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Original Article

Effect of Testosterone Replacement on Anemia and Quality of Life amongst Patients on Maintenance Hemodialysis

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ABSTRACT

Objective: To study the effect of Testosterone replacement therapy in improving the level of anemia and quality of life in males undergoing hemodialysis due to chronic renal failure (CRF).

Study Design: Randomized controlled trial (ANZCTR Trial ID ACTRN12624001137583).

Place and Duration of Study: Department of Medicine, Pak Emirates Military Hospital, Rawalpindi, Pakistan from Jan 2024 to Jun 2024.

Methodology: 160 patients were randomized into two groups, one to receive Testosterone supplementation therapy (Group A) (n=80) and one to receive placebo (Group B) (n=80). Primary variables studied were improvement in Aging Males Symptoms (AMS) scores and Hb levels. Secondary variables were changes in Testosterone levels (free and total serum levels).

Results: 160 patients were randomized into two groups, one to receive Testosterone supplementation therapy (Group A) (n=80) and one to receive placebo (Group B) (n=80). Mean hemoglobin levels between both groups were 8.38±1.12 versus 8.34±1.12 g/dl before therapy (p=0.834), 8.13±1.12 versus 8.10±1.16 g/dl at 3 months of therapy (p=0.891) and 8.10±1.10 versus 8.09±1.17 g/dl at 6 months of therapy (p=0.945). Median (IQR) values for total AMS scores between both groups were 36.00 (3.00) versus 36.00 (2.00) before therapy (p=0.954), 34.00 (2.00) versus 36.00 (4.00) at 3 months of therapy (p<0.001) and 31.00 (3.00) versus 36.00 (4.00) at 6 months of therapy (p<0.001).

Conclusion: We conclude that phycological and somato-vegetative variables in patients were considerably improved with no improvement in sexual dysfunction and levels of hemoglobin in these patients.

Keywords: Anemia, hemodialysis, Replacement, renal failure, Testosterone, quality.

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INTRODUCTION

Testosterone is one of the major male hormones regulating a diverse system of functions especially in males.[1] A decrease in circulating levels is associated with sexual dysfunction, decreased cognition, loss of bone minerals resulting in osteoporosis, and psychological disturbances including reduced cognitive function and moderate to severe depression.[2] Studies also implicate the role of Testosterone in decreasing insulin sensitization and adverse affecting the lipid profile causing decrease in high density lipoproteins (HDLs) and increase in cholesterol and low density lipoproteins (LDLs).[3] The metabolic issues associated with decrease in the circulating hormone are associated with increased incidence of developing diabetes, hypertension, cardiovascular issues resulting in considerable morbidity in patients.[4] Newer studies have linked low serum Testosterone levels with chronic kidney disease. Studies have also found causal links with morbidity as well as mortality in patients with low Testosterone levels affecting the cardiovascular system. The immune effects of low Testosterone levels have also been found to adversely affect the immune rejection in patients undergoing renal transplantation for renal failure.[5] Low levels are also associated with poor protein synthesis affecting both the muscle mass and immune responses in patients.[6]

Our study is designed in the context of newer studies having reported that low Testosterone levels are associated with adverse outcomes and all-cause mortality in male patients. Studies have also reported that dialysis patients present with considerably lower levels of Testosterone that their counterparts.[7] Local studies report that the incidence of patients presenting for dialysis is increasing every year. This is attributed to increase in co-morbidities as the chief issue in our country, the most common being diabetes since Pakistan ranks among the top five countries with the highest population suffering from diabetes.[8] The falling levels of Testosterone in hemodialysis patients

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due to chronic kidney disease are directly affected by increasing age and result in multifactorial changes collectively encompassing the late onset hypogonadism (LOH) syndrome in males. Studies show that replacement of Testosterone in these patients results in improvement in depressive episodes, improved sexual drive and improvement in immune profiles. The TRAVERSE trial reported that replacement therapy is also beneficial in correcting anemia associated with old age.[9]

