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Testosterone therapy, thrombosis, thrombophilia, cardiovascular events

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ABSTRACT

There are similar time intervals between starting testosterone therapy (TT) and development of thrombotic (~4.5 months) or cardiovascular (CVD) events (~3 months) which may, speculatively, reflect a shared pathophysiology. We have described thrombotic events 5 months (median) after starting TT in 38 men and 4 women, including 27 with deep venous thrombosis-pulmonary embolism, 12 with osteonecrosis, 1 with central retinal vein thrombosis, 1 with amaurosis fugax, and 1 with spinal cord infarction. In 8 men whose TT was continued, second thrombotic events occurred despite adequate anticoagulation with Coumadin in 8 men, 3 of whom had a third thrombotic event. Of these 42 cases, 40 had measures of thrombophilia-hypofibrinolysis, and 39 were found to have previously undiagnosed thrombophilia-hypofibrinolysis. Before beginning TT, especially in men with previous history of thrombotic events, we suggest that, at a minimum, measurements be made for the Factor V Leiden and Prothrombin mutations, Factors VIII and XI, and homocysteine, to identify men who should not receive TT. We need prospective data focused on whether there should be pre-TT screening based on history of previous venous thromboembolism or for all subjects for major gene thrombophilias. To better resolve questions about TT and all cause and cardiovascular morbidity and mortality and thrombosis, a long term, prospective, randomized, blinded study following the example of the Women's Health Initiative is needed. While we wait for prospective placebo-controlled TT outcome data, TT should be restricted to men with well-defined androgen deficiency syndromes.

1. Progressively increasing androgen use among men

Androgen use in men age ≥40 has increased more than 3-fold, from 0.81% in 2001 to 2.91% in 2011 [1]. Despite highly specific diagnostic criteria for diagnosis and therapy of hypogonadism [2], and despite lessons learned about adverse outcomes associated with sex-hormone therapy in postmenopausal women from the Women's Health Initiative [3,4], there is now rapidly expanding, often indiscriminant prescription of testosterone therapy (TT), without understanding of TT's long-term effects [5,6].

Hypogonadism is a clinical syndrome, and not just a numerical value [2]. As emphasized by Layton et al. [7], testosterone (T) levels fall with increasing age [8], with chronic disease [9,10], and with obesity [9], but smoking has been associated with higher T [11,12]. In aggregate, as men age and become heavier and more likely to be diabetic, there are an increasing number with lower T levels who do not meet diagnostic criteria [2] for hypogonadism. Part of the problem of

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increased TT use lies in determination of an age-specific lower normal range for T, since most normal ranges come from healthy younger men [13]. There are also differences in T assay methods [14,15], and recognition that adverse muscle symptoms occur at different T levels in different subjects [16].

The increasingly broad use of TT may have major public health ramifications, given recent reports of thrombotic [17–22] and cardiovascular events [23–25] related to TT.

2. Deep venous thrombosis, pulmonary embolism, spinal cord infarction, osteonecrosis, amaurosis fugax, and central retinal vein occlusion after starting testosterone therapy

In aggregate [17–22], we have described thrombotic events on TT in 42 patients, 38 men and 4 women, including 27 with deep venous thrombosis-pulmonary embolism (DVT-PE), 12 with osteonecrosis, 1 with central retinal vein thrombosis, 1 with amaurosis fugax, and 1 with spinal cord infarction, Table 1, Fig. 1. Although not conventionally known to represent a thrombotic event, osteonecrosis may be caused, in part, by thrombophilia and hypofibrinolysis-induced thrombus of the efferent veins of the head of the femur leading to increased intracortical pressure and reduced arterial inflow, with subsequent bone hypoxia and bone death [19,26,27].

None of the 42 subjects in our studies [17–22] had polycythemia or uncontrolled hypertension during TT which might have contributed to their thrombi.

In aggregate [17–22], of the 38 men, 36 were Caucasian, 2 African-American, and all 4 women were Caucasian, Table 1. Of the 38 men, 24 (63%) took TT as a gel, with 19 of the 24 (79%) taking 50 mg/day, while 13 men (34%) had TT by injection, mean 165 mg/week, Table 1. Two of the 4 women used a TT patch, and 2 had T-E2 pellet treatment, Table 1. In the 28 patients having DVT-PE, the first thrombotic event occurred 4.5 months (median) after starting TT, Table 1. ON was diagnosed in 9 men 5 months (median) after starting TT, and 2, 2, and 11 months after starting T in the 3 women with ON, Table 1. Amaurosis fugax appeared 18 months after starting TT in one man, and central retinal vein occlusion 0.5 months after starting T-E2 pellet in one woman, Table 1.

