Low Testosterone: Medical Problem or Marketing Tool?

American men aged 40 years or older tripled their use of androgen replacement therapy (ART) between 2001 and 2011, including a greater than 5-fold surge in use of the hormone testosterone as a topical gel, according to a recent analysis.

Jacques Baillargeon, PhD, from the Department of Preventive Medicine and Community Health and the Sealy Center on Aging, both at the University of Texas Medical Branch in Galveston, and colleagues report their findings in a research letter published in the August 12/26 issue of JAMA Internal Medicine (2013).

Dr. Baillargeon and colleagues studied prescription drug claims data from Clinformatics DataMart, which tracks employment-based commercial health insurance plans. Some 10.74 million men aged 40 years or older were included in the study population.

During the study period, androgen use rose among men 40 years or older from 0.81 % in 2001 to 2.91 % in 2011. «By 2011, 2.29 % of men in their 40s and 3.75 % of men in their 60s were taking some form of ART», Dr. Baillargeon and colleagues write. Androgen use was higher among men who lived in the South (3.77 % in 2010 for all men aged 40 years or older) and lower among men who lived in the Northeast (1.60 %).

«Our findings that almost 20 % of all new users received treatment for 30 days or less and that most men did not have clear evidence of a potential indication for ART suggests that the clinical reasons for initiating therapy are complex», Dr. Baillargeon and colleagues conclude. «More research is needed to determine the extent to which men with normal testosterone levels and ambiguous symptoms seek and are prescribed ART, particularly given the concerns about cardiovascular and other toxic effects from such treatment».

Indeed, in 2 accompanying commentaries, the authors suggest that the rise in prescriptions was driven by pharmaceutical companies' subtle (and sometimes surreptitious) marketing efforts to consumers.

In an editorial by Stephen R. Braun, from Braun Medical Media, Amherst, Massachusetts, explains how he was paid to «trumpet the party line» in ghostwritten articles he authored for a leading endocrinologist that ran in Life After 50, Woman's Day, Business Week, and other magazines. Braun describes a consumer-friendly booklet he wrote on behalf of Solvay, the original maker of AndroGel testosterone gel, as «a shill for the sponsor — an uncritical, unbalanced presentation of 'facts' that serves primarily to drive people to their physicians seeking the holy grail of 'energy, positive mood, and sexuality' in the form of testosterone».

Moreover, he notes that a recent market analysis of sales of testosterone replacement therapies to treat low testosterone, available as gels, transdermal patches, oral formulations, and injections given in a physician's office, have more than doubled since 2006 and are forecast to triple to $5 billion by 2017.

In an invited commentary, Lisa M. Schwartz, MD, and Steven Woloshin, MD, from the VA Outcomes Group, Department of Veterans Affairs Medical Center, White River Junction, Vermont; the Center for Medicine and the Media, Dartmouth Institute for Health Policy and Clinical Practice; and Norris Cotton Cancer Center, in Lebanon, New Hampshire, write that the «Low T» campaign follows a familiar script: medicalize ordinary life experiences, «raise the stakes» to trigger testing, and «spin the evidence» about benefit and harm.

«Whether the campaign is motivated by a sincere desire to help men or simply by greed, we should recognize it for what it is: a mass, uncontrolled experiment that invites men to expose themselves to the harms of a treatment unlikely to fix problems that may be wholly unrelated to testosterone levels», Dr. Schwartz and Dr. Woloshin write.

Metformin Linked to Fewer Prostate Cancer Deaths in Diabetics

Diabetic men with prostate cancer (PC) had a 24% decreased risk for PC-specific death for each additional 6 months of metformin treatment after cancer diagnosis, David Margel, MD, PhD, and colleagues reported online August 5 in the Journal of Clinical Oncology (2013). Cumulative metformin use was also associated with decreased risk for all-cause mortality for the first 6 months after diagnosis.

«This study adds to the growing body of evidence that prostate cancer may be a metabolic malignancy. More and more evidence is demonstrating that prostate cancer progression may be affected by obesity, metabolic syndrome, and diabetes», Dr. Margel, who is from the Division of Urology at the University of Toronto, Ontario, Canada, told Medscape Medical News.

«Metformin is safe, has minimal side effects, and is cheap. Therefore, it may be ideal as a secondary prevention strategy even among nondiabetic men with PC. We believe our study sets the foundation for such a study of metformin in PC», Dr. Margel said. However, he emphasized that currently, metformin should

be used only in accordance with current guidelines for diabetes treatment.

The researchers conducted a population-based retrospective cohort study to examine the association between cumulative duration of metformin use after PC diagnosis and all-cause and PC-specific mortality in men with diabetes. The cohort included 3837 diabetes patients older than 66 years from several Ontario healthcare administrative databases who subsequently developed PC. Median follow-up was 4.64 years (range 2.7 to 7.1 years), during which 35 % of patients died, including 7.6 % who died as a result of PC.

The investigators found that the adjusted hazard ratio (HR) for PC-specific mortality was 0.76 for each additional 6 months of metformin use. In addition, the HR for all-cause mortality declined over time from an HR of 0.76 in the first 6 months to 0.93 between 24 and 30 months. No other antidiabetic drugs affected either PC-specific or all-cause mortality.

The metformin benefit occurred regardless of cancer treatment regimen. «These results suggest that metformin may further improve survival as an adjunct therapy, even among those already receiving optimal cancer treatments», the authors wrote.

