FLAWED TESTOSTERONE ANALYSIS SPURS MISLEADING MEDIA HEADLINES

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The precipitous decline of men's testosterone levels over the years is inevitable. Unless aging men replace their diminishing testosterone, they could succumb to any of the numerous health problems linked to low testosterone levels: frailty, muscle loss, weight gain, impaired cognition, fatigue, loss of self-confidence, depression, declining bone health, increased risk of type 2 diabetes, stroke, and cardiovascular disease.[1,2]

Over the years, several studies have shown that testosterone replacement therapy improves multiple measures of men's vitality, especially related to cardio-metabolic health.[1-11]

Therefore, on November 5, 2013, we were startled to see headlines like "*Testosterone Treatments Linked to Heart Risks*" in the major news media. [12]

This headline and others like it were prompted by a retrospective, observational study by Vigen and colleagues published in the September 5, 2013, issue of the *Journal of the American Medical Association* (*JAMA*). The study suggests testosterone therapy may increase risk of death and certain cardiovascular events.[13] However, there are several significant shortcomings in the study's design and methodology, and the results conflict with an existing body of research.

WOEFULLY INADEQUATE TESTOSTERONE REPLACEMENT

The goal of testosterone restoration in most cases is to restore youthful blood levels of the hormone. Typically, Life Extension® suggests men target a blood level of testosterone between 700 and 900 ng/dL for optimal health.

In studies designed to assess the impact of testosterone replacement therapy, one of the most important considerations is to measure subjects' blood levels of testosterone regularly throughout the study period. This allows the scientists conducting the study to make sure subjects are taking their testosterone as directed and that their blood levels are rising as expected.

Unbelievably, in the flawed analysis by Vigen, only 60% of study subjects receiving testosterone had a follow-up blood test to assess their testosterone levels. Among them, average testosterone levels rose from a very low level of 175.5 ng/dL at baseline to a still far-from-optimal level of 332.2 ng/dL during testosterone therapy.

Raising testosterone levels from a paltry 175.5 ng/dL to only 332.2 ng/dL is unlikely to deliver robust health benefits. In fact, research has shown that restoring testosterone levels to 500 ng/dL or higher is associated with pronounced health benefits, whereas benefits may be less evident at lower levels. [5,6]

FAILURE TO ACCOUNT FOR IMPACT OF ESTROGEN

One of the biggest perils facing aging men is the conversion of their testosterone into estrogen by ***aromatase***.[14]

Aromatase is an enzyme that converts testosterone and other androgens into estrogen, primarily estradiol. Although some conversion of testosterone to estradiol is essential for health, too much conversion can have devastating consequences for men.

In one study, men with heart failure and high levels of estradiol had an increased risk of death compared to men whose levels of estradiol were in a balanced, middle range of 21.8–30.11 pg/mL.[15] These findings support Life Extension's long held suggested optimal estradiol level of 20–30 pg/mL. Moreover, excess estrogen promotes abnormal clot formation,[16] and high levels may be associated with an increased risk of stroke. [17]

When men take testosterone, there is a significant propensity for it to be converted into estradiol by aromatase; this is especially so for aging men. [18] It is therefore important that men undergoing testosterone therapy monitor their estradiol levels regularly and take steps like using an aromatase-inhibiting drug to keep estradiol levels in the optimal range in order to protect against the health

detriments of excess estrogen.

In the paper published by Vigen, there was no report of the subjects' estradiol levels. If estradiol was not monitored during testosterone administration, this oversight means that the men receiving testosterone could have experienced a concurrent rise in estradiol levels. This may have compromised their cardiovascular health and could partially account for the increased risk observed in the testosterone-treated group.

SIGNIFICANT DIFFERENCE IN BASELINE TESTOSTERONE LEVELS BETWEEN GROUPS

Among the men in this flawed *JAMA* study, there was a statistically significant difference in baseline testosterone levels between the "testosterone therapy" (treatment) and "no-testosterone" (control) groups.

Among the control group, testosterone levels were higher at baseline (206.5 ng/dL), whereas the average level was significantly lower at baseline (175.5 ng/dL) for those who received a prescription for testosterone.

