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Review

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

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increasing number with lower T levels who do not meet diagnostic criteria [2] for hypogonadism. Part of the problem of 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 Pellet, n = 2 (50%) 75 mg T-75 mg E2		ON after start T, n = 3 (2, 2, 11 months)	Central retinal vein occlusion after start T, n = 1, (0.5 months)

[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.