Dr. Margel and colleagues warned against overinterpretation of their data. «Finally, because our cohort was limited to patients with diabetes, we cannot conclude whether similar effects of metformin would be seen in a nondiabetic population. Thus, our study results do not demonstrate a survival benefit for diabetic men who use metformin compared with men who do not have diabetes», they wrote.

«This is an interesting publication that adds to a rapidly growing body of literature (composed mainly of retrospective studies) which has raised the hypothesis that metformin may have anticancer activity. This is a very interesting hypothesis that deserves examination in carefully designed, prospective clinical trials. Retrospective studies are well known to be affected by confounding factors, so only prospective studies in well-defined clinical settings can answer these important questions», oncologist and endocrinologist Nicholas Mitsiades, MD, PhD, told Medscape Medical News. Dr. Mitsiades, who is assistant professor, Departments of Medicine and Molecular and Cellular Biology, Baylor College of Medicine, Houston, Texas, was not involved in the study.

Dr. Mitsiades said that key unanswered questions include whether metformin has true anticancer activity, whether the results in the retrospective studies were influenced by potential differences between patients treated with metformin and those treated with insulin/sulfonylureas, and whether the anticancer activity occurs only in patients with diabetes or other metabolic abnormalities.

«Although metformin is generally a safe drug, I would not prescribe it off-label for treatment of cancer in a patient who has normal glucose metabolism», Dr. Mitsiades said.

He added that clinicians should put more emphasis on a healthy, low-fat diet and daily exercise, which have been shown in prospective studies to significantly improve clinical outcomes in several types of cancer, including PC.

ACOG Issues New Practice Bulletin on Gestational Diabetes

The American College of Obstetricians and Gynecologists (ACOG) has issued a new practice bulletin on the management of gestational diabetes mellitus.

The document «primarily serves as an update, to incorporate new clinical trials and whether or not they shed any additional light or would change management», says one of the authors, Wanda K. Nicholson, MD, from the University of North Carolina at Chapel Hill. The bottom line is that there is «no change on what was previously recommended», she told Medscape Medical News.

«The new studies that have been done since the last bulletin... reconfirm what the management has been, but we also identify areas or gaps in our knowledge for future studies», she noted.

The bulletin is published in the August issue of Obstetrics & Gynecology(2013).

Approximately 7 % of the 4 million women who give birth each year in the United States develop gestational diabetes. The condition is increasing as obesity and older age at pregnancy become more common. Other risk factors include having a family history of type 2 diabetes or belonging to an ethnic group at increased risk for the condition (such as Hispanic, Native American, South or East Asian, African American, or Pacific Islands descent).

Women with gestational diabetes are at higher risk for gestational hypertension, preeclampsia, and cesarean delivery and associated potential morbidities, and, of note, have a 7-fold increased risk of developing diabetes later in life. The offspring of women with gestational diabetes are also at increased risk for macrosomia, neonatal hypoglycemia, hyperbilirubinemia, operative delivery, shoulder dystocia, and birth trauma.

The new ACOG bulletin, together with draft guidance from the US Preventive Services Task Force issued recently, support the conclusions of a Eunice Kennedy Shriver National Institute of Child Health and Human Development Consensus Conference earlier this year, with regard to the diagnosis of gestational diabetes, which they state should remain a 2-step approach.

Despite several advantages of 1-step approaches and their widespread use outside the United States, more research is needed before any changes are made to the 2-step diagnostic approach that is the current US standard, they all conclude. One of the concerns about a 1-step approach is that it is anticipated to increase

the frequency of diagnosis of gestational diabetes 2- to 3-fold.

The 2-step approach to testing is based on first screening with the administration of 50 g of an oral glucose solution followed by a 1-hour venous glucose determination. Those women meeting or exceeding the screening threshold undergo a 100-g, 3-hour diagnostic oral glucose tolerance test (OGTT). This testing is normally done between 24 and 28 weeks' gestation in all pregnant women.

«ACOG supports this recommendation (to keep a 2-step approach) and recommends that before the testing approach and diagnostic criteria for gestational diabetes are changed, implications of such changes should be studied», the new bulletin notes.

In women in whom gestational diabetes is diagnosed — using a blood glucose level of either 135 or 140 mg/dL, with factors such as community prevalence rates of gestational diabetes determining the cutoff — initial management should be nutritional counseling by a registered dietitian, if possible, and advice on a moderate exercise program.

Once a woman with gestational diabetes begins nutrition therapy, surveillance of blood glucose levels is required to be certain that glycemic control has been established.

When target glucose levels cannot be consistently achieved through nutrition and exercise therapy, pharmacologic treatment is recommended, the bulletin states. «However, a systematic review found no conclusive evidence for the threshold value at which clinicians should start medical therapy», it notes.

When pharmacologic treatment of gestational diabetes is indicated, insulin and oral medications are equivalent in efficacy, it advises «and either can be an appropriate first-line therapy».

After delivery of the baby, the carbohydrate intolerance of gestational diabetes frequently resolves, although up to one third of affected women will have diabetes or impaired glucose metabolism at postpartum screening, which is recommended at 6 to 12 weeks after delivery.

ACOG thus proposes a new performance measure, Dr. Nicholson notes: the percentage of women in whom gestational diabetes is diagnosed who have postpartum screening for type 2 diabetes.

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