

CLINICAL STUDY

Testosterone replacement therapy (TRT) and its effect on bone marrow. How serious is it and is there a true polyglobulia?

Levcikova M¹, Breza Jr J², Luha J³, Dubravicky J⁵, Kovacova E⁴, Fillo J⁵*Department of Urology, University Hospital Bratislava, Slovakia. miskalevcikova@gmail.com***ABSTRACT**

INTRODUCTION: TRT in men with testosterone deficiency syndrome (TDS) had multiple positive effects and restore a quality of life of affected men. Polyglobulia is the most common dose-limiting adverse effect of TRT, but the mechanisms of TRT-mediated erythropoiesis remain unclear. In this study, we evaluated long term haematological side effects of TRT: polyglobulia, elevated hemoglobin (Hb) and haematocrit (Ht).

METHODS: In a cross-sectional descriptive study, the authors treated 69 men with TDS and the average age 59 years and the follow-up period 81.32 months. The men were treated with three-month i.m. injections of 1000 mg testosterone undecanoate. The elevated values were: Hb above 176 g/l, Ht above 0.52 and erythrocytes (Ery) above 6.0 mil/mcl.

RESULTS: 21 out of 69 patients (30.43 %) had an increased Hb, Ht or Ery during treatment. The interesting fact was that only five men (7.24 %) had increased the number of Ery (true polyglobulia). No men with elevated level of Hb, Ht or Ery had other side effects (like thrombosis).

CONCLUSION: It is still not clear, why in some men on TRT the feedback does not work and bone marrow production of red blood cells continues even if the upper limit is reached. Authors expect that only 7% of men had true polyglobulia, other men had elevated Hb or Ht. Based on our own experience we recommend a regular check of men on TRT on order to avoid possible serious side-effects (Tab. 1, Fig. 2, Ref. 25). Text in PDF www.elis.sk.

KEY WORDS: testosterone, testosterone replacement therapy, hemoglobin, polyglobulia, haematocrit.

Introduction

TRT of men with TDS has many beneficial effects. Overall health condition and function of many organ systems are improved significantly, among them the bone marrow function. Consequently, blood count began to improve. However, some risks have to be considered. One of the risks of TST replacement therapy is polyglobulia and hematocrit increase occurring in 4–40 % of men on TRT, and may worsen pre-existing cardiovascular complications secondary to an increased blood viscosity (1, 2). It is still not clear, why in some men on TRT feedback does not work and bone marrow production continues even if the upper limit of Hb, Ery, Ht was reached. Many studies described polyglobulia and mentioned only Hb and Ht, and not Ery (3).

Materials and methods

The authors treated 69 men with TDS after a complete urology and internal examination. They did not suffer from other serious

urological condition, mainly from nutrition problems. None of these men had an obstructive pulmonary disease or other serious internal comorbidity. The average follow-up time was 81.32 months. The mean age was 59 years. The men were treated with three-month i.m. injections of 1000mg testosterone undecanoate.

During the treatment, all men had testosterone (TST) level within the physiological range. The men were regularly checked in accordance with the EAU guidelines. The elevated values are (according to laboratory): hemoglobin above 176 g/l, hematocrit above 0.52 and erythrocytes above 6.0 mil/mcl. None of these men had an obstructive pulmonary disease or other serious internal comorbidity.

As stated in the EAU guidelines 2017, technique of blood collection is important. There should be minimal or no venous occlusion during the blood sampling.

Results

In the first year, the treatment hemoglobin rose from 151.93 g/l to 161.93 g/l and then it remained stable (Fig. 1). In 21/69 (30.43 %) men, some of the studied parameters (Ery, Hb, Ht) increased above the normal range (Tab. 1). Only five men (7.24 %) had N increased number of Ery. The others had only increased Hb and Ht. The size of Ery was not enlarged (Fig. 2). These elevated values were not only at the beginning, but also during the treatment. The men with THE elevated level of Hb, Ht or Ery had no vascular complications. In the patients with supranormal levels

¹Department of Urology, University Hospital Bratislava, Slovakia, ²Department of Pediatric Urology, University Hospital Bratislava, Slovakia, ³Institute of Medical Biology, Genetics and Clinical Genetics, School of Medicine, Comenius University Bratislava, Slovakia, ⁴Department of Internal Medicine I, Comenius University Bratislava, Slovakia, and ⁵Urology Clinic, University Hospital Bratislava, Slovakia

Address for correspondence: J. Fillo, MD, Urology Clinic, University Hospital Bratislava, Limbova 5, SK-833 05 Bratislava, Slovakia.

