LABRIX Newsletter

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New Testosterone Study Prompts the Need to Read Articles, Not Just Headlines

The importance of reading the details of research articles, particularly when the title or conclusion is contrary to general understanding, is critical to the practice of medicine. Case in point: A recent JAMA article on testosterone-replacement therapy (TRT) in older men entitled "Association of Testosterone Therapy with Mortality, Myocardial Infarction, and Stroke in Men with Low Testosterone Levels"[1] has created a wave of concern and confusion in the world of hormone replacement therapy. Simply reading the article's abstract would lead one to the conclusion that TRT increases a male's risk of adverse cardiovascular events - contrary to the numerous additional findings reporting favorable or neutral effects on cardiovascular disease markers. Reviewing this study is a good opportunity to reflect on how research is published and what makes one study different from another.

Randomized, placebo-controlled studies (RCT) are currently considered the gold standard methodology for clinical trials. It is of importance to note that, rather than being an RCT, the referenced study is observational and retrospective in nature. Thus, instead of following randomized groups of subjects who differ only by treatment(s) versus control, these findings were based off of retrospective observances with treatment and variables outside of the control of the investigator. While observational studies may demonstrate associations, causation is better observed in RCT studies.

In the JAMA study, the number of subjects appears robust at first glance, however upon further review the dwindling numbers suggest poor compliance among those initially treated. The cohort consisted of 8709 men who underwent coronary angiography between 2005 and 2011, and who had total testosterone levels less than 300 ng/dL when angiography took place. Of these men, 1223 initiated testosterone treatment over the course of the retrospective, but only a small group of men, 267, were still taking testosterone therapy 2000 days post-angiography. This closer look suggests that the conclusions of the study were based on a relatively small cohort of patients with extended follow-up time. This study is unique as it stands alone in demonstrating this type of adverse outcome among a much larger body of RCT testosterone studies. The published study demonstrates multiple inherent biases and limitations as outlined in the discussion section, including: the utilization of ICD-9 codes and no chart review to determine outcomes, a relatively small group of patients with extended follow up time, and a select group of subjects who were undergoing angiography in the VA system, limiting generalizability. As such, this study cannot prove causality.

Reading the article in its entirety brings to light another potential point of concern that causes one to question the findings. During the duration reviewed, 17.6% of subjects filled their prescription only once, with the remainder refilling their prescriptions more than once. Those subjects who did refill their prescriptions more than once averaged 376 days between refills. This is significant because testosterone refills are only valid for 180 days, suggesting the unlikelihood that therapeutic levels were attained. This concern is further strengthened by the knowledge that average total testosterone levels only increased to 332.2ng/dL - just slightly above the initial cut-off for study inclusion and definition of hypogonadism for this study.

Additionally, route of administration of TRT is of importance to note and was not accounted for in the study's conclusions. Gel usage accounted for half of the refills. Because gels and creams are immediately absorbed as free hormone and serum measures total hormone, in the 50% of the study subjects who used gels, serum values were not reflective of absorbed hormone and, as such, measured serum levels in these subjects were likely reflecting a much lower total testosterone than was actually absorbed. As well, estradiol values were not measured or accounted for. Elevated estradiol, commonly seen with TRT as a result of aromatization, increases hypercoagulability and is a known risk factor for MI and stroke, the major death categories in the study.

Though the researchers in this study concluded that testosterone supplementation was associated with an increased risk of death, MI, and ischemic stroke, association and causation are not the same thing and the associations drawn from this study were done without accounting for many important factors, as described above.

What can be confidently gleaned from this study is that further investigations and studies are necessary to be able to definitively tip the scales away from the favorable effects of testosterone supplementation. For more information on the ins and outs of advanced hormone replacement therapy including the many benefits of testosterone, please join us for our advanced hormone workshop next month in Las Vegas, NV. For more information, visit www.labrix.com/LAW.

Resources

1. Vigen, R, O'Donnell C, Baron A, Grunwalk G, et al. Association of Testosterone Therapy with Mortality, Myocardial Infarction , and Stroke in Men with Low Testosterone Levels. JAMA. 2013; 310(17)1829-1836.

2. Jones RD, Nettleship JE, Kapoor D, Jones HT, Channer KS. Testosterone and Atherosclerosis in Aging Men. Am J Cardiovasc Drugs. 2005; 5(3): 141-154.

3. Khaw K, Dowsett M, Folkerd E, et al. Endogenous Testosterone and Mortality Due to All Causes, Cardiovascular Disease, and Cancer in Men. Circulation. 2007; 2694-2701.

4. Hyde A, Norman P, Flicker L, et al. Low Free Testosterone Predicts Mortality from Cardiovascular Disease But Not other Causes: The Health in Men Study. 2012 97(1) 179-189.

5. Rouzier, Neal. Response to JAMA Article. E-Journal of Age Management Medicine, November 2013.

IMPORTANT REMINDER

Reminder: Holiday Neurotransmitter Sample Collection Guidelines

With the holiday season fast approaching we would like to extend a reminder regarding neurotransmitter sample collection and shipping.

To meet the 2013 UPS holiday shipping schedule, urine samples for neurotransmitter testing must be collected BEFORE Wednesday, December 18th and AFTER Wednesday, December 25th. Blackout dates for collection are December 18-25, 2013. Please advise your patients of the blackout dates for collection, to ensure sample has not expired.

Upcoming **events**

Labrix Advanced Workshop
January 25-26, 2014
Register Here

Save The 2014 Core Training Dates

March 1, 2014 in Atlanta, GA
April 5, 2014 in Chicago, IL