Should there be hormone replacement therapy for aging men?

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Normal male aging is associated with a decline in serum levels of a number of hormones which have anabolic and other beneficial properties when given to young adults with established hormone deficiency. The age-related decline in these hormones parallels changes in target organs and physiological functions leading to the concept that replacing these hormones might prevent, stabilize, or even reverse some of the detrimental target-organ changes seen with aging. These hormones often have been referred to as *trophic hormones*, and include testosterone, dehydroepiandrosterone (DHEA), and growth hormone (GH). The range of potential beneficial effects of trophic hormone replacement is quite extensive and includes effects on body composition, strength and physical function, sexual function, immune function, bone density, mood, and cognition. However, to date, data from actual testosterone, DHEA, and GH replacement studies in older men have demonstrated only modest effects at best, and there are potential and observed adverse effects of replacement therapies.

Testosterone

Total and free testosterone levels decline with normal aging in men (Fig. 1). Possible beneficial effects of testosterone replacement therapy (TRT) in older men include improvement in bone mass, body composition, strength, cognition, mood, and sexual function.

Bone mass declines with age in men, and hypogonadism is a risk factor for male osteoporosis. In general, TRT studies have shown a decline in bone degradation and increases in bone mineral density with replacement. There are as yet no data on the effect of TRT on fracture rates in older men.

Loss of muscle mass with age leads to decreased muscle strength and a decline in physical function. TRT studies in older men have consistently reported decline in body fat and increase in lean body mass (predominantly muscle mass) with therapy. The magnitude of the changes in both muscle and fat mass in older men appear similar in magnitude to that seen with TRT in young hypogonadal men. The strength changes with TRT in older men have not been as consistent as have been the changes in muscle mass, with many studies showing no beneficial effect. A meta-analysis of muscle strength changes with androgen therapy in older men reported a moderate increase in muscle strength, but one study influenced the mean effect size. In

terms of changes in physical function with TRT, only two studies to date have shown an improvement, and the magnitude of the changes in physical performance with TRT were far less than that which would be seen in response to exercise. The clinical significance, if any, of the fat mass changes with TRT therapy remain to be delineated.

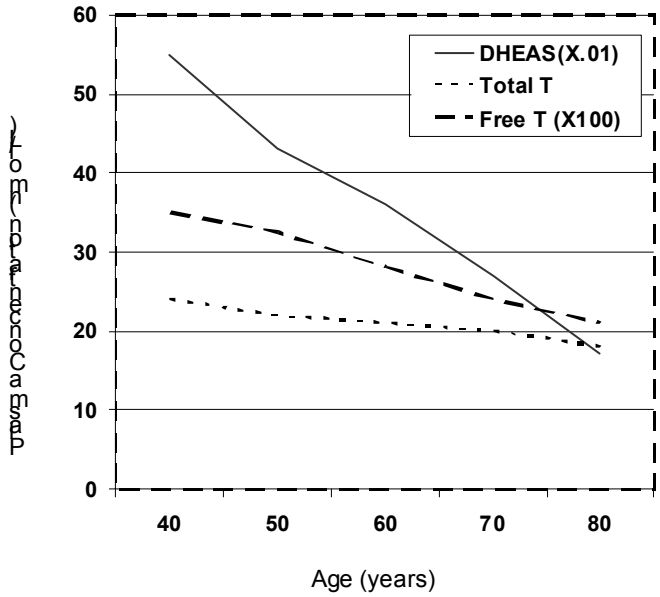

FIG. 1. Mean plasma levels of total testosterone (T), free T, and DHEAS by age in healthy men

Young men with profound testosterone deficiency have symptoms of dysphoria, fatigue, and irritability, all of which improve with normalization of testosterone levels. There have been no studies to date of TRT in depressed elderly men. In older men who were not depressed, only one of the seven clinical trials reported any mood improvement with TRT. Another five studies of testosterone therapy in older men evaluated aspects of quality of life by various scales, and none of these reported a change.

To date, there have been eight randomized controlled clinical trials evaluating cognitive function with TRT in older men without significant cognitive deficits at baseline. Half of the studies reported some improvement on aspects of cognition such as visuospatial memory, total memory, or verbal memory, and half of the studies reported no effect. There have been three small placebo controlled studies of TRT in older men with dementia. Two of

these studies reported that the TRT group did better on end of study cognitive tests than the placebo group; one study reported no difference.

