Scientific overview of hormone treatment used for rejuvenation

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A search for a hormonal fountain of youth has been hotly pursued over the last century, predominately by those who wish to market hormones to a gullible public. There is little or no benefit of hormone replacement in persons who do not have a hormone deficiency. Overall, the present state of the art suggests that the findings have been disappointing. In persons who fail to get adequate sunlight, and therefore have low vitamin D levels, vitamin D replacement appears to have positive effects, including decreasing mortality. Testosterone in hypogonadal males has a number of positive effects such as improving libido and erectile capacity, increasing strength and bone mineral density, and perhaps having a small effect on cognition. These effects need to be balanced against long-term side effects, the evidence for which studies are lacking. There is little evidence to recommend DHEA, pregnenolone, growth hormone, ghrelin, or melatonin to older persons. Overall, exercise, adequate exposure to sunlight, and adequate dietary protein appear to have at least as positive an effect as any of the hormones being used to rejuvenate older persons. (Fertil Steril® 2013;99:1807–13. ©2013 by American Society for Reproductive Medicine.)

Key Words: DHEA, exercise, growth hormone, testosterone, vitamin D

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Since the beginning of time, humans have searched for a magical way to delay or reverse aging (1). Tibetan monks believed there were seven energy centers (chakras), each of which represented one of the seven ductless glands making up the endocrine system. These centers were thought to control all of the body's functions, including the aging process (2). This concept gave rise to the hormonal fountain of youth.

Before considering the limited evidence for hormone treatment for rejuvenation, it is important to point out that a number of simple interventions have much more evidence for delaying death and improving quality of life. These include exercise, eating a balanced diet with five fruits and vegetables a day or a Mediterranean diet, and not smoking (3, 4). Exercise is especially important in frail older persons (5–9). Exercise in frail persons has been shown to increase functional performance, increase walking speed, increase chair stand, increase stair climbing, increase balance, decrease depression, improve cognition, decrease fear of falling, decrease institutionalization, and decrease mortality (10–16). There is also evidence, although less strong, that adding a leucine-enriched essential amino acid supplement to resistance exercise will improve muscle function and outcomes (17–22). Weight loss in older persons without concomitant exercise has been shown to be associated with increased hip fracture and mortality, making the recommendations for caloric restriction questionable (23–27). Shah et al. (28) have found that exercise with diet decreased the muscle and bone mass loss due to dieting. The effect of exercise on bone appears to be due to a decrease in sclerostin.

The production of many hormones decreases with aging. Almost all of these hormones, when replaced, have been claimed to ameliorate the effects of aging. However, the evidence that this is true is extraordinarily limited, and, in fact, there is no evidence to support their use in persons who are not hormonally deficient. Claims that they do so are unsubstantiated and cause financial and medical harm. Those who make claims to the contrary are charlatans, equivalent to the snake oil salesmen of the past. The rest of this article will discuss the effects of specific hormones on the aging process in persons who are hormonally deficient.

Vitamin D

The levels of 25(OH) vitamin D have been shown to decline longitudinally with aging, even in places where there is more than adequate sunshine (29). This suggests that lower vitamin D levels are a part of aging. However, use of sunblock and poor dietary intake also play a role. The Institute of Medicine has suggested that optimal vitamin D levels are between

Received March 1, 2013; revised April 4, 2013; accepted April 5, 2013.
J.E.M. has nothing to disclose.
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Fertility and Sterility® Vol. 99, No. 7, June 2013 0015-0282/$36.00

http://dx.doi.org/10.1016/j.fertnstert.2013.04.009

20 to 25 ng/dL (30). Many studies have shown that the majority of older persons have vitamin D levels lower than these recommended values (31–35). Low vitamin D levels are associated with frailty (36).

Vitamin D replacement in persons with low 25(OH) vitamin D levels appears to reduce mortality, based on meta-analysis, but this is not true in all studies (37–39). Vitamin D replacement appears to improve muscle function and decrease falls and fractures (40–43). While there is evidence that vitamin D may enhance immune function, evidence of a major effect of vitamin D replacement on age-related immune function is not very robust (44). The evidence that vitamin D supplementation reduces insulin resistance is insufficient to recommend its use at the present time (45). Vitamin D replacement can reduce myostitis due to statins (46). There is some evidence that persons with Alzheimer's disease with low 25(OH) vitamin D may have improved cognition during vitamin D replacement (47).

