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Testosterone Decreases Erythropoietin Stimulating Agent Use in Men on Hemodialysis

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Abstract

Objective: Erythropoiesis stimulating agents (ESAs) are required in most of the patients with end-stage renal disease (ESRD) for treatment of anemia. Subnormal testosterone concentrations are very common in men with ESRD. Since testosterone is erythropoietic, testosterone replacement therapy (TRT) has the potential to increase hemoglobin and decrease ESA usage in hypogonadal men with ESRD.

Methods: We reviewed charts of men on hemodialysis with subnormal testosterone concentrations at a dialysis center. The hemoglobin concentrations and ESA doses (adjusted for hemoglobin and body weight) of those who were treated with TRT ($n=10$) were compared with those who did not receive TRT ($n=10$).

Results: The average duration of TRT was 18 ± 2 weeks. Hemoglobin concentrations increased by 1.2 ± 1.3 g/dL in the treated group but did not change in the untreated group ($p=0.02$ for comparison between groups). ESA doses decreased by 20% in the TRT group but did not change in the untreated group ($p=0.03$ for comparison between groups). Four out of the 10 men in the TRT group were no longer on ESAs by the end of the study, whereas all men in the untreated group continued to require ESAs throughout the study.

Conclusion: TRT increases hemoglobin concentrations and reduces the requirement of ESAs in men with subnormal testosterone concentrations on hemodialysis.

Keywords: testosterone; anemia; renal failure; erythropoietin; hemodialysis; hypogonadism

Introduction

Anemia is present in almost all patients with end-stage renal disease (ESRD).¹ Currently, >90% of ESRD patients are on erythropoiesis stimulating agents (ESAs).² Use of ESAs to correct the severe anemia in these patients improves physiological and clinical parameters and quality of life. Although ESAs are very effective in raising hemoglobin concentrations, studies have shown that higher ESA doses tend to increase all-cause mortality.³ ESA therapy is usually started if the hemoglobin is <10 g/dL with the goal of maintain-

ing hemoglobin between 10 and 12 g/dL. Targeting higher hemoglobin levels with ESAs results in an increased risk of cardiovascular events.³ In fact, ESAs underwent a label change mandated by FDA in 2011 to reflect that association.⁴ These adverse effects may be directly mediated by the hemodynamic or rheological effects of hemoglobin. However, studies have also shown that higher ESA doses increase all-cause mortality independently of hemoglobin.⁵ It is possible that some patients are exposed to higher doses of ESAs due to "ESA hyporesponsiveness," which may

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reflect a higher underlying comorbidity burden. One of the causes of anemia in renal failure as well as hyporesponsiveness to ESAs in men is low testosterone concentrations.⁶

Subnormal testosterone concentrations are very common in men with ESRD.^{7–12} In one study of 239 patients referred to a renal center, the prevalence of subnormal total testosterone concentrations (<288 ng/dL or 10 nmol/L) was 17%, 17%, 34%, 38%, and 57% in chronic kidney disease stages 1, 2, 3, 4, and 5, respectively.⁹ The prevalence is even higher in patients with ESRD and type 2 diabetes.¹³ We have shown that 79% of diabetic men with ESRD have subnormal free testosterone concentrations (<5 ng/dL or 0.174 nmol/L). In comparison, the prevalence of subnormal testosterone concentrations was 37% in diabetic men with normal estimated glomerular filtration rate (>60 mL/[min · 1.73 m²]).¹³ There is a direct correlation between testosterone concentrations and hemoglobin in men with type 2 diabetes and renal insufficiency.¹⁴ In men on hemodialysis, testosterone concentrations are inversely related to their ESA doses.⁶ Testosterone replacement therapy (TRT) is well known to increase hemoglobin concentrations in men with and without renal failure.^{15,16} Before the advent of ESAs, androgens had been used to treat anemia in men with renal failure. However, the effect of TRT on hypogonadal men on dialysis and receiving ESA therapy has not been evaluated.