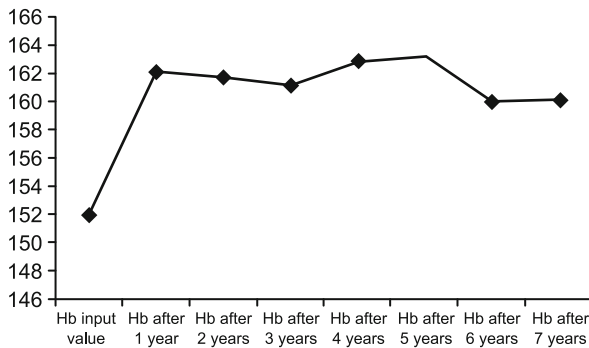


Fig. 1. The monitored level of hemoglobin.

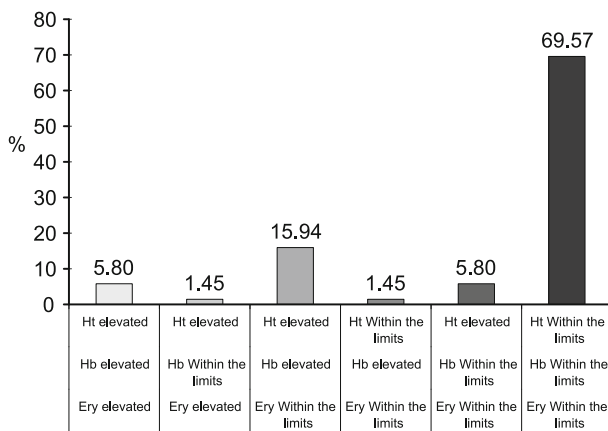


Fig. 2. Distribution of elevated Ery, Hb, Ht.

of the Hb, Ht and Ery, acetylsalicylic acid 30 mg per os daily was recommended.

Discussion

Testosterone is an anabolic hormone and besides influencing different organ systems, it stimulates also bone marrow. In some patients, the red blood components increase during the treatment. Authors proved a correlation between high testosterone levels and high hemoglobin, because testosterone stimulates erythropoiesis. Erythrocytosis can develop during testosterone treatment, especially in older men, treated by injectable testosterone preparations (4). Aghasadeh et al 2015 recommended monitoring of dihydrotestosterone level, which can be responsible for polyglobulia. They recommended therapeutic use of 5ARIs, which may inhibit the conversion of TST to dihydrotestosterone. We tried to use 5ARI (finasterid) in one men with polyglobulia and symptomatic BPH, but without a success. The testosterone-treated men were at a higher risk of developing erythrocytosis than the placebo/nonintervention group. The adverse effects of testosterone therapy include an increase in hemoglobin and hematocrit (5). A meta-analysis of 51 studies revealed that TRT is associated with an average 0.8 g/dl increase in Hb and a 3.2 % increase in Ht, but there was no significant effect on mortality, prostate size or

Tab. 1. Elevation of Ht, Hb and Ery.

Erythrocytes	Hemoglobin_	Hematocrit	n	%
Ery elevated	Hb elevated	Ht elevated	4	5.80
Ery elevated	Hb normal	Ht elevated	1	1.45
Ery normal	Hb elevated	Ht elevated	11	15.94
Ery normal	Hb elevated	Ht normal	1	1.45
Ery normal	Hb normal	Ht elevated	4	5.80
Ery normal	Hb normal	Ht normal	48	69.57
Summary			69	100.00

cardiovascular outcomes (5). It is not exactly known, which level of Ht is associated with adverse health events. In epidemiologic studies, higher Ht levels are associated with an increased risk of hypertension, cardiovascular events and stroke than lower Ht values (6, 7). As Ht levels increase from low to normal levels, plasma viscosity and tissue blood flow increase along with an increase in tissue oxygen delivery (8–11). However, as hematocrit levels rise further, plasma viscosity increases disproportionately, and at some level of hematocrit, tissue blood flow and oxygen delivery begin to decline (8–11). The Endocrine Society’s expert panel recommends that testosterone administration should be withheld in men, whose hematocrit rises above 54 % during testosterone therapy. When the hematocrit has fallen into the normal range, TRT can be reinstated at a lower dose (12). The frequency of neuro-occlusive events (stroke) in association with an increased hematocrit in testosterone trials has been extremely low (13).

Men have higher levels of hemoglobin than women, and hypogonadism causes a decline in Hb levels that can be restored with testosterone replacement therapy (14, 15). However, the elevation in haemoglobin above certain levels may lead to complications, particularly in elderly, because the increase in blood viscosity could exacerbate vascular disease in the coronary, cerebrovascular, or peripheral vascular circulation, especially in people with other diseases that cause secondary polycythemia, i.e. chronic obstructive pulmonary disease (18–20).

