Androgen Deficiency in the Aging Male: The Beginning, the Middle, and the Ongoing

consultant360.com/articles/androgen-deficiency-aging-male-beginning-middle-and-ongoing

The International Society for the Study of the Aging Male (ISSAM) defines *andropause* as "a clinical and biochemical syndrome associated with advancing age and characterized by a deficiency in serum androgen levels with or without a decrease in geriatric sensitivity to androgens."[1] It has also been described as "a man over fifty years of age who has a cluster of symptoms and a low testosterone level."[2-4]

History of Male Menopause

Testosterone deficiency was originally conceptualized in the Talmud and Old Testament.[2,5] A 16th century medical text found in China listed symptoms relating to the ideology of the male menopause syndrome. In 1944, Heller and Myers wrote what was considered a milestone paper in understanding the reversal of testosterone deficiency by testosterone replacement.[6]

Testosterone

Testosterone is the most important of the plasma androgens. Its presence is required for spermatogenesis, adult secondary sex characteristics, and pubertal development. *Androgens* are "substances that determine the differentiation of male internal and external genitalia as well as the development and maintenance of male secondary sex characteristics and male reproductive function."[7] For the most part, testosterone is bound to plasma proteins. One to two percent of testosterone is free; another 40-50% is loosely bound to albumin. In addition, 50-60% is strongly bound to sex hormone-binding globulin (SHBG).[7-9] In the aging male, there is an increase in SHBG, which can result in less available testosterone. Therefore, total testosterone levels may appear to be higher than anticipated, making evaluation of total serum testosterone levels an inadequate barometer for diagnosing hypogonadism. Free testosterone evaluation is a more sensitive measure of gonadal function.

Aging Effects on Testosterone

Change in the hypothalamic-pituitary-testicular axis is a function of aging. Worldwide research provides a consensus that aging is a major cause of testosterone decline.[10] The three primary factors affecting serum testosterone levels include "primary testicular changes with a diminished testicular secretory capacity; secondly there is an altered neuroendocrine regulation of the Leydig cells with apparent failure of the feedback mechanisms to fully compensate, and thirdly there is an independent increase of SHBG binding capacity."[7] Research has shown that there is a decrease in the number of Leydig cells in the testes in older males. "With aging there is a relative increase in aromatization of the testosterone to estradiol and in 5 alpha-reductase activity to dihydrotestosterone (DHT)."[2]

Signs and Symptoms of Male Menopause

Signs and symptoms of late-onset hypogonadism ("male menopause") can be divided into four main categories of manifestation: (1) endocrine, (2) physical, (3) sexual, and (4) psychological. These signs and symptoms may vary from patient to patient, and all may not be present in patients with late-onset hypogonadism. Since other comorbid conditions may present with any of these symptoms, exclusion of these comorbidities is mandatory prior to labeling an individual as hypogonadal. Endocrine symptoms relating to andropause include flushes, erectile dysfunction, reduced erectile quality, diminished nocturnal erections, increase in abdominal and visceral adipose tissue and waist size, joint/muscle aches, and decreased body hair. Physical symptoms relating to this syndrome include fatigue, decreased vigor and diminished strength, reduced muscle mass, reduction of lean muscle mass, and decrease in bone mineral density. Sexual symptoms include diminished libido, diminished sexual activity, diminished quality of erectile function and weakness of ejaculation, and limited quality of orgasm. Psychological symptoms include mood changes, impaired concentration, diminished motivation, reduced memory, decline in libido, and depression.[6]

Risks Attributed to Hypogonadism

Other than age-related decline, decrease in serum testosterone may be caused by various illnesses, drugs, and hereditary factors. After myocardial infarction, a significant decrease in testosterone may be observed; however, this decrease is transient in nature. Critical illness in men results in change in all areas of the hypothalamic-pituitary-testicular axis. Elevations of serum luteinizing hormone (LH) in the initial phase, transient in nature, and the presence of hypogonadotropic hypogonadism occurs in chronic illness. Aging males with diabetes commonly have decreased testosterone and SHBG levels. Chronic obstructive pulmonary disease (COPD) is commonly observed in aging males with low serum testosterone levels. Those aging males diagnosed with chronic liver disease commonly present with hypogonadism. Chronic renal failure is commonly present with hypogonadism. In the geriatric population, polypharmacy is the rule rather than the exception. Such can be seen in aging men with COPD who are being administered glucocorticoids. Gonadotropin secretion is inhibited by suppression of testosterone production by opiates and cannabinoids. Although major studies indicate that heredity is an important factor affecting testosterone levels, additional work has to be performed to pinpoint the full role of heredity pertaining to testosterone.[7]