Based on that mentioned, we planned a chart review of patients at our dialysis center who received TRT and analyzed their ESA therapy. We hypothesized that TRT will increase hemoglobin concentrations and reduce the requirement of ESAs in men with ESRD.

Methods

We reviewed the charts of all men with ESRD who had testosterone concentrations measured between January 2016 and December 2019 at a hemodialysis center (Fig. 1). It has been our clinical practice since 2016 to screen all men with ESRD for hypogonadism.¹³ Those men who have subnormal testosterone are referred to an endocrinologist for further workup and discussion about TRT. For the purposes of this analysis, we included men who (1) were between the ages of 18–80 years, (2) currently receiving ESAs, and (3) not receiving TRT before 2016. Forty-nine men received care at our dialysis center during the study period. We excluded two men because they were already on TRT before joining dialysis at our practice. Two men were excluded because they were not receiving ESAs. Twelve men were not interested in being

evaluated for low testosterone. Ten men had normal testosterone concentrations, whereas 23 men had subnormal free testosterone (<5 ng/dL; 0.174 nmol/L) on two separate occasions. These men were evaluated by an endocrinologist. Ten men had luteinizing hormone (LH) <10 IU/L and 12 men had supranormal LH concentrations. None of the patients had severe obstructive sleep apnea, panhypopituitarism, prolactinoma, Klinefelter's syndrome, or congenital causes of hypogonadism. None of the subjects were on opiates or chronic oral steroids. No patients had a history of prostate cancer.

Owing to restrictions of insurance coverage, TRT was prescribed only in the form of intramuscular injections. One man was on warfarin and could not do intramuscular injections. TRT was not started in two men because of elevated prostate specific antigen concentrations. Seven men felt that their symptoms of hypogonadism were not severe enough to try TRT at that time. Thus, 12 men were started on TRT (Fig. 1).

Treated group

We included men who had received TRT for at least 4 months. We have previously shown that TRT for this duration is sufficient to induce erythropoiesis in men without chronic kidney disease (CKD).¹⁵ We defined “study period” as starting from 2 months before the initiation of TRT and continuing for at least 4 months on TRT. Subjects who were hospitalized for a medical illness or surgery, received blood transfusion, or had a change in the type of ESAs during the study period were excluded. One man’s family complained of his aggressive behavior after 1 month of TRT and his therapy was stopped. Another man underwent coronary artery stent placement after 3 weeks of TRT and did not resume TRT. These two men were excluded from the analysis. Hence, data were available from 10 patients.

TRT was given in the form of intramuscular testosterone cypionate. Therapy was started with 200 mg every 2 weeks. The injections were given during scheduled dialysis sessions by the staff nurses. Serum-free testosterone was measured after 2 months of starting TRT to titrate the dose of testosterone injections, if needed. The blood test was done 1 week after an injection. The dose of TRT was adjusted to maintain free testosterone concentrations in the midnormal range (10–18 ng/dL; 0.35–0.63 nmol/L) as per endocrine society guidelines.¹⁸ The dose was increased or decreased in 50 mg per injection increments. The average testosterone dose at the end of the study period was 170 ± 35 mg every 2 weeks.

The average duration of TRT was 18 ± 2 weeks.

Untreated group

Eleven men did not receive TRT and were used as a comparator group. Study period in these men was defined as 2 months before the measurement of testosterone concentrations and 4 months after that. One man had prolonged hospitalization (for 3 weeks) with pneumonia and respiratory failure during the study period and he was not included in the analysis.

