



Medical Treatments for Hypogonadism do not Significantly Increase the Risk of Deep Vein Thrombosis Over General Population Risk

Parviz K. Kavoussi, G. Luke Machen, Jessica L. Wenzel, Alex M. Ellis, Mehraban Kavoussi, Keikhosrow M. Kavoussi, and Shahryar K. Kavoussi

OBJECTIVE	To evaluate the risk of deep vein thrombosis (DVT) in men treated with testosterone replacement therapy (TRT) or Clomiphene Citrate (CC) and assess other etiologies for DVT as contributing factors.
METHODS	Retrospective chart review of 1180 consecutive hypogonadal men who were treated with either TRT or CC. Sixty-four percent had mixed, 16% had primary, and 20% had secondary hypogonadism.
RESULTS	Of the 1180 men with hypogonadism, 694 were treated with TRT, while 486 were treated with CC. Overall, 10 of 1180 (0.8%) men were diagnosed with a DVT during the treatment, 9 of whom were on TRT and 1 on CC. Of the 10 men diagnosed with DVT while on treatment, 7 (70%) had potential identifiable etiologies for DVT other than treatment for hypogonadism. None of the men were found to be polycythemic at the time of DVT diagnosis. There was a higher incidence of DVT in men treated with TRT than CC, however; the overall percentages of DVT in both treatment groups were relatively low. There was no difference in the percentages of men found to have other identifiable etiologies for DVT besides being on treatment between the TRT and CC groups. There was not a difference in testosterone levels between the TRT and CC groups.
CONCLUSION	The overall rates of DVT for TRT and CC treated patients are relatively low, and the majority of patients with DVT had other identifiable etiologies for DVT. Polycythemia was not found to be a risk factor in the patients diagnosed with DVTs. UROLOGY 124: 127–130, 2019. © 2018 Elsevier Inc.

Hypogonadism has become a common diagnosis in men presenting with a constellation of symptoms which prompts an evaluation and the number of prescriptions written to treat men with hypogonadism has been on a rapid rise. Men may start to demonstrate a decline in testosterone levels at 30 years of age. Once testosterone levels begin to decline, they decrease by 1%-2% per year.¹ The overall prevalence of hypogonadism has been found to be 38.7% in men 45 years of age and older, with

hypogonadism defined as a morning drawn serum testosterone level of less than 300 ng/dL.² The overall incidence of hypogonadism ranges widely 2.1%-12.8% and the rate of testosterone use has significantly risen.^{3,4}

In June 2014, the United States Food and Drug Administration mandated that manufacturers of all testosterone replacement therapy (TRT) products add a general label warning about the increased risk for deep vein thrombosis (DVT). Prior to this general statement, the labels of TRT products warned about the risk of DVT associated with secondary polycythemia in men on treatment. Postmarket reports of DVTs in men on TRT who were not polycythemic prompted this general warning.

Besides TRT, another commonly prescribed treatment for men with hypogonadism is Clomiphene Citrate (CC), particularly for men with hypogonadism who wish to maintain fertility potential. CC is commonly prescribed

Funding Disclosure: There was no external source of funding for this work.

Author Disclosures: Parviz K. Kavoussi—Speaker bureau AYTU biosciences.

From the Reproductive Urology, Austin Fertility & Reproductive Medicine/Westlake IVF, Austin, TX; the Medical College of Wisconsin, Milwaukee, WI; the The University of Texas Dell Medical School, Austin, TX; the Texas A&M Health Sciences Center, Round Rock, TX; and the The University of Texas Southwestern Medical Center, Dallas, TX

Address correspondence to: Parviz K. Kavoussi, M.D., F.A.C.S., Reproductive Urology, Austin Fertility & Reproductive Medicine/Westlake IVF, 300 Beardsley Lane, Building B, Suite 200, Austin, TX 78746. E-mail: pkavoussi@hotmail.com

Submitted: October 9, 2018, accepted (with revisions): November 5, 2018

© 2018 The Authors. Published by Elsevier Inc.