Diagnosing Andropause

Performing a comprehensive history and physical examination is required to adequately diagnose late-onset hypogonadism. The signs and symptoms observed in the aging male are usually too vague or insufficient to make a definitive diagnosis of male andropause. Although questionnaires are commonly used as a diagnostic tool, low specificity and limited use make them a less-valuable resource. Biochemical studies must be integrated as part of the diagnostic work-up. Patients should be instructed that blood sampling should be taken

between 8:00 AM and 11:00 AM to coincide with circadian rhythm of testosterone production.[11] For the most part, evaluating total testosterone levels should be sufficient for diagnostic purposes; however, in the event that there are alterations in SHBG levels, potential for misinterpreting the study results may occur. Obtaining a free testosterone level is the most accurate method to diagnose late-onset hypogonadism. Free testosterone can be measured by ultracentrifugation, equilibrium dialysis, analog direct immunoassay, bioavailable testosterone, free androgen index, and calculated free testosterone.[12] In healthy aging men, there is a variation of 315-1000 ng/dL in morning testosterone levels. Hypogonadal to eugonadal levels range from 200 ng/dL to 600 ng/dL. When testosterone levels are low or at the lower limit of accepted value, it is wise to validate the results by performing a second testosterone level and LH for comparison.[11,13] For a complete diagnostic work-up, the following studies should be performed: urinalysis, complete blood count, biochemistry, prolactin, prostate-specific antigen (PSA) and thyroid function tests.[14] It is advisable to incorporate screening questionnaires as part of the andropause medical work-up. Commonly used questionnaires include the St. Louis University Androgen Deficiency in Aging Men (ADAM) questionnaire, the Massachusetts Male Aging study survey questionnaire, and the ISSAM Aging male survey.[15]

Comorbid Conditions

Low testosterone levels in the aging male may contribute to the development of several comorbid conditions. Examples of these conditions are myocardial infarction, coronary atherosclerosis, type 2 diabetes, obesity, hypertension, and osteoporosis.[14,16] Because of the varying presentations and associated signs and symptoms, which many times are vague in nature, diagnosing andropause can present a significant challenge.

Testosterone Administration

Although diagnosing andropause presents certain challenges, once the diagnosis is made, treatment protocols are well defined and straightforward. The delivery systems utilized for the administration of testosterone are numerous (**Table**).[17,18] One of the earliest methods of administration is injectable testosterone. Although this method, which has been available since the first half of the 20th century, remains in common use, other methods may be preferable. The following are the most commonly used delivery systems: intramuscular, transscrotal, transdermal patch, transdermal gel, subcutaneous implants, and buccal system. Pharmacokinetics associated with various routes of administration result in varied effects and side effects. For example, patients using the injectable forms may experience variations of mood, sexual function, and physical capacity resulting from fluctuations of testosterone levels, which are short-lived. Oral testosterone use is limited because it requires a fatty meal to allow for transportation through the lymphatic system. Of the newer testosterone preparations, hydroalcoholic testosterone gel provides steady serum testosterone concentrations within the physiological range.[11] Regardless of the route of administration, testosterone levels should be followed every 3 months for the first year. After the first year, yearly testosterone levels should be obtained in the absence of any

adverse effects. Efficacy should also be taken into consideration when determining frequency of testosterone testing. Following a baseline PSA, prior to initiating testosterone therapy, evaluation by digital rectal exam and assessing voiding patterns should be performed. These evaluations should be performed periodically, including periodic PSA testing, to monitor androgen therapy and response. Additional laboratory studies performed during ongoing testosterone treatment include hemoglobin, hematocrit, lipid profile, and liver function studies.

Prostate Cancer and Testosterone

The relationship between late-onset hypogonadism, treatment with testosterone, and prostate cancer should be considered.[11] There is a more frequent incidence of prostate cancer and late-onset hypogonadism after age 50. Although it has been commonly accepted that prostate cancer provides a contraindication for testosterone therapy, studies have suggested that in selected well-maintained patients, testosterone may be considered safe[6]; however, such studies have been limited. Therefore, patients must be carefully selected.[11] Subsequent to radical prostatectomy, it would be appropriate to provide counseling and initiate testosterone.[11]

Side Effects of Testosterone

As with most treatment utilizing pharmacotherapy, testosterone therapy in late-onset hypogonadic men is not without potential sequelae. Among the problems associated with testosterone therapy, the following are of most concern: lipid abnormalities, liver dysfunction, polycythemia, and sleep apnea exacerbations. Hematocrit levels are increased as a result of testosterone replacement therapy. Those patients who have low hematocrit levels may benefit; however, patients with normal or elevated hematocrit levels are at risk to develop polycythemia, which may be a precursor to stroke.[2,19] Minimal or no effect on PSA levels occur as a result of testosterone administration. Prostate size is negligibly affected. Those patients diagnosed with prostate cancer have a worsened outcome.[2] At present, there are no data to confirm that testosterone therapy causes microadenomatous prostate cancer. Gynecomastia is a common side effect associated with testosterone use. Isolated reports of hypertension and water retention have been noted in the medical literature. Although testosterone replacement therapy has been cited as a cause of sleep apnea, hypogonadal individuals have also been found to potentially develop central sleep apnea.[2] Testosterone may result in liver toxicity. The methylated oral forms of testosterone have been identified as specifically toxic to the liver; however, the esters of testosterone and the transdermal patches are primarily free of toxic hepatic effects.

