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Testosterone, Sexuality, and Erectile Function in Aging Men

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Human aging is associated with many changes, which resemble those seen with deficiencies of sex steroids or growth hormone and with cortisol excess. Among these are decreases in lean body mass (LBM) and muscle strength, loss of bone mineral, increase in body fat, and, in men, reduced libido and erectile function. Circulating total and free testosterone (T) decrease progressively with age in men, and these decreases correlate with observed changes in body composition and function. T is implicated in maintaining both male libido and erectile function, the latter effect possibly mediated by local increases in nerve nitric oxide (NO) synthase in the corpora cavernosa. Preliminary studies of T replacement in older men suggest improvements in LBM, fat, bone, libido, and erections, but more research needs to be done to better delineate benefits and potential risks before definitive recommendations can be made regarding T replacement in older men.

Typical age-related changes in body composition and function include loss of lean body and muscle mass, decreased muscle strength (Kallman et al, 1990) and fitness (Fleg and Lakatta, 1988), and loss of functional capacity (Fried et al, 1998). There is also an increase in total fat mass and percent body fat (Shimokata et al, 1989) accompanied by insulin resistance and a higher risk of type 2 diabetes (Fink et al, 1983; Kohrt et al, 1993), increased low-density lipoprotein (LDL) cholesterol, triglycerides, and fatty acids (Obisesan et al, 1997). Other changes in metabolism include negative calcium balance leading to decreased bone density and osteoporotic fractures (Wark, 1996), decreased protein synthesis, slower healing, and impaired immune system function (Scordamaglia et al, 1991). Predictably, in aging men, there also occur decreased frequency of and desire for sexual activity and a reduction in the number and quality of erections (Kaiser et al, 1988; Helgason et al, 1996; Morley et al, 2000). Behavioral and psychological manifestations of aging also include slower problem solving, lapses of memory, and increasing incidence of dementing illness.

It is unclear the extent to which alterations in hormone balance contribute to the changes enumerated above. Documented age-related changes in hormones in men include a decrease in circulating total T (Bremner and Prinz, 1983) and various measures of free or bioavailable T (Vermeulen and Kaufman, 1995), the latter decline described as steeper due to increases in circulating sex hormone binding globulin with age. The decreases in T have been observed to begin in the third decade and proceed at a more-or-less constant rate into extreme old age, whether measured

cross-sectionally (Tenover et al, 1987) or longitudinally in the Baltimore Longitudinal Study of Aging (BLSA) (Figure 1A and B) and other study populations (Morley et al, 1997; Harman et al, 2001). There are also reductions in circulating growth hormone and insulin-like growth factor I (Ho et al, 1987; O'Connor et al, 1998) and a tendency for increased cortisol secretion, especially in response to stress (Arnetz, 1985; Van Cauter et al, 1996).

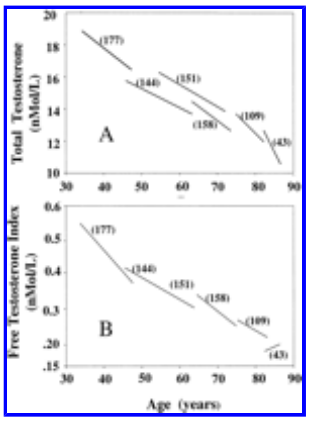

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Figure 1. Longitudinal effects of aging on date-adjusted testosterone (T) and free T index. Linear segment plots for total T and free T index vs age are shown for men with T and sex hormone binding globulin values on at least 2 visits. Each linear segment has a slope equal to the mean of the individual longitudinal slopes and is centered on the median age for each cohort of men from the second to the ninth decade. Numbers in parentheses represent the number of men in each cohort. Segments show significant downward progression at every age, with no significant change in slopes for T or free T index over the entire age range (Harman et al, 2001).

