Testosterone Replacement Therapy in the Older Male

Introduction

Similar to other endocrine deficiency states, a low testosterone level causes metabolic changes resulting in both short-term and long-term consequences. In the past, testosterone deficiency was considered a relatively uncommon problem that was limited to men with congenital causes of hypogonadism, such as Klinefelter's syndrome, or to testicular failure caused by pituitary tumors or gonadal injury. However, more recent studies have shown that marked testosterone deficiency may also develop in conjunction with a variety of other clinical situations, including diabetes mellitus, obesity, hyperthyroidism, alcoholism, as a side effect of some medications, or as a result of traumatic head injury (Seftel, 2006; Agha, 2006).

Furthermore, it is now well established that testosterone secretion gradually declines with age, even in healthy men (Harman, 2001). Popularly referred to as *andropause*, the effects reported to be associated with the phenomenon include loss of bone and skeletal muscle/strength, reduced libido, erectile dysfunction, infertility, depression, and reduced cognition (Rhoden, 2004)).

However, the event of age-related changes in men does not correspond to menopause in women. The decline of testosterone levels is subtle, and the extent to which it results in reduced physiologic function is still largely unknown. Nonetheless, it is generally accepted that subnormal serum testosterone values in symptomatic men are consistent with hypogonadism.

Prevalence of Hypogonadism Among Aging Men

Although the number of hypogonadal men in the US population has previously been reported to be 4 to 5 million (FDA Consumer Update, 1996), the prevalence may be underestimated, as the condition often goes unrecognized (AACE, 2002).

Normal male adult levels of plasma testosterone reach approximately 300 to 1,000 ng/dL in late adolescence and remain stable until around 30 to 40 years of age, at which point testosterone levels begin to decline (Merck, 2003; Harman, 2001; Feldman, 2003). Using serum samples from 890 men participating in the Baltimore Longitudinal Study on Aging, Harmon and colleagues performed an analysis based on a serum testosterone level <325 ng/dL and found that about 12, 20, 30, and 50% of men in their 50s, 60s, 70s, and 80s, respectively, to be hypogonadal (Harmon, 2001).

Based on this data and the demographic trends of increasing median age and life expectancy, the number of men with hypogonadism may reasonably be expected to increase as well. During the years between 2000 and 2050, the number of Americans age 65 and over is projected to almost double, rising from 12.4% to 20.7% of the total population, with slightly more than half of the elderly being male (US Census Bureau, 2004). Furthermore, the increased prevalence of conditions associated with testosterone

deficits, such as obesity and diabetes mellitus, may also contribute to a larger population of hypogonadal men.

Testosterone Replacement Therapy – Yes or No?

Although no specific recommendations have been established to date, the latest guidelines published by the American Association of Clinical Endocrinologists state that adult men with symptomatic hypogonadism and a total testosterone level less that 200 ng/dL are potential candidates for treatment (AACE, 2002). However, according to data published by the U.S. Food and Drug Administration (FDA), only about 5% of American men with hypogonadism receive testosterone replacement therapy (FDA Consumer Update, 1996).

Several factors may contribute to this phenomenon. As a group, men are less likely than women to interact with the healthcare system (Bertakis, 2000). Additionally, diagnosing hypogonadism in adult men is a challenge in that many clinical symptoms presenting in patients with low testosterone are also associated with the normal aging process. Further complicating diagnosis is the fact that total testosterone level determined by laboratory analysis may not indicate male hypogonadism, particularly in the elderly; the total testosterone level can remain largely unchanged, while the proportion of testosterone that is bound to sex hormone-binding globulin (SHBG) and bioavailable testosterone is unbalanced. Finally, the influence of supplemental testosterone on blood lipids and prostate health is currently unknown, raising clinician concerns regarding the potential risks of testosterone replacement therapy in aging men (Liverman, 2004).

