

# Psychosocial issues of ART in aging male

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**ABSTRACT.** The role of androgens in human sexuality as regards the mechanism of erection and the pathogenesis of impotence is under debate. In addition, it is difficult to define the psychosocial impact of both hypogonadism and androgen replacement. However, sexual hormones largely influence mood, well-being, and quality of life. For this reason, despite the methodological difficulties of assessment, testosterone replacement has a deep impact

on the social, psychological and sexual life of the treated patient. Considering the obvious characteristic of testosterone as an hormone, it appears evident that the endocrinologist is the unique experienced specialist able to diagnose and treat the hypogonadal men, monitoring potential side effects and following the psychosocial issues of androgen therapy.

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## INTRODUCTION

The psychosocial function is not easy to define scientifically. Symptoms of this "syndrome" (depressed mood, anxiety, irritability, reduced cognitive capacity, loss of sense of well-being) (1) are largely unspecific. However, a psychosocial impairment cannot be denied in neither hypogonadism nor the hypogonadism of the aging male. The decline in testosterone can be associated with some degree of dysphoria (2). This link is so strict that these symptoms can be simply attributed to the aging process (3). Furthermore, like being blocked in vicious circle, these psychosocial symptoms may be on the basis of sexual symptoms (hypoactive sexual desire, erectile dysfunction, ejaculatory dysfunction) that are peculiar of both the elderly and, to some extent, of hypogonadism. Sexual dysfunction can further exacerbate the psychosocial impairment (Fig. 1) in a perverse loop pattern that should be therapeutically approached with medical counseling on possible changes in the lifestyle (risk factors, sport, diet), by restoring sexual function, and, when necessary, with the Androgen Replacement Therapy (ART). The

social issues the elderly face further complicate this scenario. The loss of social power due to retirement and the loss of the body image due to aging itself are deeply linked with the attitude of a society - such as the Western one we live in - which is culturally unable to deal with the sexual needs of its older members. This can be considered an "antisexual syndrome" of the society against the sexuality of the old people.

### *Effects of hypogonadism on psychosocial parameters*

The majority of steroid hormones strongly impact on animal and human behavior, as well as on social attitudes. In particular, testosterone production has been closely connected to achieving dominant positions in rank-controlled animal societies.

On this basis, it has been inferred that low androgen levels may substantially affect cognitive abilities, concentration, and general mood. Psychosocial test inventories have been established to evaluate the involvement of these factors in age-related hypogonadism. Despite the claim that they are validated in different languages, cultural differences may alter homogeneity of the results. Furthermore, the words used in these psychometric tests (libido, anxiety, irritability, mood, nervousness, energy, enjoyment of life, etc) may be subjectively evaluated in completely different manners, jeopardizing the reliability of the results. The Androgen Deficiency in Aging Men (ADAM) Questionnaire by the St. Louis University is a yes/no inventory of ten questions (Table 1). If the

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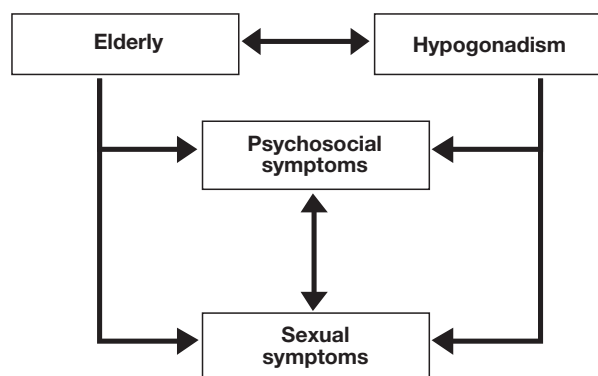


Fig. 1 - The vicious circle of amplification of sexual and psychosocial symptom rising from both elderly and hypogonadism.

questions on libido and erection plus three other questions are responded with a yes, the patients may have androgen deficiency (sensitivity: 88%, specificity <60%) (4, 5). Even if the ADAM questionnaire is useful for research purposes, in many cases careful clinical evaluation and open discussion with the hypogonadal patient before and during ART could be more reliable in assessing the psychosocial outcome of substitutive therapies.

Although it is impossible to make a definitive analysis of the psychosocial effects of testosterone, cross-sectional studies suggest a positive correlation between free testosterone and cognitive function in older men (6). The Baltimore Aging Study further suggests such a correlation, demonstrating that serum free testosterone concentration predicts memory performance and cognitive status in elderly men (7).

