The Need for a Men’s Health Initiative

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In the majority of cases, women have been excluded from or underincluded in studies. The exception to this is hormone replacement, where after the ill-fated estrogen replacement studies in men (1), women’s hormone replacement has been studied in detail, while much less attention has been given to testosterone replacement in men (2,3). At present the National Institutes of Health have asked the Institute of Medicine to study whether a large study of testosterone replacement in men is justified. Such a study will cost between $100 to $200 million and have major public health endpoints.

There is now clear evidence from 4 longitudinal studies that testosterone and, to a greater extent, free or bioavailable testosterone, declines with aging (4–7). This occurs both because of a testicular defect but also because of dysnergy in gonadotrophin-releasing hormone secretion from the hypothalamus and attenuation of its effects at the pituitary level (8–10). Because of these effects, circulating luteinizing hormone is inappropriately low for the level of testosterone. It would appear that in very old men, this is not true, with luteinizing hormone levels increasing to very high levels (4).

A problem exists in the diagnosis of hypogonadism. Variability exists in the normal values reported for hypogonadism from laboratory to laboratory. There is a need to determine standards for testosterone assays, most probably using mass spectroscopy, to make sure that the measurement of testosterone by immunoassay is accurate and the same from laboratory to laboratory. Secondly, most experts agree that some measurement of “free” testosterone (nonsex hormone globulin bound) is the measurement most closely correlated with tissue levels (11). It is agreed that analog assays for testosterone that are most widely available are grossly inaccurate. Either free testosterone by dialysis or ultracentrifugation or a bioavailable testosterone should be used. The role of calculated free testosterone remains to be determined.

At present, only a small number of placebo-controlled trials of testosterone replacement have been undertaken in older men (12–19 and reviewed in 2). These studies have lasted from 3 months to 3 years. What have these studies taught us? All studies agree (as shown in the article by Wittert and colleagues in this issue of the Journal (20)) that testosterone increases muscle mass. Testosterone also appears to increase muscle strength in truly hypogonadal men, but not in those with borderline normal levels. These findings are in keeping with epidemiological studies suggesting that testosterone and especially free testosterone levels are associated with the development of sarcopenia (21,22) and the decline in muscle strength in older males (23–27). Testosterone also decreases body fat mass and produces a decline in leptin levels.

The most clear effects of testosterone replacement are on sexual behavior. Low testosterone levels are associated with a decline in a variety of sexual behaviors (28), though a clear relationship between low testosterone and erectile function does not exist (29,30). Testosterone replacement improves libido and in some cases enhances erectile function (31,32). The effectiveness of sildenafil declines with aging (33), and this may be restored by the administration of testosterone (34).

The effects of testosterone on other systems are less clear. Testosterone appears to increase bone mineral density, at least in truly hypogonadal men (12,16).

Testosterone also may enhance cognition (17,35–37), though as is the case in women with estrogen (38–41), this is controversial. In animals, testosterone maintains synaptic spine density in the hippocampus (42), enhances performance in the alternating T-maze (43), and improves avoidance learning in the SAMP8 mouse, an animal model of Alzheimer’s disease (44–47). Recent epidemiological studies suggest that low testosterone may be associated with the development of Alzheimer’s disease and poor cognitive performance (48,49).

The major reason not to carry out a testosterone trial in older men is the fear of side effects. However, this is also the major reason to do it. The 800-pound gorilla of a side effect is the fear that testosterone will promote the development of prostate cancer. While it is clear that testosterone can promote the growth of metastatic prostate cancer and castration reduces the symptoms of metastatic prostate cancer without altering mortality (50,51), there is little evidence that testosterone promotes prostatic cancer growth in situ. Cell and animal studies suggest that there may be a U-shaped curve for testosterone with very low and high doses promoting cancer, and normal doses having no effect or suppressing it. Androgen receptors appear to play a role in differentiation and maintenance of the normal prostate and initiation, promotion, and progression of adenocarcinoma of the prostate. Cross-sectional studies have suggested that, at the time prostate cancer develops, testosterone values are low (52,53). Prospective epidemiological studies have failed to show an association of
testosterone or bioavailable testosterone with prostate cancer (54,55). One study did suggest that, after 8 years, men with higher testosterone levels had a nonstatistically significant increase in prostate cancer (56). In contrast, these and other studies have clearly shown that men with the highest quartile of insulin growth factor-I have a 1.7 to 4.3 relative risk increase in prostate cancer (57). Retrospective testosterone treatment trials have failed to show an increase in prostate cancer at 2 (31) and 10 (58) years. There is no evidence, either for or against, that benign prostatic hyperplasia and associated lower urinary tract symptomatology are associated with testosterone.