Six men continued on TT after their first DVT-PE, and despite adequate concurrent anticoagulation with Coumadin, sustained a second DVT-PE 1 month (median) after the first DVT-PE, Table 1 [17–22]. On concurrent TT and Coumadin, 3 of these 6 men had a third DVT-PE 1.5, 2, and 7 months after their second DVT-PE, Table 1 [17–22]. Two men continued on TT after their first development of ON, and despite adequate concurrent anticoagulation with Coumadin, developed ON at new sites 1 and 12 months after their first ON event, Table 1 [17–22].

After an initial thrombotic event during TT, in patients found to have thrombophilia-hypofibrinolysis, we believe that further TT is contraindicated, because of high likelihood of recurrent thrombi, even when adequate anticoagulation is maintained [17–22].

The most common thrombotic event after initiating TT in men and women with previously undiagnosed thrombophilia-hypofibrinolysis is DVT-PE, occurring in 64% (28/42) of our reported cases [17–22]. PE is expensive to diagnose and treat ($8,764/case) with a high case fatality rate (18%) [28] and approaches to reduce and/or prevent PE [19,20] are important, both medically and economically. In 596 men hospitalized over a 3 year period for DVT-PE, we previously reported that 7 men (1.2%) had taken T before and at the time of their admission [17]. Five of the 7 DVT-PE events occurred within 3 months of initiation of TT [17]. Of the 7 men treated with T, all 5 men who had evaluation of thrombophilia-hypofibrinolysis were found to have previously undiagnosed thrombophilia-hypofibrinolysis [17]. Of 123 evaluable subjects in an AndroGel trial [29], 1 (0.8%) of the cohort had “deep venous thrombosis deemed to be possibly related to T replacement.”

Table 1 – Testosterone therapy and subsequent development of thrombotic events, deep venous thrombosis-pulmonary embolus (DVT-PE),spinal cord thrombosis, osteonecrosis (ON), and ocular thrombosis in 42 patients.

	T therapy	Time intervals (months) between starting T therapy and thrombotic events		
		DVT-PE [1]	ON	Ocular thrombosis
Men, n = 38 36 C, 2 B (5%) age 53 ± 14, median 54 yrs	Gel, n = 24 (63%) (19 had 50 mg/d, 3 had 100 mg/d, 1 had 160 mg/d, 1 had 175 mg/d) Injection, n = 13 (34%) (165 ± 76 mg/wk; 1 had 50 mg/wk nandrolone) Patch 50 mg/d, n = 1 (3%)	1st DVT-PE after start T, n = 28 9.6 ± 10.1, median 4.5 25th–75th percentile (3–17) 2nd DVT-PE * after 1st, n = 6 4.5 ± 6.9, median 1.0 25th–75th percentile (1–6) 3rd DVT-PE * after 2nd, n = 3 (1.5, 2.0, 7.0 months)	1st ON after start T, n = 9 9.8 ± 19.0, median 5.0 25th–75th percentile (1–6) 2nd ON * after 1st, n = 2 (1, 12 months)	Amaurosis fugax after start T, n = 1, (18 months)
Women, n = 4 4C age 51 ± 4, median 53 yrs	Patch, n = 2 (50%) 300 μg/d		ON after start T, n = 3 (2, 2, 11 months)	Central retinal vein occlusion after start T, n = 1, (0.5 months)
	Pellet, n = 2 (50%) 75 mg T-75 mg E2			

[1] Includes 1 patient with spinal cord thrombosis, 5 days after starting T therapy.
* 2nd and 3rd events occurred on T therapy despite adequate anticoagulation with Coumadin.

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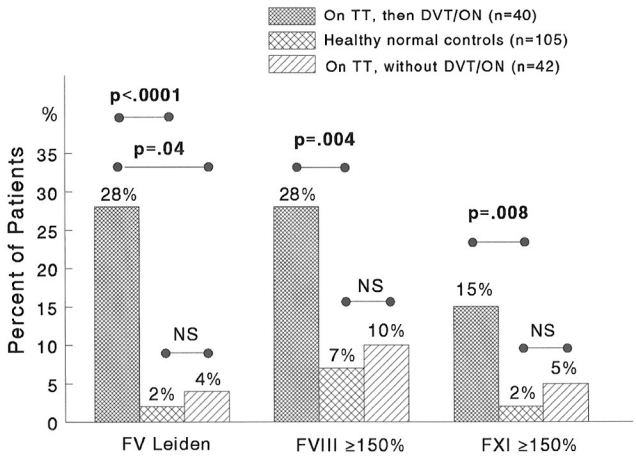

Fig. 1 – Percentage of 40 patients who sustained thrombotic events after prescription of testosterone therapy (TT) found to have Factor V Leiden heterozygosity, high Factors VIII or XI, compared to 105 healthy normal controls and to 42 patients on TT without thrombotic events. Data taken from Glueck et al. [17–22].