Injection of TST is associated with a higher potential for erythrocytosis than application of local (topic) preparations (21). Periodic hematological assessment is indicated (i.e., before treatment, then in 3 to 4 months and in 12 months in the first year of treatment and annually thereafter). While it is not yet clear, what critical threshold is a desirable, dose adjustment and/or periodic phlebotomy may be necessary to keep hematocrit below 52 % to 55 % (22).

Erythrocytosis, or polycythemia, is a known side effect of testosterone treatment. A meta-analysis of adverse effects of TST treatment in men with TDS found 11 trials that highlighted erythrocytosis as a prominent side effect of treatment with TST. However, the mechanism behind the causes of hemoconcentration, and how this may affect men, is poorly understood (5). Coviolo et al (2008) studied elevated hemoglobin and hematocrit in patients receiving TST treatment. They demonstrated that treatment with testosterone caused statistically significant increased hemoglobin levels (0.86 ± 0.31 g/dl, p = 0.01). The authors hypothesized that treatment with TST increased serum erythropoietin, leading

to erythrocytosis, yet this was disproven (-0.24 ± 2.16 mIU/ml, $p = 0.91$). Another proposed theory posits that TST has a dose dependent stimulatory effect on erythropoiesis in men that is more pronounced in older men.

Li et al (2016) studied 102,650 exogenous testosterone treated and 102,650 untreated patients. They found no significant association between the exogenous testosterone therapy and incidents of idiopathic or overall venous thrombotic events in men with hypogonadism. However, some discrepant findings exist for the association between the injectable formulations and the risk of overall venous thrombotic events.

Snyder et al (1999) noticed that erythrocytosis occurred in 5.5 % of scrotal transdermal users, and the majority of changes took place over the first three months of treatment (24). The frequency of polycythemia (hematocrit over 51 %) was related mainly to supra-physiological serum TST levels.

Testosterone increases erythropoietin levels, but the erythropoietin levels return towards baseline with a continued testosterone therapy (23). However, erythropoietin levels are elevated in relation to the increased haemoglobin levels in testosterone-treated men. Testosterone might potentially increase the sensitivity of erythroid progenitor cells to erythropoietin.

In another study, within the period of 36 months, Maggio et al (2013) reported, that there were no 'serious' patient-centered adverse events (e.g. cerebrovascular accident, vascular occlusive events, venous thromboembolisms).

There are many TDS-treated men with TST worldwide. The side effects of this treatment are also polycythemia, increase of hemoglobin and hematocrit. The increments in hemoglobin and hematocrit are related to testosterone dose and concentrations and occur more frequently in men aged 60–75 years, than in men aged 19–35 years (23).

Increasing age was associated with increasing odds for the development of polycythemia in androgen deficient men treated with testosterone. Physiological experiments, when normal men are rendered acutely with androgen deficit and then treated with graded and matched doses of TST, confirm this age association (23).

Although TRT in androgen-deficient men clearly stimulates erythrocytosis and increases the odds of polycythemia fourfold (13), the mechanism by which this occurs, remains elusive.

Physiological experiments in normal men do not show the relationship between TST dose and immunoreactive erythropoietin after five months of treatment (23). Ip et al (2010) conclude, that higher through serum testosterone levels, but not duration of treatment predict the development of polycythemia in men receiving long-acting depot TST treatment. These data inform the clinical practice. Further investigation of the mechanism by which polycythemia develops is required (25).

Conclusion

The anabolic effect of testosterone has many positive effects, including bone marrow stimulation and improvement in blood count as we documented in our patients. This helps to improve

tissue supply with oxygen and reduces fatigue. The authors found that not all components of blood count are elevated. They found only 7 % of men with polyglobulia (elevated erythrocytes count) and the rest had elevated Hb and Ht. No men with elevated blood count had thrombotic complications. Further studies will be needed to clarify, why in some men feedback does not work and bone marrow continues to increase the production of haemoglobin. It is necessary to check the blood count at regular intervals. In these cases, it is a simple solution to extend the administration interval of TST from 12 to 14 weeks or more to eliminate the potential risk resulting from an increased blood viscosity.

