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### Review Article

# Hematocrit Increase, Reduced Death in Hypogonadal Men: Implications of Testosterone Therapy (TTh) on Anemia and Complete Blood Count and Paradigm Shift of its Risk Factor

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### Abstract

Intervention with Testosterone treatment for up to 18 years, in a prospective data collection shows that long-term treatment with testosterone has significant reduction in mortality [1-3] and increase of hematocrit, which theoretically could increase risk of cardiovascular events, could not be proven [4]. Summarizing results of research results that aimed to throw the light on the relationship between hematocrit and all-cause mortality in men receiving Testosterone therapy in long-term setting [5,6].

**Keywords:** Anemia, Hematocrit, Hemoglobin, Hypogonadism, Testosterone Treatment.

### Key Points

- Can increased hematocrit increase the risk of adverse cardiovascular events?
- TTh can elevate hematocrit level! Can this be harmful?
- What is the treatment impact on Subjects receiving long-term TTh (in this report) with 1000 mg long-acting testosterone undecanoate intramuscular injections have reduced mortality despite relatively high hematocrit up to 52%.

### Testosterone, hematocrit and mortality: What is known about?

No evidence in the literature confirms the assumption that there is a link between cardiovascular disease (especially venous thromboembolism) and elevated level of hematocrit [4,7]. While some population studies suggest that high hematocrit is associated with increased risk of venous thromboembolism [8], as well as cardiovascular diseases and all-cause mortality [9] this was assumed based on explained by the presence of other medical conditions that cause both a high hematocrit and venous thrombosis or cardiovascular disease [7]. The Scottish Heart Health Extended Cohort

Study, hematocrit was significantly associated with cardiovascular disease events and mortality, however after considering and adjusting for lipids, blood pressure, type 2 diabetes, smoking status, family history of cardiovascular disease and fibrinogen, the association disappeared [10].

There is a paucity of data on the ratio between hemoglobin and hematocrit. In most individuals, hematocrit (expressed as a percentage) is about 3 times the hemoglobin value (expressed in g/dL, mg% or mg/100ml). Further studies needed to understand changes in hemoglobin, hematocrit and the

hemoglobin/hematocrit ratio during testosterone therapy, and how these changes are associated with various outcomes, such as mortality.

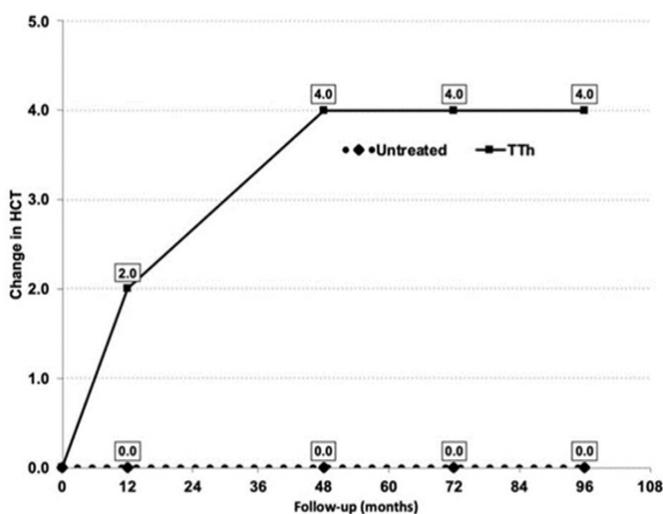
### What is this research adding to what we know?

These current data in text and references list are presenting investigation results to gain a better understanding of the clinical impact of increased hematocrit during TTh in men with hypogonadism, the relationship between baseline hematocrit, change in hematocrit over time, and all-cause mortality in 737 men who had been diagnosed with functional hypogonadism (serum total testosterone  $\leq 12.1$  nmol/L and symptoms of testosterone deficiency).

Testosterone therapy with testosterone undecanoate injection 1000 mg was started in 353 men, whereas the remaining 384 men who declined testosterone therapy served as a control group. Change in hematocrit, hemoglobin and hematocrit/hemoglobin ratio after 12, 48, 72, and 96 months of treatment with testosterone undecanoate injection was analyzed, as well as mortality.

Hematocrit levels show significant increase (+4% at month 96) in men receiving TTh. This increase occurred during the first 48 months, as illustrated in figure 1. Final assessment (month 96) resulted mean hematocrit was 49% (range 47-51%). No subject had hematocrit above 52%. No change in hematocrit noted so far in men not receiving TTh.