#### Effects of ART on sexual parameters

The key role testosterone and its metabolites have in sexual functions is based on the knowledge that: a) many animal species show correlation between androgens and penile erection (8), b) severe hypogonadism often (but not always) induces a dramatic decrease in human libido and, sometimes, in erection (9). In hypogonadal patients, sexual arousal (erotic films) activates only in the inferior temporal lobe of the thalamus (10). On the contrary, the same stimuli in eugonadal men activates, as demonstrated by blood oxygenation level-dependent functional magnetic resonance imaging, in larger central nervous system (CNS) areas, such as the inferior frontal lobe, the cingulate gyrus, the insula, the corpus callosum, the whole thalamus, the caudate nucleus, the globus pallidus, and the inferior temporal lobe. Furthermore, the thalamus is activated bilaterally. This demonstrated that the anatomical structures

Table 1 - St. Louis University androgen deficiency in aging males questionnaire (4, 5).

|    |  |        |
|----|--|--------|
| 1  | Do you have a decreased libido (sex drive)?                          | Yes/no |
| 2  | Do you lack energy?  | Yes/no |
| 3  | Do you have less strength and/or endurance?                          | Yes/no |
| 4  | Have you lost height?  | Yes/no |
| 5  | Have you noticed a decreased "enjoyment of life"?                    | Yes/no |
| 6  | Are you sad and/or irritable?  | Yes/no |
| 7  | Are your erections less strong?                                      | Yes/no |
| 8  | Have you noted a recent deterioration in your ability to play sport? | Yes/no |
| 9  | Do you fall asleep after dinner?                                     | Yes/no |
| 10 | Has there been a recent deterioration in your work performance?      | Yes/no |

governing the supraspinal, psychogenic sexual arousal are poorer and ineffective in hypogonadal men. Interestingly, after testosterone supplementation, men who were hypogonadal show an anatomical pattern of central activation to arousal completely comparable to that of eugonadal subjects. Thus, testosterone is able to restore the machinery of the "sexy brain", the dimorphic areas controlling males' sexual behavior (11).

While in the past the sexual response to androgens has been considered satisfactory in the treatment of hypogonadal impotent men (12), it has also been found disappointing, unless in patients with severe hypogonadism (13). A recent paper randomized 406 hypogonadal subjects to testosterone gel (50 and 100 mg/day), testosterone patch, and placebo, demonstrating that the restorative increases in serum testosterone levels were significantly correlated to improvements in sexual functioning. The best results were obtained with the higher doses of testosterone gel (14).

Oral testosterone therapy produced restoration of plasma androgen levels in all 23 deeply hypogonadal men but a measurable improvement of sexual attitudes and performance in only 61% (15). Furthermore, sexual function did not improve in other 17 patients when gonadotropins and androgen levels were raised with clomiphene citrate (16). Moreover, supraphysiological levels of testosterone maintained for a long period do not stimulate sexual activity in eugonadal men. A double-blind placebo controlled, cross-over study was carried out to assess the effect of biweekly injections of 200 mg of testosterone enanthate over a period of 6 weeks separated by a washout period of 4 weeks, with sexual behavior, mood, and psychological symptoms in

healthy eugonadal men with erectile dysfunction as endpoints. Blood samples for hormonal assessment, behavioral and psychological ratings were obtained prior to each injection. The luteinizing hormone remained significantly depressed but circulating testosterone had returned to baseline levels in 2 weeks following each hormonal injection. The ejaculatory frequency during the testosterone phase was statistically higher than during the placebo phase. There were marked, although statistically ns, increases in median frequency of reported sexual desire, masturbation, sexual experiences with partner, and sleep erections during the testosterone period. Testosterone did not have demonstrable effects on ratings of penile rigidity and sexual satisfaction. Mood variables and psychological symptoms did not change after hormonal administration. Results suggest that androgen administration to eugonadal men with erectile dysfunction may activate their sexual behavior without enhancing erectile capacity and without substantial effects on mood and psychological symptoms (17).

Finally, the occurrence of erections in some castrate men as well as in prepubertal boys (18, 19) suggests how the role of testosterone in erections is unclear. However, Morelli et al. for the first time demonstrated that androgens stimulate the cGMP-dependent type 5 phosphodiesterase (PDE5) both in humans and experimental animals (20), giving the rationale for the use of testosterone in hypogonadal or slightly hypogonadal men unresponsive to PDE5 inhibitors (21).

