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Editorial: Testosterone—Fountain of Youth or Drug of Abuse?

For a long time relegated to the role of poor country cousin of female hormone replacement therapy (HRT), androgen replacement has finally emerged as a hot topic in its own right. Succumbing to the pressure of perfectly sculpted, Adonis-like figures gazing down at them from news stands with captions provocatively entitled "Are You Man Enough?," men are now demanding their slice of the hormone pie.

The recent resurgence of interest in a therapy that first entered the clinical arena more than 60 yr ago reflects two major factors, the development of more patient-friendly testosterone formulations and the expansion of the clinical indications for androgen replacement. Shortly after its isolation and synthesis in 1935, it became apparent that testosterone had negligible oral bioavailability and a very short duration of action due to extensive hepatic metabolism. Attention was, therefore, focused on developing alternative modes of testosterone delivery. Initial progress in this area was slow due to the reluctance of the pharmaceutical industry to invest heavily in the limited market of male hypogonadism. However, the expansion of the indications for testosterone therapy to include wasting disorders such as human immunodeficiency virus (HIV) infection and, more controversially, the aging male has now opened up a whole new potential market for androgen therapy. Currently, there are ~34 million Americans over the age of 65 yr, and it is estimated that this number will double in the next 30 yr (1). Given these statistics, it is clear that if testosterone therapy can be shown to either slow the progression or reverse some of the features of aging, the market potential is huge.

Testosterone therapy has evolved considerably since the days of the 19th century French physiologist Charles Brown-Séquard, who extolled the virtues of a guinea pig testicular extract in restoring waning potency and virility. However, it has taken a long time to develop an optimal testosterone formulation combining favorable pharmacokinetic and safety profiles with ease of administration. To date, all available androgen formulations have had inherent limitations. Oral 17α-alkylated androgens such as methyltestosterone are rarely used due to their lack of potency and potential hepatoxicity. Although not available in the United States, testosterone undecanoate has been used in Australia, Canada, and Europe since the 1970s. The undecanoate preparation avoids first pass metabolism due to its preferential absorption through the lymphatic system, but its clinical use is limited by its short half-life, necessitating multiple daily doses. Traditionally, long-acting esters such as testosterone enanthate or cypionate have dominated the androgen market and have been used successfully to alleviate the symptoms of male hypogonadism for more than 50 yr. Testosterone esters are administered intramuscularly every 2 to 3 weeks and have the advantage of being the cheapest form of androgen replacement, provided that the patient or a family member can administer the injection. In addition to the requirement for an intramuscular injection, however, these agents have the additional disadvantage of an unfavorable pharmacokinetic profile, characterized by large fluctuations in testosterone concentrations accompanied in some men by undesired changes in mood, libido, and energy levels. In Australia, a popular method of testosterone administration involves sc insertion of pellets, which can produce normal levels of testosterone for up to 6 months, although spontaneous extrusion of the pellets may occasionally occur.

The development of transdermal testosterone preparations in the late 1980s was an important advance in androgen replacement therapy. The first patch to come on the market required application to shaved scrotal skin to permit adequate absorption. In hypogonadal men, the scrotal transdermal system (Testoderm; Alza Corp., Mountain View, CA) produces testosterone levels that are in the mid-normal range 4 to 8 h after application (2). However, many men find this site of application unacceptable. In addition, in men with hypogonadism of prepubertal onset, the surface area of the scrotum may not be large enough to accommodate the patch. In recent years, availability of nongenital patches has led to a significant decline in the use of scrotal preparations. Permeation-enhanced transdermal delivery systems with a reservoir containing testosterone in an alcohol base (Androderm, Watson Laboratory, Corona, CA) have been shown to maintain serum testosterone levels more consistently within the normal range than an equivalent intramuscular dose (3). The main drawback of this patch is skin irritation, which is encountered in up to one third of patients. Although application of triamcinolone cream to the skin before the patch can alleviate erythema and pruritus, adverse skin reactions necessitate discontinuation of therapy in ~10% of subjects. A second transdermal preparation (Testoderm TTS; Alza Corp.), which has a larger surface area and does not contain a reservoir, is associated with less skin irritation. However, this patch does not always adhere well to the skin, particularly in men who engage in strenuous exercise. Testosterone patches have the disadvantage of permitting relatively limited flexibility in dosing and are 10 times more expensive than testosterone esters.

