FEATURED NEW INVESTIGATOR

Testosterone, thrombophilia, thrombosis

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We screened previously undiagnosed thrombophilia (V Leiden–prothrombin mutations, Factors VIII and XI, homocysteine, and antiphospholipid antibody (APL) syndrome) in 15 men and 2 women with venous thromboembolism (VTE) or osteonecrosis 7 months (median) after starting testosterone therapy (TT), gel (30–50 mg/d), intramuscular (100–400 mg/wk), or human chorionic gonadotropin (HCG) (6000 IU/wk). Thrombophilia was studied in 2 healthy control groups without thrombosis (97 normal controls, 31 subjects on TT) and in a third control group (n = 22) with VTE, not on TT. Of the 17 cases, 76% had ≥1 thrombophilia vs 19% of 97 normal controls ($P < 0.0001$), vs 29% of 31 TT controls ($P = 0.002$). Cases differed from normal controls by Factor V Leiden (12% vs 0%, $P = 0.021$), by high Factor VIII (>150%) (24% vs 7%, $P = 0.058$), by high homocysteine (29% vs 5%, $P = 0.007$), and from both normal and TT controls for APL syndrome (18% vs 2%, $P = 0.023$, vs 0%, $P = 0.04$). Despite adequate anticoagulation with TT continued after the first deep venous thrombosis–pulmonary embolus (DVT-PE), 1 man sustained 3 DVT-PEs 5, 8, and 11 months later and a second man had 2 DVT-PEs 1 and 2 months later. Of the 10 cases with serum T measured on TT, 6 (60%) had supranormal T (>800 ng/dL) and of 9 with estradiol measured on TT, 7 (78%) had supranormal levels (>42.6 pg/mL). TT interacts with thrombophilia leading to thrombosis. TT continuation in thrombophilic men is contraindicated because of recurrent thrombi despite anticoagulation. Screening for thrombophilia before starting TT should identify subjects at high risk for VTE with an adverse the risk to benefit ratio for TT. (Translational Research 2015;165:537–548)

Abbreviations: APL = antiphospholipid antibody; DVT = deep venous thrombosis; E2 = estradiol; FV = Factor V; HRT = hormone replacement therapy; ON = osteonecrosis; PE = pulmonary embolus; PTG = prothrombin gene mutation; T = testosterone; TT = testosterone therapy; VTE = venous thromboembolism

INTRODUCTION

Androgen use in men aged ≥40 has increased more than 3-fold from 0.81% in 2001 to 2.91% in 2011.[1] The broad use of testosterone therapy (TT) may have major public health ramifications, given recent reports of thrombotic[2-7] and cardiovascular disease (CVD) events[8-10] associated with TT. Despite lessons learned about venous thromboembolism (VTE) and CVD associated with sex-hormone therapy in postmenopausal women from

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AT A GLANCE COMMENTARY

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Background

When testosterone therapy (TT) is given to men and women, thrombotic events occur, reflecting thrombophilic interactions between TT and familial and acquired thrombophilia-hypofibrinolysis.

Translational Significance

TT appears to interact with thrombophilia leading to thrombosis. TT continuation in thrombophilic men is contraindicated because of recurrent thrombi despite adequate anticoagulation. Screening for thrombophilia (PCR measures of the Factor V Leiden, and prothrombin gene mutations, Factors VIII and XI, homocysteine, and antiphospholipid antibodies) before starting TT should identify subjects at high risk for venous thromboembolism with an adverse risk/benefit ratio for TT.

the Women's Health Initiative,[11,12] TT is often indiscriminately prescribed to middle-age, obese men without understanding of its long-term risks.[13] Many of these men do not meet highly specific criteria for diagnosis and therapy of hypogonadism.[14] Testosterone (T) levels fall with increasing age,[15,16] with chronic disease[17,18] and obesity,[17] and rise with smoking.[19,20] Part of the problem of increased TT use lies in determination of an age-specific lower normal range for T, because most normal ranges come from healthy younger men.[21] There are also differences in T assay methods[22,23] and recognition that adverse muscle symptoms occur at different T levels in different subjects.[24]

Previously, in aggregate,[2-7] we have described VTE developing after 5 months (median) in 42 patients on TT, 38 men and 4 women, including 27 with deep venous thrombosis–pulmonary embolism (DVT-PE), 12 with osteonecrosis (ON),[4,25,26] 1 with central retinal vein occlusion (CRVO), 1 with amaurosis fugax, and 1 with spinal cord infarction. None of the 42 cases in our previous studies[2-7] had increased hemoglobin or uncontrolled hypertension during TT, which might have contributed to their thrombi. Of the 40 cases having studies of thrombophilia, 39 were found to have previously undiagnosed thrombophilia-hypofibrinolysis, including 28% heterozygous for the Factor V (FV) Leiden mutation, 28% with high Factor VIII, and 15% with high Factor XI.[7] In 8 men whose TT was continued, second thrombotic event occurred despite adequate anticoagulation with warfarin.[7]

Beyond interacting with familial and acquired thrombophilia,[2-7] TT is associated with physiological changes that predispose to clotting and thrombosis including hypertension,[27] increased hemoglobin,[28] low high-density lipoprotein cholesterol,[27,28] hyperviscosity, and platelet aggregation.[28-30] Dihydrotestosterone enhances monocyte activation,[31] further promoting acute coronary events.[32] TT also increases circulating estrogens[33] that subsequently play a role in thrombotic events.[7] Oral contraceptives and hormone replacement therapy (HRT)[34,35] have been identified as risk factors for VTE in women. Given that T is converted by aromatization to estradiol (E2),[36] it may be prothrombotic by the same mechanism as reported in women, where HRT interacts with the FV Leiden mutation to increase risk of VTE.[37]

In June 2014, on the basis of postmarketing surveillance reports including our studies,[2-7] both the US Food and Drug Administration (FDA)[38] and Canada Health[39] added a warning regarding the risks of VTE to the label of all T products. VTE, particularly PE, is associated with significant mortality risk.[40] The FDA had previously warned about a TT-associated increase in VTE in men with a diagnosis of increased hemoglobin.[28] However, the June 2014 FDA warning[38] was based on reports of VTE in men without increased hemoglobin.

In the present report, our specific aim was to further focus on thrombotic events in 17 newly reported patients on TT (1 receiving HCG injections as a form of TT[41]), subsequently found to have previously undiagnosed familial and acquired thrombophilia. Our second specific aim was to assess thrombophilia in our total cohort of 57 patients who sustained VTE on TT, 17 newly reported and 40 previously reported.[7] Our third specific aim was to compare thrombophilia in 57 cases who developed VTE on TT, in 97 healthy normal controls, in 31 men receiving TT without VTE, and in 22 cases with VTE, not taking TT.

MATERIALS AND METHODS

Patients. The procedures followed were in accordance with the ethical standards of the institutional review board of the Jewish Hospital, Cincinnati, Ohio, which approved the research protocol. The protocol was carried out with the understanding, and signed informed consent was taken from each participant.

We excluded patients and controls whose VTE was associated with cancer, polycythemia vera, recent soft