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REVIEWS

Endogenous Testosterone Levels and Cardiovascular Risk: Meta-Analysis of Observational Studies

Giovanni G. Corona,[1] Giulia Rastrelli,[2] Giuseppe Di Pasquale,[3] Alessandra Sforza,[1] Edoardo Mannucci,[2,4] and Mario Maggi[2]

ABSTRACT

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

Aim: To verify whether endogenous T levels represent a possible risk factor for CV morbidity and mortality.

Methods: We conducted a random effect meta-analysis considering all the available data from prospective observational studies comparing subjects with baseline reduced endogenous T levels to those with higher T levels as derived from an extensive MEDLINE, Embase, and Cochrane search. The identification of relevant studies was performed independently by 2 of the authors (G.R. and G.G.C.), and conflicts resolved by the third investigator (M.M.).

Main Outcome Measures: CV mortality and morbidity were investigated.

Results: After screening, 37 observational studies, published between 1988 and 2017 including 43,041 subjects with a mean age of 63.5 years and mean follow-up of 333 weeks, were considered. Low endogenous T at enrollment predicted overall and CV mortality, as well as CV morbidity, when both unadjusted and fully adjusted models were considered (odds ratio = 1.26 [1.17; 1.36], 1.54 [1.25; 1.89], and 1.17 [1.01; 1.36]; all $P < .05$ when overall mortality, CV mortality, and CV incidence and fully adjusted models were considered, respectively). The data were confirmed even when non-population-based studies were excluded from the analysis. Meta-regression analysis applied to the fully adjusted model showed that the risk of CV mortality was inversely related to mean age at enrollment (S = −0.014 [−0.017;−0.010] and I = 1.073 [0.806;1.339]; both $P < .0001$) and directly related to the prevalence of diabetes and to the proportion of active smokers.

Clinical Implications: Low endogenous T levels in aging men can represent a possible CV risk factor.

Strengths & Limitations: The present data demonstrated, for the first time, that low T predicts not only CV mortality but also CV morbidity. Data derived from studies reporting information on CV mortality suggested major publication bias although they were confirmed applying Duval and Tweedie trim and fill method. However, observational studies should be considered with caution due to the lack of complete follow-ups and due to the poor management of missing data.

Conclusion: The present meta-analysis shows that low T in aging men is a marker of CV risk. The possible benefits of T treatment in reducing this risk should be examined in longer-term, specifically designed trials. **Corona GG, Rastrelli G, Di Pasquale G, et al. Endogenous Testosterone Levels and Cardiovascular Risk: Meta-Analysis of Observational Studies. J Sex Med 2018;XX:XXX−XXX.**

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

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[1]Endocrinology Unit, Medical Department, Azienda Usl, Maggiore-Bellaria Hospital, Bologna, Italy;

[2]Sexual Medicine and Andrology Unit, Department of Experimental, Clinical, and Biomedical Sciences, University of Florence, Florence, Italy;

[3]Cardiology Unit, Medical Department, Azienda Usl, Maggiore-Bellaria Hospital, Bologna, Italy;

[4]Diabetes Agency, Careggi Hospital, Florence, Italy

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INTRODUCTION

Several epidemiological data worldwide have clearly documented that life expectancy at birth has progressively increased since 1900, being, an average, 5 years lower in men when compared to women.[1−3] Considering Europe, the observed gender differences were not present at the end of the 19th century, when life expectancy was less than 40 years, most probably because of high women's mortality due to pregnancy and child birth, which corresponded to a higher men's mortality from causes related to work, accidental injury, or violence.[4] Using

historical data from 1,763 birth cohorts from 1800 to 1935, Beltrán-Sánchez et al[5] documented that, in 13 developed countries, gender asymmetry emerged in cohorts born after 1880, with excess adult men's mortality mainly related to cardiovascular (CV) diseases (CVD). Since that time, life expectancy has increased worldwide with the maximum gender difference observed between the 1970s and the 1990s.[4] During the 1990s, life expectancy fell due to the AIDS epidemic. Since the 2000s, a new positive trend has been observed. In particular, from 2000 to 2015, the fastest increase since the 1960s was reported (5 years; World Health Organization). In the same period, the gender gap was reduced due to the narrowing of differences in risk behaviors between men and women, along with the decline in mortality rates from CVD among men.[4]

The reasons underlying such gender differences in life expectancy have not been completely clarified. Human longevity is the result of a combination between constitutional (including genetic and biological) and environmental factors, which are profoundly influenced by diet, social behavior, lifestyle and life experiences.[4] The role of the endocrine system and, in particular, of sex steroids, is still debatable. Considering the higher rate of CVD observed in men, the protective role of estrogen in premenopausal women, and the increased CV risk detected in men abusing anabolic steroids, a negative role of testosterone (T) for men overall and CV heath has been hypothesized.[6,7] On the other hand, much evidence has documented a strong relationship between age-dependent reduction of T levels and worse CV and metabolic profile,[8–11] which can be improved by the restoration of normal T levels.[13–15] However, it should be recognized that the latter observations have been recently criticized.[16] In fact, the concept of functional hypogonadism (HG) in comparison to organic (or classic) HG is emerging.[16] The first condition is essentially associated with morbidities, causing deterioration of the HPT activity. If the associated morbidities are adequately treated and removed, functional HG is potentially reversible.[16] In line with this hypothesis, the available meta-analyses failed to detect any relationship between low circulating T levels and increased incidence of CVD in aging men. During the last 5 years, several reports have documented a possible association between reduced T levels and an increased CV risk, either in the general population[17–19] or in specific sub-populations including men with CVD.[20]

The aim of the present study is to verify, using a meta-analytic method, whether low T levels represent a possible risk factor for CV morbidity and mortality, considering all the available data from prospective observational studies as derived from an extensive MEDLINE, Embase, and Cochrane search.

METHODS

This meta-analysis was performed according to the Meta-Analysis of Observational Studies in Epidemiology Guidelines for Meta-Analyses and Systematic Reviews of Observational Studies (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"[MeSHTerms]) for the selection of observational studies assessing the relationship between endogenous T levels and CV mortality and morbidity.

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. and G.G.C.), and conflicts resolved by the third investigator (M.M.). We did not employ search software. We hand-searched bibliographies of retrieved articles 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 prospective studies comparing endogenous T levels in subjects with or without CV morbidity and mortality at follow-up. All studies without any arbitrary restriction, even if CV events were not the principal end points, were included[17–53] (Supplementary Figure 1, Table 1, and Supplementary Tables 1 and 2). Studies not specifically stating the occurrence or absence of CV-related events were excluded from the analysis.

Outcome

The principal outcome of this analysis was to evaluate overall and CV mortality in subjects with baseline reduced endogenous T levels when compared to those with higher endogenous T levels. Secondary outcomes include the evolution of CV morbidity in the same populations.

Quality Assessment

The quality was assessed according to Newcastle Ottawa tool indications[54] (Supplementary Table 2). In particular, according to this tool, each study is judged on 8 items, categorized into 3 groups: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest.