Maturitas 112 (2018) 46–52

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Testosterone and sexual function in men

Giulia Rastrelli[a], Giovanni Corona[a,b], Mario Maggi[a,c,*]

[a] Sexual Medicine and Andrology Unit Department of Experimental Clinical and Biomedical Sciences "Mario Serio", University of Florence, Viale Pieraccini, 6, 50139 Florence, Italy
[b] Endocrinology Unit, Medical Department, Azienda Usl Bologna Maggiore-Bellaria Hospital, Largo Nigrisoli, 2, 40133 Bologna, Italy
[c] I.N.B.B., Istituto Nazionale Biostrutture e Biosistemi, Viale delle Medaglie d'Oro, 305, 00136 Rome, Italy

ARTICLE INFO

Keywords:
Testosterone
Erectile dysfunction
Sexual desire
Delayed ejaculation
Testosterone treatment

ABSTRACT

Testosterone (T) is deeply involved in every step of the male sexual response. However, the occurrence of sexual disorders cannot be automatically related to a decline in T levels. In fact, this relationship is complicated by organic, relational and psychological factors, which can independently impair sexual function. For example, it is recognized that erectile dysfunction (ED) can result from vascular damage as well as from low levels of T. T therapy (TTh) can improve sexual function but meta-analyses show that it improves erectile function only in men with ED and overt hypogonadism. Similarly, impaired sexual desire can result from a wide range of organic, relational and psychological factors, although it is recognized as one of the most specific symptoms of hypogonadism. Accordingly, low desire is improved by TTh in men with overt hypogonadism. The association between low T levels and delayed ejaculation has not been well studied and needs further confirmation, as does the role of TTh in such cases. Meta-analyses have found that TTh can improve orgasmic function in hypogonadal men. Clinicians should bear in mind that sexual dysfunctions have multifactorial causes and hypogonadism represents only one of these. Only hypogonadal men are likely to improve their sexual symptoms when treated with TTh. The assessment of serum T levels is mandatory before patients are prescribed TTh, as are the assessment and possible treatment of other concomitant conditions.

1. Introduction

Male hypogonadism (HG) is a clinical entity due to any condition impairing testis action, i.e. the production of sex steroids (androgens) and spermatozoa. HG can be either congenital or acquired and it can be related to any alteration in the central control of testicular function (central, secondary or hypogonadotropic HG) or to primary damage to the testis itself (primary or hypergonadotropic HG). In addition, an HG-like syndrome can also be due to any impairment in androgen activity, for example through increased levels of sex hormone binding globulin (SHBG), a protein that binds tightly to testosterone (T), thereby limiting its biological effects. The classification of HG according to the site of the impairment is clinically useful because it helps to determine choice of therapy [1]. However, it does not provide any information about the clinical features, which develop irrespective of the localization of the damage. A classification based on the time of onset of HG is more useful in this respect. In fact, when the damage leading to HG starts to exert deleterious effects on the hypothalamus-pituitary-testicular (HPT) axis during male fetal life, the resulting phenotype is characterized by specific symptoms, often dramatic, such as feminized or ambiguous genitalia, cryptorchidism or hypospadias. The clinical features are still specific when HG develops during childhood or adolescence, resulting in delayed or absent pubertal development. After completion of puberty, T is required to maintain male secondary characteristics, including sexual behavior. However, the clinical features of T deficiency in adult men are not as specific as they are in the earlier phases of life. Several symptoms and signs have been associated with low T levels in adults [2]. However, none of these can be considered specific because they widely overlap with aspects of normal ageing or with the clinical features of several chronic diseases (T tends to decline with senescence and is often low in chronic illnesses). In fact, it is not clear whether the complaints reported by ageing men or ill subjects depends, at least in part, on T decline or if low T represents only a marker of poor health, developing alongside, rather than before, the other clinical manifestations.

The difficulty in defining the pathophysiological effects of male HG has important practical consequences. According to current guidelines [3,4], the diagnosis of HG in adulthood requires the presence of low T levels and the presence of at least one symptom of androgen deficiency. This implies that physicians must ascribe a symptom to low T levels

* Corresponding author at: Sexual Medicine and Andrology Unit, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Viale Pieraccini, 6 Florence, 50139, Italy.
E-mail address: mario.maggi@unifi.it (M. Maggi).

https://doi.org/10.1016/j.maturitas.2018.04.004
Received 28 February 2018; Received in revised form 30 March 2018; Accepted 5 April 2018

each time they diagnose HG in adults. The wide overlap between androgen deficiency symptoms and the symptoms of several other common conditions can lead to both underdiagnosis and overdiagnosis of HG. Moreover, the lack of appropriate therapy can result in the persistence of symptoms and signs, with adverse consequences on quality of life, physical or mental health.

Sexual complaints are the most specific symptoms of HG and their presence can be considered a minimum criterion for diagnosing HG in adult men with low T levels [2–6]. The aim of the present narrative review is to summarize the available evidence linking T with sexual function in men.

2. Methods

An extensive search of PubMed was conducted up to 31 January 2018 using the following terms: ((“testosterone”[MeSH Terms] OR “testosterone”[All Fields]) AND (“sexual behavior”[MeSH Terms] OR (“sexual”[All Fields] AND “behavior”[All Fields]) OR “sexual behavior”[All Fields] OR “sexual”[All Fields]) AND (“physiology”[Subheading] OR “physiology”[All Fields] OR “function”[All Fields] OR “physiology”[MeSH Terms] OR “function”[All Fields])), limiting the results to studies of men (filters: humans and male) and published in English. The retrieved papers were scrutinized for evidence on the relationship between endogenous T and sexual function and the effect of T therapy (TTh) on sexual symptoms.