The effects of testosterone on cardiovascular disease appear to be mostly positive and similar to those seen with estrogen prior to the Heart and Estrogen/Progestin Replacement Study (HERS) (59) and Women’s Health Initiative (WHI) (60) trials. Low testosterone in men is associated with more heart disease and atherosclerosis, and an increase in carotid intimal medical thickness (61,62). Testosterone administration has positive effects on angina, coronary artery vasodilatation, and myocardial muscle remodeling (63,64). Testosterone increases or has no effect on brachial vascular blood flow (65,66). Master athletes have a longitudinal decline in VO2 max and performance as they age (67,68). These changes are due to alterations in lean body mass as well as cardiac output, suggesting that testosterone will improve cardiac output. Testosterone increases hematocrit, which may lead to hyperviscosity. Testosterone has minimal effects on lipids (69). Overall, the available data does not allow us to confidently predict the effects of testosterone on cardiovascular health, making it a prime target for a Men’s Health Initiative endpoint.

Given the uncertainty concerning the best method of diagnosis or the true effects of testosterone therapy or the side effects, why is a Men’s Health Initiative necessary at this time? The answer comes from the results of the WHI (60). This study clearly showed that epidemiological and small studies fail to demonstrate the true effects of a hormone that effects multiple systems. The delay in doing the WHI resulted in many women using an estrogen/progestagen combination to prevent heart disease when it clearly increased it! We have the opportunity not to make the same mistake in men.

As chronicled in the Journals (69), there has been a marked increase in testosterone prescriptions over the last few years. This has been due to the increase in testosterone products with increased pharmaceutical-driven physician education and by the availability of a simple screening test, i.e., the Androgen Deficiency in Aging Males (ADAM) questionnaire (70). At present, most men receiving testosterone are between the ages of 40 and 65 years. With more new products on the horizon such as oral products (already available in the rest of the world), buccal products, and nasal inhalation products, the market is likely to grow exponentially over the next decade. There is a strong expectation that it will become a market of over $1 billion a year within 5 years. Most of this growth is expected to come in men aged 65 years and older.

I believe that determining the safety of long-term testosterone treatment is the paramount reason for undertaking a Men’s Health Initiative at this time. The study should be adequately powered to detect potential toxic effects. Utilizing the Women’s Health Initiative (54) and the Prostate Cancer Prevention Trial (71) as examples, this should require between 16,000–20,000 men at a minimum. The trial needs to run 8–10 years. Endpoints besides prostate cancer and cardiovascular disease should include functional improvement [most probably some measurement of mobility based on data that has appeared in the Journals (72–76)], cognition, and a measurement of lumbar and spinal fractures. Persons entered into the trial should be truly hypogonadal, based on a measurement of free or bioavailable testosterone. The study should not be prematurely stopped unless there is an unacceptable increase in overall death. Failure to do this in the WHI has allowed it to be legitimately criticized.

A smaller second trial should be undertaken to determine the effects of testosterone therapy on frailty (77–80). There is epidemiological evidence that bioavailable testosterone is related to frailty (81) and sarcopenia (82), and that testosterone treatment might improve the functional index measure (FIM) in men undergoing rehabilitation (83). This study need only be short term (1-year maximum). One of the control arms should be exercise, in view of the dramatic effects that exercise can have on frailty (84–87). A combination of exercise and testosterone should involve, dependent on design, 2000–4000 people.

It should be stressed that should the National Institutes of Health (NIH) fund these studies, it does not allow them not to fund other scientifically meritorious proposals of more limited goals and shorter duration.

Thus, it is hoped that, despite limited data, the Institute of Medicine urges NIH to embark on these 2 meritorious studies as part of a Men’s Health Initiative, so that these data can be available to men by the year 2015. It should be noted that the data in favor of using testosterone in older persons is greater than that for growth hormone (88,89) and dehydroepiandrosterone (90).

ACKNOWLEDGMENT

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