#### *Effects of ART on psychosocial parameters*

Collectively, the evidence from hypogonadal men treated with ART, eugonadal men experimentally rendered hypogonadal, and transexual patients undergoing cross-gender reassignment sex hormone therapy consistently support the key role of testosterone in the establishment and maintenance of normal social, psychological, and sexual function. However, it is also clear that testosterone is neither absolutely necessary nor sufficient for some degree of these functions. Since it is difficult to firmly establish the psychosocial effects of androgens in human, it is more difficult to deduce the therapeutic effects of ART. Testosterone replacement improves positive mood and reduces negative moods in young hypogonadal men (22, 23), confirming that androgens ameliorate depression (24). However, the clinical impression that older men improve their mood by testosterone administration needs to be confirmed (25, 26), while the evidence that androgens improve spatial and verbal memory in healthy older men seems better established (27).

Some parameters, such as self-esteem, confidence, and relationship may ameliorate with ART. Many reports demonstrate that hypogonadal men respond to testosterone therapy with a marked improvement in the health-related quality of life (HRQoL). The Aging Males' Symptoms Scale (AMS) is a simple self-administered HRQoL scale developed a) to assess non-disease related symptoms of aging, b) to evaluate severity of symptoms over time, c) to measure changes after substitutive therapy, exploring the three dimensions of symptoms (psychologic, somatovegetative and sexual) (28). After 12 weeks of testosterone replacement, AMS scores increase reaching normal values in 1174 androgen-deficient males (29).

The new method of testosterone administration by gel preparation (Testogel) makes it possible to restore physiological testosterone levels with a single application per day, with the levels remaining stable for 24 h. This stable restoration of normal blood testosterone levels under gel preparation significantly improves sexual motivation and sexual libido. Furthermore, the testosterone gel significantly improves the scores for positive mood (drive, social competence, vitality, well-being), while the scores for negative mood (fatigue, anger, irritability, sadness, nervousity) decline (30).

Since improvement and stabilization of mood is one of the prime effects of testosterone substitution (31), the fluctuation in testosterone levels arising during treatment with testosterone may not be well tolerated by patients. However, in a small cohort of men with primary and secondary hypogonadism, even though long-lasting testosterone undecanoate injections initially led to slightly supraphysiological testosterone levels which decreased steadily thereafter, this did not cause clinically apparent changes in mood (32). Well-being features did not differ when they were examined at the end or half way through the injection intervals, thus suggesting that when mood is normalized by testosterone supplementation, it is unaffected by actual testosterone levels as long as they are within normal limits (33).

However and finally, since it is difficult to assess objectively self-reported psychosocial parameters - as discussed above, direct hormonal effects might be difficult to establish and might be regarded as non-specific or context-dependent (34), yet not less important for this reason.

#### *How to meet the patient's request regarding ART*

The desire of "baby boomers" to maintain vigor and health into their later yrs of age, the attention

media pay to hormone-replacement therapy in both men and women, the medical awareness of the effects of hypogonadism and the recent availability of new topical testosterone preparation raise new medical and social concerns (35). Surgeons dealing with male urogenital tract diseases demonstrated great interest in the medical approach to hypogonadism. This may lead, in some cases, to reductionism, over-simplification, and over-interpretation and to mechanistic treatments of men not requiring substitutive therapy. Furthermore, the lack of diagnostic work-up (which should consider the entire endocrine and metabolic pattern) and cultural difficulties to evaluate medical and psychosocial impact of hormonal treatment may amplify the problem. A widespread use of androgens in eugonadal subjects will surely, in the future, lead to claim of dangerous side effects and tumor risks, as it is currently happening for estrogen supplementation in menopause. Concerns about hormonal therapy were running high because a vast study of female hormone replacement (Women's Health Initiative) was halted in 2002 after the benefits proved to be outweighed by long-term risks of heart disease, breast cancer and stroke (36). If the same happens for testosterone use in men, media will amplify this (37). As a social consequence, the number of patients accepting androgen therapy will dramatically decrease. It is evident that hypogonadism, even when age-related, partial or subclinical, is an endocrine disease/symptom requiring careful diagnosis, adequate monitoring of possible side effects (from the psychosocial point of view: aggressiveness and hypersexuality), and integrated approaches taking into account social, psychological, sexual, and couple's effects of ART.

Endocrinologists are body chemistry experts, singularly equipped to understand and cope with the alterations in body chemistry responsible for the diminution of androgen levels in young and old men. Because endocrinologists are trained in the cognitive sciences, they routinely scan the complete diagnostic horizon in search of specific individual factors, or a coalition of factors, that may impair the androgen-dependent social, psychological, and sexual function. Indeed, the endocrinologist should be the evaluating physician who supervises the medical and hormonal treatment and who refers the patient, as necessary, to other members of a multidisciplinary team.

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