Since chronic renal failure is associated with osteoporosis, anemia and immune issues especially in older males with LOH symptoms, we aim our study to evaluate the effect of Testosterone replacement therapy (TRT) in improvement of anemia as well as effect on the quality of life assessed by the aging males' symptoms (AMS) scores in older males suffering from LOH since studies on the subject are scarce in our demographic setups and this study would help define treatment guidelines in this specific sub set of patients.[10]

METHODOLOGY

This randomized controlled trial was carried out at the Department of Medicine, Military Hospital, Rawalpindi Pakistan from January 2024 to June 2024 after approval from the ethical review board (vide letter no. A/28/ERC/598/23 and ANZCTR Trial ID ACTRN12624001137583). Minimal sample size was calculated keeping the confidence interval at 95%, power of test at 80% with the anticipated improvement in AMS scores in patients with Testosterone replacement therapy versus those without therapy at 86% versus 32% respectively.[11] Minimum sample size came out to be 10 patients for each group. We included 80 patients randomized in each of the two groups making the total study sample of 160 patients using simple random sampling in one of the two groups after completing requirements of the inclusion criteria furnished.

Inclusion Criteria: Included all male patients over the age of 40 years, with late onset hypogonadism evidenced by low serum Testosterone levels (<250 mg/dl) with anemia (Hb low for age) and AMS scores of >27 assessed pre-study undergoing hemodialysis for chronic renal failure (CKD grade 5 and above with a disease duration of more than 2 years requiring dialysis 2-3 times a week)

Exclusion Criteria: Excluded patients with acute renal failure on dialysis, patients with uncontrolled diabetes or hypertension, patients with metastatic diseases, patients already on some form of Testosterone replacement therapy, patients on supplementation therapy for anemia, patients lost to follow-up or patients not giving consent to be included in the study

The study method included all patients as per the inclusion criteria furnished. The patients were randomized into two groups, one to receive Testosterone supplementation therapy (Group A) (n=80) and one to receive placebo (Group B) (n=80). Before inclusion in the study protocol, all patients had their blood panel and initial AMS scores done to see whether they met the inclusion criteria to be included in the study. The AMS scoring system included 17 question items encompassing psychological, sexual and somato-vegetative areas with higher scores corresponding to greater debility in quality of life defined as low (17-26 points), mild (27-36), moderate (37-49) and severe (>50 points).

This was a double blind study. Blood complete picture, total serum Testosterone and free serum Testosterone levels were taken in all patients and AMS scores were endorsed by a resident medicine unaware of the study protocol or its study outcomes pre-intervention. All patients evaluated and meeting the inclusion criteria were then counseled regarding the study protocol, addressing all ethical concerns with all patients blinded to which treatment group they were assigned to prevent bias. They were also counselled to follow up for a period of six months as requirement for the study.

Patients in Group A (n=80) received supplementation of Testosterone enantholactam acid ester 250 mg administered as intramuscular injection every two weeks, before the appointment for the next dialysis cycle. Patients in Group B (n=80) received normal saline as placebo in similar doses and timeframe as Group A to ensure blinding and prevent bias. Follow-up visits included measurement of serum total Testosterone, free serum Testosterone and Hb levels on Blood complete picture. AMS scores were re-assessed at 3 months and 6 monthly follow-up visits respectively. The questionnaire consisted of 17 questions to assess psychological, sexual and somatovegetative symptoms with scores of 0-26 suggesting no significant symptoms, 27-36 suggesting mild symptoms, 37-49 suggesting moderate symptoms and scores more than 50 suggesting severe symptoms of testosterone deficiency. Serum testosterone levels were analyzed using liquid chromatography-tandem mass spectrometry in the lab. Primary variables

studied were improvement in AMS scores and Hb levels. Secondary variables were changes in Testosterone levels (free and total serum levels) (Figure).