References

1. **Rhoden EL, Morgentaler A.** Risks of Testosterone-Replacement Therapy and Recommendations for Monitoring. *N Engl J Med.* 2004; 350: 482.
2. **Bassil N, Alkaade S, Morley JE.** The benefits and risks of testosterone replacement therapy: a review. *Ther Clin Risk Manag* 2009; 5: 427.
3. **Aghazadeh M, Pastuszak AW, Johnson WG, McIntyre MG, Hsieh TM, Lipshultz LL.** Elevated Dihydrotestosterone is Associated with Testosterone-induced Erythrocytosis. *J Urol* 2015; 194 (1): 160–165.
4. **Wang C, Nieschlag E, Swerdloff R et al.** Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA and ASA recommendations. *Eur J Endocrinol* 2008; 159: 507–514.
5. **Fernández-Balsells MM et al.** Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. *J Clin Endocrinol Metab* 2010; 95: 2560–2575.
6. **Strand A et al.** Increased hematocrit before blood pressure in men who develop hypertension over 20 years. *J Am Soc Hypertens* 2007; 1: 400–406.
7. **Gagnon DR, Zhang TJ, Brand FN, Kannel WB.** Hematocrit and the risk of cardiovascular disease –the Framingham study: a 34-year follow-up. *Am Heart J* 1994; 127: 674–682.
8. **Hagl S et al.** The effect of hemodilution on regional myocardial function in the presence of coronary stenosis. *Basic Res Cardiol* 1977; 72: 344–364.
9. **Danesh J, Collins R, Peto R, Lowe GD.** Hematocrit, viscosity, erythrocyte sedimentation rate: meta-analyses of prospective studies of coronary heart disease. *Eur Heart J* 2000; 21: 515–520.
10. **Burch GE, DePasquale NP.** Hematocrit, viscosity and coronary blood flow. *Dis Chest* 1965; 48: 225–232.
11. **Woodward M, Rumley A, Tunstall-Pedoe H, Lowe GD.** Does sticky blood predict a sticky end? Associations of blood viscosity, hematocrit and fibrinogen with mortality in the West of Scotland. *Br J Haematol* 2003; 122: 645–650.
12. **Bhasin S et al.** Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2010; 95: 2536–2559.
13. **Calof OM et al.** Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. *J Geront A Biol Sci Med* 2005; 60: 1451–1457.
14. **Sih R, Morley JE, Kaiser FE, Perry III HM, Patrick P, Ross C.** Testosterone replacement in older hypogonadal men: a 12 months randomized controlled study. *J Clin Endocrinol Metab* 1997; 82: 1661–1667.
15. **Basaria S, Dobs AS.** Risks versus benefits of testosterone therapy in elderly men. *Drugs Aging* 1999; 15: 131–142.

- 16. Viillard JF, Marit G, Mercie P, Leng B, Reiffers J, Pellegrin JL.** Polycythaemia as a complication of transdermal testosterone therapy. *Br J Haematol* 2000; 110: 237–238.
- 17. The Endocrine Society.** Clinical bulletins in andropause: benefits and risks of treating hypogonadism in the aging male. *Endocr Rep* 2002; 2: 1–6.
- 18. Kim YC.** Testosterone supplementation in the aging male. Testosterone supplementation in the aging male. *Int J Impot Res* 1999; 11: 343–352.
- 19. Dobs AS, Meikle AW, Arver S, Sanders SW, Caramelli KE, Mazer NA.** Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. *J Clin Endocrinol Metab* 1999; 84: 3469–3478.
- 20. Bassil et al,** publisher and licensee Dove Medical Press Ltd. This is an Open Access article which permits unrestricted non commercial use, provided the original work is properly cited. *Ther Clin Risk Manag* 2009; 5: 427–448.
- 21. Li H, Benoit K, Wang W, Motsko S.** Association between Use of Exogenous Testosterone Therapy and Risk of Venous Thrombotic Events among Exogenous Testosterone Treated and Untreated Men with Hypogonadism. *J Urol* 2016; 195 (4P1): 1065–1072. Doi:10.1016/j.juro.2015.10.134. Epub 2015 Oct 31.
- 22. Snyder PJ, Peachey H, Hannoush P, Berlin JA, Loh L, Lenrow DA.** Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab* 1999; 84: 2647–2653.
- 23. Coviello A, Kaplan B, Lakshman K, Chen T, Singh A, Bhasin S.** Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. *J Clin Endocrinol Metab* 2008; 93: 914–919.
- 24. Maggio M, Snyder P, Ceda G, Milaneschi Y, Luci M, Cattabiani C et al.** Is the haematopoietic effect of testosterone mediated by erythropoietin? The results of a clinical trial in older men. *Andrology* 2013; 1: 24–28.
- 25. Ip FF, Pierro I, Brown R, Cunningham I, Handelsman DJ, Liu PY.** Through serum testosterone predict the development of polycythemia in hypogonadal men treated for up to 21 years with subcutaneous testosterone pellets. *Eur J Endocrin* 2010; 162: 185–390.

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