3. Testosterone and sexual function

In men, T can be considered to drive sexual behavior because it enhances several key steps of the entire male sexual response (see below). Based on this assumption, finding a deterioration of sexual function in men with HG would not be surprising. However, this relationship is not straightforward, because it is affected by several other factors in the determination of sexual dysfunction. Fig. 1 shows total and free T levels (TT and FT, respectively) in men reporting mild, moderate or severe symptoms of three conditions, erectile dysfunction (ED), impaired morning erections and low sexual desire, in a population of 4890 men seeking medical care for sexual dysfunction at the University of Florence [5]. According to these results, men with the most severe symptoms are characterized by lower T levels than those without or with a milder form of the symptom, independent of age. Whereas both TT and FT are significantly lower in men with severely reduced morning erections or sexual desire, only a trend towards significance can be observed for severe ED. Moreover, a similar non-significant trend is observed also for the reduction of TT in men with a mildly decreased sexual desire, whereas the difference achieves statistical significance when a moderate reduction in sexual desire is considered. Overall, these results suggest that the three sexual disorders, previously demonstrated to be those most directly related to low T in the general European population [6], do not entirely depend entirely on androgen deficiency and a multifactorial pathogenesis should be advocated. Nonetheless, undoubtedly, androgen deficiency has a role in their development, and it is likely to be the most important pathogenic component when a severe sexual dysfunction is reported.

3.1. Testosterone and erectile dysfunction

Penile erection relies on the integrity and functioning of the vasculature of the corpora cavernosa. T has an important role in regulating penile integrity and functioning. It is known that T is involved in the development of the human penis during fetal life [7] and in its growth during the first months of life (mini-puberty) [8] as well as during puberty [9]. Conversely, T levels are not correlated with penile length during adulthood. However, T is still greatly involved in penile function in adults. In fact, the mechanisms on which the erectile process is based are deeply affected by T. Nitric oxide (NO) is the key mediator for erectile function. NO is synthesized by the enzyme NO synthase (NOS), which is produced by endothelial cells (eNOS) and non-adrenergic/non-cholinergic (NANC) nerves (nNOS). Once produced, NO diffuses into penile smooth muscle cells, where it stimulates the formation of cyclic guanylate monophosphate (cGMP), which in turn promotes their relaxation. Both eNOS and nNOS have been shown to be up-regulated by T in animal models [10,11]. In addition, T down-regulates the activity of RhoA-ROCK (Ras homolog gene family member A-Rho-associated, coiled coil containing protein kinase) pathway [12], which is involved in the sensitization to calcium of penile smooth muscle cells, allowing

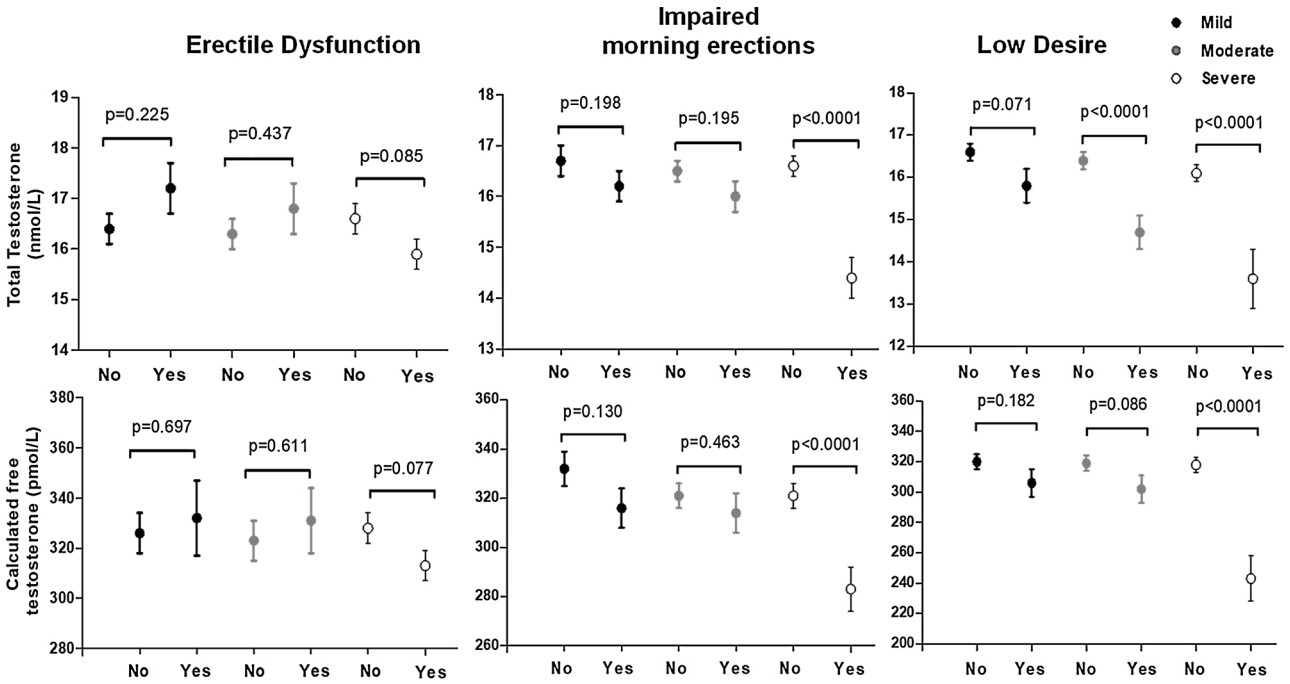

Fig. 1. Age-adjusted differences in total and calculated free testosterone between subjects with or without erectile dysfunction, impaired morning erections or low desire categorized as mild, moderate or severe. Data are expressed as mean ± standard error. The figure is adapted from [5] with permission.