Clinical Biochemistry 47 (2014) 960–966

Contents lists available at ScienceDirect

Clinical Biochemistry

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

Review

Testosterone Deficiency Syndrome: An overview with emphasis on the diagnostic conundrum

Alvaro Morales *

Queen's University, Kingston, Ontario, Canada

ARTICLE INFO

Article history:
Received 20 August 2013
Received in revised form 16 November 2013
Accepted 26 November 2013
Available online 16 December 2013

Keywords:
Testosterone
Testosterone deficiency
Hypogonadism
Laboratory diagnosis
Clinical diagnosis

ABSTRACT

Objectives: To review the controversial issues of the Testosterone Deficiency Syndrome (TDS) with an emphasis on the concerns about the diagnosis.

Design and methods: The relevant literature was reviewed with particular attention to matters related to the clinical manifestations of the syndrome, the need for biochemical assessment and questions of biological and analytical variation that have to be taken into account. Therapeutic options were also appraised.

Results: There are numerous difficulties with the clinical diagnosis of TDS due to the lack of specificity and subtlety of the manifestations when the degree of deficiency is not severe. Confirmation of the clinical impression requires laboratory evaluation but the choice of assays remains an unsettled issue although there is a general consensus that both free testosterone and bioavailable testosterone best reflect the degree of androgenicity. The laboratory diagnosis enjoys a great deal of credibility among clinicians but shortcomings in the interpretation of the assays need to be reiterated and the need for close collaboration between the clinician and the clinical biochemist is important for diagnostic accuracy. Even when the clinical picture is convincing, the laboratory may produce inconclusive results. The option of a therapeutic trial should be contemplated in this situation. Treatment options should be decided between the physician and the patient considering issues of availability, tolerance, efficacy and cost.

Conclusions: TDS is a prevalent condition but a matter of persistent controversy due to the vagaries of the clinical and laboratory diagnosis. Symptomatic men with documented T deficiency deserve treatment to improve their quality of life.

Contents

Introduction . . . 961
Overview of hypogonadism . . . 961
Definition . . . 961
Manifestations of TDS . . . 961
Diagnosis . . . 961
History and physical examination . . . 961
Diagnostic questionnaires . . . 962
Laboratory diagnosis . . . 962
The test of choice . . . 962
Total testosterone . . . 962
Bioavailable T . . . 962
Free T . . . 962
Interpretation of laboratory results . . . 963
Biological variation . . . 963
Analytical variability . . . 964
The borderline conundrum . . . 964
Treatment . . . 964
Testosterone therapy . . . 964
Alternatives to T therapy . . . 965

* 59 Lakeshore Blvd., Kingston, Ontario K7M 6R4, Canada.
E-mail address: moralesa@queensu.ca.

0009-9120/$ – see front matter
http://dx.doi.org/10.1016/j.clinbiochem.2013.11.024

Conclusions. 965
References 965

Introduction

Alterations in endocrine profiles accompanying advancing age translate in a decline in testosterone (T) production in males. These changes are common and impact in a significant proportion of men over 40 years old. It is generally accepted that total serum T values decrease at the rate of approximately 0.8%/year of age while free and bioavailable T declined by 2% [1]. The Baltimore Longitudinal Study of Aging found low levels of T in about 20% of men 60 to 69 years old [2]. The Massachusetts Male Aging Study (MMAS) estimated a crude prevalence of T deficiency at the onset of the study and at follow-up of 6.0 and 12.3%, respectively or about 2.4 million of 40 to 60 year old American men while the crude incidence was 12.3 per 1000 person-years, expecting 481,000 new cases per year [3]. Of course, not all develop significant manifestations, the reported prevalence of *symptomatic* T deficiency in the study was 5.6% [4]. The European Male Aging Study estimated an overall prevalence of low T levels of 2.1% increasing to 5.1% for those between 70 and 79 years old [5]. Despite the wide acceptance of the existence of the Testosterone Deficiency Syndrome (TDS) or Late Onset Hypogonadism (LOH), few areas in medicine attract as much heated controversy and misunderstanding as the management of TDS. In addition, probably none experiences the influx of "expert" views from all walks of life: from endocrinologists and psychiatrists to urological surgeons and gerontologists, from the lay press to the regulatory agencies and from the pharmaceutical to the film industries. The dismal result of all this free-for all cacophony of opinions has caused a great deal of confusion, erroneous information and significant detriment to patients and physicians alike [6]. This problem has afflicted all aspects of TDS, from diagnosis to treatment for almost 7 decades [7].