Laboratory measurements

Blood tests were performed by clinical laboratories as part of standard of care. Total testosterone concentrations (normal range 250–1100 ng/dL; 8.7–38.2 nmol/L) were measured by liquid chromatography tandem mass spectrometry (LC-MS/MS). A detailed description of the methodology has previously been published.¹⁹ The sensitivity of the assay (limit of quantification), set at a coefficient of variation (CV) of $\leq 20\%$, was

0.3 ng/dL (0.01 nmol/L). The intra-assay CV ranged from 7.6% to 10.8% and interassay CV ranged from 9.8% to 13.4% at total testosterone concentrations between 10 and 1200 ng/dL (0.35–41.7 nmol/L). Tracer equilibrium dialysis is considered the gold standard for measuring free steroid hormone concentrations and this methodology was used to determine the free testosterone concentrations (normal range 5–25 ng/dL; 0.174–0.868 nmol/L) in our subjects. A detailed description of these methodologies has previously been published.¹⁹ Total testosterone was measured by LC-MS/MS and free testosterone was separated by equilibrium dialysis at a commercial laboratory. LH was measured by solid-phase chemiluminescent immunometric assay (IMMULITE 2500; Siemens). Hemoglobin and iron studies were measured by well-established clinical laboratory assays.

Statistical analysis

The aim of this study was to evaluate the change in hemoglobin concentrations and ESA doses after TRT. We defined the baseline period as 8-week period immediately preceding TRT. End of the study period was defined as the last 8 weeks of follow-up.

Two men in the untreated group were on darbepoetin alfa. One man in the treated group was on methoxy polyethylene glycol-epoetin beta. Rest of the patients were on short-acting epoetin alfa, intravenously three times a week. The direction, magnitude, and frequency of epoetin alfa dose adjustments were determined by the level of hemoglobin and the rate of rise or fall of hemoglobin as per the protocol of the dialysis unit. Hemoglobin was measured every 2 weeks. Epoetin alfa was held if the hemoglobin was >12 g/dL. Iron studies (ferritin, iron, and transferrin saturation) were also measured every 4 weeks and iron was replaced intravenously as needed. Iron was replaced weekly unless ferritin was >200 ng/mL, saturation was $>50\%$ or hemoglobin was >13 g/dL.

The primary end point of the study was to compare the change in ESA dose from baseline after TRT. Doses of epoetin beta and darbepoetin in micrograms were converted to equivalent international units of erythropoietin for purposes of tabulation in the analysis. Typically, a conversion factor of 200–400 is used, with higher doses requiring a higher conversion factor.^{20–22} We chose a conversion factor of 300 in our study. ESA equivalent dose is presented as U per week as well as U/kg/Hb/week (adjusted for body weight and hemoglobin) in the following analyses. ESA doses were not normally distributed and were log transformed for

statistical tests. Secondary end points of the study were to compare the change in hemoglobin concentrations, ferritin, iron, transferrin saturation, and iron replacement after TRT. Data are presented as mean $\pm$ standard deviation for normally distributed data (mean $\pm$ standard error in graphs) and median [25th, 75th percentile] for non-normal data. SPSS software (SPSS, Inc., Chicago, IL) was used for the analyses.

The study protocol was approved by the institutional review board of Saint Louis University.

Results

Type 2 diabetes was present in 80% of the men whereas 60% had coronary artery disease. Data on age, body mass index, testosterone concentrations, hematological parameters, and ESA dose in testosterone treated and untreated groups at baseline and end of study are depicted in Table 1.

Hemoglobin concentrations increased by 1.2 ± 1.3 g/dL in the treated group but did not change in the untreated group (0.06 ± 0.48 g/dL, $p = 0.02$ for comparison between groups). The hemoglobin concentrations appeared to start increasing at week 8 and were significantly higher than baseline by week 16 (Fig. 2). As a response to the

increase in hemoglobin, ESA doses decreased in the treated group. The ESA doses (adjusted for body weight and hemoglobin) were lower by 15% at week 12 and by 30% at week 16 (Fig. 3). Overall, the ESA doses were lower by $\sim 20\%$ in the treated group (Table 1) but did not change in the untreated group ($p = 0.03$ for comparison between groups). The change in ESA was not related to the baseline ESA dose in the testosterone treatment group ($r = -0.19$, $p = 0.58$).