Conclusion

The female menopause is an accepted syndrome in women; however, through the ages, as far back as biblical times, a syndrome that can be likened to the male menopause has been documented. In the aging male population, male menopause (hypogonadism) should be

differentiated from various emotional disorders and other medical comorbidities. Therefore, when screening for hypogonadism, a total testosterone and, if possible, a free testosterone level should be considered in addition to the usual blood screen studies. Not to be excluded are a comprehensive history, including family history, and a complete physical examination that includes digital rectal exam and an examination of the scrotum and testes. Testosterone replacement therapy is the treatment of choice when hypogonadism has been identified; however, the systemic side effects, including hepatic sequelae, lipid abnormalities, cardiovascular effects, sleep apnea, and clotting disorders, should be monitored. Research pertaining to hypogonadism and testosterone deficiency should be given a higher priority in the research agenda. More training and education targeting primary care physicians should be encouraged. Andrology clinics, similar to menopause clinics, should be created to serve the needs of the aging male population.

References

1. Morales A. The andropause: Bare facts for urologists. BJU Int 2003;91(4):311-313.
2. Morley JE, Perry HM 3rd. Andropause: An old concept in new clothing. Clin Geriatr Med 2003;19:507-528.
3. Matsumoto AM. Andropause: Clinical implications of the decline in serum testosterone levels with aging in men. J Gerontol A Biol Sci Med Sci 2002;57:M76-M99.
4. Morley JE. Andropause: Is it time for the geriatrician to treat it? J Gerontol A Biol Sci Med Sci 2001;56:M263-M265.
5. Morley JE, Perry HM 3rd. Androgen deficiency in aging men: Role of testosterone replacement therapy. J Lab Clin Med 2000;135:370-378.
6. Charlton R. Ageing male syndrome, andropause, androgen decline or mid-life crisis? The Journal of Men's Health and Gender 2004;1:55-59.
7. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocr Rev 2005;26(6): 833-876. EPub 2005 May 18.
8. Vermeulen A, Verdonck L. Studies on the binding of testosterone to human plasma. Steroids 1968;11:609-635.
9. Dunn JF, Nisula BC, Rodbard D. Transport of steroid-hormones: Binding of 21 endogenous steroids to both testosterone binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab 1981;53:58-68.
10. Liu PY, Swerdloff RS ,Wang C. Relative testosterone deficiency in older men: Clinical definition and presentation. Endocrinol Metab Clin North Am 2005;34:957-972, x.
11. Jockenhovel F, Kaufman JM, Mickisch GH, et al. The good, the bad, and the unknown of late onset hypogonadism: The urological perspective. The Journal of Men's Health and Gender 2005;3:292-301.
12. Elin RJ, Winters SJ. Current controversies in testosterone testing: Aging and obesity. Clin Lab Med 2004;24:119-139.
13. Morales A, Lunenfeld B; International Society for the Study of the Aging Male. Investigation, treatment and monitoring of late-onset hypogonadism in males. Official

recommendations of ISSAM. International Society for the Study of the Aging Male. Aging Male 2002;5(2);74-86.
14. Petty R, Angwin R. How real is the male menopause? Practitioner 2004;248:452-456.
15. Morley JE, Perry HM 3rd, Kevorkian RT, Patrick P. Comparison of screening questionnaires for the diagnosis of hypogonadism. Maturitas 2006;53(4):424-429. Epub 2005 Sep 2.
16. Philips GB, Pinkernell BH, Jing T-Y. The association of hypotestosteronaemia with coronary artery disease in men. Arteriocsler Thromb 1994;14:701-706.
17. Bhasin S, Cunningham GR, Hayes FJ, et al. Testosterone therapy in adult men with androgen deficiency syndromes: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2006;91(6):1995-2010.
18. Margo K, Winn R. Testosterone treatments: Why, when, and how? Am Fam Physician 2006;73(9):1591-1598.
19. Eyler AE, Biggs WS. Sexuality in family medicine. In: Rakel RE, ed. Textbook of Family Practice. Philadelphia, PA: W.B. Saunders; 2002.