The clinical manifestations of TDS are not specific and the telling signs often are not evident until the deficiency in T is profound. For this reason, the clinician puts a great deal of emphasis on the biochemical diagnosis and accepts the laboratory results at face value. This review of TDS will focus on the pitfalls of diagnosis and possible ways to circumvent them.

Overview of hypogonadism

Definition

TDS is defined as a clinical and biochemical syndrome associated with advancing age and characterized by a deficiency in serum T levels with or without a decrease in tissue sensitivity to androgens. It may result in significant alterations in the quality of life and adversely affect the function of multiple organ systems [8]. Not to be extrapolated with the menopause since TDS is subtle, gradual in its occurrence and is not universal. Unfortunately, frequently there is lack of appreciation of the considerable differences in the genomic and non-genomic actions of T and the peculiarities in the metabolism of sex hormones by males and females. In most cases TDS is the result of testicular aging and, as such it would be labeled as primary hypogonadism which is characterized by low serum T and elevated follicle-stimulating (FSH) and luteinizing (LH) hormones or gonadotropin serum levels. Secondary hypogonadism results from abnormalities in the hypothalamus–pituitary axis in which case serum T levels are low but there is not a concomitant elevation in LH and FSH. Neither the hypothalamus nor the pituitary is impervious to the effects of aging, therefore not infrequently adult hypogonadism is the result of senescence of the whole hypothalamus–pituitary–gonadal axis. Central alterations have long been documented in the neuroendocrine control of Leydig cell function in aging males, exemplified by blunting of the circadian rhythm of T production and decreased frequency and amplitude of LH pulses which might be the result of diminished stimulation from hypothalamic gonadotropin-releasing hormone (GnRH) resulting from depopulation of GnRH secreting neurons [5]. This issue is important because older men may not fit the simple definition of primary or secondary hypogonadism but have a "mixed" type, characterized by low T and normal, elevated or subnormal gonadotropins [9].

The term "andropause" is inappropriate but entrenched in the public mind. Its use, in my view, should be reserved for individuals in which bilateral gonadal function has ceased as a result of an acute condition (testicular torsion, orchitis) or for therapeutic reasons (medical or surgical castration for advanced prostate cancer). In these situations a full blown clinical and biochemical picture with well recognized consequences and incontrovertible evidence of a "pause" in sex hormone production occurs.

Table 1
Common signs and symptoms of TDS in adults.

1. Normal or slightly low testicular volume; soft testicles
2. Thinning facial, axillary and pubic hair
3. Gynecomastia
4. Diminished libido and erectile function
5. Low bone mineral density
6. Low muscle mass, increased % of body fat
7. Mild anemia
8. Hot flushes
9. Decreased sense of well being
10. Depression, irritability

Manifestations of TDS

Although there is a relationship between the severity of T deficiency and the clinical picture, there is also a great deal of inter-individual variation on the display of such manifestations. It is also generally accepted that a correlation exists between the degree of T deficiency and the appearance of the clinical signs and symptoms (Table 1). Thus, an early indicator is a decrease in sexual interest while, paradoxically, alterations on erectile function can only be attributed, in the absence of other comorbidities (vascular insufficiency) to the presence of a profound hypogonadism. Not all the manifestations need to be present and the degree of severity can be very variable and dependent on other factors such as age, general health, and medications.

Diagnosis

History and physical examination

The signs and symptoms of TDS are heterogeneous and unspecific. For this reason the history and physical examination are of limited usefulness in reaching the diagnosis. It is only when the production of T is

Table 2
Conditions associated with adult hypogonadism.

1. Type II diabetes mellitus
2. Metabolic Syndrome
3. HIV
4. Use/abuse of opioids
5. End-stage renal disease/dialysis
6. Infertility
7. Sellar region mass, disease, radiation or trauma
8. Use of glucocorticoids
9. Ketoconazole
10. Gonadotropin releasing hormone agonist and antagonists
11. Severe liver disease