice.** The reported monthly cost of clomiphene (50 mg every other day) is \$83 compared to testosterone therapies, Testim 1% (5 gm daily) at \$270 and Androgel 1% (5 gm daily) at \$265, according to the *Journal of Sex Medicine*.

A 2010 systematic review published in the *Journal of Clinical Endocrinology and Metabolism* of 37 randomized, controlled studies found testosterone replacement did cause an increase in hemoglobin, hematocrit, and PSA and a decrease in HDL cholesterol.

Infertility is also a concern for young men because another common side effect of therapy is lowered sperm count. Glenn Braunstein, MD, Cedars-Sinai’s vice president of Clinical Innovation, says a reduction in testicular size is another consequence.

“It is important in evaluating a male with infertility associated with oligospermia or azospermia to ask about testosterone or anabolic steroid use,” says Braunstein. “If a patient who initially had normal testicular function has used exogenous androgens, it often takes three months and some times even up to a year for

normal testosterone and sperm production to recover.”

In efforts to preserve fertility in young men with hypogonadism, many doctors are turning to alternative medications to testosterone (see sidebar left).

### Observing the Benefits

While there are several risks of testosterone replacement, the therapy has proven beneficial for many men. In their study, Miner and his colleagues found men on testosterone therapy had positive health outcomes after one year of use.

The researchers followed more than 800 men, between the ages of 21 and 85, who used either 5 or 10 grams of testosterone gel per day. The men had significant improvements in sexual function and mood after three months. By 12 months, their body mass indexes, waist circumferences, and glucose levels improved as well. And while there was a significant increase in the mean PSA levels over 12 months, the researchers concluded the changes were “well within guidelines.”

“If a patient who initially had normal testicular function has used exogenous androgens, it often takes three months and sometimes even up to a year for normal testosterone and sperm production to recover.”

— Glenn Braunstein, MD,  
vice president, clinical innovation, Cedars-Sinai

“PSA changes with testosterone are rather negligible and are based on the degree of testosterone deficiency present,” Miner explains. “Usually, if PSA rise does not exceed 0.4 ng/ml, men do not usually experience an exacerbation of their lower urinary tract symptoms.”

A 2013 randomized, controlled study in the *Journal of Clinical Endocrinology and Metabolism* also found men over age 60 who used testosterone gel had improved fat mass and upper body strength after 12 months compared with the placebo group.

Yet, the controversy over the therapy continues. Experts emphasize that all the benefits and risks of testosterone therapy are unknown due to the lack of large-scale, long-term clinical trials. Many in the field are anticipating more answers next year, however, with the conclusion of The Testosterone Trial, an National Institute on Aging (NIA)-sponsored randomized, double-blind, placebo-controlled study being conducted in 800 men, aged 65 and older, from 12 cities across the U.S. The trial promises to determine if testosterone gel treatment (vs. placebo) will improve their walking, vitality, sexual function, memory, blood count, and cardiovascular risk. Participants will be followed for one year during the trial and followed up for one additional year. **EN**

— Fauntleroy is a freelance writer in Carmel, IN, and a regular contributor to Endocrine News.

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## Treatment Options, Environmental Factors, and Trial Results Dealing with

**T**he current epidemic of pediatric obesity is a major contributor to the increased prevalence of insulin resistance, prediabetes, and type 2 diabetes mellitus in adolescents. Insulin resistance and type 2 diabetes are associated with an increased risk of cardiometabolic complications, leading to increased morbidity and mortality across the lifespan. Defining and diagnosing prediabetes and type 2 diabetes remains a challenge in this vulnerable population where the incidence ranges from 8% to 46% of all new diabetes cases referred to pediatric centers. Furthermore, lifestyle interventions do not appear

as effective in children as in adults, and treatment options are more limited.

In this article, three experts discuss the challenges and advances in diagnosis and management of type 2 diabetes mellitus in adolescents: A clinical practitioner considers patient management, including treatment options and goals. A clinical researcher discusses the results of three clinical trials and their implications. Finally, a basic researcher reviews recent advances in our understanding of genetic and environmental factors contributing to disease risk.



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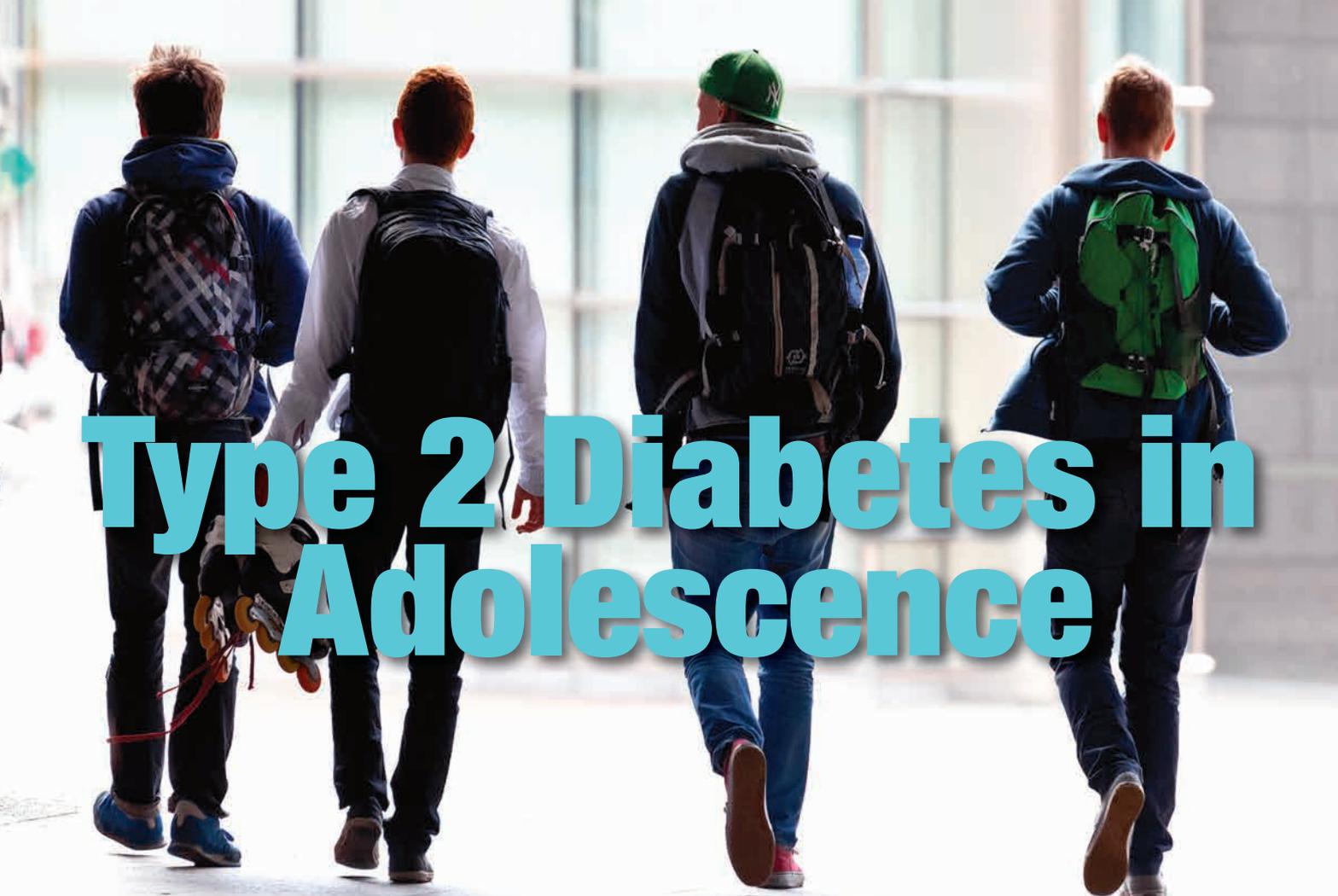
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# Type 2 Diabetes in Adolescence

## CLINICAL PRACTITIONER PERSPECTIVE

### HIGHLIGHTS

- Type 2 diabetes is increasing among adolescents, yet **diagnostic criteria and therapeutic regimens are poorly defined** for this age group.
- Type 2 diabetes in adolescence poses a **significant medical risk for cardiovascular comorbidities** in adolescence and young adulthood.
- New guidelines for the clinical management of type 2 diabetes in adolescence **emphasize increased use of autoimmune markers** to clarify diagnostic type and continued use of insulin as first line therapy when blood sugar is markedly elevated and in unclear situations.
- Little is known regarding the **use of oral hypoglycemic agents** in this age group; therefore, much research is needed.

While type 2 diabetes remains rare in adolescents, the obesity epidemic in childhood has introduced pediatric practitioners to an alarming increase in the number of adolescent patients with type 2 diabetes. These patients present with widely varying degrees of metabolic dysregulation; this presents diagnostic and therapeutic challenges in both the near and long term.

### Clinical Presentation

Type 2 diabetes in childhood may present variably as an incidental finding on a blood sugar assessment of an obese adolescent with a dark, velvety skin rash and strong family

history of diabetes, or with classical diabetic symptoms of polyuria, polydipsia, and weight loss in an obese pubertal child that may progress to ketoacidosis or hyperosmolar syndrome. The polyuria, polydipsia, weight loss, or ketoacidosis picture is similar to new onset type 1 patients, who may also present with obesity, thereby creating considerable confusion as to type of diabetes. Pinhas-Hamiel et al. have itemized frequent commonalities and differences between the two disorders, pointing out that the comorbidities of hypertension and dyslipidemia, in addition to the presence or absence of antibodies, may provide helpful clues to distinguish which form of diabetes is present.

## Comorbidities and Complications

The comorbidities and complications of type 2 diabetes may present at the time of diagnosis. The TODAY trial, a study of the management of type 2 diabetes in adolescents with an average of seven months duration of diabetes, found that 26% of patients had blood pressure greater than the 90th percentile with 13.2% greater than the 95th percentile at baseline. At the same time, 79% had low HDL cholesterol (<40mg/dl for males, <50mg/dl for females) and 10% had high triglycerides (>200mg/dl). Eppens et al. observed earlier onset of hypertension and microalbuminuria in type 2 diabetics with similar duration of diabetes and better measures of blood glucose control compared to an age-matched type 1 diabetes population. These findings are supported by epidemiological data from Canada showing a fourfold increase in renal failure compared to age-matched type 1 diabetics as well as decreased 10-year survival.

Management guidelines are of major importance given the difficulties of accurate diagnoses and implementation of appropriate management strategies, particularly as data demonstrate early and rapid progression of complications.

## Management

Consensus guidelines representing the collaborative efforts of the American Academy of Pediatrics, the American Diabetes Association (ADA), the Pediatric Endocrine Society, the American Academy of Family Physicians, and the Academy of Nutrition and Dietetics (formerly the American Dietetic Association) were recently published and address both diagnosis and management. The guidelines use the established diagnostic

criteria of the ADA with emphasis on the need for repeated testing in the absence of symptomatology, and are composed of six key action statements [see table below] that highlight: 1) the need for insulin therapy in many patients with type 2 diabetes; 2) criteria for blood sugar and HgbA1c monitoring; 3) recommendations for nutritional counseling; and 4) the need for lifestyle modification along with medication as initial therapy. They identify, however, the limited repertoire of *approved* medications for use in the pediatric age group (insulin, metformin).

Furthermore, the TODAY trial documents a limited ability of lifestyle modification with or without metformin to slow the progression of diabetes in these adolescents, with 45.6% reaching treatment failure at a mean of 3.86 years (defined as a HgbA1c  $\geq$  8% for at least six months or metabolic decompensation requiring the use of insulin). Indeed, the most effective therapy made use of metformin and rosiglitazone, the latter of which is no longer available for use due to an increased risk for cardiovascular events in older adults.

## Summary

Clearly, we have much to learn regarding the best treatment for these adolescents. Recognition of the disorder and appropriate management decisions regarding blood glucose control are of major importance to their future well-being. Given the ever increasing number of pharmacologic treatments available to treat type 2 diabetes in adults, research is needed to evaluate the safety and efficacy of these agents in adolescents, with an emphasis on those options that might slow the decline in pancreatic beta cell function. **EN**

### Key Action Statements\*

STATEMENT	CONDITION
1. Ensure insulin therapy	Ketoacidosis, ketosis Blood glucose $\geq$ 250mg% HgbA1c >9% Diagnosis type 1 versus type 2 unclear
2. Lifestyle modification + Metformin	All other conditions than #1 above for first line therapy
3. Monitor HgbA1c every three months	All patients
4. Monitor fingerstick blood sugar	Patients taking insulin or medication with risk of hypoglycemia Initiating or changing diabetes treatment Have not met treatment goals Have intercurrent illness
5. Provide nutrition counseling as recommended by the Academy of Nutrition and Dietetics in their "Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines"	All patients at diagnosis and ongoing management
6. Moderate to vigorous exercise for 60 min. daily, and limit non-academic screen time to 2hrs/day	All patients

\* Adapted from K. C. Copeland, J. Silverstein, K. R. Moore, G. E. Prazar, T. Raymer, R. N. Shiffman, et al. Management of Newly Diagnosed Type 2 Diabetes Mellitus (T2DM) in Children and Adolescents. *Pediatrics*. 2013;131:364-382.



# CLINICAL RESEARCHER PERSPECTIVE

## HIGHLIGHTS

- Type 2 diabetes in adolescence remains rare, and progression **rate from risk to overt disease is low.**
- Type 2 diabetes in adolescence disproportionately affects individuals with **low socioeconomic status.**
- Development of diabetes-related **complications is faster in adolescence than in adults** with type 2 diabetes.

## The Contribution of Large Clinical Studies

It is now almost two decades since the first reports of type 2 diabetes and other obesity-related comorbidities in children and adolescents began to appear. During this time, a first wave of important studies began to clarify the parameters of the problem and allowed us to move beyond anecdote and assumption. The largest of these studies, SEARCH, HEALTHY, and TODAY, illustrate the power of well-supported research consortia to address complex and diverse pediatric health problems, particularly when these disorders remain relatively rare.

SEARCH, a population-based registry and observational study supported by the Centers for Disease Control (CDC) and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), consists of a consortium of six centers reflecting geographic and race/ethnicity diversity of the U.S. population. To date, SEARCH has provided reliable incidence and prevalence data for type 2 diabetes in adolescence and confirmed the age, gender, and race/ethnicity distributions suggested by earlier case reports. Furthermore, SEARCH demonstrated that, despite a substantial rise in incidence during the late 1990s, type 2 diabetes remains a rare disorder in adolescence, with less than 4,000 new cases diagnosed in the U.S. annually. SEARCH has also provided insight into the clinical course of type 2 diabetes in adolescence and the prevalence of comorbidities.

HEALTHY, a NIDDK-supported study of school-based interventions to prevent diabetes in sixth to eighth graders, showed, first of all, that undiagnosed diabetes is rare even in at-risk adolescents, unlike in adults where nearly 50% of cases are undiagnosed. This suggests that type 2 diabetes in adolescence does not have an extended asymptomatic prodrome. In addition, HEALTHY demonstrated the challenges in changing the trajectory of obesity and metabolic risk even with comprehensive interventions.