Four out of the 10 men in the TRT group were no longer on ESAs by the end of the study, whereas all men in untreated group continued to require ESAs throughout the study ($p = 0.09$ for comparison among groups by Fisher Exact probability test). The average baseline hemoglobin concentration was 10.0 g/dL in the six subjects in the TRT group who continued to require ESAs during the study, whereas it was 10.9 g/dL in the other four subjects who were not on ESAs at the end of the study. Hence the latter four subjects were more likely to reach the threshold hemoglobin concentration of 12 g/dL, beyond which ESA is held in hemodialysis patients. Those four men also had lower baseline ESA doses (5219 vs. 9550 U/week). They went off ESAs after a mean of 7 weeks and did not require ESAs again during the study period.

Table 1. Demographics, Testosterone Concentrations, Iron Studies, and Erythropoiesis Stimulating Agent Dose in Testosterone Treated and Untreated Groups at Baseline and End of Study

	Testosterone (n = 10)			Untreated (n = 10)			p for baseline comparison between groups*
	Baseline	End of study	p	Baseline	End of study	p	
Age (years)	59 $\pm$ 9			58 $\pm$ 7			0.75
Body mass index (kg/m ²)	33.0 $\pm$ 6.0	33.1 $\pm$ 6.3	0.76	30.2 $\pm$ 5.6	30.1 $\pm$ 5.4	0.45	0.30
Weight (kg)	92 $\pm$ 16	93 $\pm$ 16	0.88	94 $\pm$ 27	94 $\pm$ 27	0.44	0.87
Total testosterone (ng/dL; nmol/L)	213 $\pm$ 91; 7.4 $\pm$ 3.2	771 $\pm$ 194; 26.8 $\pm$ 6.7	<0.001	262 $\pm$ 155; 9.1 $\pm$ 5.4			0.39
Free testosterone (ng/dL; nmol/L)	2.8 $\pm$ 1.0; 0.097 $\pm$ 0.035	11.8 $\pm$ 5.6; 0.410 $\pm$ 0.194	0.01	3.0 $\pm$ 1.3; 0.104 $\pm$ 0.045			0.63
LH (IU/L)	19 $\pm$ 24			15 $\pm$ 13			0.69
SHBG (nmol/L)	51 $\pm$ 32			47 $\pm$ 21			0.75
Hemoglobin (g/dL)	10.3 $\pm$ 1.0	11.5 $\pm$ 1.6	0.02	10.5 $\pm$ 0.7	10.6 $\pm$ 0.9	0.69	0.67
Hematocrit (%)	31.0 $\pm$ 2.9	35.0 $\pm$ 4.6	0.01	31.5 $\pm$ 2.2	31.7 $\pm$ 2.6	0.69	0.72
Ferritin (ng/mL)	761 $\pm$ 545	794 $\pm$ 363	0.71	605 $\pm$ 242	563 $\pm$ 296	0.50	0.42
Iron (μ g/dL)	58 $\pm$ 15	47 $\pm$ 18	0.15	59 $\pm$ 34	52 $\pm$ 27	0.69	0.93
Iron saturation (%)	26 $\pm$ 7	26 $\pm$ 11	0.82	24 $\pm$ 11	21 $\pm$ 8	0.28	0.61
TIBC (μ g/dL)	239 $\pm$ 39	233 $\pm$ 32	0.52	238 $\pm$ 55	244 $\pm$ 51	0.37	0.99
UIBC (μ g/dL)	190 $\pm$ 28	191 $\pm$ 25	0.88	185 $\pm$ 43	188 $\pm$ 34	0.46	0.78
ESA dose (U/Kg/Hb/week)	6.05 [4.59, 11.01]	4.93 [0, 13.3]	0.04	15.80 [6.66, 42.04]	21.30 [5.11, 28.87]	0.83	0.26
ESA dose (U per week)	5300 [4438, 14,050]	4950 [0, 15,000]	0.04	15,450 [6188, 30,000]	15,738 [4550, 30,000]	0.43	0.19
Iron dose (mg per week)	42 $\pm$ 19	52 $\pm$ 36	0.52	69 $\pm$ 50	60 $\pm$ 33	0.60	0.13

Within-group comparisons were performed with paired t-test. Between-group comparisons for changes were performed by unpaired t-tests; ESA doses were log transformed for comparison.