This is an open access article under the CC BY-NC-ND license. (<http://creativecommons.org/licenses/by-nc-nd/4.0/>)

<https://doi.org/10.1016/j.urology.2018.11.009>

127

0090-4295

for hypogonadism in men as an off-label indication. Although the package insert for CC was not designed for the treatment of hypogonadism in men, it includes pulmonary embolism (PE), an end sequela of DVT. Polycythemia has been reported as a potential side effect of TRT products and has been shown to not be a significant side effect with CC use.⁵

Despite these warnings, there is not a large body of data on the risk of DVT associated with the treatment of men with hypogonadism, including TRT and CC, in the medical literature. The goal of the study was to evaluate the risk of DVT in a population of men who presented for a hypogonadism evaluation and who were treated with TRT or CC. A secondary goal was to assess the presence of other etiologies for DVT to be the potential factor in men who are on TRT or CC and to evaluate the association of secondary polycythemia with the occurrence of DVT in these men.

MATERIALS AND METHODS

After Institutional Review Board exemption was obtained, a retrospective chart review was performed from a reproductive urology/andrology clinic of 1180 consecutive men presenting for a hypogonadism evaluation who were treated with either TRT or CC, after being deemed a candidate for treatment based on Endocrine Society guidelines for diagnosing hypogonadism, between July 2011 and December 2017. All men underwent an evaluation including a symptoms questionnaire, a complete history, a complete physical examination, 2 separate serum total testosterone levels drawn in the morning along with follicle stimulating hormone, luteinizing hormone (LH), prolactin, estradiol, prostate specific antigen (PSA), and hemoglobin and hematocrit prior to initiating treatment. Sixty-four percent of the men were diagnosed with mixed hypogonadism defined as normal LH, 16% were categorized as primary hypogonadism with elevated LH, and 20% with secondary hypogonadism with low LH. Patients were then counseled on Food and Drug Administration approved options for TRT including transdermal gels, intramuscular injections, and subcutaneous pellets. Men who desired to maintain fertility potential, wanted to avoid testicular atrophy, or did not want a treatment that would decrease the hypothalamic-pituitary-gonadal axis function opted for an off-label treatment with CC. Serum laboratory evaluation and follow-up clinic visits were at intervals of 1 month after initiation of treatment followed by repeat laboratory testing and follow-up every 6 months while remaining on treatment. There was a high compliance rate as prescription refills would not be allowed without laboratory testing and follow-up visits at these intervals. DVT events were recorded by review of the Duplex ultrasound confirming the diagnosis of DVT based on clinical suspicion by a physician at an outside facility.

Student *t* test and Chi-square test were used for statistical analyses between groups where appropriate. A *P* value of <.05 was considered to be statistically significant.

RESULTS

From June 2011 to December 2017, 1180 men presenting for an evaluation were diagnosed with hypogonadism. Six hundred and ninety-four of these men were treated with TRT,

while 486 were treated with CC for hypogonadism. The mean age of all men treated was 43 years \pm 12 with a mean follow-up interval of 25 months \pm 21. Overall, 10 of 1180 (0.8%) men who were treated were diagnosed with a DVT during the treatment interval. Of the 10 men diagnosed with DVT while on treatment, 7 of them (70%) had potential identifiable etiologies for DVT other than being on a medical treatment for hypogonadism. Other potential etiologies for DVT included risk factors that resulted in venous stasis, endothelial injury, or a hypercoagulable state. These other etiologies included a DVT following ankle reconstruction, 2 men had DVTs following international flights, 1 had a DVT following a lower extremity trauma, 1 patient presented with a DVT following a road trip that was 12 hours in duration 1 week following abdominal surgery, 1 man had Klinefelter's Syndrome, and another was diagnosed with Factor V Leiden deficiency. One patient had 2 potential etiologies including having Klinefelter's syndrome, which increases the risk of DVT, as well as presenting with his DVT 1 week following knee surgery.⁶⁻¹⁰ One of the 10 patients had a resultant PE from his DVT, this was the man with Klinefelter's syndrome. All of the men who were diagnosed with DVTs were referred for hematologic evaluation. None of the men were found to be polycythemic, defined as a hematocrit greater than 52, at the time of DVT diagnosis. None of the men diagnosed with DVT had elevated estradiol levels greater than 60 pg/mL, therefore; none of these men required aromatase inhibitors. None of the men who were diagnosed with DVT were smokers.