Each of the hormonal alterations mentioned above, occurring in young adults, can present a clinical picture having certain features in common with typical age-related changes in body composition and function. In particular, male hypogonadism is associated with loss of muscle mass and strength, increased total and (especially) truncal and visceral body fat (accompanied by mild insulin resistance), and reduced libido and erectile capacity. The relationship between impaired pituitary-gonadal axis function and diminished sexual response during aging is not fully delineated, but it has become clear recently that the decline in free/bioavailable T levels is sufficient to make a substantial fraction of men over the age of 65 hypogonadal, at least by standard criteria for serum hormone levels (Figure 2) (Harman et al, 2001).

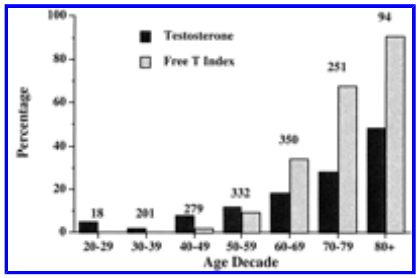

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Figure 2. Hypogonadism in aging men. Bar height indicates the percentage of men in each 10-year interval from the third to the ninth decades with at least 1 testosterone (T) value in the hypogonadal range by the criteria of total T < 300 ng/dl (shaded bars) or T/SHBG (free T index) < 5.74 (striped bars). Numbers above each pair of bars indicate the number of men studied in the corresponding decade. The fraction of men with hypogonadism increases progressively from the 20s to the 80s by either criterion. More men have hypogonadaism by free T index than by total T after age 50, and there is a progressively greater difference with increasing age between the 2 criteria (Harman et al, 2001).

The decline in sexual activity levels and erectile function with aging has been well documented in a number of studies. Martin (1977) followed total self-reported male "sexual outlet," including

heterosexual and homosexual intercourse, masturbation, etc, in BLSA men and documented a profound decrease in rates of sexual activity with age. This change was accompanied by an expressed decrease in desire for sexual activity and an increase in the period men reported being comfortable without sex. These same BLSA men also reported a decrease in frequency of erections such that by age 70 and above, over 50% had no erections whatsoever. In a more recent study by Panser et al (1995), approximately 80% of men ages 40 to 49 reported adequate erectile function "all the time," whereas less than 20% of men ages 70 and older did so. Conversely, fewer than 5% of men ages 40 to 49 rated their erectile function as "little/none," whereas this level of deficiency occurred in nearly 40% of men ages 70 and older. In the same study, over 70% of the younger men reported desire for sex more than once weekly, but only about 15% of men over 70 had this level of libido. The number of men ages 40 to 49 with no interest in sex was less than 5%, but approximately 35% of men ages 70 and older expressed no desire for sexual activity. The decrease in erectile function with age has also been documented in a study by Feldman et al (1994) (Figure 3), in which approximately 50% of men ages 70 to 79 reported moderate or complete erectile dysfunction (ED) compared with 25% of men ages 40 to 49.

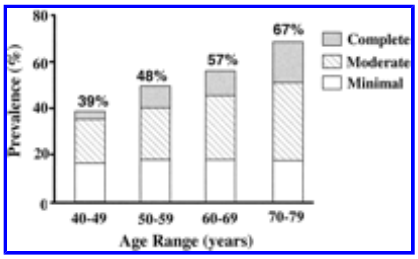

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Figure 3. Prevalence in percentage of men of various ages from 40 to 79 years reporting minimal, moderate, or complete ED. Total bar height represents number of men with any degree of erectile dysfunction (ED) and is indicated by numbers above bars. Prevalence of minimal ED remains constant across the age spectrum, whereas prevalences of moderate and complete ED increase progressively with age (Feldman et al, 1994).

Although the decrease in free/bioavailable T levels with age has been shown in some studies to be correlated with the loss of muscle strength (Roy et al, 2002) and the decrease in bone mineral density (Scopacasa et al, 2000), even when age is adjusted for as a covariate, the finding of such associations does not prove causality. This is also true for the relationship of hormonal alterations to sexual function. In one study of BLSA men (Tsitouras et al, 1982) there did appear to be a weak relationship between total serum T levels and self-reported sexual activity, such that men over 60 in the lowest age-adjusted tertile for sexual outlet had lower serum T levels ($P < .05$) than those in the middle or upper tertiles (Figure 4). This relationship did not hold true for younger men. The concept that hormonal alterations underlie a significant fraction of age-related male sexual disability is further supported by data (Morley, personal communication) showing that the fraction of men complaining of ED who have an identifiable endocrine etiology increases from 43% in men less than 60 years of age to 83% of men more than 60 years of age.