3. Role of underlying thrombophilia

Of 42 patients who sustained thrombotic events after starting TT [17–22], 40 had measures of thrombophilia-hypofibrinolysis, and 39 were found to have previously undiagnosed thrombophilia-hypofibrinolysis. When compared to 105 healthy normal controls and to 42 controls on TT but with no thrombotic events, the 40 cases with thrombotic events were more likely to have Factor V Leiden heterozygosity ($p < .0001$, $p = .042$), Fig. 1. Compared to the 105 healthy normal controls, the 40 cases with thrombotic events were more likely to have high Factor VIII ($p = .004$), and high Factor XI ($p = .008$), Fig. 1.

The 105 healthy normal controls did not differ from the 42 TT controls for Factor V Leiden or Factors VIII and XI, $p > 0.05$ for all, Fig. 1.

We speculated [17–22] that TT selected out subjects with previously undiagnosed, underlying thrombophilia, leading to DVT-PE. In a parallel fashion, Douketis et al. [30] reported that in women who were estrogen-progestin hormone replacement therapy users, "… the presence of the factor V Leiden mutation or an elevated factor VIII level appears to have a multiplicative effect on their overall risk of DVT, increasing it 17-fold compared to women without these blood abnormalities who are HRT users."

Before beginning TT, especially in men with previous history of thrombotic events, we suggest [13–18] that, at a minimum, measurements be made for the Factor V Leiden and Prothrombin mutations, Factors VIII and XI, and homocysteine, to identify men who should not receive TT. We need prospective data focused on whether there should be pre-TT screening based on history of previous venous thromboembolism or for all subjects [31,32] for major gene thrombophilias (Factor V Leiden, Prothrombin gene, Factors VIII and XI), issues which have been addressed, but not resolved in women given exogenous estrogens [30–33].

4. Association of TT with physiologic changes predisposing to thrombosis

Beyond interacting with familial thrombophilia [17–22], TT is associated with physiologic changes that predispose to clotting and thrombotic disorders including increased blood pressure [34], polycythemia [35,36], reductions in HDL cholesterol [34,36], hyperviscosity of the blood, and platelet aggregation [36–38]. Intramuscular TT in healthy men increases platelet thromboxane A2 receptor density and platelet aggregation [39], promoting adhesion to the coronary artery endothelium and thrombus formation leading to plaque rupture and acute coronary syndrome [40]. Dihydrotestosterone enhances monocyte activation [41] further promoting acute coronary events [42].

5. Role of aromatization of testosterone to estradiol (E2)

TT increases circulating estrogens [19,43,44] that may play a role in increasing thrombotic [45] and cardiovascular-related events [46–48]. In the Coronary Drug Project trial in men, 2.5 mg estrogen increased cardiovascular events and was discontinued [49]. When 5 mg diethylstilbesterol was used in the Veteran's Administration prostate cancer trial, there was an increased rate of cardiovascular disease death [50].

Increased E2 increases resistance to activated protein C [51], a major thrombophilic factor. We have suggested [19] that some of the thrombophilia mediated by TT comes from its aromatization of testosterone to estradiol (E2). The major source of E2 in men comes from the aromatization of T (endogenous or exogenous) to E2 [52]. We have previously reported [19] that of 20 men having total and free testosterone and E2 measured before and during exogenous TT, 2 (10%) had high pretreatment E2 (≥42.6 pg/mL), but with all men receiving testosterone gel (50 mg/day, ≥3 months), 9 (45%) developed high E2. In a second group of 30 men with measures of T and E2 before and after TT, median T rose from 211 to 421 ng/dl ($p < .001$), E2 rose from 23 to 36 pg/ml ($p < .05$), Whereas, 8% of men had high pre-treatment E2 (≥42.6 pg/ml), 31% had high E2 on TT, McNemar $p = .025$. Change in T and change in E2 on TT were closely correlated, $r = 0.45$, $p = .02$.

In 9 of the 38 men in our aggregate studies [13–18] with measures of E2 on TT, E2 was high in 7 (78%), with median E2 50 pg/ml in the 9 men.

Finkelstein et al. have concluded that benefits of TT may rest on increasing both serum T and E2 [16]. However [19], when exogenous T is aromatized to E2, and E2-induced thrombophilia [45] is superimposed on familial thrombophilia, thrombosis occurs. We have concluded that increases in E2 via aromatization from testosterone may interact with familial and acquired thrombophilia to produce deep venous thrombosis, pulmonary emboli, osteonecrosis, ocular thrombosis, and spinal cord thrombosis [17–22]. If high E2 after administration of exogenous T is associated with thrombosis in patients with previously undiagnosed thrombophilia [17–22], concurrent use of an aromatase inhibitor to lower otherwise high E2 might have theoretical utility. However,

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aromatase inhibitors are themselves thrombogenic [22], although less so than tamoxifen [53].