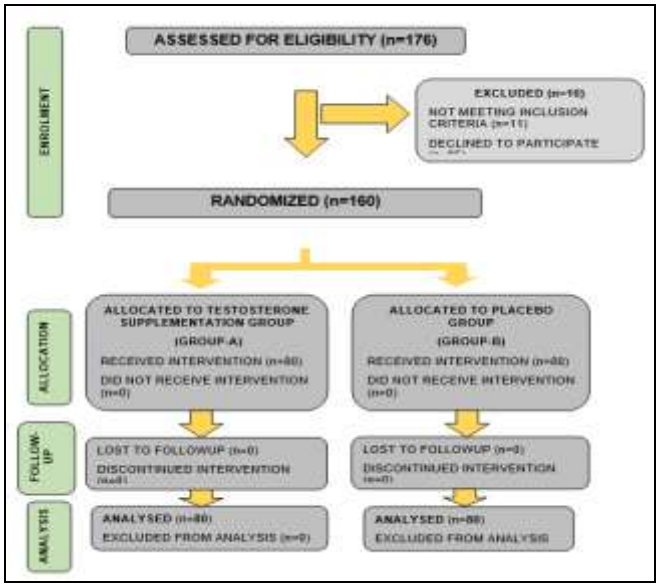

Figure: Patient Flow Diagram

All statistical calculations were performed using Statistical Package for the Social Sciences (SPSS) 26.0. Demographic data were statistically described in terms of Mean±SD, frequencies, and percentages. t-test was used to compare statistically significant demographic means and Chi-square test was used for frequency variables. Normality of data was checked using Shapiro Wilk test. Independent samples t-test was used to compare secondary variables while Median values for AMS scores were compared using Mann-Whitney U test. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

A total of 160 patients were included in the final study protocol divided into the treatment group receiving Testosterone (Group A) (n=80) and the placebo group receiving normal saline (Group B) (n=80). Mean age of patients was 59.04±6.55 years in Group A versus 59.64±6.31 years in Group B (*p*=0.556). Mean BMI was 22.35±2.03 kg/m² in Group A versus 21.98±1.82 kg/m² in Group B (*p*=0.222) (Table-I).

Laboratory investigations done showed that mean total Testosterone levels between both groups before therapy were 4.48±0.40 ng/ml versus 4.44±0.40 ng/ml (*p*=0.555), levels at 3 months of therapy were 10.70±0.41 ng/ml versus 4.40±0.39 ng/ml (*p*<0.001) and levels done at 6 months of therapy were 10.73±0.43 versus 4.48±0.39 ng/ml (*p*<0.001). Mean values of free serum Testosterone levels between both groups were 5.53±0.46 pg/ml versus 5.50±.046 pg/ml before therapy (*p*=0.646), 21.30±0.75 versus 5.46±0.45 pg/ml at 3 months of therapy (*p*<0.001) and 19.87±0.54 versus 5.64±0.47 pg/ml at 6 months after therapy (p<0.001). Mean hemoglobin levels between both groups were 8.38±1.12 versus 8.34±1.12 g/dl before therapy (*p*=0.834), 8.13±1.12 versus 8.10±1.16 g/dl at 3 months of therapy (*p*=0.891) and 8.10±1.10 versus 8.09±1.17 g/dl at 6 months of therapy (*p*=0.945) (Table-II).

Table-I: Demogrpahic Parameters Between Both Groups (n=160)

Variables	Group-A (n=80)	Group-B (n=80)	*p*-value
Mean Age (Years)	59.04±6.55	59.64±6.31	0.556
Mean BMI (kg/m²)	22.35±2.03	21.98±1.82	0.222

Table-II: Comparison of Testosterone and Hemoglobin Levels Before and After Therapy Between Testosterone Supplementation and Placebo Groups (n=160)

Variables	Group-A (n=80)	Group-B (n=80)	*p*-value
Total Testosterone (ng/ml)			
Before Therapy	4.48±0.40	4.44±0.40	0.555
At 3 Months	10.70±0.41	4.40±0.39	<0.001
At 6 Months	10.73±0.43	4.48±0.39	<0.001
Free Serum Testosterone (pg/ml)			
Before Therapy	5.53±0.46	5.50±0.46	0.646
At 3 Months	21.30±0.75	5.46±0.45	<0.001
At 6 Months	19.87±0.54	5.64±0.47	<0.001
Mean Hemoglobin Level (g/dl)			
Before Therapy	8.38±1.12	8.34±1.12	0.834
At 3 Months	8.13±1.12	8.10±1.16	0.891
At 6 Months	8.10±1.10	8.09±1.17	0.945