Although this final point has stirred considerable debate, to date there is no compelling evidence that testosterone replacement therapy is associated with either cardiovascular disease or prostate cancer (Rhoden, 2004). Conversely, research suggests that testosterone replacement therapy may be beneficial for several health outcomes, including positive effects on body composition, strength, bone density, frailty, cognitive function, mood, sexual function, and quality of life (Liverman, 2004).

Treatment Approach

The therapeutic goal of testosterone replacement in hypogonadal men over the age of 50 years include improvement in libido, mood and feelings of well-being, strength and stamina, muscle mass, and preservation of bone mass (Tenover, 1998).

Current knowledge of risks and benefits of testosterone treatment in older men is limited to data from a relatively small number of short-term studies (Matsumoto, 2002). Because testosterone has actions in a wide variety of organs and tissues, prospective candidates for therapy require screening for parameters related to any potential risks prior to the initiation of treatment. Absolute contraindications include a history of prostate cancer, breast cancer, or a hematocrit above 55% (MacIndoe, 2003). Relative contraindications include benign prostatic hyperplasia, sleep apnea, congestive heart failure, and erythrocytosis (Matsumoto, 2002; Tenover, 1998).

The FDA has approved a variety of testosterone compounds that are used in the treatment of hypogonadism, all of which are designated as Schedule III controlled substances due to abuse potential. Androgen delivery systems available in the US allow for oral, intramuscular, and transdermal administration (AACE, 2002). Ideally, these products are designed to provide a safe, effective, convenient treatment, resulting in prolonged physiologic range serum testosterone levels with the least possible side effects (Liverman, 2004).

However, the available forms of treatment vary in risk profile as well as several other key areas. For example, oral preparations are infrequently prescribed due to issues both in efficacy and safety. Orally administered testosterone is so rapidly metabolized by the liver that it is prevented from achieving sufficient blood levels. Alkylated androgen compounds, such as methyltestosterone and fluroxymesterone, are associated with substantial hepatic toxicity and are therefore rarely prescribed (Rhoden, 2004).

Several testosterone formulations can be delivered by intramuscular injection, including testosterone enanthate and testosterone cypionate. Both of these preparations are esterified, increasing lipid solubility and extending action. The typical adult regimen of 150 to 300 mg every 2 to 3 weeks can yield transient supraphysiological testosterone levels in the first few days after injection, sometimes resulting in a "roller coaster" effect in personal experience, as well as acne and polycythemia (AACE, 2002; Liverman, 2004). Lower doses given at more frequent intervals usually produced more sustained testosterone levels; however, this may be undesirable to patients due to an increase in number of needle sticks and doctors office visits required (Rhoden, 2004).

Transdermal testosterone, available in a scrotal skin patch, a non-scrotal skin patch, and topical gel, requires daily administered. Patches are typically applied in the evening (non-scrotal) or morning (scrotal) and usually result in normal-range serum testosterone levels that mimic the diurnal testosterone changes in normal men (AACE, 2002). Although easy to use, patches have been associated with skin irritations due to the addition of enhancers for increased absorption, a problem that may ultimately result in discontinuation of therapy for some patients (Tenover, 1998). Comparatively, skin irritation from the use of gel preparations is uncommon . As in patches, daily application of testosterone gel to skin has been shown to result in physiological serum testosterone levels (Matsumoto, 2004). Additionally, a recent long-term study of 1% testosterone gel (Testim®, Auxilium Pharmaceuticals, Norristown, PA) reported that therapeutic benefits in sexual function, mood, and body composition were successfully maintained over a 12-month treatment period with a safety profile similar to that of the previous short-term study (Dean, 2004).

Of note, a new class of compounds in development, selective androgen receptor modulators (SARMs), may provide a future alternative to testosterone therapy for hypogonadism in men. The discovery of SARMs offers an opportunity to design molecules that target androgen receptors to elicit a desired biologic response in a tissue-specific way. This tissue-selective activation has potential to treat symptoms associated with hypogonadism with less concern for the stimulation of potential diseases, such as

prostate cancer. Furthermore, SARMs are expected to provide the option of a safe and effective oral therapy that is missing from current treatment choices (Negro-Vilar, 1999).