TODAY, a 15-center, NIDDK-supported study of approaches to treatment of type 2 diabetes in adolescence, demonstrated that type 2 diabetes in adolescence is characterized by more rapid deterioration of beta cell function than in adults, with a majority of adolescents failing oral monotherapy within one year. In addition, lifestyle intervention does not add significantly to oral monotherapy in this population. TODAY has also shown

that comorbidities, such as hypertension, dyslipidemia, retinopathy, and albuminuria, are prevalent at diagnosis in adolescents with type 2 diabetes and rise rapidly over the first few years.

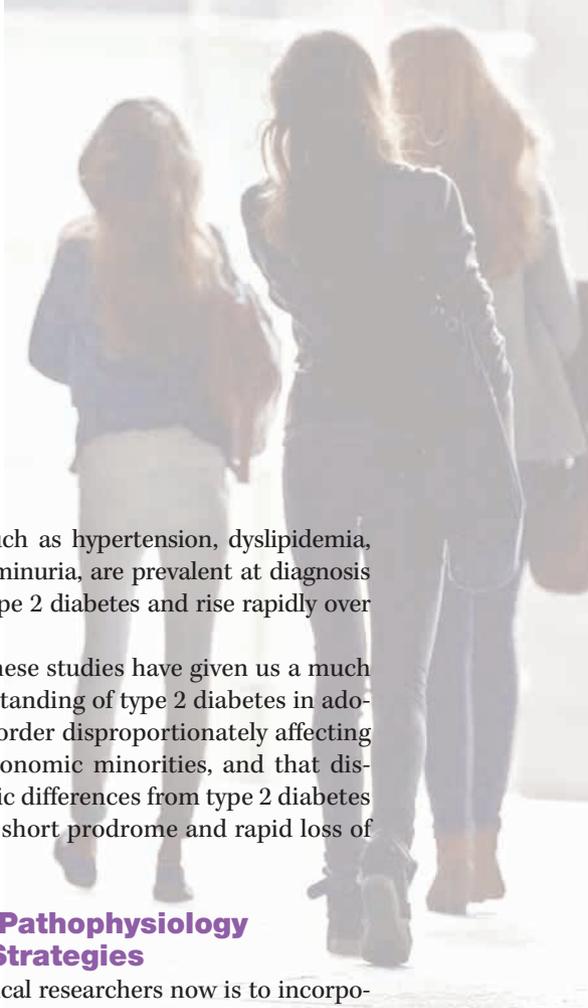
Taken together, these studies have given us a much more rigorous understanding of type 2 diabetes in adolescence as a rare disorder disproportionately affecting ethnic, racial, and economic minorities, and that displays apparent biologic differences from type 2 diabetes in adults, including a short prodrome and rapid loss of beta cell function.

## Implications of Pathophysiology for Prevention Strategies

The challenge for clinical researchers now is to incorporate the information from this first wave of studies into the design of the next round of prevention and treatment trials. In particular, the observation that type 2 diabetes remains rare, even among at-risk adolescence, implies that the progression from at-risk states to overt diabetes is limited, a fact that must be taken into account in the design and testing of prevention strategies.

If progression rates are low, then the most robust interventions will need to be tested in a sufficiently large cohort of the most at-risk adolescents for a sufficiently long duration to demonstrate any effect on the occurrence of overt diabetes. Given this, it is certainly reasonable to question whether such a large-scale trial would be financially and logistically realistic, particularly as type 2 diabetes in adolescents remains a relatively rare disorder. On the other hand, reliance on surrogate outcomes of “risk” for diabetes, such as insulin sensitivity and secretion, or extrapolating from adult interventions brings problems in the face of demonstrated differences in the pathobiology of type 2 diabetes in adolescence.

Investigators will need to consider whether to directly target prevention of diabetes, with the implications for study design that this entails, or whether it is more appropriate to target prerequisites for diabetes, such as obesity and its more common comorbidities such as hypertension, dyslipidemia, and fatty liver disease, with the assumption that successful prevention of prerequisites will inevitably lead to reduction in rates of diabetes without directly testing the latter. As of now, there has been no resolution of this conundrum.



## Implications of Demographics for Clinical Trial Design

The second important observation from the first wave of studies, which has implications for the design of clinical research in this population, is the overwhelming predominance of low socioeconomic status in affected individuals. Successful research enrollment and retention in this population requires a high level of cultural sensitivity and experience, as well as sufficient staff and infrastructure to accommodate the frequently disorganized and stressful family situations in which these adolescents live. Therefore, study design and staff training must take into account what is realistic for these adolescents, while being attentive to the requirements of good clinical science.

## Implications for Obesity Prevention

Finally, HEALTHY and TODAY have shown that it is difficult to reverse established obesity in at-risk children, and once type 2 diabetes is diagnosed, progression to requiring multiple medications to treat hyperglycemia, hypertension, dyslipidemia, and microalbuminuria is rapid. Above all else, these results make clear that the primary focus of efforts must be on prevention of diabetes through primary

prevention of childhood obesity. A large societal effort will be required to accomplish this goal, with particular urgency to reduce pregnancies complicated by obesity and diabetes, which are known to be important risk factors for offspring.

## Summary

SEARCH, HEALTHY, and TODAY have demonstrated the importance of well-supported clinical trials for the study of rare pediatric disorders that cannot be studied at a single institution. Taken together, these trials have provided rigorous insight into early onset type 2 diabetes and delineated the parameters for the next cycle of studies addressing this biologically fascinating, but socioeconomically troubling disorder. The design of future studies in the prevention and treatment of type 2 diabetes in adolescence will need to address the low prevalence of type 2 diabetes in the population, the apparent rapid progression of beta cell failure in those individuals who develop diabetes, and, above all, the challenging sociodemographics of the at-risk population. However, lessons learned from SEARCH, HEALTHY, and TODAY will prove invaluable. EN

## BASIC RESEARCHER PERSPECTIVE

### HIGHLIGHTS

- Millennia of genetic pressure to maintain "thrifty" genes in the population may now render individuals, including children and adolescents, **vulnerable to type 2 diabetes mellitus**, given the overabundance of food in our modern world.
- Current research is focusing on dietary fats, carbohydrates, commensal microbes, and disruptive environmental chemicals and toxins as environmental factors that enhance type 2 diabetes risk. Understanding how genetics and environmental factors interact to promote the pathogenesis of type 2 diabetes is an **emerging area of metabolic research** that is particularly relevant to young people.
- As an example, the accumulation of certain lipid species, such as saturated fatty acids, diacylglycerols, and ceramides, in tissues such as the abdominal fat, liver, and skeletal muscle is likely to play an important role in driving inflammation in these tissues that then leads to insulin resistance and type 2 diabetes. **Determining what genetic factors** can control this inflammation is a key area for future type 2 diabetes research.

At the heart of the epidemic of obesity and type 2 diabetes is a harmful interaction between components of an "obesogenic" environment and one's individual genetic predispositions. This interaction is highlighted by classic examples such as the high rate of type 2 diabetes among individuals of Pima ancestry living in the Southwestern U.S. versus genetically matched counterparts living in rural Mexico. We are now beginning to understand the science behind how environmental factors and genes interact to create a "perfect storm" that, along with inactivity, sets children up for obesity and associated metabolic complications.

## Genetic Factors

Millenia of genetic pressure have rendered human beings efficient at storing calories in white adipose tissue in order to survive periods when food is scarce. Unfortunately, the maintenance of these "thrifty" genes in the population may now render some individuals vulnerable to the ill effects of excess energy storage, given the overabundance of food in the developed world.

Though we do not know all the polymorphisms in our genome that are beneficial during starvation but detrimental when food is abundant, new genome-wide approaches are allowing us to tackle this important

question. Although genome-wide association studies have been successful in finding single nucleotide polymorphisms (SNPs) in various genes that predict type 2 diabetes risk, these SNPs only account for a minority of the overall risk predicted based on family history alone. Therefore, there is much to the genetic risk that is still not understood. However, with newer deep sequencing technologies, we are now able to survey the entire genome with much higher resolution in order to identify a wider array of genetic alterations that predispose to type 2 diabetes and other diseases associated with obesity.

Additionally, we can now analyze the entire genome for transcriptional modulators and epigenetic factors that affect gene regulation and the pattern in which genes are turned “off” and “on.” In this way, we are beginning to approach an era of “precision medicine” in which we will be able to provide infants and children with a genetic analysis of their diabetes risk and make appropriate patient-specific interventions.

### Environmental Factors

What are the interacting environmental factors that enhance type 2 diabetes risk? Emerging research is focusing on dietary fats, carbohydrates, commensal microbes, and disruptive environmental chemicals and toxins. Dietary fats have been extensively studied for their metabolic impact. Obese individuals who never develop type 2 diabetes are more likely to accrue fat in subcutaneous depots (e.g., thighs, buttocks), whereas individuals who develop type 2 diabetes tend to accrue fat preferentially in visceral depots deep within the abdomen.

Such visceral adiposity is associated with fatty build-up in insulin-responsive, non-adipose tissues such as the liver, skeletal muscle, and pancreas, and in immune cells such as macrophages. This ectopic fat deposition alters the function of these cells and tissues, promoting inflammation and insulin resistance. Recent studies have focused on the predisposition of individuals to developing visceral and ectopic lipid deposition as independent risk factors for the development of type 2 diabetes. As an example, magnetic resonance spectroscopy showed that the lean, disease-free offspring of patients with known type 2 diabetes are more likely to have ectopic lipid deposition in their skeletal muscle than are children born to disease-free parents. Determining what factors promote ectopic lipid deposition and how these lipids alter cellular function may lead to new ways to mitigate type 2 diabetes.

### Storage and Inflammatory Effects of Fats

Ectopic lipid deposition is associated with low-grade inflammation in insulin-responsive tissues, and the intersection of immune and metabolic function is a major area in diabetes research. Beyond macrophages, this inflammatory response involves several immune cell types and secreted factors, including cytokines such as IL-1 $\beta$  and chemokines such as monocyte

chemoattractant factor 1 (MCP-1). Many of these factors are being studied as biomarkers, and recent advances in high-throughput screening hold promise for discovering what circulating type 2 diabetes biomarkers are best at predicting type 2 diabetes risk in children.

What fats promote type 2 diabetes? A burgeoning literature points to saturated and trans fats as fueling tissue inflammation and metabolic compromise. In addition to red meat, these pro-inflammatory fats are enriched in processed foods. The ability to feed a large, growing global population relies on mass-produced processed foods, which particularly in emerging nations are sold primarily to children. Scientists, clinicians, and policy makers will want to focus on how to reduce the metabolic impact of pro-inflammatory fats present in these foods.

### Sugars, Toxins, and the Obesogenic Enterotype

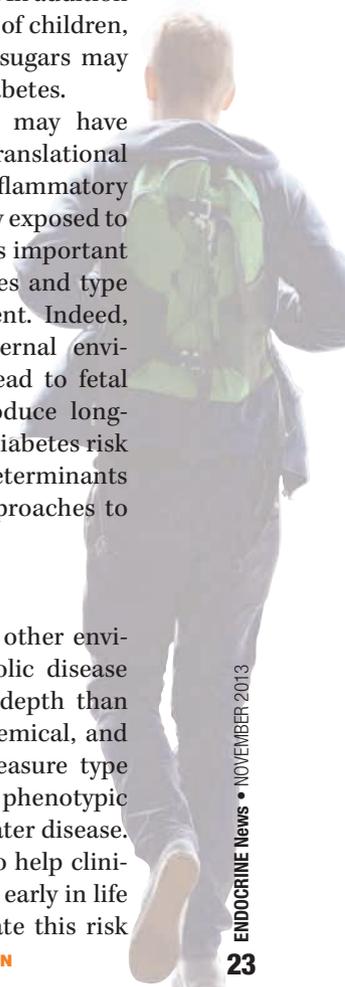
Commensal gut bacteria may also mediate diet-induced inflammation. The gut bacterial “enterotype” of an individual shifts in response to diet-induced obesity. This shift has the potential to modulate intestinal immune function and influence metabolic pathways. Interestingly, emerging research is focusing on whether shifts in gut microbiota can occur in response to exposures early in life, setting up a predisposition to obesity.

Excess sugars in foods and beverages can also alter cellular metabolism, for example in the liver. In addition to removing sugary products from the lives of children, determining the cellular effects of excess sugars may help identify new ways to prevent type 2 diabetes.

Environmental toxins and chemicals may have genetic, epigenetic, and potentially post-translational effects that also alter metabolic and inflammatory function. Given that young people are highly exposed to such agents, from pesticides to plastics, it is important to explore the link between these exposures and type 2 diabetes throughout human development. Indeed, recent work strongly suggests that maternal environmental exposures and nutrition can lead to fetal metabolic “reprogramming” that can produce long-standing consequences and impact type 2 diabetes risk after birth. Understanding the molecular determinants of fetal reprogramming may yield new approaches to control type 2 diabetes risk in children.