Median values for total AMS scores between both groups were 36.00 (3.00) versus 36.00 (2.00) before therapy (*p*=0.954), 34.00 (2.00) versus 36.00 (4.00) at 3 months of therapy (*p*<0.001) and 31.00 (3.00) versus 36.00 (4.00) at 6 months of therapy (*p*<0.001). The psychological part of the scoring system showed median values of 8.00 (1.00) versus 8.00 (1.00) before therapy (*p*=0.433), values of 6.00 (1.00) versus 8.00 (2.00) at 3 months of therapy (*p*<0.001) and 5.00 (0.00) versus 8.00 (1.00) at 6 months of therapy between both groups (*p*<0.001). The somato-vegetative part of the scoring system showed median values of 15.00 (2.00) versus 15.00 (2.00) before therapy (*p*=0.834), values of 14.00 (1.00) versus 15.00 (2.00) at 3 months of therapy (*p*<0.001) and 13.00 (1.00) versus 15.00 (2.00) at 6 months of therapy (*p*<0.001) between both groups. The

part of the scoring system denoting sexual improvement showed values of 15.00 (2.00) versus 15.00 (2.00) before therapy (p=0.801), values of 14.00 (1.00) versus 14.00 (1.00) at 3 months of therapy (p=0.693) and values of 13.00 (1.00) versus 13.00 (1.00) at 6 months of therapy (p=0.948) between both groups (Table-III).

Table-III: Comparison of AMS Scores before and after Therapy between Testosterone Supplementation and Placebo Groups (n=160)

Variables	Group-A (n=80) Median (IQR)	GROUP-B (n=80) Median(IQR)	*p*-value
Total AMS Score			
Before Therapy	36.00(3.00)	36.00 (2.00)	0.954
At 3 Months	34.00 (2.00)	36.00 (4.00)	<0.001
At 6 Months	31.00 (3.00)	36.00 (4.00)	<0.001
AMS-Psychological Score			
Before Therapy	8.00 (1.00)	8.00 (1.00)	0.433
At 3 Months	6.00 (1.00)	8.00 (2.00)	<0.001
At 6 Months	5.00 (0.00)	8.00 (1.00)	<0.001
AMS-Somatovegetative Score			
Before Therapy	15.00 (2.00)	15.00 (2.00)	0.834
At 3 Months	14.00 (1.00)	15.00 (2.00)	<0.001
At 6 Months	13.00 (1.00)	15.00 (2.00)	<0.001
AMS-Sexual Element Score			
Before Therapy	15.00 (2.00)	15.00 (2.00)	0.801
At 3 Months	14.00 (1.00)	14.00 (1.00)	0.693
At 6 Months	13.00 (1.00)	13.00 (1.00)	0.948

DISCUSSION

The study concluded that while Testosterone supplementation therapy considerably improved the phycological and somato-vegetative variables for our patient group, there was no statistically significant improvement in sexual issues and the degree of anemia in these patients' undergoing dialysis. The non-availability of quality healthcare and delay in diagnosis is also linked to more patients being impacted by the renal complications of the disease. Compared to the previous decade, survival with chronic renal disease has increased especially in the developing world, and associated disturbances which can affect mortality need to be addressed to ensure better survival and effective patient care.[12]

Multiple studies have reported that chronic kidney disease (CKD) is associated with decreasing levels of Testosterone and are associated with poor outcomes in patients undergoing dialysis. The associated sexual dysfunction is also reported by many patients, but reports suggest that due to the increasing age, multiple other factors come into play in improving the specific cause apart from Testosterone levels which include hormonal issues, renal disease associated deficiency of zinc and diabetes associated peripheral vascular disease.[13] The impact of testosterone supplementation on sexual dysfunction in patients with end-stage renal disease or those who have undergone transplants remains a topic of debate, with research indicating mixed results. A key consideration is whether testosterone can serve as a viable therapeutic target for men undergoing hemodialysis and if there exists a critical period for influencing treatment outcomes. Therefore, this study aimed to explore the effects of testosterone supplementation therapy in men who are on hemodialysis.