From Strange RC, König CS, Ahmed A, et al. Testosterone Therapy: Increase in Hematocrit is Associated with Decreased Mortality. *Androgens: Clinical Research and Therapeutics*. 2021/12/01 2021;2(1):150-159. HCT, hematocrit; TTh, testosterone therapy; TTh group = 353 men; Untreated group: 384 men



**Figure 1:** Change in hematocrit at 12, 48, 72 and 96 months in men receiving testosterone therapy vs. untreated men.5

Among subjects under TTh, a surprising finding was that those who died during the follow-up had significantly ( $p=0.021$ ) lower hematocrit than men who survived, and baseline hematocrit and change in hematocrit were inversely associated with mortality, even after adjustment for age. Men with final hematocrit above 49% up to 52% suffered lower mortality than men with hematocrit 46-49%. The higher the baseline hematocrit and the greater the increase in hematocrit during testosterone therapy (up to 52%), the lower the risk of mortality. Results were the same when the group of testosterone-treated men was stratified by type 2 diabetes prevalence. These research outcomes suggest that there is a reduction in mortality risk takes place, even at relatively higher hematocrit levels up to 52%.

Notworthy, the hematocrit/hemoglobin ratio increased significantly ( $p < 0.0001$ ) at all time points compared to baseline. It could be, possibly, due to increased red blood cell life span, as suggested by the investigators of the T4DM study.

### Conclusive Discussion

The present study showed that increased hematocrit (up to 52% at final assessment) was independently associated with reduced mortality [5]. This confirms the current clinical guidelines recommendation of using 54% as a threshold for change in management of men receiving testosterone therapy (e.g. dose reduction or therapeutic phlebotomy) [11-15]. It should be kept in mind that dehydration can cause a temporary elevation in hematocrit [16] and therefore a high hematocrit reading should be confirmed in a second blood test, ensuring the patient is in a well hydrated state, before action is taken.

The finding that the hematocrit elevation stabilized at month 48 is reassuring [5] This is congruent with results from another long-term real-world evidence study, in which treatment with testosterone undecanoate injection for 10 years increased hematocrit by 3.6% [3].

Meta-analyses of randomized controlled trials which showed that despite a higher incidence of elevated hematocrit in men receiving testosterone therapy compared to placebo, no difference in clinical adverse events were reported [17,18]. The present study provides reassurance regarding the safety of testosterone therapy and suggests that long-term TTh can reduce mortality even in the context of relatively high hematocrit levels. Support for this comes from other long-term real-world evidence studies showing that despite increases in hematocrit, there was no increased risk for venous thromboembolism, myocardial infarction, stroke, or mortality [2,19].

A possible reason for the lack of adverse effects of testosterone-induced elevation of hematocrit in men receiving testosterone therapy could be that the association between testosterone therapy and increased hemoglobin and hematocrit may be mediated by other mechanisms besides erythropoiesis. For example, it has been shown that testosterone

therapy may increase red blood cell lifespan [20]. In healthy subjects, there is a loss of 20% of erythrocyte hemoglobin, a phenomenon that increases during the second half of red blood cell life span [21,22]. In the context of increased red blood cell life span, the loss of hemoglobin would increase, which in turn would increase the hematocrit/hemoglobin ratio. This could impact not only the accuracy of HbA1c - for more information see our report of the T4DM study [23] - but possibly also the link between hematocrit and adverse outcomes. For example, the increased red blood cell lifespan during testosterone therapy may occur as a result of beneficial testosterone-induced modification of the composition and fluidity of red blood cell membranes, contributing to improvement in blood rheology and possibly reduced thrombosis risk [24] If this is the case, an increased hematocrit/hemoglobin ratio could be a marker for beneficial outcomes in the context of hematocrit elevation during testosterone therapy. In contrast to the present study, where no subject receiving treatment with testosterone undecanoate injection experienced hematocrit above 52%, in the T4DM study 23 22% of subjects (106 men) in the testosterone group had at least one reading of hematocrit  $\geq 54\%$ , compared to 1% (6 men) in the placebo group. A possible explanation for this is that the T4DM study was conducted in Australia, where the prevalence of dehydration due to hot weather is relatively common, which may have contributed to rising hematocrit to  $\geq 54\%$ . In contrast, the registry study was conducted in Germany, where dehydration prevalence due to hot weather is likely non-existent. Another possible explanation is that blood testing for measurement of hematocrit was done at different time points between injections. This study has a limitation as registry design. Furthermore, the sample is relatively small. Large scale, placebo-controlled studies with large cohort over prudential period is needed to robustly confirm these results.

More studies, both randomized controlled trials and real-world evidence studies, are needed to further investigate the association between hematocrit and mortality, and whether testosterone-induced hematocrit elevation is a cause of concern or just an innocent bystander [7].

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