### Summary

The link between genetic, nutritional, and other environmental factors on obesity and metabolic disease is being studied with more breadth and depth than ever before. New genetic, lipidomic, biochemical, and imaging modalities are being used to measure type 2 diabetes risk and to characterize early phenotypic changes that may serve as biomarkers for later disease. These approaches show promise as tools to help clinicians accurately detect type 2 diabetes risk early in life and offer personalized strategies to mitigate this risk and/or prevent type 2 diabetes altogether. **EN**



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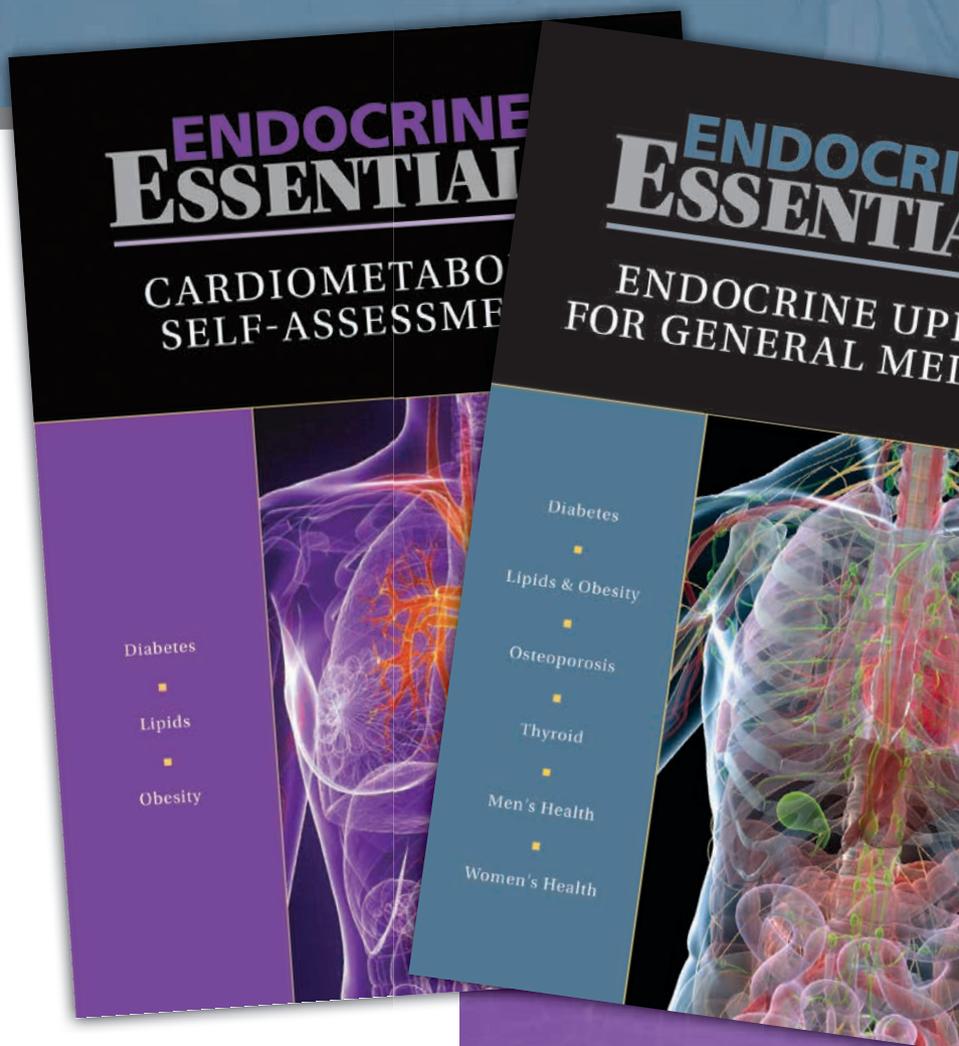
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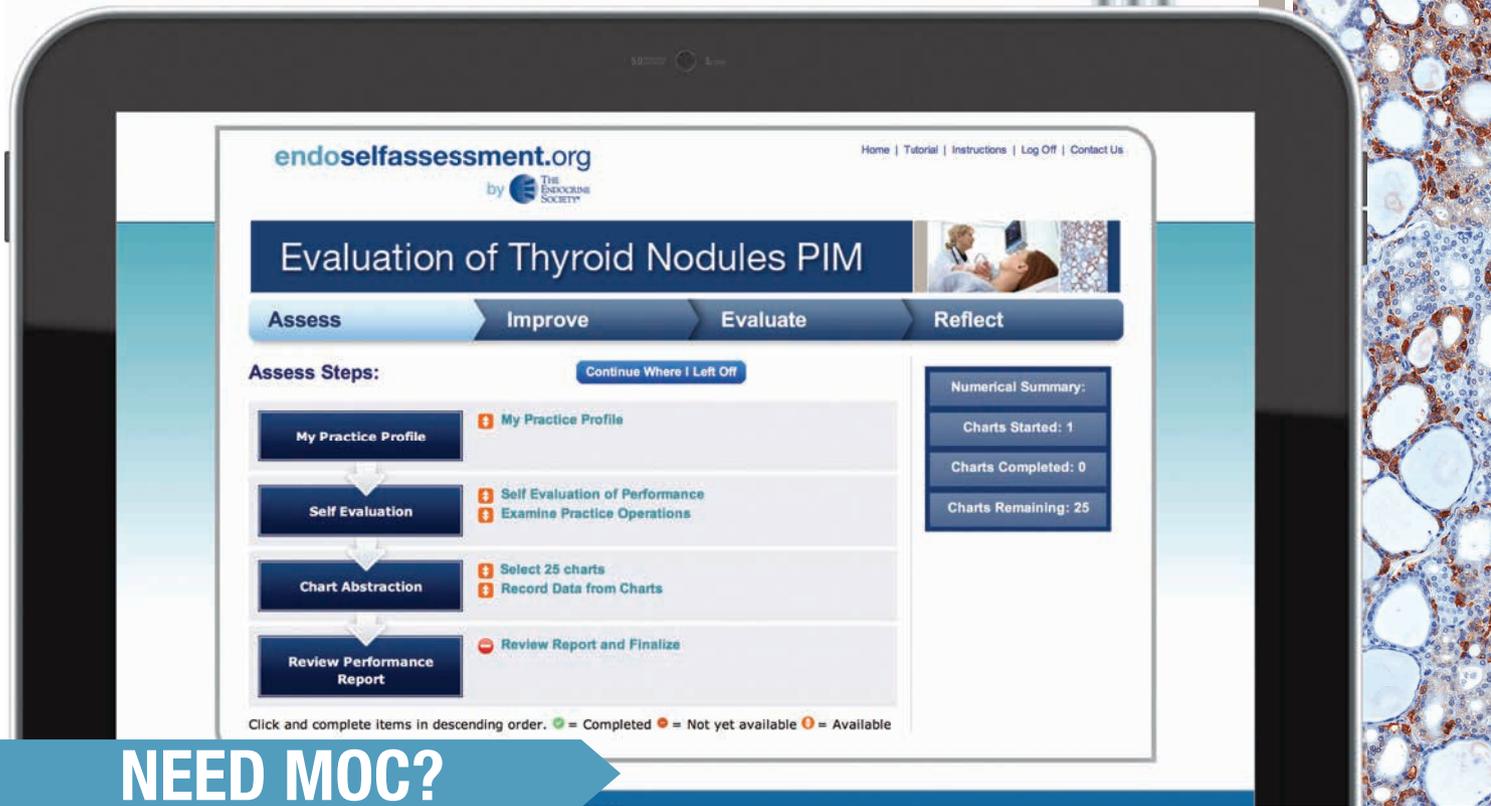
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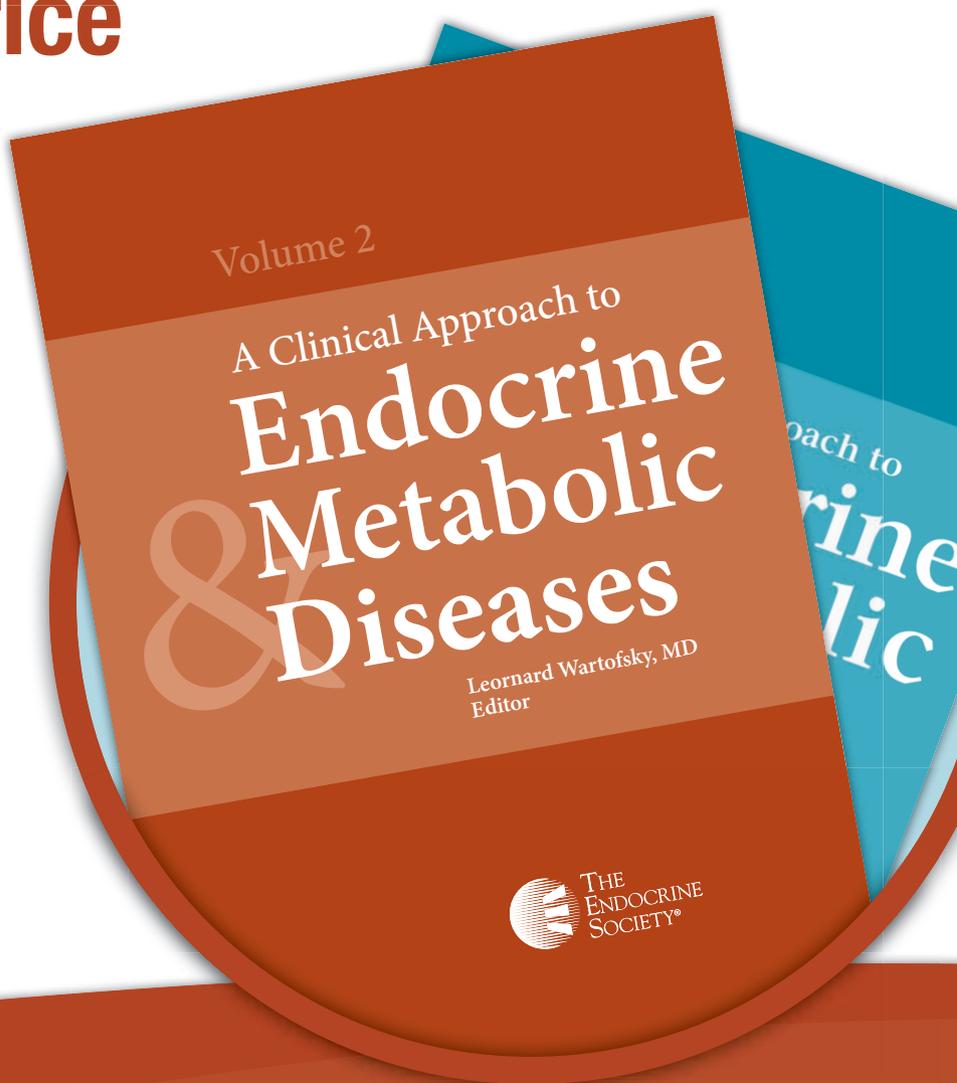
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**The Clinical Course of Treated Hyperparathyroidism Among Patients Receiving Hemodialysis and the Effect of Cinacalcet: The EVOLVE Trial •**

Patrick S. Parfrey,

Glenn M. Chertow, Geoffrey A. Block, Ricardo Correa-Rotter, Tilman B. Drüeke, Jürgen Floege, Charles A. Herzog, Gerard M. London, Kenneth W. Mahaffey, Sharon M. Moe, David C. Wheeler, Bastian Dehmel, Marie-Louise Trotman, Dennis M. Modafferi, and William G. Goodman • *Severe unremitting HPT develops frequently in patients on hemodialysis despite conventional therapy, and cinacalcet substantially reduces its occurrence.*

**The IGSF1 Deficiency Syndrome:**

**Characteristics of Male And Female Patients •** S.D. Joustra, N. Schoenmakers, L. Persani, I. Campi, M. Bonomi, G. Radetti, P. Beck-Peccoz, H. Zhu, T.M.E. Davis, Y. Sun, E.P. Corssmit, N.M. Appelman-Dijkstra, C.A. Heinen, A.M. Pereira, A.J. Varewijck, J.A.M.J.L. Janssen, E. Endert, R.C. Hennekam, M.P. Lombardi, M.M.A.M. Mannens, B. Bak, D.J. Bernard, M.H. Breuning, K. Chatterjee, M.T. Dattani, W. Oostdijk, N.R. Biermasz, J.M. Wit, and A.S.P. van Trotsenburg • *In males, the X-linked IGSF1 deficiency syndrome is characterized by CeH, hypoprolactinemia, delayed puberty, macroorchidism, and increased body weight. A subset of female carriers also exhibits CeH.*

**Disuse Impairs the Muscle Protein Synthetic Response to Protein Ingestion in Healthy Men •** Benjamin T. Wall, Tim Sniijders, Joan M.G. Senden, Chris L.P. Ottenbros, Annemie P. Gijsen, Lex B. Verdijk, and Luc J.C. van Loon • *A short period of muscle disuse impairs the muscle protein synthetic response to dietary protein intake in healthy young men. Thus, anabolic resistance to protein ingestion contributes significantly to the loss of muscle mass that is observed during disuse.*

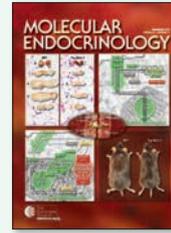


**Growth Hormone Secretion Is Correlated With Neuromuscular Innervation Rather Than Motor Neuron Number in Early-Symptomatic Male Amyotrophic**

**Lateral Sclerosis Mice •** F. J. Steyn, K. Lee, M. J. Fogarty, J. D. Veldhuis, P. A. McCombe, M. C. Bellingham, S. T. Ngo, and C. Chen • *Our data imply that increased GH secretion at symptom onset may be an endogenous endocrine response to increase the local production of muscle IGF-I to stimulate reinnervation of muscle, but that in the latter stages of disease this response no longer occurs.*

**Antagonistic Roles of Dmrt1 and Foxl2 in Sex Differentiation via Estrogen Production in Tilapia as Demonstrated by TALENs •** Ming-Hui Li, Hui-Hui Yang, Meng-Ru Li, Yun-Lv Sun, Xiao-Long Jiang, Qing-Ping Xie, Ting-Ru Wang, Hong-Juan Shi, Li-Na Sun, Lin-Yan Zhou, and De-Shou Wang • *Taken together, our data demonstrate that TALENs are an effective tool for targeted gene editing in tilapia genome. Foxl2 and Dmrt1 play antagonistic roles in sex differentiation in Nile tilapia via regulating cyp19a1a expression and estrogen production.*

**Inhibition of Hippocampal Aromatization Impairs Spatial Memory Performance in a Male Songbird •** David J. Bailey, Chunqi Ma, Kiran K. Soma, and Colin J. Saldanha • *Hippocampal aromatization, much of which is achieved at the synapse in this species, is critical for spatial memory performance.*



**Smad3 Induces Atrogin-1, Inhibits mTOR and Protein Synthesis, and Promotes Muscle Atrophy In Vivo •**

Craig A. Goodman, Rachel M. McNally, F. Michael Hoff-

mann, and Troy A. Hornberger • *This study provides the first evidence that Smad3 is sufficient to regulate many of the events associated with myostatin-induced atrophy and therefore suggests that the Smad3 signaling may be a viable target for therapies aimed at preventing myostatin-induced muscle atrophy.*

**Forkhead Box O1 Is a Repressor of Basal and GnRH-Induced Fshb Transcription in Gonadotropes •**

Danalea V. Skarra, David J. Arriola, Courtney A. Benson, and Varykina G. Thackray • *In summary, our data demonstrate that FOXO1 can negatively regulate Fshb transcription and suggest that FOXO1 may relay metabolic hormonal signals to modulate gonadotropin production.*

**Salt-Inducible Kinases 1 and 3 Negatively Regulate Toll-Like Receptor 4-Mediated Signal •**

So Yong Kim, Sookyung Jeong, Kyong-Hwa Chah, Eunyu Jung, Kwan-Hyuck Baek, Seong-Tae Kim, Jae-Hyuck Shim, Eunyong Chun, and Ki-Young Lee • *These results suggest that SIK1 and SIK3 negatively regulate TLR4-mediated signaling through the interruption of TAB2-TRAF6 complex and, thereby, the inhibition of ubiquitination of TRAF6. The present findings can be useful for a better understanding of multilevel interactions between the metabolic and immune systems.*

# Partly CLOUDY

As patients' electronic data migrates to the cloud, will issues of privacy and access supersede the system's ease of use and convenience?

By Melissa Mapes

Across the deserts of Arizona, data fields have been popping up left and right. Hard drives stacked floor to ceiling are humming away with billions of pieces of coded information on people, diseases, and insurance coverage. These buildings full of black boxes comprise what developers call the "healthcare cloud." Once a far-off aspiration of tech-savvy medical professionals, the cloud is poised for implementation, and software companies are fighting tooth and nail to win the bids of hospitals and private practices.

