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REVIEW

Testosterone and Cardiovascular Risk: Meta-Analysis of Interventional Studies

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ABSTRACT

Background: The relationship between testosterone (T) and cardiovascular (CV) risk in men is conflicting.

Aim: To verify whether T therapy (TTh) represents a possible risk factor for CV morbidity and mortality.

Methods: We conducted a random effect meta-analysis considering all available data from pharmaco-epidemiological studies as well as randomized placebo-controlled trials (RCTs).

Outcomes: CV mortality and morbidity were investigated.

Results: After screening, 15 pharmaco-epidemiological and 93 RCT studies were considered. The analysis of pharmaco-epidemiological studies documented that TTh reduces overall mortality and CV morbidity. Conversely, in RCTs, TTh had no clear effect, either beneficial or detrimental, on the incidence of CV events. However, a protective role of TTh on CV morbidity was observed when studies enrolling obese (body mass index >30 kg/m^2) patients were scrutinized (Mantel-Haenszel odds ratio 0.51 [95% CI 0.27−0.96]; $P = .04$), although this association disappeared when only high-quality RCTs were considered (Mantel-Haenszel odds ratio 0.64 [95% CI 0.22−1.88]; $P = .42$). Finally, an increased risk of CV diseases was observed in RCTs when T preparations were prescribed at dosages above those normally recommended, or when frail men were considered.

Clinical Implications: Pharmaco-epidemiological studies showed that TTh might reduce CV risk, but this effect was not confirmed when RCTs were considered.

Strengths & Limitations: Meta-analysis of pharmaco-epidemiological studies indicates that TTh reduces overall mortality and CV morbidity. In addition, even in RCTs, a protective role of TTh on CV morbidity was envisaged when studies enrolling obese (body mass index >30 kg/m^2) patients were considered. Pharmaco-epidemiological studies should be considered with caution due to the lack of completeness of follow-up and of the management of missing data. In addition, properly powered placebo-controlled RCTs with a primary CV end point, in men with late-onset hypo-gonadism, are not yet available. Finally, the duration of all studies evaluated in the present meta-analysis is relatively short, reaching a maximum of 3 years.

Conclusions: Data from RCTs suggest that treatment with T is not effective in reducing CV risk, however, when TTh is correctly applied, it is not associated with an increase in CV risk and it may have a beneficial effect in some sub-populations. **Corona G, Rastrelli G, Di Pasquale G, et al. Testosterone and Cardiovascular Risk: Meta-Analysis of Interventional Studies. J Sex Med 2018;15:820−838.**

Key Words: Testosterone; Cardiovascular Risk; Obesity; Late-Onset Hypogonadism

INTRODUCTION

Several population-based studies have documented an age-dependent, modest reduction of circulating testosterone (T) levels in men. "Late-onset hypogonadism" (LOH) is the most frequently used term to describe this phenomenon.[1−3] This condition has been associated with several symptoms and signs, including sexual dysfunction, reduced vitality and cognition, depressive symptoms, as well as visceral obesity, and metabolic syndrome.[3,4] In the past 2 decades, the introduction and use of newer user-friendly T preparations has dramatically expanded the