The latest development in androgen replacement is an open testosterone delivery system using a 1% hydroalcoholic gel (AndroGel; Unimed Pharmaceuticals, Inc., Buffalo Grove, IL). Pharmacokinetic studies of this gel indicate that application to hypogonadal men increases testosterone levels to the normal range within 30 min with steady-state levels achieved by 24 h (4). In the August 2000 issue of *JCEM* (**85**:2839–2853), the same

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Address correspondence and requests for reprints to: Frances J. Hayes, MB, MRCPI, Reproductive Endocrine Unit and National Center for Infertility Research, Massachusetts General Hospital, 55 Fruit Street, Boston, Massachusetts 02114. E-mail: Hayes.Frances@MGH.Harvard.edu.

investigators report that 6 months treatment with this testosterone gel formulation improves sexual function, increases lean body mass and muscle strength, and decreases fat mass in a large cohort of hypogonadal men (5). Whereas similar beneficial effects were observed with the testosterone patch, the gel was better tolerated and associated with less skin irritation and a lower discontinuation rate. The main adverse effect observed was a significant, dose-related increase in hematocrit levels, which exceeded the normal range in 18% of subjects who received the higher testosterone gel dose. Prostate-specific antigen (PSA) levels also increased in a dose-dependent fashion but remained within the normal range. No significant changes were observed in the lipid profile following testosterone therapy.

It is important to put the benefits of this new mode of testosterone delivery into perspective. The testosterone gel is clearly an important advance in androgen replacement in that it is more user-friendly than existing formulations and, therefore, likely to improve patient compliance. However, the lay press is already attributing far-reaching clinical implications to this formulation in the absence of strong scientific data. The concept that a relative hypogonadism (*i.e.* testosterone levels in the low-normal range) may account for many of the symptoms of aging has recently gained popularity. The normal aging process is accompanied by physiological changes in target organs that are sites of androgen action. Given the decline in androgen levels with aging that has been documented in many epidemiological studies, it is tempting to attribute some of the features of aging to androgen deficiency (6). However, symptoms of aging, such as decrease in muscle strength, energy levels, libido, and potency, are nonspecific and are more likely to be multifactorial in origin as opposed to reliable indices of androgen status. In addition, there is considerable interindividual variation in the decline in testosterone with aging, and in many instances mean levels remain well within the normal adult male range.

If an absolute or relative androgen deficiency does, indeed, contribute to age-related physiologic changes, one could argue that a trial of testosterone therapy should be considered for all older men with testosterone levels in the low-normal range. There are three main problems with this approach. First, assessment of androgen status by a single testosterone level can be misleading. Second, the potential benefit of testosterone in the aging male is a question that is more appropriately addressed by large, prospective, randomized trials than by anecdotal experience. Third, testosterone is a Schedule III controlled substance with the potential to cause significant adverse effects if prescribed for inappropriate indications and without proper medical supervision.

In the absence of good biologic markers of androgen action, androgen status has traditionally been assessed by measurement of plasma testosterone levels. Whereas hypogonadism is easy to diagnose when testosterone levels are markedly diminished (*i.e.* $<$100 ng/dL), it is more difficult to interpret the biological significance of testosterone levels just below or in the low-normal range. When assigning a diagnosis of androgen deficiency based on a single testosterone measurement, it is important to be cognizant of the fact that as many as 15% of healthy young men with normal sexual function have a testosterone level below the normal range at some point during a 24-h period of blood sampling (7). In younger men in whom testosterone levels may fall by as much as 30% in the course of a day, the time at which the blood sample is drawn is critical for its interpretation. In many instances, samples that fall below the normal range when measured in the late afternoon will be normal when repeated in a morning sample. Obtaining a morning testosterone level may be less critical in older men given that the diurnal rhythm of testosterone secretion is significantly attenuated with aging (8). Given this normal pulsatile and diurnal rhythm of testosterone secretion, a more careful characterization of the hypothalamic-pituitary-testicular axis may be necessary, in some instances, to prevent misdiagnosis of hypogonadism and the institution of inappropriate therapy.