The cloud operates by downloading data over a wireless connection to the hard drives in Arizona and other parts of the country. Rather than store patient files onsite at hospitals, administrators can send them to a remote information bank with the click of a button. Physicians and researchers then have access to datasets on all their patients, which could allow them to track progress, outcomes, and conduct in-depth studies. Though still a long way off in the future, a universal cloud containing patient data from across the country or even the world would have priceless value to researchers, from epidemiology to pharmacology.

## Blocked by HIPAA?

But one large issue stands in the way: the Health Insurance Portability and Accountability Act (HIPAA). Joyce Lee, MD, MPH, associate professor at the University of Michigan and a

practicing endocrinologist, has looked into privacy concerns in her research on the healthcare cloud and other medical applications. "I believe that the biggest barrier to date to having a seamless cloud solution linking patients and providers is HIPAA," she says.

Many software developers — like Amazon, Dell, and ClearData — are claiming their clouds to be HIPAA compliant, but providers and hospital administrators remain wary.

Violating HIPAA is a legitimate fear. In addition to the ethical obligation to protect the privacy of one's patients, failing to uphold the law could incur up to \$1.5 million in fees in a single year. Add to that the cost of converting to a cloud-friendly form of electronic health records (EHR) and developers wind up with a hard sell.

Without a federally dictated selection of EHR programs to choose from, providers have no guarantee that the EHR they choose will stay in business, let alone be cloud-compatible in the future. Luckily, a few early-adopters have climbed on board and are paving the way for the rest of the medical world.

Kaiser Permanente has developed its own custom EHR, which allows for cloud storage across all of its hospitals. Kaiser has begun processing the metadata collected through its electronic records to test the viability for possible large-scale studies.



### AT-A-GLANCE

- Rather than store patient files on site at hospitals, administrators can send them to a remote information bank with the click of a button.
- Files on a cloud are accessible any place and any time, instantaneously.
- Despite concerns for patient privacy, some experts claim that the healthcare cloud actually offers more secure options for transmitting sensitive information.

Should it succeed, the Kaiser example may become a crucial basis for the decisions of other hospitals and medical businesses.

### Affordable and Efficient

The reticence on the side of the medical community does not seem to be mirrored in the business realm. ClearData recently received \$7 million in investor funds for its Phoenix-based operations. Amazon has taken the lead among major tech companies such as Microsoft and Google for healthcare cloud computing and major data studies. These tech companies are leveraging the power of their data centers and computers to attract researchers, especially big pharmaceutical companies. The strategy is paying off.

Pharmaceutical companies rent the vast computing resources of companies such as Amazon by the hour to conduct fast, cheap studies that might usually cost millions. The investment seems to be bringing savings of time and money to the world of research. In one example, as described by National Public Radio, a study required the screening of 21 million chemical compounds. The power of 50,000 computers virtually processed the study in three hours, and the cost was under \$15,000 — an unheard of accomplishment a decade ago.

The affordability and efficiency of such studies has demonstrated the value of cloud computing in the present day. Other projects hint at where big data may be heading in the near future. Pathwork Diagnostics, for example, exercises its computer database of cancer tissues when a provider sends in a patient sample. In one day, doctors can have a high-probability diagnosis of the cancer a patient faces.

### Easy Access

The healthcare cloud poses other benefits beyond research and diagnosis. The organization of files has long since been an arduous task requiring daily maintenance. By storing files on a cloud, they can be automatically sorted and searched — saving on paper and labor costs, and creating space in the office by removing the need for hefty filing cabinets.

Files on a cloud are accessible any place and any time — instantaneously. Providers can work from home or find patient information at a moment's notice. "One of the biggest barriers that we face as medical providers is the exchange of relevant medical information with our patients between healthcare visits," Lee claims. The cloud would revolutionize this process and alleviate the time wasted from digging for files. Conceivably, medical history for an incapacitated patient could be transferred from one hospital to another, which is an especially valuable tool in the emergency room. iPads and other mobile devices make such access even more efficient.

### Recent Developments in the HEALTHCARE CLOUD

**Kaiser Permanente** has developed a custom EHR and is converting its files to cloud storage

**Amazon** rents out its massive computing service by the hour to run big data studies

**ClearData** recently received \$7 million for their healthcare cloud data centers in Arizona

Despite concerns for patient privacy, some experts claim that the healthcare cloud actually offers more secure options for transmitting sensitive information than traditional means. Files and prescriptions sent via fax may be improperly disposed of or accidentally sent to the wrong number. Cloud access provides password protection to keep unintended eyes off of patient information.

The many benefits of the healthcare cloud seem to be overwhelming HIPAA concerns, but it may be some time before we see a universal database — if ever. For now, commercial research is showing off the powers of big data and cloud computing. And, of course, the data fields in Arizona keep on growing. **EN**

— Mapes is a freelance writer in Washington, D.C., and a regular contributor to Endocrine News.



# PQRS Moves From Carrot to Stick

What happens between now and the end of 2013 may have major financial impacts on practices for many years to come.

By Kurt Ullman

**I**n 2007, the Physician Quality Reporting Initiative was started as part of the Tax Relief and Health Care Act of 2006. In 2010, the name was changed to the Physician Quality Reporting System (PQRS). It is set up to provide a financial incentive to physicians and physician extenders.

“PQRS was put in place by the Centers for Medicare and Medicaid Services (CMS) as part of their efforts to attach a value to the healthcare provided,” says Bettina Berman, RN, MPH, CPHQ, project director for quality improvement at Thomas Jefferson University’s School of Population Health in Philadelphia. “PQRS is a group of quality metrics being used by physicians to report on their practice. Currently, you can get an incentive payment for participation.”

## Small Incentives, Big Work

Some practices have declined to participate in the PQRS program because of what many viewed as a small incentive for quite a bit of work. For example, a recent article on 2011 participation published in *American Medical News* found that while the average payment was \$5,463 for endocrinologists, the lowest payment was 37 cents. This may be one reason why only one eligible provider in three participated.

“One huge problem with PQRS is that compliance can be time consuming,” says Bradley Scheel, practice administrator for Raleigh Endocrine Associates in

Raleigh, N.C. “It means paperwork and documentation that is often not in line with what a doctor does on a daily basis. If the doctors put the burden on someone else in the practice, that means they are spending money and time on things other than patient care.”

There is also some concern about whether PQRS is ready for prime time and how that might have adverse effects on providers. “While PQRS is a lot better than it was, there is still a long way to go,” says Ardis Hoven, MD, current president of the American Medical Association (AMA). “If you look at the success rate of those currently involved, it has not been very high. That indicates a problem with the system.”

However, in 2015 there will be changes, and the carrot is being replaced by a stick. At that time CMS will institute what it is calling the PQRS negative adjustment. Failure to qualify or participate will result in a 1.5% penalty based on total Allowable Medicare Charges. That rises to 2.0% in 2016 and beyond.

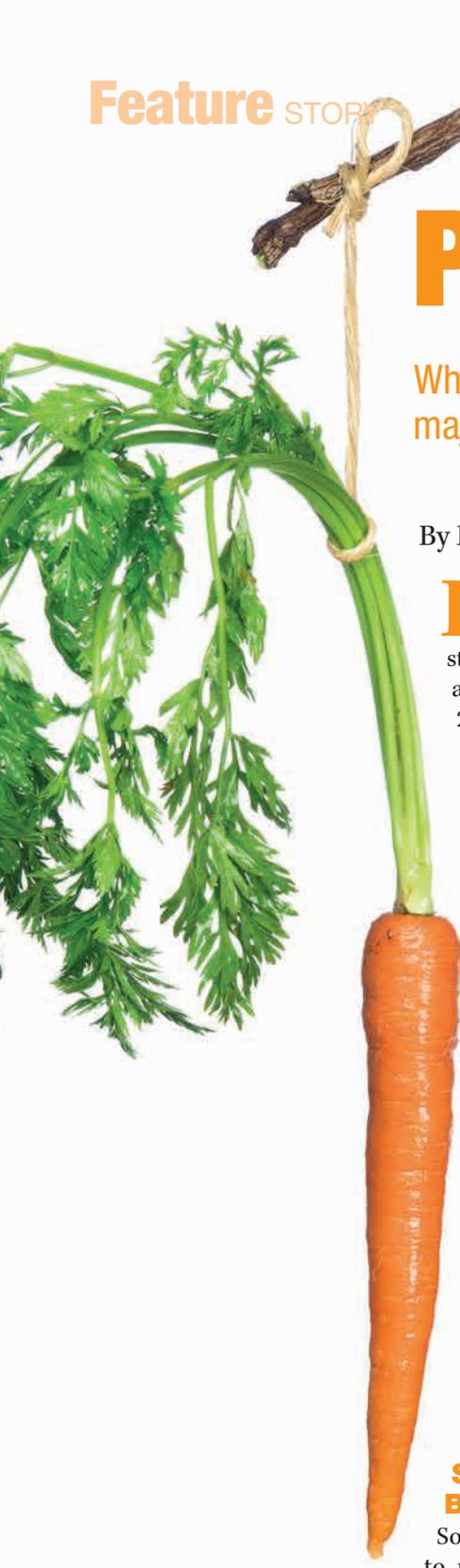
## 2015 Penalties Based on 2013 Performance

One of the concerns is that many physicians do not realize the 2015 payment penalties are based on 2013 performance. So, practices have only until Dec. 31, 2013 to avoid taking the hit two years later.

“If you do not participate in 2013, you obviously do not qualify for this year’s .5% bonus,” says Lawrence Ward, MD, MPH, FACP, vice chair for clinical affairs and quality in the Department of Medicine at Thomas Jefferson. “However, you will also receive the penalty later on. While not participating can have a neutral impact this year, the impact in 2015 may be much worse.”

There are indications that most practices may not be ready. The *American Medical News* noted that of those endocrinologists who participated in PQRS for 2011, around 18% did not qualify for the bonus. Between those not participating, and the group that did not qualify, perhaps as many as 72% of endocrinologists could be looking at a penalty in 2015.

So, with only a few weeks left in the year, what can a practice do now to salvage 2015? Depending on how your specific practice operates, there are still a few alternatives.



## Ways to Report Quality Measures

“There are a number of ways to report quality measures,” says Jennifer Gasperini, senior group governmental affairs representative with Medical Group Management Association’s Washington, D.C., office. “Whether you participate through claims, a qualified registry, or have a qualified electronic health records system (EHR), you can still report in 2013 to avoid a 2015 penalty. Information on this and the other available ways to qualify are available at the CMS website

Each of these options does require that a certain number or percentage of your patients be included in reporting to qualify for the extra money. A practice might be able to get the incentive and qualify for 2015. However, because of the work required to compile this information, it may be too late to start and most likely will only be useful to the practice if the method is already in use.

If none of these other options is available, CMS has put in place one last opportunity to avoid the sanctions in 2015. A practice can report one indicator on one patient seen before Dec. 31, 2013. Although that won’t mean any extra money, it does give practices additional time to put future alternatives in place. All of those interviewed see this as being a one-time offer from CMS, and they are very unlikely to have this in place in 2014.

“The era of massive data collection is already here.

**If you don’t want to comply, perhaps the only alternative is a concierge practice that only accepts cash.”**

— Bradley Scheel, practice administrator, Raleigh Endocrine Associates, Raleigh, N.C.

## Penalties Add Up

Although most of the focus has been on PQRS and the penalties directly attached to that program, other financial issues are involved.

“Participating in PQRS will fulfill the quality indicator section requirements for meaningful use,” notes Ward. “In 2015, practices with more than 100 eligible providers will be subject to penalties under the Physician Value-based modifier; and those with 100 will follow by 2017.”

These penalties from different programs are cumulative. For example, those who don’t qualify under PQRS this year miss out on the 0.5% bonus. However, when the penalty phase begins in 2015, they will incur a 1.5% penalty. Additionally, they may be subject to a 1.0% penalty for failing to participate in the EHR incentive program (Meaningful Use). All programs involved will total 6% of Medicare reimbursement at risk by 2016.

## AT-A-GLANCE

- Failing to qualify for PQRS by the end of 2013 means Medicare payment penalties two years later in 2015.
- CMS is allowing practices to avoid the 2015 penalties by reporting one measure on one patient seen by December 31, 2013
- CMS website and help desk can assist practices in meeting the requirements for 2015.

“This overlap is not only a down side, because you can also use it to spread the costs around a little,” says Jonathan D. Leffert, MD, managing partner of North Texas Endocrine Center in Dallas. “Because of the push toward electronic records, for instance, adding the infrastructure for PQRS is largely a marginal cost.”

If you manage to rescue your practice during the waning days of 2013, early 2014 is the time to begin working toward a system that can be in place so you aren’t running around putting out fires later in the year. What resources are available to the practice?

## What to do in 2014?

One of the best places is the “getting started” part of the CMS PQRS website ([www.cms.gov](http://www.cms.gov)). It also has a help desk available to answer questions. In addition, the AMA has a wide-ranging area about this on its website. Other organizations, such as the Medical Group Management Association, have information and may present seminars from time to time. Perhaps the best resource is colleagues who have already gone through the process.

“When we started looking into this, it seemed very daunting,” says Leffert, whose small practice includes two physicians, two nurse practitioners, and a dietician. “Physicians are already busy seeing patients and dealing with day-to-day operations. When you add these extra loads, there is plenty of reason to put it off for a while. As with many things in business, once you find the process that best fits your particular situation, it isn’t really an overwhelming task.”

Add in other stressors such as the changeover to the International Classification of Diseases, Tenth Revision, the rise of Accountable Care Organizations, and implementation of the Patient Protection and Accountable Care Act, it is small wonder that practices let PQRS slide until the last minute.

“All carriers are looking at participating or instituting some form of this program sooner rather than later and will favor those practices that comply,” says Scheel. “The era of massive data collection is already here. If you don’t want to comply, perhaps the only alternative is a concierge practice that only accepts cash.” **EN**

— Ullman, RN, MHA, is an Indiana-based freelance writer with nearly 30 years of experience.



# The FRENZY Over FRUCTOSE

The debate rages on over the sweetener's role in obesity and disease.

By Terri D'Arrigo

Ask a clinician about the dietary effects of fructose, and you'll likely get an impassioned response. Not since the low-fat vs. low-carb wars of the 1990s has a nutritional topic received so much media attention and garnered so much debate in the medical and scientific communities. At the heart of the debate lies the role of fructose in America's battle with obesity and its related metabolic disorders. Some researchers say fructose is particularly lethal, while others question the value of singling fructose out, and maintain that obesity is driven simply by consuming more energy than one needs.

"The people who say a sugar is a sugar are calorie-centric, and it's probably true from a caloric standpoint that fructose and other sugars are equal," says Michael I. Goran, PhD, professor of preventive medicine, physiology and biophysics, and pediatrics at the University of Southern California's Keck School of Medicine. "But that misses the consequences of the metabolic fate of different sugars. This issue goes well beyond calories."

