CLINICAL COMMENTARY

Safe T—A Heartfelt Perspective

Janet Winikoff, M.D.

Like a vampire who periodically arises from the dead to attack its victims, the issue of testosterone safety keeps rebounding from what ought to be a final resting place, and instead, repeatedly intimidates would be prescribers of this hormone. Two recent articles[1,2] have once again resurrected the argument over the cardiovascular safety profile of testosterone. The allegations in these articles, namely that testosterone replacement presents unjustified cardiovascular risks, have been largely answered,[3] but not before they created a near national panic, which was among other things responsible for the initiation of an FDA safety review,[4] opinion pieces in at least two prominent national newspapers,[5,6] and most worrisome, the precipitous cessation of this medicine by patients in whom it is unequivocally beneficial.

It is generally agreed and not disputed that testosterone is necessary for the development and maintenance of male secondary sex characteristics, reproductive function, libido, muscle, size, and strength; furthermore, it has been shown as a precursor to estrogen and has a critical role in prevention of fat accumulation.[7] It is also accepted that as a precursor to estrogen, it has a critical role in the maintenance of bone mineral density.

To clarify one's understanding, it would be useful to consider different clinical circumstances under which testosterone is prescribed and to acknowledge that a one-size-fits-all approach might not be suitable for addressing concerns about the safety profile of testosterone replacement. Consider the following brief modified vignettes of 2 actual of patients who sought testosterone treatment:

A 46-year-old man who underwent pituitary surgery at age 4 for a craniopharyngioma. He had initially been on pituitary hormone replacement, which had been stopped and then restarted. However, he heard about the cardiovascular dangers of testosterone on TV and abruptly stopped his testosterone therapy. Total testosterone < 10 ng/dL (241-827) LH 0.1 mIU/mL (1.14-8.75) FSH 0.4 mIU/mL (1.37-13.58) PRL 8.30 ng/mL (3.46-19.40)

A 56-year-old man complains of the gradual onset of decreased libido and sexual dysfunction consisting of suboptimal erections. He was started on testosterone and initially felt that he had improved but then his libido started waxing and waning. The testosterone treatment was stopped, and after 6 months, he requested reinstitution of the testosterone. Laboratory studies were repeated before considering reinstitution of testosterone treatment. LH 7.3 (1.5-9) mIU/mL Total T 376 ng/dL (348-1197) Bioavailable T 110 ng/dL (95-285).

There is no controversy in the literature about the benefits of testosterone therapy in the group of men who have pituitary or testicular pathology causing profound testosterone deficiency such as our patient #1 above. Testosterone therapy improves the metabolic and clinical profile of clearly testosterone-deficient men and possibly improves clinical outcomes as well.[3] Furthermore, any number of studies in the past, too numerous to review here, have concluded that testosterone deficiency is not associated with an increase in cardiovascular risks and mortality in such men. So it is necessary to be clear that testosterone therapy in this group of men is not controversial and that unequivocally these men barring some other specific reason should be reassured and counseled to continue their testosterone.

But what of men who have no particular identifiable pathology in either of these organs? Do they have a syndrome that requires treatment or the treatment of which would be of benefit to them? At least 2 papers[9,10] have shown that testosterone declines with age in both longitudinal and cross-sectional studies. While it is well-accepted that low testosterone from clear pathological conditions of the pituitary or testicle contributes to cardiovascular risk, low bone density, low muscle mass, and mortality, it is less clear that the age-related decrement in testosterone in otherwise healthy men has a meaningful clinical correlate and whether its replacement is beneficial.

Among previous papers, two have suggested that for such men there are cardiovascular risks due to testosterone. One was a study, Basaria et al,[8] in which testosterone gel was given to community dwelling men over age 65 with limited mobility in an effort to increase strength and endurance. However, the trial was stopped early because of concerns about the cardiovascular safety. However, the concerns with regard to safety were criticized[3] because most of the adverse events were not defined before hand, the events were subjective without systematic collection of data, and the events were of questionable clinical importance. While there were also more serious objective adverse cardiac events (1 death, 2 MI's, 1 stroke), which occurred solely in the treatment arm, it was

thought that due to the small sample size and small number of events, and lack of a consistent pattern of events, this distribution could have occurred by chance alone.