Although measurement of total testosterone by RIA has traditionally been considered the most reliable method of diagnosing androgen deficiency, there are situations where it may be misleading. More than 98% of testosterone is protein bound: ~40% to sex hormone-binding globulin (SHBG) and 60% to albumin. Aging is associated with an increase in SHBG levels and consequently a slower decline in total testosterone (~0.4% per yr) than in the free fraction (~1.2% per yr) (9). For this reason, some investigators have advocated use of free testosterone to diagnose hypogonadism on the basis that it is the most sensitive marker of androgen status. However, accurate measurement of free testosterone involves a dialysis procedure, a requirement that makes the assay both time-consuming and inconvenient. The alternative, which is to measure free testosterone by one of the widely used commercial kits, is notoriously unreliable. In some studies, use of free testosterone kits has been shown to underestimate plasma free testosterone levels by as much as 100% (10). Therefore, reliance on these kits to diagnose male hypogonadism has the potential to markedly overestimate the true prevalence of androgen deficiency. A third measure of androgen status is provided by bioavailable or non-SHBG-bound testosterone. This assay, which involves ammonium sulfate precipitation, does not suffer from the methodological limitations of the free testosterone kits and may be a better marker of androgen status than total testosterone in states of altered SHBG secretion, such as obesity. Whereas androgen status is typically defined solely on the basis of plasma testosterone levels, the androgen receptor (AR) is clearly another important determinant of androgen action. Indeed, whereas the majority of studies demonstrate no correlation between endogenous testosterone levels and the subsequent development of prostate cancer, an inverse correlation has been established between the length of the AR polyglutamine tract and both an increased risk and earlier onset of prostate cancer (11). Therefore, polymorphisms in the AR may be as important as absolute testosterone levels in mediating androgen effects.

When discussing the physiologic role of testosterone, it is important to make a distinction between overt hypogonadism and the more subtle decline in testosterone levels seen with aging. It is clear that overt hypogonadism has a significant negative impact on a variety of parameters, including body composition, bone mineral density (BMD), and sexual function, and that these effects can be reversed with androgen replacement. However, it is not clear what impact the age-related decline in testosterone has on these same parameters. In the last decade, a number of studies have tried

to address this question by examining the impact of testosterone supplementation in the aging male. To date, these studies have yielded inconsistent results. The discrepancy in results may reflect the relatively small number of patients studied, variable selection criteria and definitions of "hypogonadism," differences in dose and duration of androgen therapy, and the different methodologies used to assess study end points.

Given the prevalence of osteoporosis in elderly men and its associated morbidity and mortality, determining whether testosterone therapy may have a beneficial impact on bone in men with testosterone levels in the low normal range is an important public health issue. Based on current data, the proportion of the variance in BMD in healthy elderly men that is due to testosterone is controversial (12). Some, but not all, studies have demonstrated a positive correlation between BMD and either total or free testosterone. Overall however, hormone levels were estimated to account for only ~5% of the age-and weight-adjusted variance in BMD in a large cohort of healthy, elderly men (13). The largest and longest study of testosterone administration to a cohort of healthy, elderly men with a baseline testosterone level of less than 475 ng/dL failed to show any significant improvement in BMD after 36 months of therapy (14). However, subset analysis of this study demonstrated that subjects with baseline testosterone levels less than 200 ng/dL had a significant improvement in BMD in the lumbar spine, whereas the latter did not change in those with a baseline testosterone level more than 400 ng/dL. Regardless of the baseline testosterone level, however, no change was observed in BMD at the hip. The absence of a beneficial effect of testosterone on BMD at the hip is particularly important given that most of the morbidity and mortality of osteoporosis relates to hip fracture. Therefore, a convincing role for testosterone has yet to be definitively established in reversing the decline in BMD with aging. Some argue that the testosterone levels achieved in this study were not high enough to see an effect, although mean levels almost doubled. An alternative possibility is that it is estradiol rather than testosterone that is the major steroid regulator of bone in the male. This hypothesis is supported by the demonstration of osteoporosis in men with congenital estrogen deficiency despite high levels of testosterone. In addition, some epidemiological studies demonstrate a better correlation between BMD and estradiol than testosterone (15). Estradiol does not demonstrate the same age-related decline as testosterone (9). The failure of estradiol produced by aromatization of exogenously administered testosterone to have a significant beneficial effect on BMD in men with normal baseline hormone levels suggests that there may be a threshold for estrogen's beneficial effect on bone.