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T market.[5,6] The opportunity to release drug- and disease-related specific advertisements has clearly influenced T sales, especially in the United States. A recent ecologic study, conducted in designated market areas in the United States, has demonstrated that between 2009 and 2013 exposure to televised direct-to-consumer advertising was associated with greater T testing, new initiation of therapy and, especially, initiation of therapy without prior T testing.[7] These data appear even more surprising considering that the clinical significance of LOH is still debated. In fact, it is not thoroughly known whether the reduced T levels observed in elderly men contribute to age-related morbidities and symptoms, or whether low T and associated morbidities are concomitant conditions, both associated with the aging process.[8] To better clarify this point, in 2004 the Institution of Medicine recommended conducting clinical trials to evaluate the efficacy and safety ratio of T therapy (TTh) in older men.[9] The data published in the last 20 years have not definitively clarified this issue. In particular, the debate about LOH has been further complicated by the data published in the last 5 years, emphasizing a possible increase in cardiovascular (CV) risk. In its final 2015 release, the U.S. Food and Drug Administration (FDA) cautioned that the benefits and safety of treatment with T products have not been clearly established for the treatment of low T levels due to aging.[10] In particular, the FDA stated that TTh should be considered only for men with "classical hypogonadism," ie, due to primary or secondary T deficiency resulting from known problems within the testis, pituitary, or hypothalamus.[10] This position has been endorsed by Health Canada[11] and more recently by the Australian Society of Endocrinology.[12] In addition, supporting these views, the concept of *functional hypogonadism* has been introduced.[13] The latter includes all LOH conditions associated with potentially modifiable morbidities impairing hypothalamus-pituitary-testis axis function.[13] In other words, functional hypo-gonadism represents a diagnosis of exclusion when and no identifiable organic problem is detected.[13] These positions have not been supported by the European Medicine Agency, which, after a specific review of the available data, did not find sufficient evidence for declaring a TTh-associated CV risk.[14]

The aim of the present study is to verify, using meta-analytic methods, whether TTh represents a possible risk factor for CV morbidity and mortality, considering all available data from intervention studies, including randomized placebo-controlled trials (RCTs) and pharmaco-epidemiological studies.

METHODS

This meta-analysis was performed in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Supplementary file 1). The protocol of this study (CRD42017054353) was published on the website of the University of York (Center for Reviews and Dissemination): http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017054353.

Search Strategy

An extensive MEDLINE, Embase, and Cochrane search was performed including the following words ((“testosterone”[MeSH Terms] OR “testosterone”[All Fields]) AND (“cardiovascular system”[MeSH Terms] OR (“cardiovascular”[All Fields] AND “system”[All Fields]) OR “cardiovascular system”[All Fields] OR “cardiovascular”[All Fields]) AND (“risk”[MeSH Terms] OR “risk”[All Fields])) AND (“humans”[MeSH Terms] AND English[lang] AND “male”[MeSH Terms]) for the selection of interventional pharmaco-epidemiological studies evaluating the effect of TTh on CV mortality and morbidity. In addition, a second separate search was performed including the following words (‘testosterone’[MeSH Terms] OR ‘testosterone’[All Fields]) AND (Clinical Trial[ptyp] AND ‘humans’[MeSH Terms] AND English[lang]AND ‘male’[MeSH Terms]) for the selection of all placebo-controlled RCTs for the analysis of the same end points.

The search, which accrued data from January 1, 1969, up to March 31, 2017, was restricted to English-language articles and studies of human participants. The identification of relevant studies was performed independently by 2 of the authors (G.R., G.C.), and conflicts resolved by the third investigator (M.M.). We did not employ search software. We hand-searched bibliographies of retrieved studies for additional references. The principal source of information was derived from published articles. If data were missing from a publication, an attempt at retrieval was made through clinicaltrials.gov website.

Study Selection

We included all pharmaco-epidemiological studies or placebo-controlled RCTs evaluating the effects of TTh vs placebo on different end points. All studies without any arbitrary restriction, even if CV events were not the principal end points, were included[15−121] (Supplementary Figure 1A and B; Tables 1 and 2; and Supplementary Tables 1−3). Studies not specifically stating the occurrence or absence of CV-related events were excluded from the analysis. Studies using androgens other than T, as well as studies with simultaneous treatment with other hormones and drugs, were excluded, unless there was a clearly defined treatment arm that received only T treatment. In addition, to reduce possible bias in the statistical analysis, the open-label phase of RCTs was not considered in the analysis of pharmaco-epidemiological trials. Finally, since phosphodiesterase type 5 inhibitors (PDE5is) have been reported to play a possible positive influence on CV outcomes, RCTs evaluating the effect of TTh as an add-on to PDE5i were excluded from the analysis.

Outcome

The principal outcome of this analysis was to evaluate the effect of TTh on CV morbidity and mortality as derived from pharmaco-epidemiological and RCTs studies. In particular, in RCTs, the effect of TTh, as compared to placebo, on the incidence of new major adverse CV events (MACE) was evaluated.