The other often cited prior worrisome study was a meta-analysis performed by Xu et al[9] that was criticized[3] for having included only studies in which one or more cardiovascular events occurred. Since studies without any cardiovascular events were excluded, it was felt this prejudiced the conclusions. In addition, the paper was criticized because 2 of the 27 reports it included in its meta-analysis accounted for 35% of the adverse events; without these 2 studies, the rates of adverse cardiovascular events between the placebo group and the treatment groups would have been similar. One of the two papers was the paper by Basaria[8] with the analytic and data collection problems cited above.

Against this background, the two new studies cited at the beginning of this paper have once again raised the specter of cardiovascular risks associated with testosterone therapy. The first of these by Vigen et al,[1] which was a retrospective cohort study, purported to show that in a group of VA patients who had undergone coronary angiography the subsequent use of testosterone was associated with an increased number of cardiovascular events. The study has since been roundly criticized[3] for using an unproven statistical methodology. As a consequence, the data were interpreted to mean that the rate of cardiovascular events was higher in the treatment group even though there was a higher rate of such events in the untreated group. In addition, subsequent to publication, the authors acknowledged they had inappropriately excluded over 1,000 men with adverse events from the untreated group and that 10% of the study population consisted of women in what was intended to be an all male group.

The second of the two papers,[2] which, parenthetically, was published in a non-peer reviewed journal, involved extracting data from an insurance data base in which the MI rate one year prior to testosterone and 90 days after the use of testosterone were compared. The MI rates pre- and post-testosterone prescriptions were compared, and they were in turn compared with the MI rate pre- and post-phosphodiesterase inhibitor prescription. This paper[3] was criticized because there was no information about other risk factors in the various cohorts (i.e., smoking, diabetes, hypertension, etc.), and because the rate of MI in the testosterone treated group was approximately one-third the expected rate while there was no comparison with a completely untreated control group. The validity of the comparison with the phosphodiesterase inhibitor treated group was questioned because the patients, indications for treatment, and mechanisms of actions of the medications may not have been equivalent. The possibility that the phosphodiesterase inhibitor itself might have decreased cardiovascular risk via its vasodilator properties was not addressed. Finally, the duration of the study post-prescription was so short that it was thought that the testosterone was unlikely to have acted rapidly enough to be the causative agent of the post-prescription MI rate and that the MI's might have been due causative factors other than the testosterone treatment itself.

These two weak papers with substantial methodological and analytic problems have become the cornerstone of a movement to deny testosterone treatment to all men. The popular media have done a clear disservice to men such as our patient #1 by frightening them into abandoning a useful and safe therapy for no good reason. A much more important but insufficiently addressed issue is whether men, such as described in patient #2, would benefit from testosterone therapy. Although their gonadotropins may be slightly elevated, these men generally do not have any significant pathology identified in the hypothalamic-pituitary-testicular axis

At least 2 studies[10,11] have shown that testosterone declines with age in both longitudinal- and cross-sectional analysis. While it is well-accepted that low testosterone from pathological conditions contributes to cardiovascular risk, low bone density, low muscle mass, and mortality, it is less clear that the age-related decrement in testosterone in otherwise healthy men has a meaningful clinical correlate and whether its replacement is beneficial. In fact, in one of the above studies,[11] dihydrotestosterone (the active metabolite of testosterone) levels did not decrease but whether the serum levels and the specific tissue levels correlate is less clear. One set of investigators[12] did try to determine the relationship between low testosterone and specific clinical syndromes by looking at nine candidate symptoms, 3 sexual (decreased frequency of morning erections, erectile dysfunction, decreased frequency of sexual thoughts); 3 physical (decreased vigorous activity, difficulty walking > 1 kilometer, inability to bend); and 3 psychological (sadness, loss of energy, fatigue), and determining how these symptoms correlated with testosterone levels. As it turned out, psychological symptoms had virtually no association with the testosterone level. Low physical vigor was associated with a level of total testosterone below 374 ng/dL and sexual symptoms clustered with a level of testosterone below 317 ng/dL, close to the lower limit of normal for young healthy men, in many assays. However, the prevalence of the sexual symptoms was also high in men with clearly normal testosterone, making it difficult to know whether there is a cause and effect relationship between the low levels of testosterone measured and the sexual symptoms. It underscores the difficulty of distinguishing true symptoms of hypogonadism and the potentially unrelated nonspecific symptoms of aging.