In clinical practice, most men are referred for testosterone replacement therapy because of declining sexual function. Contrary to what is being suggested by the lay press, current data do not support a beneficial role of testosterone therapy for middle-aged men with sexual dysfunction and testosterone levels in the low-normal range. The study by Wang *et al.* (5) as well as previous studies using other modes of testosterone delivery demonstrate that libido and potency are diminished in hypogonadal men and are restored with testosterone therapy (6). However, the majority of studies have demonstrated no correlation between libido or potency and testosterone levels within the normal range. Similarly, increasing testosterone levels within the normal range rarely has been reported to have a beneficial impact on sexual function. In the study by Wang *et al.* (5), the improvement in sexual function was independent of the dose or mode of testosterone delivery despite the fact that serum testosterone levels were almost 2-fold higher in the group that received the high-dose testosterone gel compared with those who received the patch. These data, therefore, support the concept of a threshold level of testosterone in the low normal range, below which libido and sexual function are impaired and above which there is no further enhancement of response.

Several studies have demonstrated that testosterone administration has a beneficial impact on body composition. This anabolic effect of testosterone is seen in both hypogonadal men treated with physiologic doses of testosterone as well as eugonadal men receiving pharmacologic levels of testosterone (16). Studies of androgen administration to older men have demonstrated a consistent increase in lean body mass, but a variable improvement in muscle strength (17). None of these studies have attempted to correlate the changes in muscle strength to functional performance. However, to date, all of the studies of androgen replacement have been done exclusively in healthy older men. Therefore, it remains to be seen what impact testosterone administration will have on frail, elderly men, who, in general, tend to have testosterone levels 10–15% lower than healthy, age-matched controls (9). This may well be the population that will derive most benefit from testosterone replacement. It will be particularly interesting to see if changes in muscle strength in this group can translate into an improvement in functional activity and potentially a reduction in falls and fractures.

Testosterone therapy has the potential to cause a number of adverse events, which is why it is classified as a Schedule III controlled substance. Almost all studies of androgen therapy have demonstrated a significant increase in hematocrit levels due to stimulation of erythropoiesis, which has the potential to cause symptoms related to hyperviscosity. Administration of testosterone to hypogonadal men also causes a modest increase in prostate volume comparable with that seen in age-matched eugonadal men. To date, testosterone administration has not been reported to produce clinical symptoms of benign prostatic hypertrophy, although it is important to bear in mind that men with any suggestion of prostatic outflow obstruction have been excluded from these studies. Despite an increase in PSA levels within the normal range, there are no data to suggest a link between testosterone administration and prostate cancer, although longer follow-up is needed. The impact of androgens on lipids seems to vary depending on the dose, route of administration, and whether aromatizable or nonaromatizable androgens are used. To date, most studies of testosterone administration to healthy, older men have demonstrated a decrease in total cholesterol, with either no change or a slight decrease in high-density lipoprotein cholesterol. Abnormalities in liver function tests are generally limited to the orally administered androgens. Therefore, all patients on androgen replacement require monitoring with hematocrit levels, liver function

tests, a lipid profile and PSA, and should be under the supervision of a physician with expertise in this area.

In summary, therefore, androgen replacement therapy in men is a new and exciting field of study. As "designer androgens" become available it should be possible to develop formulations with a desired profile of activity such that they are stimulatory to the desired target organ (*e.g.* bone) but have a neutral effect on erythropoiesis or the prostate. Available data are still insufficient to permit any major conclusions about the role of androgen replacement in the treatment of age-related physiological changes. In designing intervention studies on androgen replacement in men, it is imperative to learn from the studies of the impact of HRT in women. Whereas several observational studies had suggested that HRT was associated with a significant reduction in cardiovascular mortality, the one prospective, randomized, placebo-controlled trial of estrogen replacement demonstrated no cardiovascular benefit in terms of secondary prevention (18). Therefore, a large, randomized, placebo-controlled, multicenter study would be the optimal way to address the potential benefit of androgen replacement in the male.

Frances J. Hayes
Reproductive Endocrine Unit and National Center for Infertility Research
Massachusetts General Hospital
Boston, Massachusetts 02114

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