Understanding Andropause: Diagnosis and Possible Therapies

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Introduction

In both sexes, aging is associated with a progressive reduction in skeletal muscle mass and strength, although this may be masked by increases in subcutaneous fat or abdominal obesity that give the impression of stable body weight. Progressive frailty, however, occurs on a more global level with seniors "affected by multiple chronic diseases which cause physical and functional limitations."[1] These comorbid diseases may cause a systemic stress, which by itself (excess cortisol secretion), or by virtue of its suppressive action on the pituitary-gonadal axis, leads to a decline in androgen production. While the tendency to associate andropause and androgens has become increasingly common, the causal link between male hormone deficiency and the clinical disorder andropause still remains a weak one. A medical anthropologist is certainly likely to qualify the association as a reductionist vision of the frailty syndrome. In a sense, this vision serves the interests of both patients and physicians: it facilitates the diagnostic approach and the treatment strategies in an aged population, estimated at 20%, that seeks medical attention because of frailty, low mental and physical energy, depression-like symptoms and sexual hypofunction.

Diagnosis of Andropause

If andropause is the result of an imbalance between glucocorticoids and androgenic hormones, ignoring for the moment major issues such as obesity and sedentary lifestyle, it becomes relatively easy to focus on testosterone. It is common knowledge that the cortisol secretion rate remains constant throughout the lifespan of human beings, while systemic stressors and prednisone therapy elevate free corticoid concentrations in blood by down-regulating transcortin (the globulin that binds cortisol in circulation). The physician is then left with one variable, namely adrenal and gonadal androgens. What is their relative importance late in life?

In men aged 70 years or older, dehydroepiandrosterone (DHEA), and its sulfate (DHEA-S), is drastically reduced to one-tenth of the measured value in young adults. This suggests the loss of DHEA-producing cells in the

Table 1

Clinical Symptoms of Andropause Classified According to Four Areas of Investigation

Vasomotor and nervous symptoms
Hot flushes
Unexplained episodes of sweating
Insomnia
Nervousness
Mood disorders
Sadness and grumpiness
Lethargy, irritability
Decreased sense of well-being
Low mental energy (unusual fright and anxiety, decreased capacity to make decisions, delayed activities)
Pessimism and proneness to solitude
Depressive symptoms
Difficulties with short-term memory
Masculinity and virility
Decreased vigor and physical activity
Frequent arthralgias and myalgias
Diminished muscle mass and strength
Abdominal obesity
Loss of sexual body hair
Sexuality
Decreased interest in or desire for sex, leading to decreased sexual performance and activity
Erectile dysfunction (decreased rigidity and rapid flaccidity)
Decreased ejaculation (weakness and decreased volume)
Decreased quality of orgasm
Decreased sensibility of external genitalia

zona reticularis of the adrenal cortex. The other two cell types of the adrenals, located in the zona glomerulosa and the zona fasciculata, retain normal function. Thus, **reduced DHEA levels should contribute to the diagnosis of andropause** because of the role DHEA plays as a precursor of hormones (testosterone and estradiol) that have important functions in the brain, muscle and bone.

An even more important feature of andropause is the decline of testosterone production (from peripheral conversion) and secretion (gonads) as men age[2] (Figure 1, page 34). Life would be much easier if the secretion rate of testosterone could be measured routinely using isotopic dilution techniques. Instead, physicians must rely on serum testosterone concentrations, which are measured using commercially available kits having a high degree of inter-kit variability.[3]

To make things more complex, as men age, sex hormone-binding globulin (SHBG) concentrations can either increase[4] or decrease (obesity). Thus, serum total testosterone (TT) concentrations are largely influenced by SHBG, making serum testosterone measurements inappropriately high (aging) or low (obesity). Generally speaking, **the aging process is associated with a progressive decline of the free or bioavailable testosterone concentrations.**[5] The full impact on health of these age-related androgen variations in older men remains to be determined, but the temptation to link them to the decreased anabolism leading to sarcopenia in older men is strong. What is the evidence in favour of this association?

Chronically institutionalized older men have lower testosterone concentrations compared to their healthy counterparts,[6] and some believe that the severity of sarcopenia correlates with testosterone concentration.[7] However, it could be argued that the differences result from varied levels of physical activity between the two groups. Over the past decade several reports demonstrated that the success of strength training in older people of both sexes is positively correlated with serum testosterone concentration.[8] We propose that the free fraction of testosterone, in association with growth-promoting hormones, may increase nitrogen retention (anabolic property) and lean body mass in aged men who invest in exercise and diet to optimize their quality of life.