$p < 0.05$ is depicted in bold.

ESAs, erythropoiesis stimulating agents; LH, luteinizing hormone; SHBG, sex hormone binding globulin; TIBC, total iron binding capacity; UIBC, unsaturated iron binding capacity.

FIG. 2. Hemoglobin concentrations (mean $\pm$ SE) in treated and untreated groups. Hemoglobin concentrations at each time point are an average of the past 4 weeks. For example, week 12 hemoglobin is an average of weeks 9, 10, 11, and 12. * $p < 0.05$ as compared with 0 weeks. SE, standard error.

FIG. 3. Percentage change in ESA dose (mean $\pm$ SE, U/Kg/Hb/week) from baseline (which is depicted as 100% for both groups). ESA doses at each time point are an average of the past 4 weeks. For example, week 12 ESA dose is an average of weeks 9, 10, 11, and 12. * $p < 0.05$ as compared with 0 weeks and as compared with the untreated group.

Follow-up after the study period

In the treated group, only 3 out of 10 are still continuing TRT. One man died due to complications of graft revision surgery, one got a kidney transplant, two men have moved out of town, and three men have been inconsistent with their follow-up with endocrinology for dose titration and prescriptions.

Discussion

Our data suggest that TRT in hypogonadal men on hemodialysis can decrease requirement of ESAs. This observation is of clinical importance since (1) almost all patients on dialysis therapy are treated with ESAs for anemia and (2) ~50–80% of men with ESRD have subnormal testosterone concentrations.^{9,13} It is remarkable that 40% of the men were able to stop their ESAs all together due to the improvement in hemoglobin concentrations within 4 months.

A few studies have tried to assess the effect of androgens on erythropoiesis in renal failure. Brockenbrough et al. gave transdermal testosterone to 40 patients who were on hemodialysis and being treated with ESAs.²³ However, the treatment dose was inadequate and serum testosterone concentrations did not increase significantly. ESA dose also did not change. A study of intramuscular TRT for 6 months in men with hemodialysis showed improved symptoms of hypogonadism but did not change the hemoglobin concentrations.²⁴ ESA doses were not analyzed in that study. Testosterone concentrations during the treatment increased from 135 ng/dL (4.7 nmol/L) to only 300 ng/dL (10.4 nmol/L, low end of normal range). In contrast, the post-treatment testosterone concentrations in our study were 771 ng/dL (26.8 nmol/L). Thus, adequate replacement allowed us to detect a change in hemoglobin and ESAs. To the best of our knowledge, there are no other trials with TRT, but a few investigators have studied other androgens (nandrolone and oxymetholone) in addition to ESA treatment. In a randomized placebo controlled trial of oral oxymetholone in combination with ESAs in patients on peritoneal dialysis, hemoglobin and lean body mass in patients improved but significant increases in liver enzymes were also observed.²⁵ Intramuscular nandrolone treatment in combination with low dose human recombinant erythropoietin in men on hemodialysis showed an increase in hematocrit by 8% after 3²⁶ or 6 months²⁷ of treatment. In comparison, the increase in hematocrit was ~3% in the group who received low dose ESAs without nandrolone. A small study with nandrolone in six patients did not show

an increase in hematocrit after nandrolone therapy for 4 months.²⁸ Two of those six patients stopped nandrolone due to occurrence of acne. The dose of human recombinant erythropoietin was not adjusted in these studies to achieve a particular hemoglobin target. A Cochrane review in 2014 found a paucity of studies on this topic and insufficient evidence to recommend androgen therapy for improving renal failure-associated anemia.²⁹ In view of the large magnitude of the problem and accompanying economic implications, it is surprising that the effect of testosterone on anemia of renal failure has not been investigated systematically. Unlike oral androgens, administration of testosterone by alternative routes (intramuscular and transdermal) does not lead to hepatotoxicity.³⁰