Table 1 represents the demographics and outcomes of the men treated with TRT versus CC. This includes the number of men who had DVTs during treatment with TRT versus CC, the percentage of men who had other identifiable etiologies for DVT in each treatment group, and the mean total testosterone levels for both treatment groups. Men treated with TRT were older than men treated with CC. There was a statistically significant higher incidence of DVT in men treated with TRT than in men treated with CC, however; the overall percentages of DVT in both treatment groups was low. There was not a significant difference in the percentages of men found to have other identifiable etiologies for DVT besides being on treatment for hypogonadism between the TRT and CC groups. The man on CC who developed a DVT had it diagnosed following an international flight. The remaining etiologies were found in the men on TRT with DVTs. There was not a significant difference in total testosterone levels between the TRT and CC groups. Table 2 represents the characteristics of the men who developed DVT while on a medical treatment for hypogonadism. The mean time men were on treatment for hypogonadism prior to being diagnosed with DVT was 22 months \pm 8.

DISCUSSION

The incidence of DVT in the general population has been stratified by age with 1 study revealing an incidence of DVT of 0.5% by the age of 50 and as high as 10.7% incidence by the age of 80 years.¹¹ The mean age of the men in our current study was 43 \pm 12 years of age with an overall 0.8% incidence of DVT in these men. Another study reported an incidence of DVT in the general population 0.2% per year which doubles beyond the age of 40 years.¹² Another epidemiological study reported the

Table 1. Demographics and outcomes of men treated with testosterone replacement therapy versus Clomiphene Citrate including the percentage of men who had deep vein thrombosis on either treatment, what percentage of men on either treatment had an identifiable etiology for besides treatment, and the serum testosterone levels. Results are expressed as means +/- standard deviations

	Age (y)	DVT	Other Etiologies for DVT	Testosterone Levels
TRT (n = 694)	47 +/- 11	1.3% (9/694)	66.7% (6/9)	656 +/- 248
CC (n = 486)	38 +/- 11	0.2% (1/486)	100% (1/1)	662 +/- 248
P value	.0001	.044	.66	.068

CC, clomiphene citrate; DVT, deep vein thrombosis; TRT, testosterone replacement therapy.

incidence of DVT in the general population as 0.2%.¹² In this current study, the overall rate of DVT in patients on TRT or CC was 0.8% with 70% of these men having another identifiable etiology for DVT. If the men with DVT and with other potential etiologies are excluded from the men with DVT with the only risk potentially being treatment for hypogonadism, the incidence of DVT in this population would be 0.2%, equivalent to the lowest reported general population rate of DVT in the previous studies. The incidence of DVT was 1.3% in the TRT patients versus 0.2% in the CC patients with 66.7% and 100%, respectively, having other identifiable etiologies for DVT.

Despite the labeling on all TRT products and CC indicating a risk of DVT/PE with these medical treatments for hypogonadism, there is not a large body of data in the medical literature associating these treatments with DVT. There have been reports of DVT with PE associated with anabolic steroid use, but with supratherapeutic testosterone levels, which implies different inherent risks.¹³ A study including 14 patients diagnosed with DVT while on TRT revealed only 1 of these men without an identifiable clotting abnormality. The other 13 men were diagnosed with thrombophilic-hypofibrinolytic conditions including 3 who were factor V Leiden heterozygotes, 3 with high factor VIII, 3 with plasminogen activator inhibitor 1 4G4G homozygosity, 2 with high factor XI, 2 with high homocysteine, 1 had low antithrombin III, 1 had the lupus anticoagulant, and 1 had anticardiolipin antibody Immunoglobulin G. The study revealed other etiologies

but also raised the concern of ruling out thrombophilia prior to administering TRT and the potential risk of DVT in men with a thrombophilia on TRT.¹⁴ The patient population diagnosed with DVT in our current study only included 1 patient with a thrombophilic-hypofibrinolytic condition, factor V Leiden deficiency, and the remainder of the potential etiologies for DVT included risk factors for venous stasis, trauma, or a genetic disorder, specifically Klinefelter's syndrome.