Studies have reported that low Testosterone levels are associated with falling levels of hemoglobin in patients.[14] Our study found no statistically significant difference in improving the levels of hemoglobin in patients undergoing Testosterone therapy. While the levels were considerably improved and the psychological and somato-vegetative elements were improved significantly, longer treatment protocols may attain improvement in levels in these patients for which we recommend further studies. Despite these negative results, we still strongly propose Testosterone replacement therapy in patients with low levels undergoing dialysis since improvement in AMS scores in these patients are associated with a better quality of life.[15]

Studies done by Carrero *et al*., also concluded that low Testosterone levels are implicated in causing decreased sensitivity to erythropoiesis stimulating agents especially in men with chronic kidney disease and this can indirectly affect the levels of circulating hemoglobin in these patients.[16] Further studies are warranted in our local demographic setups to have more conclusive results to establish this important causal relationship. The study also identifies hypogonadism as an additional issue causing resistance to erythropoiesis stimulating agents. Other studies done by McCollough et al also concluded that in patients with cardiorenal syndrome suffering from chronic kidney disease, low Testosterone levels have been implicated in causing anemia.[17] The results of study were concluded over a longer duration of 3 years and long term follow-up in our study may provide evidence of statistically significant improvement in hemoglobin levels in our patients

which were not seen in the 6 month duration of our study.

The findings from the study and corresponding literature suggest that there are no statistically significant differences in hemoglobin levels when comparing the placebo group to those receiving testosterone supplementation among patients undergoing dialysis. This observation is particularly noteworthy given that all participants in the study had previously been treated with erythropoietin-stimulating agents, which are commonly used to manage anemia in patients with chronic kidney disease18. The lack of significant changes in hemoglobin levels raises important questions about the role of testosterone in this specific patient population. It may indicate that the testosterone levels achieved through supplementation were not sufficient to elicit a measurable impact on hemoglobin production or that the underlying mechanisms of anemia in dialysis patients are complex and not solely dependent on testosterone levels. Furthermore, the findings suggest that a higher baseline testosterone level might be necessary to observe any potential clinical benefits in men undergoing hemodialysis. Additionally, the study raises the possibility that prolonged testosterone therapy in male hemodialysis patients could lead to gradual improvements in hemoglobin levels over time. This suggests that while immediate effects may not be evident, sustained testosterone treatment could potentially enhance erythropoiesis and improve anemia management in this population. Long term studies have shown this particular benefit and our demographic area could use this long term follow-up as treatment guideline in this patient population.[19] Overall, these findings highlight the need for further research to explore the optimal dosing and duration of testosterone therapy, as well as its long-term effects on hemoglobin levels and overall health outcomes in dialysis patients. Understanding the interplay between testosterone, erythropoiesis, and anemia in this context could lead to more effective treatment strategies for managing anemia in men undergoing hemodialysis. The study recommends Testosterone replacement therapy in patients with low levels undergoing dialysis since improvement in AMS scores in these patients are associated with a better quality of life.

LIMITATIONS OF STUDY

Our study found no statistically significant difference in improving the levels of hemoglobin in patients undergoing Testosterone therapy. While the levels were considerably improved and the psychological and somato-vegetative elements were improved significantly, longer treatment protocols may attain improvement in levels in these patients for which we recommend further studies.

CONCLUSION

We conclude that phycological and somato-vegetative variables in patients were considerably improved with no improvement in sexual dysfunction and levels of hemoglobin in these patients.

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MHL & ARA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

QUAA & MNAK: Conception, data analysis, drafting the manuscript, approval of the final version to be published.

HB & MUY: Data acquisition, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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