Earlier this year Goran and colleagues published a paper in *Global Public Health* in which they noted that countries that use high fructose corn syrup (HFCS) in their food supplies have a 20% higher prevalence of diabetes than countries that do not — even though there

were no significant differences between them in terms of body mass index (BMI) or other dietary variables such as caloric intake and total sugar intake.

Another study, appearing earlier this year in *PLOS One* by Sanjay Basu, MD, PhD, assistant professor of medicine at the Stanford Prevention Research Center and his colleagues, found that every 150-calorie increase per person per day in sugar availability was associated with increased diabetes prevalence by 1.1%.

## Metabolic Mayhem

Fructose has been the subject of research going back to the 1950s, when a team at Harvard University demonstrated that fructose could induce insulin resistance in rats, results replicated in enough laboratories since then that it's accepted as fact.

"There is unequivocal evidence in careful biologic studies in animals and cell culture that clearly document that fructose has effects independent of its calories," says Richard J. Johnson, MD, professor in the Department of Medicine at the University of Colorado-Denver. "If you feed animals either fructose or glucose and they all eat the same number of calories, the ones that eat fructose will have worse metabolic features

than those that eat glucose.”

Johnson adds that fructose is well-known to cause other problems in animals as well, such as fatty liver, high triglycerides, and resistance to leptin, a hormone that helps to control appetite. Last year, he and his colleagues published a paper in the *Journal of Biological Chemistry* in which they suggest that high levels of uric acid induced by fructose play a role in metabolic syndrome and the development of diabetes by causing oxidative stress in cells.

Research has borne similar results in humans. Several small studies, such as a trial in women led by the University of Pennsylvania’s Karen Teff, PhD, in 2004, suggests that fructose contributes to obesity because it does not stimulate insulin and leptin.

Leptin is of great concern for Robert Lustig, MD, MSL, professor of pediatrics in the Division of Endocrinology at the University of California, San Francisco, member of the Endocrine Society’s Obesity Task Force, and one of Basu’s co-authors.

“Leptin tells the brain to burn energy at normal levels. It’s the signal to the brain of peripheral energy adequacy. When insulin goes up, it interferes with brain leptin signaling, which the brain reads as starvation,” Lustig says.

As a result, consuming fructose does not lead to a feeling of fullness and instead promotes a distinct lack of energy that makes it difficult for people to find the motivation to exercise, he adds. “The biochemistry actually changes the behavior.”

In the January 2 issue of the *Journal of the American Medical Association*, research at Yale University led by Kathleen Page, MD (now with USC’s Keck School of Medicine) suggests that fructose and glucose affect the brain differently. In a small, blinded study of healthy adults who were given drinks with either fructose or glucose, the team found that after glucose-sweetened drinks, the participants’ bodies produced insulin and activity slowed in the hypothalamus, the area of the

brain that stimulates appetite. The participants also said they didn’t feel as hungry. However, after the fructose-sweetened drink, they experienced almost no increase in insulin, the hypothalamus remained active, and they said they felt hungrier.

Evidence has begun to point to a darker side of fructose. Kimber Stanhope, PhD, RD, associate research nutritional biologist in the Department of Molecular Biosciences at the University of California at Davis, has led two studies that fuel the debate. In one, the team compared the effects of consuming 25% of calories from either fructose or glucose in overweight and obese participants — the maximal intake level of calories from added sugar suggested in the 2010 Dietary Guidelines for Americans. As described in the May 2009 issue of *The Journal of Clinical Investigation*, the team found that although both groups of patients gained similar amounts of weight, the fructose group experienced increased fat production in the liver and increased intra-abdominal fat, which raises cardiovascular risk

more than subcutaneous fat. Fasting glucose and insulin levels increased and insulin sensitivity decreased in the fructose group as well.

In the other study, appearing in the October 2011 issue of the *Journal of Clinical Endocrinology and Metabolism*, the team compared the effects of fructose, HFCS, and glucose

as 25% of total calories in adults between 18 and 40 years old with a lower average BMI than the participants in the previous study, including participants with BMIs as low as 18. This time, the fructose and HFCS groups experienced increased risk factors for cardiovascular disease such as higher post-meal triglycerides and higher fasting and post-meal concentrations of LDL cholesterol compared to the glucose group.

Stanhope points to fructose metabolism in the liver as a likely culprit. “Fructokinase, the enzyme that regulates the uptake and metabolism of fructose in the liver, is turned on all the time. Therefore whether the liver

**“Fructose *per se* is not likely to be the problem, but rather the manner in which we consume it.**

Unprocessed sources of fructose, as in fruit, digest more slowly and do not overwhelm the liver.”

— David S. Ludwig, MD, PhD, director of the New Balance Foundation Obesity Prevention Center and the Optimal Weight for Life Clinic, Boston Children’s Hospital

## AT-A-GLANCE

- Studies suggest that overloading the liver with highly processed fructose increases risk for diabetes and cardiovascular disease.
- Some researchers question the value of singling fructose out because fructose is usually consumed with glucose.
- Americans consume 240 more calories per day today than they did in 1971, which some researchers say is the real problem driving obesity and its related diseases.

needs energy or not, nearly all the fructose from the beverages ends up in the liver. The metabolic pathways become overloaded and the result is increased fat and uric acid production.”

Studies such as these are enough to make Goran leery of fructose. “You can’t dispute the metabolic machinery of the cell,” he says.

“The question is now about tipping the balance. How much more fructose do you need to produce a metabolically damaging effect and send you down the path toward diabetes? We should all be consuming less sugar, but if you had to choose, [know that] added sugar that contains fructose is going to be more damaging [in general],” Goran adds, noting that current food labeling does not spell out how much fructose or HFCS is in a product. “In a previous study, we measured fructose in sodas and showed that it may be higher than we think.”

### Fructose in a Vacuum?

Some critics of current fructose research question the usefulness of singling out fructose.

“The effects [of fructose and glucose] may be somewhat different based on chemical structures, but rather than substitute one for the other, let’s instead focus on reducing all highly processed carbohydrates because they all have adverse effects,” says David S. Ludwig, MD, PhD, director of the New Balance Foundation Obesity Prevention Center and the Optimal Weight for Life Clinic at Boston Children’s Hospital.

Ludwig stresses that fructose occurs naturally in fruit, and that people who eat several servings of fruit daily tend to have better health.

“Fructose per se is not likely to be the problem, but rather the manner in which we consume it. Unprocessed sources of fructose, as in fruit, digest more slowly and do not overwhelm the liver,” Ludwig says, adding that it would be a disservice to tell patients not to eat fruit.

“We don’t consume fructose by itself. We always consume it with glucose,” says James Rippe, MD, professor of biomedical sciences at the University of Central Florida, who also serves as a consultant to the Corn Refiners Association. “Sucrose, the leading sweetener worldwide, is half fructose and half glucose. High-fruc-

tose corn syrup, the second-leading sweetener, is also glucose and fructose, with the most common form being 55% fructose and 45% glucose.”

Rippe says what happens in the lab is different than what happens on the plate. “A lot of confusion comes into this because people compare large amounts of pure fructose to large amounts of pure glucose to show that they behave differently, but we don’t consume them separately.”

He adds that studies that supply 25% of calories as either fructose or glucose, as Stanhope and other researchers have done, exceed average consumption. “It’s an artificial condition, and it’s not relevant to human nutrition.”

Nonetheless, Rippe and his colleagues conducted a study in which participants with an average age of 42 were assigned one of three different levels of sucrose or HFCS at 8%, 18%, or 30% of the calories required for weight maintenance. Their results, published in the June 2013 issue of *Applied Physiology, Nutrition, and Metabolism*, indicated no change over the course of 10 weeks in the fat content of the liver or several major muscle groups.

“I’m not in any way recommending that people consume excessive amounts of sugar, but I’m saying that there is no demonstrated harm from up to 25% of calories from added sugar,” Rippe says, adding that researchers should instead consider the overall increase in daily calories consumed by Americans in the last 30 years.

According to survey data from the nine National Health and Nutrition Examination Surveys conducted between 1971 and 2010, average daily total intake rose 314 calories from 1971 to 2003. Although it then fell 74 calories between 2003 and 2010 — with no corresponding dip in obesity rates — there remains a net gain of 240 more calories per day in 2010 compared to 1971.

“When you look at the increase in calories, focusing on fructose is like chasing a zebra in a herd of horses,” Rippe says. “The fact is that we [as a nation] are eating too much of everything, and until we get people to pay attention to their overall diet, that isn’t going to change. If I could wave a magic wand and take away all fructose, I don’t think anything would change.” **EN**

— *D’Arrigo is a health and science writer based in Holbrook, N.Y., and a regular contributor to Endocrine News*



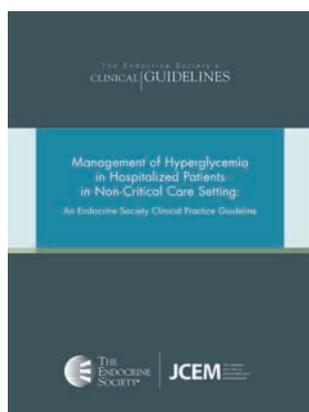
“How much more fructose do you need to produce a metabolically damaging effect and send you down the path toward diabetes? WE SHOULD ALL BE CONSUMING LESS SUGAR, but if you had to choose, added sugar that contains fructose is going to be more damaging.”

— *Michael I. Goran, PhD, professor of preventive medicine, physiology and biophysics, and pediatrics, University of Southern California’s Keck School of Medicine*

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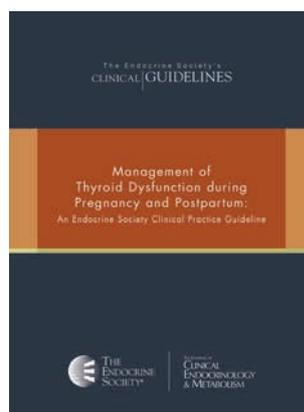
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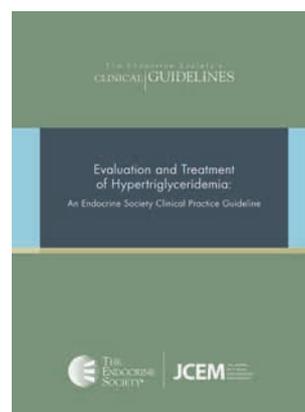
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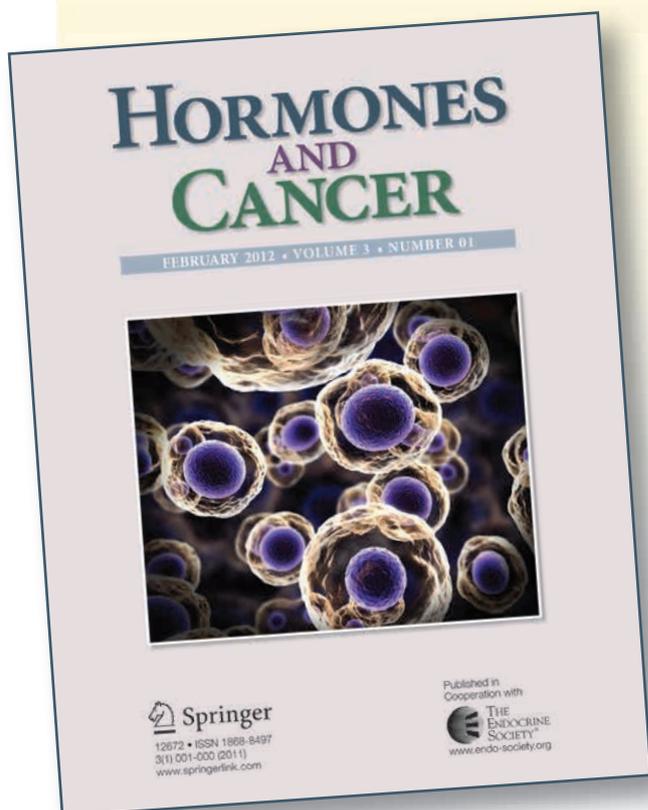
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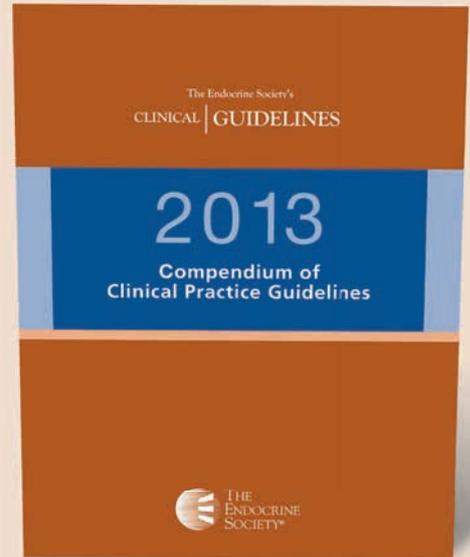
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- Endocrine and Nutritional Management of the Post-Bariatric Surgery Patient
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- Evaluation and Management of Adult Hypoglycemic Disorders
- Endocrine Treatment of Transsexual Persons
- Evaluation and Treatment of Adult Growth Hormone Deficiency
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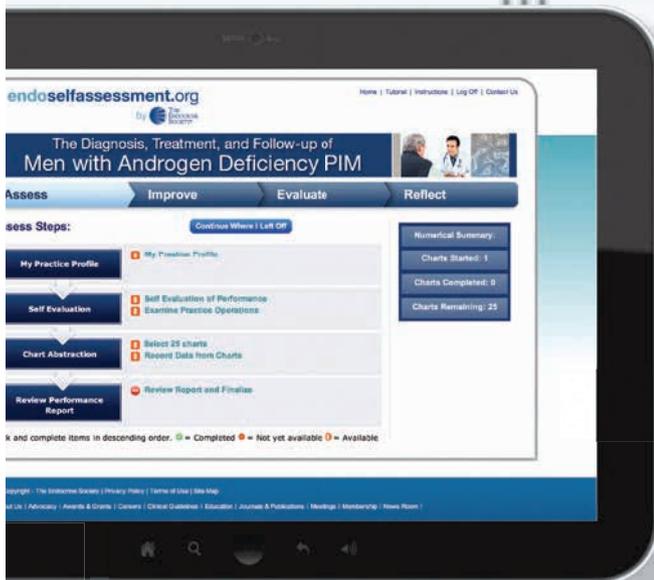
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### **About the Position at Geisinger-Patton Forrest**

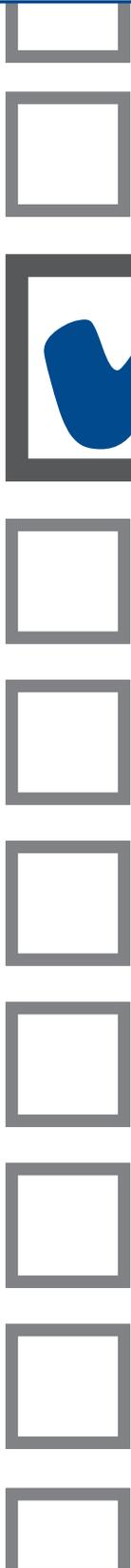
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# VOTE

## 2014 ELECTION FOR OFFICERS AND COUNCILS

The polls are now open for the 2014 Election and you are encouraged to vote. All members with voting privileges were sent an electronic ballot in early November. You can access online voting instructions by visiting [www.endocrine.org/election](http://www.endocrine.org/election).