The treatment group may have had significantly lower levels of testosterone than the control group for years prior to entering the study. The damage caused by years of potentially lower testosterone levels was not accounted for in the study and may have skewed the results.

ACHIEVING HIGHER TESTOSTERONE LEVELS HAS CLEAR CARDIOVASCULAR BENEFITS

Testosterone restoration is an important step aging men can take to retain good health.

In a revealing study, researchers identified 2,416 men (aged 69–81 years) who were not on any kind of testosterone-affecting treatment. These men were subjected to a battery of blood tests that included total testosterone and estradiol.

The first observation was that men with *increasing* levels of testosterone had a *decreased* prevalence of diabetes, hypertension, and body fat mass. Compared to men with the highest testosterone levels, those with low testosterone were twice as likely to have a history of cardiovascular disease. It was also observed that men with the *highest* testosterone levels were the most *physically active*.[5]

This large group of men was followed for an average of 5.1 years. Men in the highest quartile of total testosterone (above 550 ng/dL) had a 30% lower risk of cardiovascular events. Any level of total testosterone below 550 ng/dL resulted in significantly increased risk, thus helping establish a minimal baseline as to where total testosterone should be to guard against heart attack or stroke.

Estradiol levels measured in this group appeared to be mostly in safe ranges and did not impact incidence of cardiovascular events.

Data was tabulated based on hospital reports and/or death certificates for:

1. Acute myocardial infarction (heart attack)
2. Unstable angina (chest discomfort caused by a lack of oxygen flow to the heart)
3. Revascularization procedure (bypass surgery or stenting)
4. Transient ischemic attack (mini-stroke)
5. Stroke

The four quartiles of total testosterone in this large group of older men were:

Quartile 1: Total testosterone below 340 ng/dL
Quartile 2: Total testosterone between 341 and 438 ng/dL
Quartile 3: Total testosterone between 439 and 549 ng/dL
Quartile 4: Total testosterone above 550 ng/dL

Of interest was the finding that Quartiles 1, 2, and 3 had about the same risk of cardiac adverse events. It was only in Quartile 4 (when total testosterone exceeded 550 ng/dL) that the 30% reduction in cardiovascular events occurred.

This finding showed that it did not matter if these men's total testosterone was very low (below 340 ng/dL) or moderately low (up to 549 ng/dL) … they all had a similar increased risk for suffering a cardiovascular event. Only when total testosterone exceeded 550 did cardiovascular risk plummet.

This finding remained consistent for cerebrovascular disease incidence, where men with the highest total testosterone (Quartile 4)

had a 23% reduced risk of transient ischemic attack or full blown stroke. The researchers noted this association with reduced cerebrovascular risk remained after adjustment for traditional risk factors.

The conclusions by the researchers who conducted this study were:

> " *Higher serum testosterone levels are associated with a reduced risk of fatal and non-fatal cardiovascular events in community dwelling elderly men* ."[5]

ADDITIONAL STUDIES DEMONSTRATE THE BENEFITS OF MAINTAINING HIGHER TESTOSTERONE LEVELS

Another study found the threshold level for benefit with testosterone replacement therapy was >500 ng/dL. This randomized, double-blind, placebo-controlled trial on 50 male subjects with low testosterone and metabolic syndrome found that testosterone administration reduced fasting glucose and waist circumference, and improved markers of atherosclerosis. The authors concluded: "Clinical efficacy of T [testosterone] replacement therapy in hypogonadal men with MS [metabolic syndrome] is reached when its plasmatic levels approach into the medium-high range of normality (>5 ng/mL [or >500 ng/dL])."[6]

Asymmetric dimethylarginine (ADMA) is a metabolic compound that contributes to atherosclerosis and cardiovascular disease. In a study of 10 men with low testosterone levels at baseline (115.27 ng/dL), testosterone administration for 2 weeks caused testosterone levels to rise to 648.41 ng/dL and ADMA levels to drop to a statistically significant degree. The study authors noted: " *The outcome of this study may be viewed as a favorable effect of normalization of plasma testosterone on plasma ADMA since even small elevations of plasma ADMA significantly increase cardiovascular risk."* [7]

STUDY CONFLICTS WITH PREVIOUS RESEARCH

Vigen and colleagues note, "The association between testosterone therapy use and adverse outcomes observed in this study differs from the association observed in a prior retrospective VA study [Shores et al.]"

