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ORIGINAL ARTICLE

Normalization of Testosterone Levels After Testosterone Replacement Therapy Is Not Associated With Reduced Myocardial Infarction in Smokers

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Abstract

Objective: To examine the effect of cigarette smoking (CS) status and total testosterone (TT) levels after testosterone replacement therapy (TRT) on all-cause mortality, myocardial infarction (MI), and stroke in male smokers and nonsmokers without history of MI and stroke.

Participants and Methods: Data from 18,055 males with known CS status and low TT levels who received TRT at the Veterans Health Administration between December 1, 1999, and May 31, 2014, were grouped into (1) current smokers with normalized TT, (2) current smokers with nonnormalized TT, (3) nonsmokers with normalized TT, and (4) nonsmokers with nonnormalized TT. Combined effect of CS status and TT level normalization after TRT on all-cause mortality, MI, and stroke was compared using propensity score–weighted Cox proportional hazard models.

Results: Normalization of serum TT levels in nonsmokers was associated with a significant decrease in all-cause mortality (hazard ratio [HR]=0.526; 95% CI, 0.477-0.581; $P<.001$) and MI (HR=0.717; 95% CI, 0.522-0.986; $P<.001$). Among current smokers, normalization of serum TT levels was associated with a significant decrease in only all-cause mortality (HR=0.563; 95% CI, 0.488-0.649; $P<.001$) without benefit in MI (HR=1.096; 95% CI, 0.698-1.720; $P=.69$). Importantly, compared with nonsmokers with normalized TT, all-cause mortality (HR=1.242; 95% CI, 1.104-1.396; $P<.001$), MI (HR=1.706; 95% CI, 1.242-2.342; $P=.001$), and stroke (HR=1.590; 95% CI, 1.013-2.495; $P=.04$) were significantly higher in current smokers with normalized TT.

Conclusion: We conclude that active CS may negate the protective effect of testosterone level normalization on all-cause mortality and MI after TRT.

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At any given age, men are more vulnerable than women to death from cardiovascular disease (CVD).[1] Male gender is thought to be a strong independent risk factor for coronary artery disease (CAD), myocardial infarction (MI), and stroke.[2] The male sex hormone testosterone is postulated to play a role in the observed incidence of CAD, MI, and stroke in men.[2-4] *Ex vivo* studies showing increased human platelet thromboxane A2 receptor density and aggregation in response to testosterone lend support to this hypothesis.[5] However, other studies have provided data that highlight the importance of normal testosterone levels for cardiovascular (CV) health specifically in symptomatic subjects with persistently low testosterone levels.[6-9] The significance of testosterone replacement therapy (TRT) in CV health is a topic of ongoing debate as

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several studies have reported higher CV events with TRT.[10,11] In contrast, we and others have found that normalization of testosterone levels after TRT is associated with a significant decrease in all-cause mortality and MI.[6,7]

Lifestyle choices such as cigarette smoking (CS) could also contribute to this disparity in CVD between men and women. Historically, CS rates are higher in men than in women.[12] Our group and others have shown that CS is associated with increased atherothrombotic events.[13-18] In an experimental study using rabbit aorta it was reported that physiologic levels of testosterone augmented the endothelial dysfunction associated with environmental tobacco smoke exposure.[19] Therefore, it is conceivable that a combination of testosterone and CS could additively increase the risk of MI and stroke in male smokers *via* their reported prothrombotic effects. However, to our knowledge, no study has specifically examined the combined effect of CS and testosterone level on mortality, MI, or stroke in humans after TRT. It is also unclear whether normal testosterone levels indeed potentiate the active CS-related adverse effect on the mortality and CV events as suggested by some *ex vivo* and preclinical data.[5,19]

In this study, we examined whether CS status modulated the risk for all-cause mortality, MI, and stroke in men in relation to normalized testosterone level after TRT.

PARTICIPANTS AND METHODS

We conducted a retrospective cohort study of male veterans who received medical care in the Veterans Health Administration (VHA) from December 1, 1999, to May 31, 2014. Data were retrieved from Veterans Administrations Corporate Data Warehouse (CDW) through the Veterans Administrations Informatics and Computing Infrastructure.[20] The VHA provides care to veterans at more than 1400 establishments across the United States and each veteran is assigned a unique identifier in the CDW database. The Institutional Review Board of the Veterans Affairs Medical Center, Kansas City, MO, approved the study. The quality of data from these sources is well documented, and the data have been widely used by investigators for retrospective longitudinal studies.[21]

Study Design

This study was designed to determine the effect of the interaction between smoking and testosterone levels on CV events by determining the incidence of MI, stroke, and all-cause mortality in subpopulations of patients who received TRT. Cardiovascular events and comorbidities in patients were identified according to *International Classification of Diseases, 9th Revision* (*ICD-9*) codes. Patients included in the study had their testosterone levels checked on at least 2 separate occasions as recommended by guidelines.[22]

Determination of Exposure to TRT and Smoking. Patients' medical records were used to ascertain prescriptions for TRT administration. For this study, patients who received any form of TRT (injection, gel, or patch) were considered as treated. Smoking status was obtained from HealthFactors files in the Veterans Administrations Informatics and Computing Infrastructure database. Only those patients whose smoking status could be verified from the database were included in the study. Patients were classified as current smokers (smoking at the beginning of the study and at every encounter throughout the study period), nonsmokers (never smoked or had quit smoking at the beginning of the study and did not resume smoking throughout the study period).

Determination of Total Testosterone Levels. Total testosterone (TT) levels were considered low when the reported serum TT values were below the lower limit of normal laboratory reference range for each test result. This approach permitted inclusion of results from most laboratories in the Veterans Administration (VA) health system over the study period ($\geq$14 years). The available test results from such a long period of follow-up lacked a uniform laboratory range for normal TT level and reporting units in the database. We chose to use this method rather than a discrete cutoff value because we found that facilities within the VHA system used different assay methods with different reference ranges and reporting units.[23,24] Even in the same hospital, the assay used could change over time. Moreover, lack of standardized values for serum testosterone levels and other stoichiometric measures made

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