Questions should be directed to Elizabeth Kan at 301.941.0206 or [ekan@endocrine.org](mailto:ekan@endocrine.org).

**BALLOTS WILL BE ACCEPTED  
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Look for the electronic ballots in your e-mail.





## SPOTLIGHT ON SOCIETY POLICY:

### Heinz Center Recognizes Society's Pioneering Work on EDCs



President-elect Santen gives remarks.

The Heinz Center and fellow honorees unanimously recognized the Society's pioneering role in bringing the issues of chemical contaminants into the mainstream through all its efforts to raise awareness of endocrine-disrupting chemicals.

President-elect Richard Santen, MD, represented the Society, giving remarks about the Society's dedication to increasing knowledge of endocrine-disrupting chemicals (EDCs) and their effects. Society members John Peterson (Pete) Myers, PhD, and Tracey Woodruff, PhD, are active in efforts to raise awareness of EDCs — working both with the Society and independently — and were instrumental in planning and coordinating the event. CEO Scott Hunt and Senior Director of Advocacy and Policy Programs Mila Becker also attended on behalf of the Society.

### Society Instrumental in Advancing Global EDC Action

The Endocrine Society is committed to improving awareness and understanding of EDCs in the U.S. and globally. Since the 2009 release of its Scientific Statement on EDCs, the Society has advocated for more research on EDCs and for the endocrine perspective to be incorporated into chemical risk assessment paradigms.

In August, the Society participated in an important policy meeting in Mexico City to convey its messages to officials in the Latin American and Caribbean region. Meeting participants, comprising representatives of more than 25 countries, industry, and civil society, passed a resolution to advance regional knowledge of EDCs under the Strategic Approach to International Chemicals Management (SAICM), a global policy framework to protect people and the environment from hazardous chemicals. Introduced by IPEN (International POPs Elimination Network), the resolution calls for concrete action pursuant to a 2012 decision by SAICM's governing body on the need to protect "humans, ecosystems, and their constituent parts" around the world from EDCs. It is an important step in raising awareness of EDCs among global policymakers; it will be a foundation for discussions in the upcoming regional SAICM meetings in Europe, Africa, and Asia to be held through early 2014. IPEN has indicated that the Society's presence and commitment to this issue are very influential in advancing key policy actions such as this resolution.

The Society can only accomplish its global policy goals through the dedication of its members. For this meeting, Society member Patricia Joseph-Bravo, PhD, served as the Society's regional representative, network-



Left to right: Linda Giudice, MD, PhD, MSc, ASRM president; Richard Santen, MD; Alison Carlson, Forsythia Foundation president; Society member Tracey Woodruff, PhD, UCSF School of Medicine; Society member Pete Myers, PhD, Heinz Center Chair; Jeanne A. Conry, MD, ACOG president; and Conn Nugent, Heinz Center president.

### President-Elect Santen Gives Remarks

On October 2, the H. John Heinz III Center for Science, Economics and the Environment sponsored a high-profile event titled "Presidents for Prevention." The event was supported by the Forsythia Foundation and held at 101 Constitution Avenue in Washington, D.C., amidst the early chaos of the government shutdown. Despite the unexpected challenges brought on by the shutdown, the room was filled with interested and engaged individuals from key stakeholder groups.

The Heinz Center honored the Society, American College of Obstetricians and Gynecologists, and American Society of Reproductive Medicine for their dedication to improving public health through increased awareness of environmental contributors to disease.



## SEQUESTER, SHUTDOWN and more

ing with prospective partners and identifying steps to improve knowledge in her home country of Mexico. As a first step, Joseph-Bravo has initiated discussions with colleagues to institute a monitoring program to identify sources of exposure to EDCs in Mexico City. Such a program would be a big step forward in increasing awareness of the risks of EDC exposure in the area.

Society member R. Thomas Zoeller, PhD, presented evidence of EDC effects in humans, drawing heavily from the recent report from the World Health Organization and United Nations Environment Program, on which Zoeller served as a primary editor. He also presented information from The Endocrine Society's 2012 Statement of Principles and from reports published in the Society's journals. **EN**

The Endocrine Society has been extremely active in advocacy to protect the National Institutes of Health (NIH) from further budget cuts. During September, the Society:

- Conducted three Hill Days and visited dozens of congressional offices
- Published letters-to-the-editor in *The New York Times* and local newspapers across the country
- Conducted an e-advocacy campaign that sent hundreds of emails to Congress
- Conducted a call-in campaign to Congress
- Provided Society members with up-to-date information about how the shutdown would affect their research grants

For the latest information about federal budget cuts and how you can join the Society's advocacy efforts, please visit [www.endocrine.org](http://www.endocrine.org) and "click" the Advocacy & Outreach button.



### Rally for MEDICAL RESEARCH

The Endocrine Society participated in a "Rally for Medical Research" Hill Day on October 18. Andrea Gore, MD and Joanna Spencer-Segal, MD and Society GPA staff joined hundreds of other representatives from research and patient advocacy groups in visits to congressional offices to discuss the need to protect biomedical research from further federal budget cuts. During September the Society met with dozens of congressional offices to share our message and has been recognized as one of the most visible professional medical societies on the Hill.

## EndoCareers

### How to Expedite the Process of Translational Medicine From Discovery Into Action

The term “translational research” first appeared in *PubMed* in 1993, and since then, more than 9,000 citations can be found with the terms “translational medicine” or “translational research.” Given the fact that translational medicine is a new discipline, this is a remarkable achievement.

There are many definitions for translational medicine or translational research. Perhaps the broadest definition is from the NIH, which defines translational research as “the process of applying discoveries generated during research in the laboratory (preclinical studies) to the development of trials and studies in humans, and then enhancing the adoption of best practices in the community.”

This process of translation from the laboratory to clinical practice, then to the community and back, involves a wide array of professionals such as basic scientists, biotechnologists, clinicians, financial investors, ethicists, regulators, policy-makers, and politicians.

#### Why is Translational Medicine Important?

There are many obstacles in the process by which traditional research is conducted and translated into real-life applications. Research is compartmentalized: Basic scientists are not generally trained to think of the clinical application of their work; clinicians are often not taught to formulate research studies based on clinical observations; public health scientists may not have a strong background in basic or clinical research (but have the knowledge of the community the other two groups may lack); and policy-makers/politicians do not under-

stand the research process.

Essentially, there is no effective communication between the professionals involved in the different steps of research, making the translation into real-life applications lengthy, ineffective, and expensive. Most potential drugs do not make it to market, creating what is known as a “valley of death,” where ideas die for lack of funding.

The importance of translational medicine on human health has been wisely delineated in an editorial by Fontanarosa and DeAngelis in 2002 in *JAMA*: “Effective translation of the new knowledge, mechanisms, and techniques generated by advances in basic scientific research into new approaches for the prevention, diagnosis, and treatment of disease is essential for improving health.”

By promoting the development of new methods and approaches that allow effective interactions between professionals and researchers across disciplines, translational medicine promotes the movement away from a small-scale industry of individual efforts to a systematic, cross-disciplinary effort. In that way, translational medicine turns research into one smooth and rapid process of discovery, clinical application, and public knowledge. Ultimately, research breakthroughs can become available to humanity sooner and at lower costs.

Beginning in 2000, translational medicine gained prominence and appeared in several hundred articles each year. In the U.S., the NIH launched the CTSA (Clinical and Translational Science Awards) program to construct a consortium of 60 Clinical and Translational Science Centers (CTSCs) at universities and medical centers across the

country, aiming at making translational research an integral part of biomedical research. In addition, several translational research journals have been created to spread knowledge that is able to fill the gaps of both basic and human research.

#### Where Does Translational Medicine Fit in Endocrinology?

The Endocrine Society, a trans-disciplinary society that fosters endocrine research at all stages, has a strong track record in supporting translational research and in promoting the integration between basic and clinical researchers, leading to the acceleration of discovery and to its application toward human health. The Endocrine Society acknowledges the importance of the CTSA program and has been providing input to the National Center for Advancing Translational Sciences (NCATS) on how to better structure and position the CTSA program.

Multidisciplinary articles are published by all of The Endocrine Society’s journals, and translational studies are particularly highlighted in *Translational Endocrinology & Metabolism*, *Hormones and Cancer* (published by Springer in cooperation with The Endocrine Society), and *Translational Research in Endocrinology & Metabolism*, all freely accessible by members. Moreover, in the last few years, sessions at our Annual Meeting have been categorized into Basic, Clinical, and Translational, making it easy for attendees to identify translational endocrinology sessions. **EN**

— Gilberto Paz-Filho, MD is research fellow and convenor of the Master of Translational Medicine Program, The Australian National University.



THE ENDOCRINE SOCIETY'S 96th ANNUAL MEETING & EXPO

## ICE/ENDO 2014

### Key Dates and Deadlines

**Member registration opens:**  
October 23, 2013

**General registration opens:**  
November 14, 2013

**Abstract submission opens:**  
December 3, 2013

**Abstract submission closes:**  
January 29, 2014

**Early registration closes:**  
April 9, 2014

**Registration closes:**  
May 14, 2014

**URL:**  
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**At the time of submission, no abstract may contain data already accepted for publication in any online or PubMed Indexed venue. Furthermore, abstracts may not contain data previously presented at a national meeting within the U.S. at the time of submission.**

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Is your research ready for the big stage? **ICE/ENDO 2014**, coming to Chicago in June, is a rare opportunity to gain exposure for your work and experience presenting at the world's largest gathering of endocrinologists.

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NETWORK

For more than ten years, the Hormone Health Network has been the go-to resource for delivering trusted, clinically accurate, patient-friendly information on endocrine-related disorders.

With more than 100 **FREE** Fact Sheets and Patient Guides in both English and Spanish, the Hormone Health Network and The Endocrine Society are committed to helping patients better understand their condition and treatment options.

Your contribution is a vital part of creating and distributing these valuable resources.

**Making a donation to the Hormone Health Network has never been easier. Here's how to give:**

1. Use the form provided and send your gift via mail
2. Visit our website at [www.hormone.org/donatenow](http://www.hormone.org/donatenow)
3. Use your annual Society membership renewal form and check the box for Network donations





# Medicines and Bone Loss

Some types of medicines can cause bone loss, making your bones weak, if used for a long time. Use over a short time is usually not a problem. When you have weak bones—a condition called osteoporosis—your risk of bone fractures goes up. Broken bones can lead to pain and disability. For example, some older people who break a hip may lose their ability to function independently.

## DID YOU KNOW?

**Normally, your body continuously removes old bone and replaces it with new bone. Bone loss occurs when old bone breaks down faster than new bone can form.**

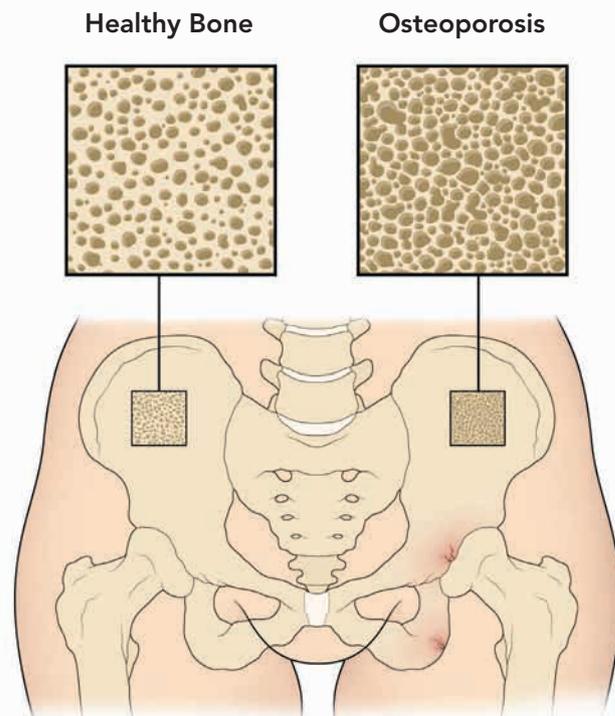
## WHICH MEDICINES CAN CAUSE BONE LOSS?

A number of medicines can cause bone loss if used over the long term (several years). Some common ones include

- Glucocorticoids, also called steroids, such as cortisone and prednisone. They are used to treat arthritis, asthma, lupus, multiple sclerosis, and other conditions.
- Some medicines such as phenytoin and phenobarbital, used to treat epilepsy.
- Gonadotropin-releasing hormone agonists (GnRH agonists), such as goserelin acetate and leuprolide acetate. They are used to treat endometriosis, prostate cancer, or female infertility.
- Aromatase inhibitors, such as anastrozole, exemestane, and letrozole. They are used to treat breast cancer.

Some people who take thyroid hormone worry about bone loss. The doses of thyroid hormone used to treat hypothyroidism (underactive thyroid) don't harm bone and shouldn't be cause for concern. Only high doses, used for thyroid cancer treatment, can cause bone loss.

High doses or long-term use of medicines called proton pump inhibitors (PPIs) can raise the risk of bone loss. PPIs, such as esomeprazole, lansoprazole, and omeprazole, are used for GERD (acid reflux), peptic ulcer, or heartburn. However, getting enough calcium and vitamin D may be enough to lower the risk.



Experts don't know yet whether selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine and escitalopram, increase fracture risk. Some studies show a small effect on bone but others do not. SSRIs are used for depression and obsessive-compulsive disorder. Talk to your doctor if you take an SSRI and are concerned about bone loss.

### OTHER MEDICINES THAT MAY CAUSE BONE LOSS

Medicine	Used For
Antacids that contain aluminum	Heartburn
Chemotherapy drugs	Cancer
Cyclosporine and tacrolimus	Preventing rejection of organ transplant
Heparin	Preventing blood clots
Loop diuretics such as furosemide and torsemide	Heart failure, edema (tissue swelling), some kidney problems
Medroxyprogesterone acetate	Contraception
Methotrexate	Cancer and rheumatoid arthritis
Thiazolidinediones such as pioglitazone and rosiglitazone	Diabetes

### HOW IS BONE STRENGTH MEASURED?

A bone mineral density test called a DEXA scan—a type of very low dose X-ray—checks bone mass (the amount of calcium and other minerals in your bones). This test can show early bone loss before the more serious condition of osteoporosis occurs.