The increase in hemoglobin after TRT in our study is similar to the increase noted in men without renal insufficiency.^{30,31} Meta-analyses show that TRT usually increases hemoglobin by 0.8 g/dL.¹⁶ This effect is dose dependent and is evident within a few weeks of starting TRT.^{32,33} Recent studies have shed some light on the mechanisms that underlie testosterone's erythropoietic effect. Testosterone increases erythropoietin and enhances the mobilization of iron from its stores by suppressing hepcidin. This induces an increase in the expression of ferroportin in macrophages.³⁴ In the presence of erythropoietin, this translates into increased iron incorporation into red blood cells and erythropoiesis.^{35,36} We have previously shown that TRT in hypogonadal men with type 2 diabetes leads to a significant increase in plasma erythropoietin concentrations, reduction in plasma hepcidin concentration, increase in ferroportin expression, and increase in transferrin receptor in mononuclear cells.¹⁵ In our study, we did not observe an increase in the dose of iron infusion or a change in ferritin after TRT. Future studies need to investigate whether TRT decreases hepcidin concentrations and increases ferroportin in men with renal failure.

Our study suffers from many limitations inherent in a retrospective study. The two groups were not similar at baseline. Specifically, the median ESA doses were much higher in the untreated group than in the treated group. This is likely due to chance since the hemoglobin levels were similar in the two groups. A major difference in their comorbidities or iron stores was also not apparent. We did not find a relationship between the baseline ESA dose and change in ESAs after testosterone treatment. However, interpretation of such relationship is severely limited due to the small sample size. It is not clear whether testosterone-induced reduction in ESA dose

would be more or less likely in those with high ESA doses. The short study duration of 4 months is also a significant limitation in our report. It is possible that longer duration of treatment may have a greater magnitude of effect in the reduction of ESA dose and the number of patients requiring ESAs. Nevertheless, we found that the dose of ESAs decreased by ~20% after TRT for 4 months. This can have significant financial implications for health care of ESRD patients. ESAs are the single largest drug expenditure program in Medicare, with total annual expenditures >2 billion dollars for dialysis patients.⁴ The annual average cost per person of ESAs to Medicare is ~\$6000.³⁷ Intramuscular testosterone is generic and costs ~\$200 per patient per year. A 20% reduction in ESA requirements would potentially save \$1000 per person per year. There are currently 267,000 men in the United States on dialysis.³⁸ Conservatively assuming that 60% of men with ESRD are hypogonadal and that only half of them would get treated, TRT will reduce the annual expenditure on ESAs by \$80 million. This analysis is an underestimate because it does not include nondialysis CKD 4 and 5 patients who are receiving ESAs. In addition, an increase in hemoglobin can positively impact the clinical state and quality of life. Although we did not collect data on these parameters in this study, these would be important to measure in a prospective trial.

Conclusion

We conclude that TRT increases hemoglobin concentrations and reduces the requirement of ESAs in hypogonadal men on hemodialysis. These preliminary short-term data need to be confirmed in trials involving a longer duration of therapy and larger number of subjects.

Author Disclosure Statement

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Abbreviations Used

CKD	= chronic kidney disease
CV	= coefficient of variation
ESAs	= erythropoiesis stimulating agents
ESRD	= end-stage renal disease
LC-MS/MS	= liquid chromatography tandem mass spectrometry
LH	= luteinizing hormone
SE	= standard error
TRT	= testosterone replacement therapy

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