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A Critical Analysis of the Role of Testosterone in Erectile Function: From Pathophysiology to Treatment—A Systematic Review

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Abstract

Context: Androgen modulation of erectile function (EF) is widely accepted. However, the use of testosterone replacement therapy (TRT) in men with erectile dysfunction (ED) has generated an unprecedented debate.
Objective: To summarize the relevant data on the incidence, diagnosis, and management of ED coexisting with hypogonadism and to develop a pathophysiology-based treatment algorithm.
Evidence acquisition: We reviewed the relevant medical literature, with a particular emphasis on original molecular studies, prospective observational data, and randomized controlled trials performed in the past 20 yr.
Evidence synthesis: Testosterone modulates nearly every component involved in EF, from pelvic ganglions to smooth muscle and the endothelial cells of the corpora cavernosa. It also regulates the timing of the erectile process as a function of sexual desire, coordinating penile erection with sex. Epidemiologic studies confirm the significant overlap of hypogonadism and ED; however, most guidelines do not consider the differential diagnosis of hypogonadism or the relevance of subclinical disease. Various clinical tools can help the physician to assess and restore androgen levels in men with ED. Special attention is given to fertility-sparing treatments, due to the increasing number of older men desiring fatherhood. The simultaneous use of phosphodiesterase type 5 inhibitors (PDE5-Is) and TRT has recently been questioned. Originally proposed as a salvage therapy for nonresponders to PDE5-Is, this approach has been inappropriately transformed into a combination therapy. Clinical data are consistent when reinterpreted in the proper framework, whereas molecular evidence remains controversial.
Conclusions: A body of molecular and clinical evidence supports the use of TRT in hypogonadal patients with ED, although the benefit–risk ratio is uncertain in advanced age. Critical appraisal of this evidence enabled the development of a pathophysiology-oriented algorithm designed to avoid inappropriate treatments and support whether to start with TRT, PDE5-I only, or both. Apparently divergent findings are reconciled when TRT is correctly indicated. An improved diagnosis and individualized management is desirable in light of the many available options.

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1. Introduction

Erectile dysfunction (ED) has emerged as an important marker of cardiovascular (CV) and overall health, independently of other known conventional risk factors [1]. Normal sexual activity throughout the adult lifespan has been associated with a reduced incidence of CV events, suggesting a protective role [2]. Coronary artery disease is preceded by ED in half of the affected subjects, underlining the need for proper screening [3]. Sexual dysfunction is the most specific symptom of late-onset hypogonadism (LOH) [4] in the aging man, a condition also associated with an increased mortality for CV events [5]. However, ED still remains largely underdiagnosed and untreated. The Global Study of Sexual Attitudes and Behavior showed that < 30% of men with ED had sought medical help, due to high social and personal barriers [6].

Public awareness of the benefits of phosphodiesterase type 5 inhibitors (PDE5-Is) has significantly shortened the time lag between the onset of ED and the seeking of medical help [7]. The same cannot be said for testosterone replacement therapy (TRT) in LOH, despite the availability of excellent multifaceted treatment options, due to the long-standing controversies surrounding safety versus efficacy in male sexual dysfunction. The scientific community is sharply divided into those for or against TRT, with a proliferation of studies with apparently contradictory findings, generating a debate without comparison in any other hormone deficiency.

These considerations prompted us to perform a critical appraisal of the major studies of TRT in sexual dysfunction, focusing on three of the critical questions: (1) Is TRT worthwhile in ED patients? If so, how and when? (2) Does testosterone (T) act centrally or peripherally? (3) What are the underlying facts and beliefs about the combination of T and PD5-I therapy? Is it safe?

2. Evidence acquisition

We reviewed the relevant medical literature, with a particular emphasis on original molecular studies, prospective observational data, and randomized controlled trials (RCTs) performed in past 20 yr that included the search terms *testosterone* or *hypogonadism and erectile function* (EF). We provide a systematic review and critical appraisal of the data (see Supplement).

3. Evidence synthesis

3.1. Hormonal assessment in erectile dysfunction patients

The European Male Ageing Study (EMAS) found that 30% of European men experienced ED and two-thirds of them were eugonadal [4]. In representative samples, the prevalence of hypogonadism ranges between 23% and 36% of ED subjects [8] and varies according to the cut-off value adopted for the diagnosis, respectively 7%, 23%, 33%, or 47% for T levels of <7, 10.4, 12, or 14 nmol/l [9]. These figures, however, are simple associations that do not imply any causal association between the two conditions.

Detractors of universal screening of androgen deficiency in ED subjects point out that, in addition to the known causes of hypogonadism (Fig. 1), the frequent real or

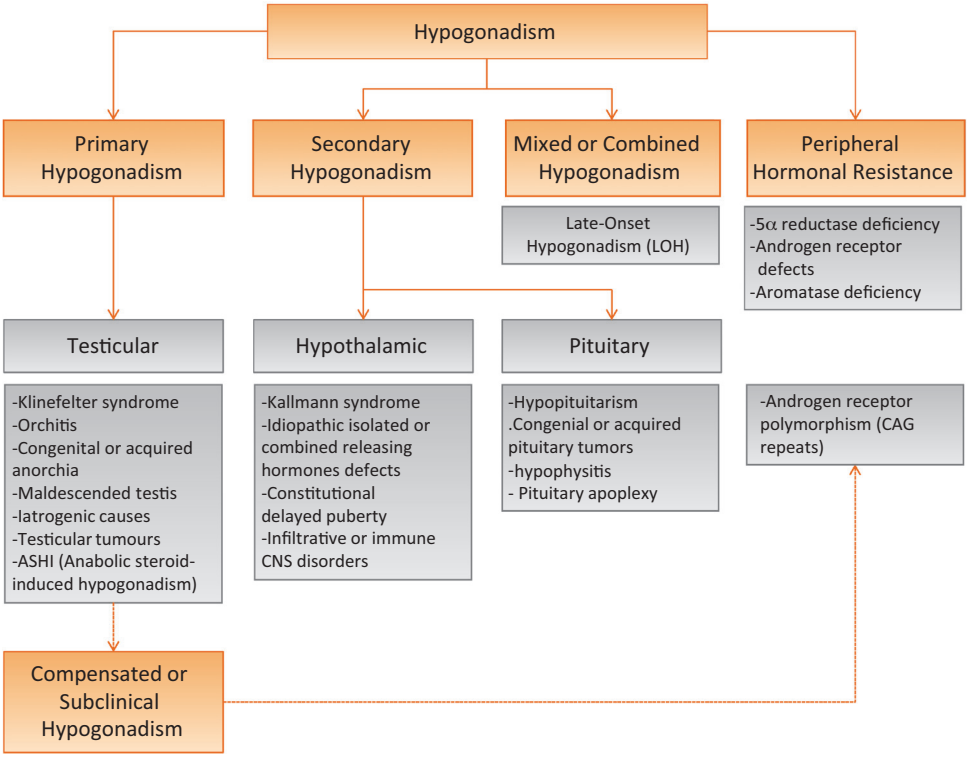

Fig. 1 – Causes of reduced androgen levels in men with erectile dysfunction. CNS = central nervous system.