Similarly, Araujo et al[13] used data from the Boston Area Community Health Survey to evaluate the relationship between testosterone levels and "specific" symptoms, which included low libido, erectile dysfunction, and osteoporosis, and "non-specific" symptoms, which was comprised of lethargy, sleep disturbance, depressed mood, and low physical performance. While about 5.6% of men had both symptoms of androgen deficiency and low testosterone levels, the majority of men with these symptoms had normal testosterone levels. Nearly half of men with low testosterone levels had no androgen deficiency signs or symptoms at all. The symptoms of purported androgen deficiency doubled in men over 50 compared to those under 50. While a greater percentage of men over 50 compared with those under 50 with such symptoms also had a higher percentage of androgen deficiency, still 48% of those older than age 50 with low testosterone level did not have symptoms. The lack of

consistency between androgen related signs and symptoms on the one hand, and low serum testosterone levels on the other, has led to the Endocrine Society Clinical Practice Guidelines[14] suggesting that a diagnosis of androgen deficiency be made in men only with consistent symptoms *and* unequivocally low serum testosterone levels.

All of the above should make one realize that many ostensible symptoms often attributed to testosterone deficiency do not correlate well with testosterone levels. It is very unclear whether low testosterone is the cause of complaints often seen in the aging male. The concept of "T deficiency" has entered the popular culture, and middle aged men and others clamor for the use of testosterone to treat their symptoms such as lethargy, depression, lowered physical performance, loss of libido, and sexual performance, all of which, to some extent, invariably accompany aging. So it would seem that we have "medicalized" existential life problems by attributing them to modestly low testosterone levels to which they have, at best, a tenuous connection. Then we are asking doctors to accept responsibility for ameliorating these life problems by administering testosterone which may or may not be contributing to these problems.

But one may ask if there is no or little risk, at least from a cardiovascular standpoint (and probably other perspectives which are beyond the discussion in this paper), why not just prescribe the testosterone on request? Well, there is just one very inconvenient truth that precludes doing so, and that is that testosterone is a schedule III substance. A schedule III substance is "defined as drugs with a (moderate to low) potential for physical and psychological dependence" and includes "products containing less than 90 milligrams of codeine per dosage unit, ketamine, anabolic steroids, testosterone" on the DEA website.[15] The nature of the potential physical or psychological dependence of testosterone is not identified; why this substance should be classified with drugs containing codeine while benzodiazepines, tramadol, carisoprodol, propoxyphene, and LSD are classified as schedule IV substances is not comprehensible. The history of this classification is apparently related to the public outrage at the use of testosterone as a performance enhancing substance in competitive sports in the 1980's. However, why that should be translated into the idea that testosterone is a dangerous substance that needs to be controlled, or the idea that men should not be able to obtain it to improve their sense of well being and subjective sense of sexual capability without making low testosterone levels into a disease that we cannot define, is not evident.

So let's stop the hypocrisy. Let's admit that we are not sure of the relationship between testosterone levels and the purported symptoms of androgen deficiency in middle aged men. Let's stop talking about the problems of aging as if they constitute a medical disease. Let's take this apparently safe drug and de-classify it as a controlled substance; let's consider making it available in low doses over the counter so that men can get it or doctors can prescribe it without worrying about the legal consequences of doing so. Let's put a stake through the heart of the monster that roams the earth intimidating would be prescribers of testosterone and end, once and for all, the unwarranted obstacles to testosterone usage.