The essential components of andropause diagnosis include: gathering clinical data with "The Aging Male's Symptoms Rating"[9] (Table 1);[10] androgen measurements, including bioavailable testosterone (≤ 2.5nmol/L)[5] and calculated free testosterone (≤ 225pmol/L).[5] Both proposed threshold values are merely indicative and must be weighed in light of the characteristics of the methods used to measure total testosterone and/or SHBG.[11]

Drug Therapy for Andropause

Prior to considering hormonal replacement therapy (HRT) for symptomatic elderly men experiencing andropause, the physician should eliminate any confounding diseases that can mimic andropause (depression, hypothyroidism, iatrogenic hypercortisolism, obstructive pulmonary conditions, etc.). The diagnosis should be supported by low values of calculated free testosterone[5] in association with several symptoms (Table 1). There is, however, no absolute requirement to experience symptoms in all four areas of investigation.

The commonly available androgen treatment options illustrate the progress made over the past five decades: injectable testosterone esters have been available since the 1950s; oral testosterone tablets since the 1970s; and transdermal testosterone preparations (in the form of a patch or a gel) since the 1990s (Table 2).

Injectable testosterone esters require deep intramuscular injections of 150–200mg every two to three weeks. They induce supraphysiological testosterone levels soon after the injection and their efficacy has been proven in the treatment of hypogonadism and/or andropause.

Among the testosterone tablets, fluoxymesterolone (Halotestin) and mesterolone (Proviron) either show liver toxicity or are not supported by data for the treatment of andropause. Testosterone undecanoate (Andriol) is commonly used in over 80 countries for the treatment of hypogonadism, and recent data on its efficacy for the treatment of andropause (120 to 160mg in divided doses on a daily basis) are available.

The transdermal preparations include Testoderm (1994, Alza Corp), Androderm (1995, Watson; 2002, Paladin Lab) and AndroGel (1999; Unimed, 2002, Solvay). Recent efficacy data are available on these preparations for the treatment of andropause.[12,13] When prescribing these preparations, the physician must

Table 2

Hormonal Preparations and Commonly used Dosages of Testosterone for the Treatment of Andropause or Testosterone Deficiency in the Aging Male

Testosterone esters (enanthate: Delatestryl) (cypionate: Depo-Testosterone)	150–200mg i.m. every 2 or 3 weeks
Testosterone Undecanoate (Andriol)	80mg, twice a day, with meal One brown capsule = 40mg
Testosterone USP (Androderm)	2.5 or 5.0mg patches/day, at night
Testosterone USP 1% (AndroGel)	2.5 or 5.0g gel per packet/day

keep in mind that there are associated inconveniences, namely scrotal shaving, skin irritation or testosterone transfer to a sexual partner.

For many decades, physicians were limited to prescribing intramuscular testosterone injections; recently developed delivery systems also demonstrate efficacy in the treatment of hypogonadism and / or andropause. However, the newer preparations do not eliminate the safety concerns associated with HRT, in the context of geriatric practice, as outlined by The Canadian Andropause Society.[14] These include a variety of genetic disorders such as prostate cancer. When HRT is recommended either for partial strength deficits of muscles or for osteoporosis, the patient's tolerance of the medication is of paramount importance. Thus, the various testosterone preparations should be presented to each patient in order to cater to individual requirements. When considering intervention programs for the elderly experiencing testosterone deficiency, androgen therapy in combination with nutrition, exercise and a sound psychosocial environment should maximize energy and health-related quality of life.