### WHAT CAN I DO TO PREVENT BONE LOSS AND AVOID FRACTURES?

Talk with your doctor about what's best for you. Your doctor may advise you about

- **Adjusting your current medicines.** If your medicines may cause bone loss, make sure that you are taking the lowest possible dose for the shortest possible time.
- **Taking osteoporosis medicines.** Some medicines can prevent or treat osteoporosis. The most common type, called a bisphosphonate, is taken as a pill by mouth or as a liquid through a vein. This type of medicine keeps bones strong by helping the bones retain calcium.
- **Getting enough calcium and vitamin D.** Calcium and vitamin D are found in some foods. Good sources of calcium include milk, yogurt, cheese, collard greens, and foods with added calcium, such as cereal and soy drinks. Vitamin D, which helps the body absorb calcium, is made in the skin when people

spend time in the sun. It's also found in salmon, shrimp, and milk with added vitamin D. You may also need dietary supplements to get enough calcium and vitamin D.

- **Exercising regularly.** Two kinds of exercise help keep bones strong: weight-bearing exercise, such as walking, running, dancing, and climbing stairs; and exercise that strengthens muscles, such as lifting weights.
- **Choosing a healthy lifestyle.** Avoiding smoking can help keep bones strong. Smoking may lower the amount of calcium that the body can absorb. Some studies also show that drinking a lot of alcohol might weaken bones.

### Questions to ask your doctor

- Do any of my medicines cause bone loss?
- Are there different medicines I can take?
- Do I need a bone density test?
- What should I do to protect my bones?
- Should I be taking medicine to protect my bones?
- Should I see an endocrinologist?

### RESOURCES

- Find-an-Endocrinologist: [www.hormone.org](http://www.hormone.org) or call 1-800-HORMONE (1-800-467-6663)
- Hormone Health Network information about glucocorticoid-induced osteoporosis: [www.hormone.org/Resources/upload/FS\\_OBH\\_Glucocorticoid\\_induced\\_Osteoporosis\\_EN-6-12.pdf](http://www.hormone.org/Resources/upload/FS_OBH_Glucocorticoid_induced_Osteoporosis_EN-6-12.pdf)
- Hormone Health Network information on osteoporosis: [www.hormone.org/Osteoporosis/index.cfm](http://www.hormone.org/Osteoporosis/index.cfm)
- Mayo Clinic information about osteoporosis: [www.mayoclinic.com/health/osteoporosis/DS00128](http://www.mayoclinic.com/health/osteoporosis/DS00128)
- National Osteoporosis Foundation: [www.nof.org](http://www.nof.org)
- National Institutes of Health:
  - MedlinePlus (about osteoporosis): [www.nlm.nih.gov/medlineplus/osteoporosis.html](http://www.nlm.nih.gov/medlineplus/osteoporosis.html)
  - MedlinePlus (about medicines): [www.nlm.nih.gov/medlineplus/druginformation.html](http://www.nlm.nih.gov/medlineplus/druginformation.html)
  - Osteoporosis and Related Bone Diseases National Resource center: [www.niams.nih.gov/Health\\_Info/Bone/Osteoporosis/overview.asp](http://www.niams.nih.gov/Health_Info/Bone/Osteoporosis/overview.asp)

### EDITORS

Jens Bollerslev, MD  
Steven T. Harris, MD  
Benjamin Z. Leder, MD

April 2013

The Hormone Health Network offers free, online resources based on the most advanced clinical and scientific knowledge from The Endocrine Society ([www.endo-society.org](http://www.endo-society.org)). The Network's goal is to move patients from educated to engaged, from informed to active partners in their health care. This fact sheet is also available in Spanish at [www.hormone.org/Spanish](http://www.hormone.org/Spanish).

Medicines and Bone Loss Fact Sheet



[www.hormone.org](http://www.hormone.org)

## Hunt Testifies Before D.C.'s COMMITTEE ON FINANCE & REVENUE

On September 24, Endocrine Society CEO Scott Hunt spoke before the District of Columbia's Committee on Finance & Revenue regarding over \$15 million in tax-exempt revenue bonds that would finance a portion of the cost of the Society's move from its current location in suburban Maryland into Washington D.C.

Hunt, a District resident for almost 30 years, said that he was pleased to bring the Society "from the suburbs to my city, in the heart of town." Accompanying Hunt to make his case in the council chamber at the John A. Wilson Building were Society COO John Heberlein and legal counsel Richard Newman of Arent Fox.

According to Hunt, the Society would use the proceeds of the bonds to finance the majority of the costs associated with the purchase, build-out, and equipping a portion of the new headquarters located at 2055 L Street NW. The Society will acquire the sixth floor of the building on November 1; the move-in is scheduled for February 2014. "The bonds would allow the Society to reduce its costs, without adding any direct or indirect financial burden or risk to the District government or its citizens," Hunt explained.

Councilperson Jack Evans, who represents Ward 2, serves as the chair of the Committee on Finance and Revenue and presided over the meeting. "I am pleased to have a company of your stature move into D.C.," he said, adding that he was pleased to put his support behind the bond issue.



(L to R) Society CEO Scott Hunt, Washington D.C. Councilperson Jack Evans, and Society COO John Heberlein.

When the Society makes the move into the District, it will literally be right next door to another major medical society, the American Society of Hematology, and within a short walk or cab ride of several others including the American College of Cardiology, the American College of Obstetricians and Gynecologists, the Society for Neuroscience among many more. "The Society's presence will reinforce to other peer societies the value of being located in the District," Hunt said. **EN**

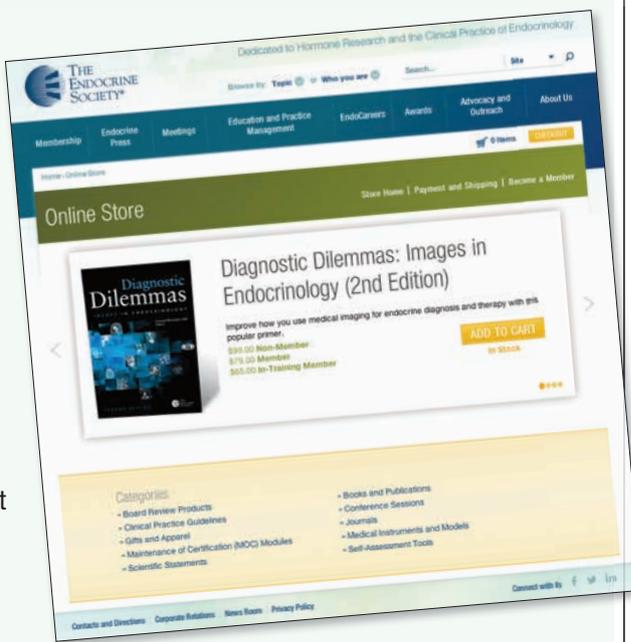
## BETTER ONLINE FUNCTIONALITY for Members

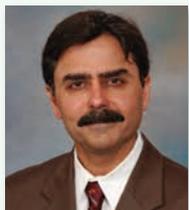
The Endocrine Society has two great new technology advances that will help both you and Society staff — a new database and a new online store.

The database, powered by Avectra's netFORUM software, is a key component of "Direction IV: Capacity to Lead" in Strategic Plan III. This new technology allows the Society to better serve the many diverse needs of our members. It also allows you to easily find pertinent information on the website, locate like-minded professionals, and update your profile and account information whenever you like. You can now use either your Member ID or email address to log on and will be prompted to update your password the first time you sign in.

The new online store lets you check out fast and easy with a new single-page checkout process — you'll be amazed at how quickly you can complete transactions. Plus, there are lots of great new products to discover!

Visit [endocrine.org](http://endocrine.org) to see the improvements and [endocrine.org/store](http://endocrine.org/store) to explore all of the products available.





**Sundeep Khosla, MD**  
Laureate Awards  
Committee Chair

## Announcing the 2014 Laureate Award Winners

It gives me great pleasure to announce the 2014 Laureate Award recipients and congratulate each on their outstanding accomplishments. The Endocrine Society's Laureate Awards are presented in recognition of extraordinary achievements in the field of endocrinology. Award recipients are the top clinical and basic scientists, innovators, leaders, educators, and practitioners whose dedication and accomplishments are unmatched. The winners will be honored at ENDO in Chicago, June 21–24, 2014. The 2015 Call for Nominations is now open! To nominate and learn more about the exciting changes to the Laureate Awards, visit [www.endocrine.org/laureate](http://www.endocrine.org/laureate).

### CONGRATULATIONS TO THE 2014 LAUREATE AWARD RECIPIENTS!

Fred Conrad Koch Award

**George P. Chrousos, MD**

Robert H. Williams

Distinguished Leadership Award

**Leslie J. DeGroot, MD**

Sidney H. Ingbar

Distinguished Service Award

**Elliot J. Rayfield, MD**

Distinguished Educator Award

**John P. Bilezikian, MD**

Distinguished Physician Award

**Robert G. Dluhy, MD**

Outstanding Achievement

in Endocrine Science Award

**Ming-Jer Tsai, PhD**

**Sophia Tsai, PhD**

Outstanding Clinical Practitioner

**Paul M. Copeland, MD**

International Excellence Award

**Yutaka Seino, MD**

Edwin B. Astwood Award Lecture

**Domenico Accili, MD**

Gerald D. Aurbach Award Lecture

**Peter J. Tontonoz, MD, PhD**

Roy O. Greep Award Lecture

**David M. Altshuler, MD, PhD**

Clinical Investigator Award Lecture

**James A. Fagin, MD**

Ernst Oppenheimer Award

**W. Lee Kraus, PhD**

Richard E. Weitzman Memorial Award

**Antonio Moschetta, MD, PhD**

### Endocrine Society and AACE Recommend Best Practices in *Choosing Wisely* Campaign

The Endocrine Society was joined by the American Association of Clinical Endocrinologists (AACE) in releasing a list on October 16 of five procedures, tests, or treatments that are often overused and should be given serious consideration by physicians and patients before being used.

The list is part of the American Board of Internal Medicine Foundation's *Choosing Wisely* campaign, which aims to promote conversations between physicians and patients by helping patients choose care that is supported by evidence, not duplicative of other tests or procedures already received, free from harm, and truly necessary. Nearly 60 organizations have participated in the *Choosing Wisely* campaign.

The recommendations identified by the joint task force include:

- Avoid routine multiple daily self-glucose monitoring in adults with stable type 2 diabetes on agents that do not cause hypoglycemia.
- Don't routinely measure 1,25 dihydroxyvitamin D unless the patient has hypercalcemia or decreased kidney function.
- Don't routinely order a thyroid ultrasound in patients with abnormal thyroid function tests if there is no palpable abnormality of the thyroid gland.
- Don't order a total or free T3 level when assessing

levothyroxine (T4) dose in hypothyroid patients.

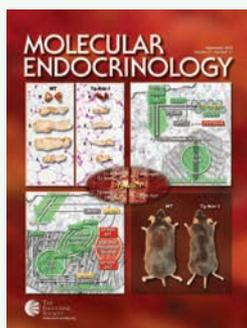
- Don't prescribe testosterone therapy unless there is biochemical evidence of testosterone deficiency.

"These recommendations give endocrinologists a platform to engage patients in important discussions about their health and the benefits of various treatment options," says Endocrine Society President Teresa K. Woodruff, PhD. "We are pleased to be empowering patients and physicians to be true partners in determining the wisest course of care for each individual."

Members of The Endocrine Society along with representatives of AACE formed a joint task force to identify tests or procedures that should only be used in specific circumstances. With input from members of the Society's Council, Clinical Affairs Core Committee, and AACE's Board of Directors and other leaders, the task force selected the final list based on the amount of evidence supporting each item, the value of the recommendation to practitioners, and the potential for cost savings.

Society members who worked on compiling this list were Robert Lash, MD, (chair), Nelson Watts, MD, Steve Nagelberg, MD, Grazia Aleppo, MD, Fran Kaiser, MD, Daniel Einhorn, MD, FACP, FACE, Doug Ross, MD, and J. Woody Sistrunk, MD.

To learn more about *Choosing Wisely* and to view the complete lists and additional detail about the recommendations and evidence supporting them, visit [www.ChoosingWisely.org](http://www.ChoosingWisely.org).



## MOLECULAR ENDOCRINOLOGY IS MOVING TO ONLINE ONLY

### JANUARY 2014

Beginning in January 2014, *Molecular Endocrinology* will only be available in the format that appeals most to its readers: online, linked, and easily searchable. December 2013 is the last issue of *Molecular Endocrinology* that will be published in print format.

Members won't need to adjust anything — this will happen automatically and the online subscription will be noted during the annual membership renewal. Members who receive a print copy of the journal will be given the option to switch to another print journal or choose online-only access.

*Molecular Endocrinology* online — enhanced search ability, efficient functionality, and now it's going green, too!

Questions? Please contact Society Services via email at [SocietyServices@endocrine.org](mailto:SocietyServices@endocrine.org) or via phone at +1.301.941.0210 (1.888.363.6762 toll-free in the U.S.), Monday-Friday, 8:30 a.m. – 5:00 p.m. ET.

Subscribers will have an option to purchase hard copies of the journal using a print-on-demand feature.

## Event CALENDAR

**NOVEMBER 2, 2013, PHOENIX, ARIZ.**  
Endocrine Essentials for Primary Care  
[www.endocrine.org/meetings/regional/endocrine-essentials-live](http://www.endocrine.org/meetings/regional/endocrine-essentials-live)

**NOVEMBER 9-13, 2013, SAN DIEGO, CALIF.**  
Society for Neuroscience Annual Meeting  
[www.sfn.org/](http://www.sfn.org/)

**NOVEMBER 12-15, 2013, CANCUN, MEXICO**  
Highlights of ENDO: Mexico; Mexican Endocrine Society Mtg.  
[www.endocrine.org/meetings/international/highlights-of-endo/mexico](http://www.endocrine.org/meetings/international/highlights-of-endo/mexico)

**NOVEMBER 13-16, 2013, JAKARTA, INDONESIA**  
AFES 2013, The 17th Congress of The ASEAN Federation of Endocrine Societies  
[www.afes2013.org/](http://www.afes2013.org/)

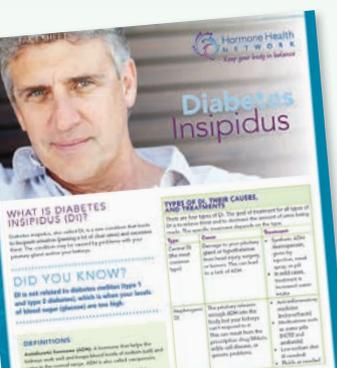
**NOVEMBER 13-16, 2013, NASHVILLE, TENN.**  
ABRCMS — Annual Biomedical Research Conference for Minority Students  
[www.abrcms.org/](http://www.abrcms.org/)

**DECEMBER 2-6, 2013, MELBOURNE, AUSTRALIA**  
World Diabetes Congress  
[www.idf.org/worlddiabetescongress](http://www.idf.org/worlddiabetescongress)

## HHN Fact sheet DIABETES INSIPIDUS

Diabetes insipidus, also called DI, is a rare condition that leads to frequent urination and is characterized by excessive thirst, despite drinking plenty of fluids. The Hormone Health Network's fact sheet, *Diabetes Insipidus*, explains how the kidneys and bladder typically regulate fluids in the body and how the different forms of DI can disrupt this system by lowering sodium levels in the blood, which can lead to headache, nausea, confusion, seizures or, in rare cases, death. The four main types of DI are listed, including their causes and specific treatment options. While long-term outlook depends on the type of DI, the fact sheet reassures patients that most adults do not have serious problems unless they do not have access to water or other fluids. Brief definitions and a list of suggested questions help patients have more informed conversations with their doctors.