Another previous study evaluated 596 men who were admitted for DVT/PE over a 3-year period and found a 1.2% (7/596) prevalence of DVTs in men on TRT with a mean interval between initiation of TRT and DVT/PE of ≤ 3 months for 5 of the 7 cases and mean time of all included patients on TRT to DVT/PE being 6.7 months. This may lessen the potential of a limitation of our current study being a follow-up interval of 25 months \pm 21. Of the 7 men with DVT/PE in the previous study, 5 had identifiable thrombophilic/hypofibrinolytic etiologies including 1 with lupus anticoagulant, 3 with hypofibrinolytic 4G4G mutation of the plasminogen activator inhibitor gene, 2 had high factor VIII, 1 had high factor XI, and 1 had MTHFR C677T homozygosity. This study suggests a thrombotic interaction between exogenous TRT and thrombophilia-hypofibrinolysis.¹⁵ Again, being that our population of men with DVTs only included 1 with a thrombophilia identified by an evaluation by a hematologist following DVT, this may not be as relevant as a factor in the DVT patients in our current study. This study cannot rule out the possibility of medical treatment for

Table 2. Characteristics of patients who developed DVT while on treatment for hypogonadism

Patient	Age (y)	Treatment	Testosterone (ng/dL)	Estradiol (pg/mL)	Identifiable Etiology for DVT
1	32	TRT injections	774	32	Following ankle reconstruction
2	47	CC	693	51	International flight
3	34	TRT injections	921	48	None identified
4	39	TRT gel	368	17	Lower extremity trauma
5	58	TRT injections	428	36	None identified
6	35	TRT gel	908	31	Following knee surgery/ Klinefelter's Syndrome
7	45	TRT injections	878	34	12 h drive after abdominal surgery
8	52	TRT gel	937	49	International flight
9	47	TRT pellets	847	42	None identified
10	39	TRT injections	643	37	Factor V Leiden deficiency

hypogonadism being an additional potential etiology for DVT concomitantly with the identifiable etiology other than the medical treatment. A large case control study of men in the United Kingdom with a mean age of 64.8 who had 2 years of baseline medical data, reported an increased risk of DVT with starting TRT which peaks at 6 months after initiating TRT and then declined.¹⁶ In our current study, the mean time to DVT following initiation of treatment for hypogonadism was 22 months \pm 8, and the mean follow-up interval was 25 months \pm 21.

Ramasamy et al reported an increase in all-cause mortality in hypogonadal men not treated with TRT compared to men treated with TRT, and found no difference in PE rates between patients treated with TRT versus those who remained hypogonadal and were not treated in a cohort of 217 hypogonadal men of ages greater than 65.¹⁷ Another study revealed no difference in DVT/PE incidences in men who were treated with TRT to normalized serum testosterone levels (0.5%), versus those treated with TRT but who remained hypogonadal (0.4%), versus those who were hypogonadal and were not treated with TRT (0.4%).¹⁸

Although there are reports of DVT in women on CC with ovarian hyperstimulation syndrome, data on DVT in men on CC for hypogonadism is scarce. A case report of a 32-year-old man who was diagnosed with a DVT while on CC, with a hypogonadal total serum testosterone level of 224 ng/dL has been reported.¹⁹ Our current study reports a DVT in 1 out of 486 men treated with CC, who had an additional potential etiology of venous stasis due to an international flight.

Although the body of evidence in the medical literature is not very robust, the majority of data are in agreement with the data of the current study. There is not a significantly increased risk of DVT in men on TRT or CC versus general overall population risk. Some studies indicate that men with baseline thrombophilia/hypofibrinolysis may increase the risk of DVT with TRT, however; the men in our current study had other potential etiologies for their DVTs such as venous stasis, trauma, or Klinefelter's syndrome, with only 1 man with a thrombophilic condition.

Other limitations to this study include the retrospective nature with its inherent biases as well as the possibility that men could have experienced this complication or had the diagnosis of DVT at a facility outside of the home institution. However, all follow-up patients receive an interval history update form which asks about any new medical diagnoses, imaging studies, procedures, or new medications since the last visit, which should capture any DVT diagnosed outside of the home institution. All patients being treated for hypogonadism are seen every 6 months while on treatment.