The effects of TRT on aspects of the cardiovascular system are varied. Epidemiologic studies have demonstrated that low, rather than high, serum testosterone levels are associated with an increased risk of cardiovascular disease in older men. TRT studies have shown that testosterone tends to improve many cardiovascular risk parameters, such as decreasing platelet aggregation, dilatation of vessels, and improvement in total and LDL cholesterol levels. The ultimate impact of TRT on cardiovascular disease events in older men, however, is unknown.

A meta-analysis of studies of erectile dysfunction and testosterone treatment demonstrated that the prevalence of testosterone as a reversible cause of erectile dysfunction was low. TRT is not the primary treatment for the majority of older men with erectile dysfunction, but may be beneficial in some older men where decreased libido is a significant complaint, where serum testosterone levels are very low, or if testosterone therapy is used as adjunctive therapy in men who have failed PDE-5 inhibitor therapy alone (Chapter 35).

Potential or reported adverse effects of TRT in older men include fluid retention, gynecomastia, polycythemia, exacerbation of sleep apnea, and exacerbation of prostate disease. Most are rare occurrences or controllable with monitoring and with testosterone dosage adjustment. It is the potential for exacerbation of benign prostatic hyperplasia (BPH) and prostate cancer that are the main concerns with TRT. A meta-analysis of adverse events from double-blind, placebo controlled testosterone replacement trials in middle-aged and older men demonstrated that rates of prostate cancer, the number of prostate biopsies performed, and a rise in PSA were not statistically significant different between TRT and placebo treatment groups.

Summary: TRT improves bone density and may prevent or treat osteoporosis; however, other therapies are available. Clinically important effects of TRT on fat and muscle, such as improvement in metabolic syndrome and/or physical function, have not yet been demonstrated. TRT effects on mood and cognition are inconsistent, although it may be helpful in some older men. Cardiovascular effects of TRT may be beneficial, but there are no data on meaningful clinical outcomes such as stroke and myocardial infarction. Most adverse effects are predictable and/or manageable. The possibility of prostate cancer or BPH exacerbation by TRT remains a concern, although there are no data to support this has occurred.

DHEA

DHEA(S) levels markedly decline with normal aging (Fig.1), and epide-

miological studies have reported associations between better overall health and higher DHEA levels. While early small human studies suggested DHEA supplementation might be beneficial for a variety of clinical parameters, larger randomized controlled trials of DHEA in older adults have not demonstrated any clear evidence of meaningful benefits. A recent 2-year study of DHEA supplementation in men and women over 60 years of age found no notable effects on body composition, physical performance, insulin sensitivity, or quality of life. Other randomized trials of DHEA replacement in older adults also have failed to demonstrate improvements in mood, well-being, and cognition. Several DHEA replacement studies have reported small increases in bone density, but the effects are minimal compared to established osteoporosis treatments. There have been inconsistent small effects of DHEA supplementation in older adults on immune function.

There are no reports of significant adverse effects from DHEA in the clinical trials, but these studies have utilized physiological replacement doses of high quality grade DHEA. DHEA can be metabolized to sex steroids, but deleterious effects, such as elevation in PSA or increase in prostate volumes, have not been reported.

Summary: DHEA supplementation may lead to small improvement in bone density, but much less than traditional therapies; there are no significant or consistent effects on any other clinical parameters. No significant adverse effects at physiological replacement doses of high quality DHEA.

Growth hormone

While there are reasonable data to support GH replacement therapy in adults with documented GH deficiency and hypothalamic-pituitary disease, there are few data to support any use of GH supplementation for age-related changes in muscle, strength, bone, and other parameters. Currently, it is illegal in the United States to give GH as an anti-aging therapy.

A recent review of randomized controlled clinical studies of GH therapy reported small increases in muscle mass and decreases in fat mass compared to placebo treated older men. However, no improvements in strength, endurance, or function were found with GH therapy. Cholesterol levels tend to decrease with GH therapy, but other serum lipid levels, bone density, and quality of life did not change.

Side effects of GH therapy in older persons include peripheral edema, arthralgias, carpel tunnel syndrome, gynecomastia, and impaired fasting glucose levels. No study of GH therapy in older persons has been of sufficient duration to evaluate cancer risk.

Suggested reading

Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Gerontol Med Sci.* 2005; 60A: 1451-57.

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