Visit [www.hormone.org](http://www.hormone.org) to view this fact sheet and sign up for *Hormone Hotline*, our monthly e-update, for the latest news on Hormone Health Network publications and events.



**Kathleen Caron**  
Named Chair at UNC  
School of Medicine

The University of North Carolina School of Medicine named Kathleen Caron, PhD, as the new chair of its Department

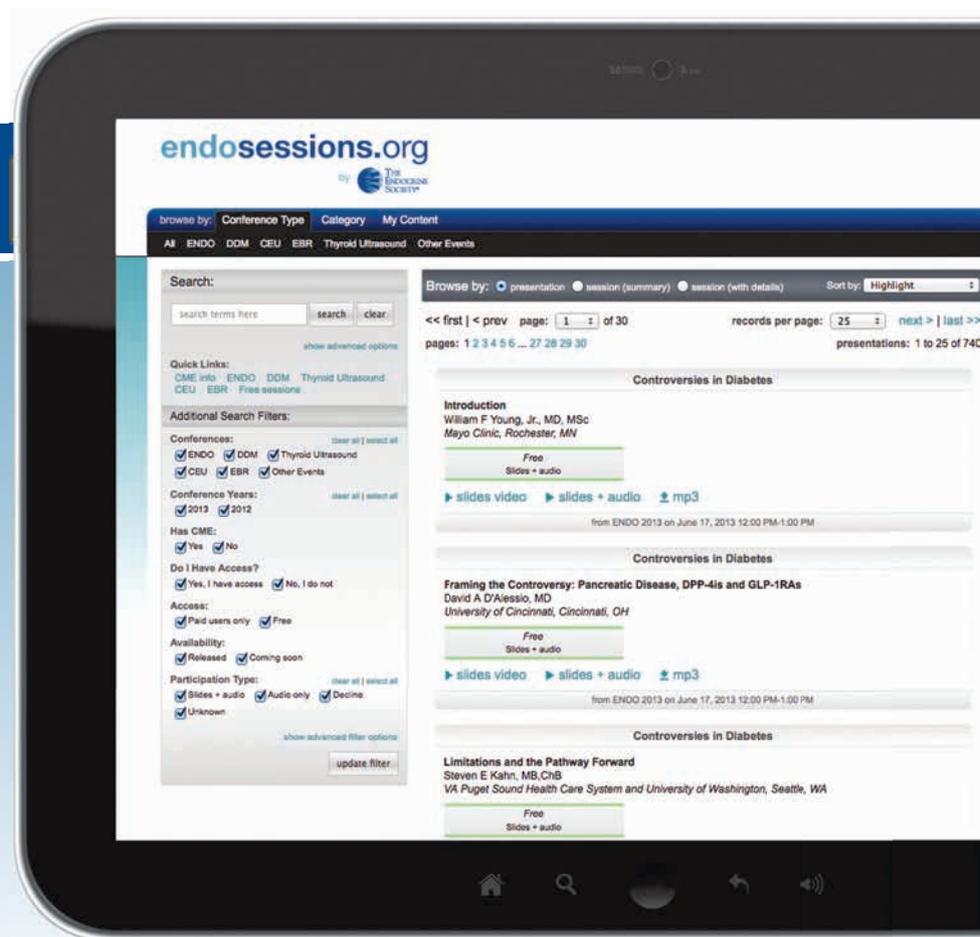
of Cell Biology and Physiology, effective October 1. In her new position, Caron is charged with providing academic and administrative leadership for the research and teaching programs of the department. She will be responsible for the financial health of the department, as well as the recruitment of new faculty to further the missions of the department and the School of Medicine. "Our department has terrific strengths in the areas of neurosciences, cell biology and imaging, and cardiovascular sciences," Caron says. "I look forward to building on those strengths and working with existing and new faculty to expand into new research areas, such as diabetes and endocrinology, degenerative diseases, and aging."

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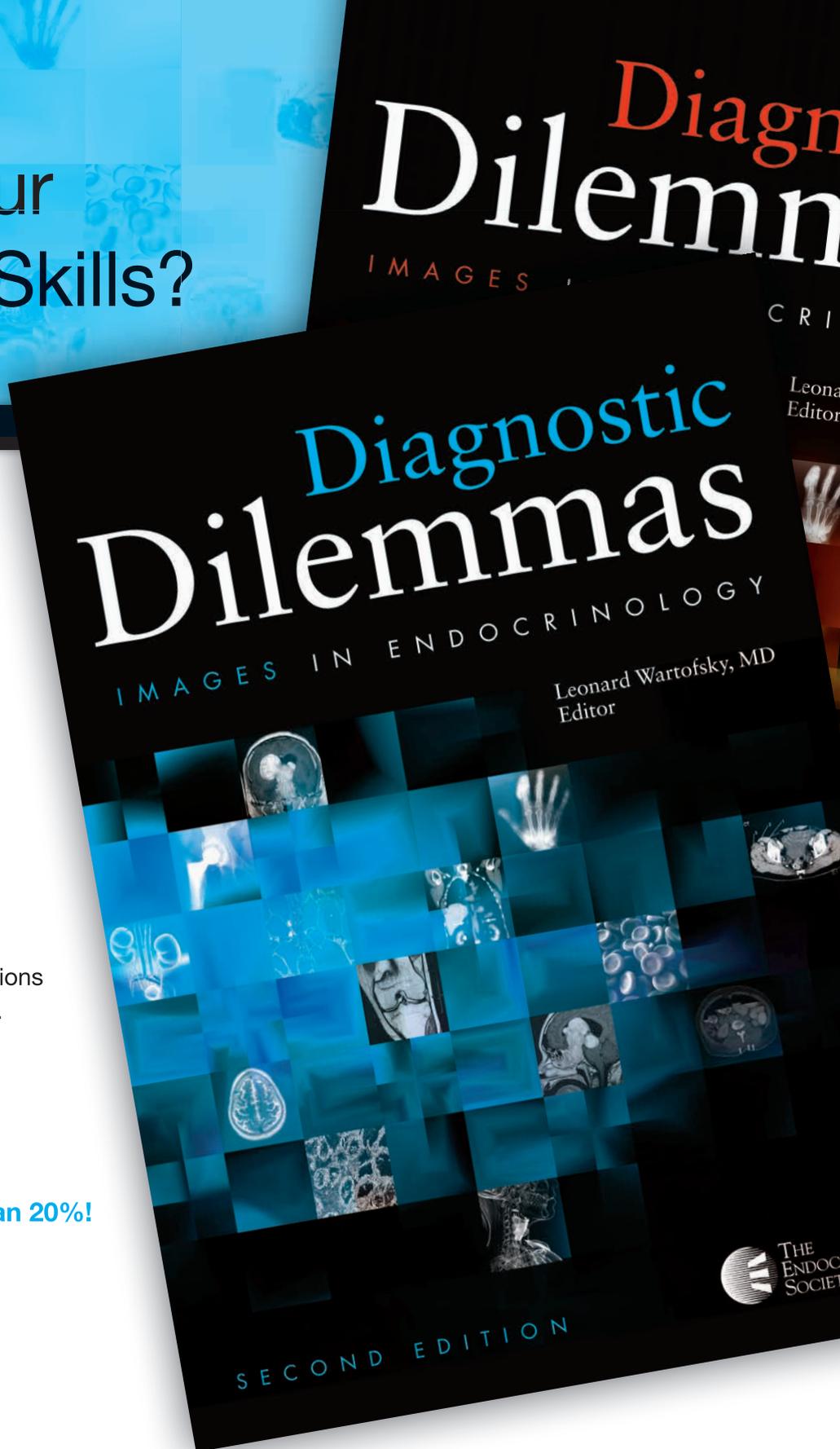
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# Victoza®—a force for change in type 2 diabetes.

For patients like Laura who are uncontrolled on metformin, **Victoza® provides quick and lasting control:**

- HbA<sub>1c</sub> reductions and the additional benefit of weight loss were seen within 12 weeks and sustained for 52 weeks\*<sup>1</sup>

Laura's baseline HbA<sub>1c</sub>

**7.6%**

**BMI**  
32 kg/m<sup>2</sup>

FPG 9.2 mmol/L



**\*Victoza® is not indicated for the management of obesity, and weight change was a secondary end point in clinical trials.**

**Reference:** 1. Pratley R, Nauck M, Bailey T, et al; for the 1860-LIRA-DPP-4 Study Group. One year of liraglutide treatment offers sustained and more effective glycaemic control and weight reduction compared with sitagliptin, both in combination with metformin, in patients with type 2 diabetes: a randomised, parallel-group, open-label trial. *Int J Clin Pract* 2011;65(4):397-407.

#### Prescribing Information

**Victoza®**  
Liraglutide.

Victoza® 6 mg/ml pre-filled pen

1 ml of solution contains 6 mg of liraglutide. One pre-filled pen contains 18 mg liraglutide in 3 ml.  
**Indication:** Treatment of adults with type 2 diabetes mellitus in combination with metformin or a sulphonylurea, in patients with insufficient glycaemic control despite maximal tolerated dose of metformin or sulphonylurea monotherapy; or in combination with metformin and a sulphonylurea, or metformin and a thiazolidinedione in patients with insufficient glycaemic control despite dual therapy. **Posology and administration:** Victoza® is administered once daily by subcutaneous injection and at any time independent of meals however it is preferable to inject around the same time of day. Victoza® should not be administered intravenously or intramuscularly. Recommended starting dose is 0.6 mg daily, after at least one week, the dose should be increased to a maintenance dose of 1.2 mg. Based on clinical response, after at least one week the dose can be increased to 1.8 mg. Daily doses higher than 1.8 mg are not recommended. When added to existing sulphonylureas or in combination with metformin and sulphonylureas, a reduction in the dose of sulphonylurea may be necessary to reduce the risk of hypoglycaemia. Victoza® can be used in the elderly (>65 years) without dose adjustment but therapeutic experience in patients ≥75 years is limited. No dose adjustment for patients with mild renal impairment (creatinine clearance (CrCl) 60-90 ml/min). Due to lack of therapeutic experience Victoza® is not to be recommended for use in patients with moderate (CrCl of 30-59 ml/min), severe (CrCl <30 ml/min) and end-stage renal disease or patients with hepatic impairment or children <18 years. **Contraindications:** Hypersensitivity to the active substance or any of the excipients. **Special warnings and precautions for use:** Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Victoza® is not a substitute for insulin. The addition of Victoza® in patients already treated with insulin has not been evaluated and is therefore not recommended. Limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II and no experience in patients with NYHA class III-IV. Due to limited experience Victoza® is not recommended for patients with inflammatory bowel disease and diabetic gastroparesis. Victoza® is associated with transient gastrointestinal (GI) adverse reactions. GLP-1 analogues have been associated with pancreatitis; patients should be informed of symptoms of acute pancreatitis if pancreatitis suspected, Victoza® and other suspect medicinal products should be discontinued. Thyroid adverse events, including increased blood calcitonin, goitre and thyroid neoplasm reported in clinical trials particularly in patients with pre-existing thyroid disease. Risk of dehydration in relation to GI side effects; take precautions to avoid fluid depletion. No studies on effects on ability to drive and use machinery. Patients advised to take precautions to avoid hypoglycaemia while driving and using machines, in particular when Victoza® is used in combination with sulphonylureas. In the absence of compatibility studies Victoza® must not be mixed with other medicinal products. **Fertility, pregnancy and lactation:** If a patient wishes

to become pregnant, pregnancy occurs or is breast feeding, treatment with Victoza® should be discontinued; use of insulin is recommended instead. Apart from a slight decrease in number of live implants in animal studies no harmful effects on fertility observed. **Undesirable effects:** The most frequently observed adverse reactions from long term phase 3 controlled studies and spontaneous (post-marketing) reports were: Very common (≥1/10): nausea, diarrhoea, hypoglycaemia when used in combination with sulphonylureas, headache when used in combination with metformin and vomiting when used in combination with metformin and rosiglitazone; Common (≥1/100 to <1/10): vomiting, constipation, abdominal pain, discomfort and distension, dyspepsia, gastritis, flatulence, gastroesophageal reflux disease, gastroenteritis viral, toothache, headache, dizziness, nasopharyngitis, bronchitis, hypoglycaemia, anorexia, appetite decreased, fatigue, pyrexia and rash; Not known (cannot be estimated from the available data): Increased heart rate. GI adverse reactions are more frequent at start of therapy but are usually transient. Patients >70 years or with mild renal impairment (CrCl 60-90 ml/min) may experience more GI effects. Consistent with medicinal products containing proteins/peptides, patients may develop anti-liraglutide antibodies following treatment but this has not been associated with reduced efficacy of Victoza®. Few cases of: angioedema (0.05%), acute pancreatitis (<0.2%), injection site reactions (usually mild, approx. 2%). Rates of thyroid adverse events - 33.5, 30.0 and 21.7 events/1000 subject years of exposure for liraglutide, placebo and total comparators; Thyroid neoplasms, increased blood calcitonin and goitres are the most frequently reported thyroid adverse events/1000 subject years of exposure were 6.8, 10.9 and 5.4 of liraglutide treated patients in comparison with 6.4, 10.7 and 2.1 of placebo treated and 2.4, 6.0 and 1.8 of total comparator treated. Few cases of allergic reactions (including urticaria, rash and pruritus) and anaphylactic reactions with additional symptoms (such as hypotension, palpitations, dyspnoea, oedema) have been reported with marketed use of Victoza®. The Summary of Product Characteristics should be consulted for a full list of side effects. **MA numbers and Basic NHS Price:** 2 x 3 ml pre-filled pens EU/1/09/529/002 £78.48; 3 x 3 ml pre-filled pens EU/1/09/529/003 £117.72. **Legal Category:** POM. **Further prescribing information can be obtained from:** Novo Nordisk Limited, Broadfield Park, Brighton Road, Crawley, West Sussex, RH11 9RT. Marketing Authorisation Holder: Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark. **Date last revised:** March 2013.

**Adverse events should be reported. Reporting forms and information can be found at [www.mhra.gov.uk/yellowcard](http://www.mhra.gov.uk/yellowcard). Adverse events should also be reported to Novo Nordisk Limited (Telephone Novo Nordisk Customer Care Centre 0845 6005055). Calls may be monitored for training purposes.**

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July 2013



changing  
diabetes®

At Novo Nordisk we are changing diabetes. In our approach to develop treatments. In our commitment to operate profitably and ethically and in our search for a cure.

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