Addendum

Concerns About Long-term Androgen Therapy

Dr. Carruthers of the United Kingdom and Dr. Gooren of The Netherlands have, respectively, 10 and 20 years experience in andropause treatment, with a cohort of more than 1,500 hypogonadal aged male patients. No adverse changes have been reported in lipid profile, in cardiovascular risk factors or on prostate specific antigen (PSA) or other prostate-

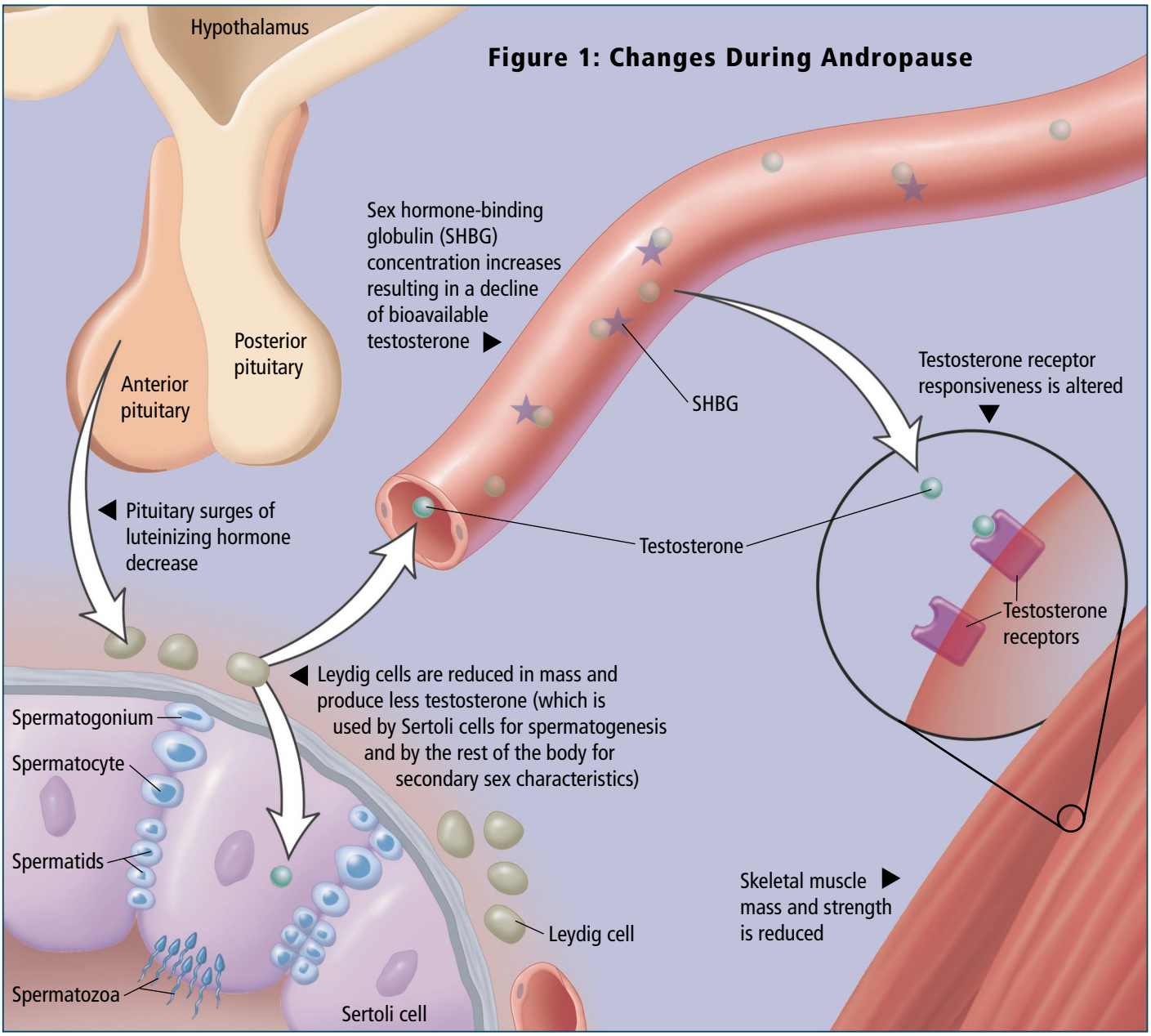


Figure 1: Changes During Andropause

related variables, with the exception of those associated with age. Typically, prostate cancers are detected in prescreening, although Dr. Carruthers has reported that seven cases of prostate cancer occurred during testosterone treatment. Early detection is important in these cases.

Recent concerns regarding the results of the five-year HRT study in women cannot easily be extrapolated to HRT in men. In 30 years of clinical experience prescribing testosterone to young, adult or elderly patients, I have had only positive experiences with the therapy, although I pay close attention to changes in hemoglobin and hematocrit, in blood pressure and prostate health. ◆

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