REFERENCES

1. **Vigen R, O'Donnell CI, Barón AE, Grunwald GK, Maddox TM, Bradley SM, Barqawi A, Woning G, Wierman ME, Plomondon ME, Rumsfeld JS, Ho PM**. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*. 2013 Nov 6;310(17):1829-36. doi:10.1001/jama.2013.280386. Erratum in: JAMA. 2014 Mar 5;311(9):967. PubMed PMID:24193080.
2. **Finkle WD, Greenland S, Ridgeway GK, Adams JL, Frasco MA, Cook MB, Fraumeni JF Jr, Hoover RN**. Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. *PLoS One*. 2014 Jan 29;9(1):e85805. doi:10.1371/journal.pone.0085805. eCollection 2014. PubMed PMID: 24489673; PubMed Central PMCID: PMC3905977.
3. **Morgentaler A, Miner MM, Caliber M, Guay AT, Khera M, Traish AM**. Testosterone therapy and cardiovascular risk: advances and controversies. *Mayo Clin Proc*. 2015 Feb;90(2):224-51. Review. PubMed PMID: 25636998.
4. **FDA**. Safety Announcement: FDA evaluating risk of stroke, heart attack and death with FDA-approve testosterone products. 2014 www.fda.gov/drugs/drugsafety/ucm383904.htm.
5. **Woloshin S, Schwartz LM**. 'Low T' and the Peril of Medicating Grumpy Old Men. *The Los Angeles Times*. 2014; Op-Ed February 16.
6. **The Editorial Board, The New York Times.** Overselling Testosterone, Dangerously. *The New York Times*. The Opinion Pages, Editorial. 2014; February 4.
7. **Finkelstein JS, Lee H, Burnett-Bowie SA, Pallais JC, Yu EW, Borges LF, Jones BF, Barry CV, Wulczyn KE, Thomas BJ, Leder BZ**. Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med*. 2013 Sep 12;369(11):1011-22. doi: 10.1056/NEJMoa1206168. PubMed PMID: 24024838; PubMed Central PMCID: PMC4142768.
8. **Basaria S, Coviello AD, Travison TG, Storer TW, Farwell WR, Jette AM, Eder R, Tennstedt S, Ulloor J, Zhang A, Choong K, Lakshman KM, Mazer NA, Miciek R, Krasnoff J, Elmi A, Knapp PE, Brooks B, Appleman E, Aggarwal S, Bhasin G, Hede-Brierley L, Bhatia A, Collins L, LeBrasseur N, Fiore LD, Bhasin S**. Adverse events associated with testosterone administration. *N Engl J Med*. 2010 Jul 8;363(2):109-22. doi: 10.1056/NEJMoa1000485. Epub 2010 Jun 30. PubMed PMID: 20592293; PubMed Central PMCID: PMC3440621.
9. **Xu L, Freeman G, Cowling BJ, Schooling CM**. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. *BMC Med*. 2013 Apr 18;11:108. doi:10.1186/1741-7015-11-108. PubMed PMID: 23597181; PubMed Central PMCID:PMC3648456.
10. **Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR; Baltimore Longitudinal Study of Aging**. Longitudinal effects of aging on serum total and

free testosterone levels in healthy men. *Baltimore Longitudinal Study of Aging*. J Clin Endocrinol Metab. 2001 Feb;86(2):724-31. PubMed PMID: 11158037.

11. **Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, Bremner WJ, McKinlay JB**. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. *J Clin Endocrinol Metab*. 2002 Feb;87(2):589-98. PubMed PMID: 11836290.
12. **Wu FC, Tajar A, Beynon JM, Pye SR, Silman AJ, Finn JD, O'Neill TW, Bartfai G, Casanueva FF, Forti G, Giwercman A, Han TS, Kula K, Lean ME, Pendleton N, Punab M, Boonen S, Vanderschueren D, Labrie F, Huhtaniemi IT; EMAS Group**. Identification of late-onset hypogonadism in middle-aged and elderly men. *N Engl J Med*. 2010 Jul 8;363(2):123-35. doi: 10.1056/NEJMoa0911101. Epub 2010 Jun 16. PubMed PMID: 20554979.
13. **Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, Williams RE, Clark RV, McKinlay JB**. Prevalence of symptomatic androgen deficiency in men. *J Clin Endocrinol Metab*. 2007 Nov;92(11):4241-7. Epub 2007 Aug 14. PubMed PMID:17698901.
14. **Bhasin S, Cunningham GR, Hayes FJ, Matsumoto AM, Snyder PJ, Swerdloff RS, Montori VM; Task Force, Endocrine Society**. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2010 Jun;95(6):2536-59. doi: 10.1210/jc.2009-2354. Review. PubMed PMID: 20525905.
15. www.DEA.gov/druginfo/ds.shtml.

Submitted April 19, 2015