- "In the study by Shores, investigators noted a 39% reduction in mortality risk among patients treated with testosterone therapy."[8] Unfortunately, the testosterone levels achieved in this study were not reported.
- A comprehensive review of data from 4 randomized controlled trials on men with chronic heart failure found that testosterone therapy was associated with improved functional capacity with no adverse events reported after up to 52 weeks of treatment.[9]
- French researchers found that lower bioavailable testosterone levels (i.e., the fraction of circulating testosterone that readily enters cells [free testosterone plus weakly bound testosterone]) in men 65 and older were linked to increased carotid artery intima-media thickness, which is a known marker of cardiovascular risk.[10]
- A randomized, controlled, 12-month study on 13 men with low testosterone levels and chest pain (i.e., angina) found that testosterone restoration therapy resulted in greater reductions in carotid artery plaques and improvements in time to myocardial ischemia (i.e., decreased blood flow to the heart) during exercise testing; the benefits were maintained throughout the duration of the study.[11] The average range of total testosterone achieved during the 12 month period was approximately 461 ng/dL to 548 ng/dL.
- In a study of 24 men with low baseline testosterone, intramuscular injections with 200 mg of testosterone every 2 weeks for 3 months were associated with improvements in insulin sensitivity and glycemic control as well as a reduction in total cholesterol and visceral adiposity. The scientists noted " *Improvements in [glycemic] control, insulin resistance, cholesterol and visceral adiposity together represent an overall reduction in cardiovascular risk.* "[19]
- A 2013 study confirmed the increase of metabolic syndrome in men that are testosterone deficient.[3] *Metabolic syndrome* is a cluster of cardiovascular risk factors that include insulin resistance, hypertension, elevated triglycerides/LDL and low HDL. This study found that men treated with testosterone showed across the board improvements as indicated by:
  - Reduced LDL
  - Reduced triglycerides
  - Reduced glucose
  - Reduced C-reactive protein

- Reduced liver enzymes
- Reduced blood pressure
- Reduced hemoglobin A1c
- Increased HDL (removes cholesterol buildup from arterial walls)

RETROSPECTIVE OBSERVATIONAL STUDY — UNMEASURED CONFOUNDING OR HIDDEN BIAS MIGHT EXIST

The study by Vigen et al. was retrospective and observational. This study design limits the interpretation of the findings because subjects were treated in a clinical setting and not randomized to treatment. Bias may be introduced if confounding factors (*e.g.,* those associated with both treatment initiation and mortality) are not adequately accounted for. Although the authors attempted to control for confounding factors, unmeasured or hidden factors likely still exist. The extent that these unmeasured variables bias the association reported is unknown.

UNNATURAL FORMS OF TESTOSTERONE USED BY 1/3 OF SUBJECTS

Of men receiving testosterone therapy in the study by Vigen et al., only 1.1% were prescribed testosterone gel, 63.3% received patches, and 35.7% received injections. Commonly prescribed testosterone injectables can produce a peak, often supraphysiologic, level of testosterone that then declines slowly to an often subnormal level in 1 to 2 weeks.[20,21] This "peak and trough" effect is an unnatural rhythm for testosterone. A testosterone cream or gel, on the other hand, gradually releases into the bloodstream, which is more analogous to the natural secretion of testosterone by the testes. More than a third of men in this analysis received testosterone injections, which may cause unusual fluctuations in testosterone levels. In addition, testosterone injectables are comprised of non-bioidentical testosterone compounds. Life Extension advocates that men use a daily bioidentical testosterone gel (eg, Androgel® or compounded version) to avoid unnatural fluctuations in testosterone levels.

Based upon an analysis of this study and the existing research, Life Extension continues to recommend male members restore testosterone levels to youthful ranges for optimal health.

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