Independent of treatment modality, patient follow-up at 3 to 4 month intervals during the first year is recommended to monitor the clinical response to therapy and any side effects that occur. Routine visits should also include examination of the prostate, as well as an annual prostate symptom assessment. In addition, the serum testosterone level should be measured at midpoint between treatments in patients receiving injections to ensure that the value is within the normal range (AACE, 2002).

Conclusions

Clearly, a progressive decline in serum testosterone levels takes place during aging in healthy men which may result in a substantial number of hypogonadism cases. The deficiency in testosterone may contribute to age-related changes in physiological function, and subsequently have a detrimental affect on quality of life.

Although the risks and benefits have not been well established, data suggests that testosterone replacement therapy may offer symptomatic, aged men a variety of benefits, including protection from osteoporosis, increased libido, and improvement in mood, sense of well-being, and cognitive function. To mitigate potential risks associated with testosterone supplementation, potential candidates should be carefully screened prior to treatment initiation and regularly monitored during the treatment program. Due to changing demographics and the current state of under diagnosis, more attention to research and clinical awareness regarding hypogonadism in elderly men is warranted.

References

Seftel, AD. Male hypogonadism. Part I: Epidemiology of hypogonadism. *Int J Impot Res*. 2006;18(2):115-20.

Agha, A, Thompson CJ. High Risk of Hypogonadism After Traumatic Brain Injury: Clinical Implications. *Pituitary*. 2006 Feb 9; [Epub ahead of print].

Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. *J Clin Endocrinol Metab*. 2001;86(2):724-31.

US Food and Drug Administration. Skin patch replaces testosterone. Consumer Updates, available at http://www.fda.gov/fdac/departs/196_upd.html. Accessed March 6, 2006.

American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hypogonadism in adult male patients: 2002 update. *Endocr Pract*. 2002;8:440-456.

MacIndoe JH. The challenges of testosterone deficiency: uncovering the problem, evaluating the role of therapy. *Postgrad Med*. 2003;114(4):51-62.

Bertakis KD, Azari R, Helms LJ, Callahan EJ, Robbins JA. Gender differences in the utilization of health care services. *J Fam Pract*. 2000;49(2):147-52.

Liverman CT, Blazer DG. 2004 Testosterone and aging: clinical research directions. Washington DC: National Academies Press. Available online at http://darwin.nap.edu/books/0309090636/html/R1.html. Accessed March 6, 2006.

Rhoden EL and Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. *N Engl J Med*. 2004;350:482-92.

Merck. 2003. Male hypogonadism. In: Beers MH, Berkow R, eds. *The Merck Manual of Diagnosis and Therapy.* 17th ed. Whitehouse Station, NJ: Merck & Co., Inc.

Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. *J Clin Endocrinol Metab*. 2002;87(2):589-98.

US Census Bureau. US interim projections by age, sex, race, and Hispanic origin. 2004. Available online at http://www.census.gov/icp/www/usinterimproj/ . Accessed March 6, 2006.

Tenover, JL. Male hormone replacement therapy including "andropause". *Endocrinol Metab Clin North Am*. 1998;27(4):969-87.

Matsumoto, A. Andropause: clinical implications of the decline in serum testosterone levels with aging in men**. .***J Gerontol A Biol Sci Med Sci*. 2002;57(2):M76-99.

Dean JD, Carnegie C, Rodzvilla J, Smith T. Long-term effects of Testim® 1% testosterone gel in hypogonadal men. *Reviews in Urology.* 2004: 6(Suppl. 6):S22-S29.

Negro-Vilar A. Selective androgen receptor modulators (SARMs): a novel approach to androgen therapy for the new millennium. *J Clin Endocrinol Metab*. 1999;84(10):3459-62.