Because vitamin D deficiency has become so common in most developed populations, it would appear that vitamin D replacement in older persons is likely to improve the aging process. For most persons, 1,000 IU of vitamin D appears to be a sufficient replacement dose. Measuring parathyroid hormone to ensure it is within the normal range is most probably a better measure of whether vitamin D replacement is sufficient, rather than measuring 25(OH) vitamin D levels.

Testosterone

In males, T declines at the rate of approximately 1% per year from the age of 30 years (48, 49). Sex hormone–binding globulin increases in older persons, making it essential to measure either a calculated free T or a bioavailable T (50). The prevalence of hypogonadism is controversial, with a study of 40- to 79-year-old European men finding a 2.1% prevalence, while studies focusing on total T levels have reported hypogonadism in 20% of men in their 60s and 50% of those in their 80s (51, 52). Whether these changes in T are due to underlying disease or not is controversial, but they have been found to be present in multiple large cohorts using liquid chromatography tandem mass spectrometry (53–55). It is controversial whether the low levels in aging men are "normal" for them. However, it appears that true low T levels define hypogonadism at any age. Older men with low T levels have been shown to be more likely to be frail than those who have normal values (56–58). Data for the association of mortality with low T in older males are not clear, but there is no evidence that low T improves mortality (59–62). Shores et al. (63) found that hypogonadal males treated with T had a lower mortality than those who were not treated. However, this was not a controlled trial.

Sarcopenia, loss of muscle mass and function, is a major problem for older men (64–69). Low T is associated with a decline in muscle mass and strength (70). T treatment in low doses increases muscle mass (71) and in high doses improves muscle strength and power (72, 73). T given to frail persons improves strength (74–76). In heart failure patients, T improves walking distance (77). Of interest, this is also true in females with heart failure (78). In persons (male and female) in assisted living who received T and a caloric supplement there was a markedly decreased hospitalization rate (79).

Half of the males with low libido are T deficient, but the other half are not deficient (80). The value of individual reports of reduced libido as an indicator of low T is open to question. Males with low T cannot increase their nitric oxide synthase activity, which results in softer erections, and they are less responsive or unresponsive to phosphodiesterase inhibitors (81, 82). However, a study by Spitzer et al. (82) did not find that sildenafil plus T was superior to sildenafil alone, although many of these men would not be considered truly hypogonadal. In older males with hypogonadism, T improves libido and erectile function (83).

Bone mineral density decreases with age in males, and hip fractures occur approximately 10 years later than in females (84). Low T is associated with having a hip fracture in males (85). T replacement increased bone mineral density at the hip over 3 years (86). There is no evidence that T replacement decreases hip fracture.

Bioavailable T levels in males are highly predictive of cognitive function (87). Persons with amnestic mild cognitive impairment and Alzheimer's disease have lower bioavailable T levels than those males with normal cognition (88). Males with low bioavailable T levels and amnestic mild cognitive impairment tend to very rapidly develop Alzheimer's disease (89). SAMP8 mice are an animal model of Alzheimer's disease (90). They have both increased amyloid precursor protein and increased oxidative damage in the brain (91, 92). The SAMP8 mouse has low T, and its cognitive defects can be reversed by T replacement (93). T replacement in the SAMP8 mouse reduced amyloid precursor protein. A number of small studies in humans have suggested that T may produce small improvements in cognition in males, although this has not been found in all studies (94).

Hemoglobin levels fall by 1–2 g/dL with aging. T increases hemoglobin in hypogonadal men. In some males it can cause polycythemia leading to stroke and other negative cardiovascular effects. Older persons have a reduction in total water volume, and T causes fluid retention. Both of these factors can be considered side effects or positive effects of T. There is limited evidence that prostate cancer can be aggravated by T (95). While some studies have suggested T may accelerate atherosclerotic disease, others suggest it may be protective (96).

T has been available since the 1930s. Overall, with reasonable doses, it seems to be safe in hypogonadal men (97). Many of the effects of T may be beneficial to older males, although it appears that relatively high doses may be necessary. At present, long-term T replacement placebo-controlled studies in older males are not available, although a single National Institutes of Health study is presently in progress. Thus, at present it would seem that T should be considered only in hypogonadal older males who have symptoms suggestive of hypogonadism (98).

The effect of T on the cardiovascular system is uncertain. One study suggested a marked increase in cardiovascular disease, but much of this was due to peripheral edema and