CONCLUSION

The overall rate of DVT for TRT and CC treated patients was 0.8%, and the majority of patients with DVT in our

study population had other identifiable etiologies for DVT. Accounting for those patients, the risk of DVT without another identifiable potential etiology for DVT other than medical treatment for hypogonadism, is similar to general population DVT risk. Polycythemia was not found to be a risk factor in the patients diagnosed with DVTs.

References

1. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. *J Clin Endocrinol Metab.* 1983;56:1278–1281.
2. Mulligan T, Frick MF, Zuraw QC, Stenhagen A, McWhirter C. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract.* 2006;60:762–769.
3. Zarotsky V, Huang MY, Carman W, et al. Systematic literature review of the risk factors, comorbidities, and consequences of hypogonadism in men. *Andrology.* 2014;2:819–834.
4. Mohr BA, Guay AT, O'Donnell AB, McKinlay JB. Normal, bound and nonbound testosterone levels in normally ageing men: results from the Massachusetts Male Ageing Study. *Clin Endocrinol.* 2005;62:64–73.
5. Wheeler KM, Smith RP, Kumar RA, Setia S, Costabile RA, Kavoussi PK. A comparison of secondary polycythemia in hypogonadal men treated with clomiphene citrate versus testosterone replacement: a multi-institutional study. *J Urol.* 2017;197:1127–1131.
6. Valasek AE, Warren P, Kumar R. Klinefelter syndrome as a risk factor for recurrent deep vein thrombosis in an adolescent male: significance of a thorough physical examination. *Pediatr Blood Cancer.* 2018;65:e27080.
7. Glueck CJ, Jetty V, Goldenberg N, Shah P, Wang P. Thrombophilia in Klinefelter syndrome with deep venous thrombosis, pulmonary embolism, and mesenteric artery thrombosis on testosterone therapy: a pilot study. *Clin Appl Thromb Hemost.* 2017;23:973–979.
8. Zoller B, Ji J, Sundquist J, Sundquist K. High risk of venous thromboembolism in Klinefelter syndrome. *J Am Heart Assoc.* 2016;5:1–6.
9. Seth A, Rajpal S, Penn RL. Klinefelter's syndrome and venous thrombosis. *Am J Med Sci.* 2013;346:164–165.
10. Campbell WA, Price WH. Venous thromboembolic disease in Klinefelter's syndrome. *Clin Genet.* 1981;19:275–280.
11. Hansson PO, Welin L, Tibblin G, Eriksson H. Deep vein thrombosis and pulmonary embolism in the general population. 'The Study of Men Born in 1913'. *Arch Intern Med.* 1997;157:1665–1670.
12. Kearon C. Epidemiology of venous thromboembolism. *Semin Vasc Med.* 2001;1:7–26.
13. Liljeqvist S, Hellden A, Bergman U, Soderberg M. Pulmonary embolism associated with the use of anabolic steroids. *Eur J Intern Med.* 2008;19:214–215.
14. Glueck CJ, Richardson-Royer C, Schultz R, et al. Testosterone, thrombophilia, and thrombosis. *Clin Appl Thromb Hemost.* 2014;20:22–30.
15. Glueck CJ, Richardson-Royer C, Schultz R, et al. Testosterone therapy, thrombophilia-hypofibrinolysis, and hospitalization for deep venous thrombosis-pulmonary embolus: an exploratory, hypothesis-generating study. *Clin Appl Thromb Hemost.* 2014;20:244–249.
16. Martinez C, Suissa S, Rietbrock S, et al. Testosterone treatment and risk of venous thromboembolism: population based case-control study. *BMJ.* 2016;355:i5968.
17. Ramasamy R, Scovell J, Mederos M, Ren R, Jain L, Lipshultz L. Association between testosterone supplementation therapy and thrombotic events in elderly men. *Urology.* 2015;86:283–285.
18. Sharma R, Oni OA, Chen G, et al. Association between testosterone replacement therapy and the incidence of DVT and pulmonary embolism: a retrospective cohort study of the veterans administration database. *Chest.* 2016;150:563–571.
19. Subedi BH, L.uldashev A. A case of clomiphene-induced DVT in a young man. *J Hosp Med.* 2014;9(suppl 2).