In contrast to exogenous T, endogenous T is not associated with thrombosis in men [54,55] or in women [55].

6. Klinefelter's syndrome: a potential model to further explain thrombosis during testosterone therapy

We speculate that Klinefelter's syndrome, with a 13% prevalence of post-thrombotic syndrome [39], provides a model that will further help to explain thrombotic events occurring with TT. Increased thrombotic events in Klinefelter's syndrome have been attributed to low levels of plasminogen activator inhibitor associated with low serum testosterone levels [56,57]. However, we and others [56,58–62] have speculated that leg ulcers, DVT, and PE associated with Klinefelter's syndrome reflect interaction of TT therapy (universally used in treatment of hypogonadism in Klinefelter's syndrome) with underlying thrombophilia, including antiphospholipid antibody syndrome, Factor V Leiden heterozygosity, compound Factor V Leiden and Prothrombin gene heterozygosity, and high Factor VIII.

7. Testosterone, thrombophilia, thrombosis, associations with all-cause mortality, and cardiovascular morbidity and mortality

There are similar time intervals between starting TT and either thrombotic events (median 4.5 months [17–22]) or cardiovascular events (~3 months [19–21,58]). We speculate that the short duration between starting TT and development of thrombotic and CVD events [23–25,63] may indicate a shared thrombotic pathophysiology, since CVD events occurring ~3 months after starting TT cannot reflect a conventional arterial atherosclerotic event.

Three recent studies [23–25] and a meta-analysis [63] have raised serious concerns about adverse cardiovascular disease (CVD) outcomes within 3 to 6 months after TT was started. Basaria et al. [23] studied 209 community-dwelling men ≥ age 65 in a randomized trial of testosterone gel on muscle function. During a 6-month treatment period, CVD events occurred in 23 subjects in the TT group vs 5 in the placebo group (OR 10.6, 95% CI 1.3-84.5), and there was rapid divergence in rates of CVD adverse events by 3 months with a progressive increase over the 6-month treatment period. The study was discontinued before enrollment was completed because of the increased CVD events in the TT group [23]. A subsequent meta-analysis of TT in predominantly older men suggested excess CVD event rates [63], which, congruent with Basaria et al. [23], appeared soon (~3 months) after beginning TT [63].

Vigen et al. [24] completed a retrospective study in the Veteran's Administration health care system of men (average age >60) who had undergone coronary angiography, 80% of whom had documented coronary artery disease (CAD). At 3 years after coronary angiography, the Kaplan-Meier estimated cumulative percentages of men with events including all-cause mortality and CVD morbidity, were 25.7% in the TT group and 19.9% in men not receiving TT, hazard ratio 1.29, 95% CI 1.04-1.58.

Finkle et al. [25] conducted a cohort study of the risk of acute non-fatal myocardial infarction (MI) 90 days after an initial TT prescription in a large health-care database (n = 55,593). They compared the MI incidence rate in the 90 days following the initial T prescription (post-prescription interval) with the rate in the one year prior to the initial prescription (pre-prescription interval) (post/pre). They also calculated post/pre MI rates in a cohort of men prescribed phosphodiesterase type 5 inhibitors (PDE5I n = 167,279), and compared TT prescription post/pre rates with the PDE5I post/pre rates, adjusting for potential confounders [25]. In all subjects, the post/pre-prescription MI rate ratio (RR) for TT was 1.36 (1.03, 1.81). Comparing TT to PDE5I subjects, the ratio of the post/pre MI rate ratios (RRR) was 1.90 (1.04, 3.49) for all subjects.

There is a prospective ongoing study "Testosterone Trial in Older Men (NCT00799617)," with 800 men ≥ age 65 randomized to TT (gel) or placebo for 1 year. Unfortunately, this trial will lack adequate power to determine whether TT affects CVD event rates.

8. Conclusion

The increasingly broad use of TT may have major public health ramifications, given recent reports of thrombotic [17–22] and cardiovascular events [23–25] related to TT. We need prospective, cost-effectiveness data [31,32] to determine whether all men or only those with history or family history of venous thromboembolism should have pre-TT screening for major gene thrombophilias. The comparable short time courses between initiation of TT and either thrombotic (~4.5 months) or cardiovascular events (~3 months) suggests a shared pathophysiology.

To better resolve questions about TT and all cause and cardiovascular morbidity and mortality and thrombosis, a long term, prospective, blinded study following the example of the Women's Health Initiative [3,4] is needed. While we wait for prospective placebo controlled TT outcome data, TT should be restricted to men with well-defined androgen deficiency syndromes [2].

Conflict of interest

The authors have no conflicts of interest.

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