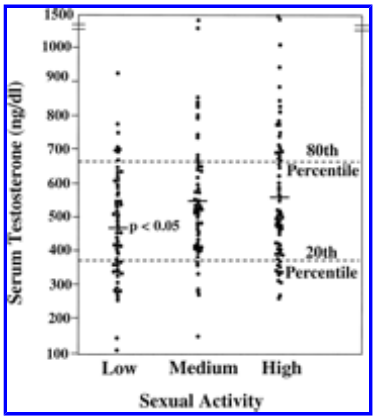

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Figure 4. Distributions of individual values for total serum testosterone (T) in men over 60 years of age in the Baltimore Longitudinal Study of Aging, classified into tertiles for self-reported sexual activity levels by 5-year age group. Men in the low activity tertile have significantly lower mean T values ($P < .05$) than those in the 2 upper tertiles (Tsitouras et al, 1982).

An important step in establishing plausibility of a causal relationship between decreased T and altered erectile function and libido is the identification of biological mechanisms by which T-action alters each of these sexual functions. In the case of libido, it has long been known that exposure to T alters both brain function, and, in some species, structure (Xiao and Jordan, 2002; Cooke et al, 2003). There are both androgen and estrogen receptors on neurons in various areas of the brain, including those known to be involved in mediation of male sexual activity. It also appears, from experiments in a number of species, that T affects sexual behavior both directly and after local aromatization to estradiol in the brain (Vagell and McGinnis, 1997; Roselli and Chambers, 1999). In addition, a direct local role for T in erectile function is suggested by recent data derived from animal studies, which have shown that exposure to T increases, and deprivation of T decreases, the activity of constitutive NO synthase in the nonadrenergic, noncholinergic autonomic vascular nerve endings of the corpora cavernosa (Chamness et al, 1995; Zvara et al, 1995; Park et al, 1999). NO is an important mediator of the erectile response and directly activates guanyl cyclase in the vascular smooth muscle cells, leading to production of cyclic guanosine monphosphate (cGMP) from guanosine triphosphate. Increased cGMP relaxes smooth muscle, allowing the sinusoids of the corpora cavernosa to dilate, causing erection. Thus, the erectile response is augmented by T and impaired in its absence (Seo et al, 1999). The relevance of the above relationships to human physiology is likely but not proven at this point in time.

Final confirmation of the importance of T in mediating changes in sexual function with age await definitive data documenting the extent to which T replacement does or does not ameliorate this deficiency. Preliminary studies appear promising. In one study (Seo et al, 1999), 80% of older men (mean age 71) perceived their libido as improved after treatment with T, compared with about 8% receiving placebo. In another trial (Kunelius et al, 2002), 150 men ages 50 to 70 years were treated with placebo or dihydrotestosterone (DHT) (which is not aromatized to estrogen and hence is less likely to have effects at the central nervous system). Early morning erections improved transiently in the DHT group at 3 months of treatment, and the ability to maintain erection improved in the DHT group compared with the placebo group.

In summary, aging is associated with changes in body composition similar to those observed in men with hypogonadism. These changes include 1) loss of libido and decreased sexual function, 2) decreases in LBM, muscle strength, and endurance, 3) decreases in bone density, and 4) increases in body fat and insulin resistance

Total and free T levels also decrease with age in men. In older men, circulating T or free T correlate positively with sexual function, LBM, muscle strength, $\dot{V}O_2$max, and bone density and correlate negatively with body fat. ED is frequently associated with low T in older men. Relationships of endogenous androgen measures to clinical outcome variables suggest that some deleterious age-related changes may be caused by androgen depletion. Finally, T replacement appears to improve both sexual desire and erectile capacity in some older men with low T levels. Further studies of the risks and benefits of androgen replacement in aging men, emphasizing clinical outcomes, especially ED and libido, are justified and should further clarify these issues.

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