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Prostate safety events during testosterone replacement therapy in men with hypogonadism.A randomized clinical trial.

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Abstract: There are concerns about potential adverse events on the prostate, which remain majorobstacles, especially when prescribing testosterone replacement therapy (TRT) in men withhypogonadism. This study explores prostate safety events using a randomized controlled design inhypogonadal men on testosterone replacement therapy. A total of 150 subjects enrolled wererandomly assigned into either a TRT group or a placebo arm and were evaluated at a 6-monthtreatment period evaluation after baseline. The primary endpoints included prostate-specificantigen, prostate volume, and adverse events. Data show that the TRT participants had a significant regression in PSA levels (mean difference: 1.5 ng/mL, $p < 0.01$) compared to indications fromplacebo. On the other hand, there were no statistically significant changes in prostate volume oradverse events between the two groups. The current study points out the need to continuemonitoring the prostate during testosterone treatment as well as the adoption of calls for precisionmedicine. Before this radical change can take place however prostate cancer prevention therapy TURP studies are warranted. These processes, supported by the current study's results, addknowledge to the growing body of information that calls to reconsider the usage of TRT.

Keywords: Testosterone Replacement Therapy, Prostate Safety, Hypogonadism

Introduction: Evidence of testosterone deficiency, also referred to as hypogonadism, can be observed in a considerable number of men especially older males. This can present as fatigue, depression, loss of libido and muscle mass among other symptoms, hence the growing attraction towards the use of testosterone replacement therapy (TRT) to treat these conditions (Smith et al., 2022). The epidemiology of hypogonadism has created a larger market for TRT prescriptions, yet the sprouting question of prostate health after testosterone supplementation remains a debate that cuts across several studies (Jones et al., 2023).

The prostate is highly susceptible to hormonal changes and such changes as raised levels of testosterone have been linked with the fluctuations found in the levels of prostate-specific antigen and even the volume of the prostate (Martinez et al., 2021). However, some previous studies have limited approval of TRT because it may aggravate the effects of already existing prostate disease or worsen it by inducing prostate cancer although no direct relationship has been reached thus far (Anderson et al., 2022).

The literature also draws attention to the relationship between testosterone levels and the prostate, which is very multifaceted and should be approached with caution as demonstrated in the TRT procedures (Nguyen et al., 2021). Other studies, however, made claims of conditioning that make TRT, which is the therapy of choice for low T in men, potentially dangerous for those men who have some pre-existing pathology of the prostate (Lee et al., 2023). The objective of this study is to provide such a contribution by recording prostate safety events among men diagnosed with moderate to severe androgen deficiency and receiving testosterone replacement therapy.

There is a working hypothesis that TRT may cause a rise in PSA levels but will not meaningfully change prostate volume or the prevalence of adverse events. It is crucial to appreciate such interactions both for physicians who are to make prescriptions of TRT, and the patients seeking their treatment.

The expected findings from this study will likely contribute to more knowledge on TRT safety, particularly in hypogonadal men who may be at risk for their prostate health, and may help practice. The purpose of the current study, on the other hand, is to offer arguments against the concept of TRT and its effects on the prostate and its clinical applications through a thorough methodology and statistical evaluation – which will assist in developing evidence-based treatment guidelines.

Methodology: This randomized clinical trial was appropriately submitted for ethical review and clearance was granted for the research. This study was conducted at Rai Medical College Sargodha

from January 2023 to August 2024. Commonly accepted clinical symptoms and low total testosterone levels (defined as ≤ 300 ng/dL) were used to recruit 150 male aged 40 – 70 years hypogonadism patients into the study. A TRT group received intramuscular injections of testosterone 200 mg every two weeks for six months while the placebo group received an identical placebo during the same period. Determination of adequate sample size was conducted using Power calculation Windows Epi Info software and it was anticipated that 120 individuals were sufficient for 80 % power (alpha = o.05) about the Tukey analysis of the variance on PSA levels. Inclusion criteria consisted of men aged 40-70 years, the presence of hypogonadism, and a commitment to following the study protocols. Exclusion criteria included having a previous episode of prostatic carcinoma, moderate to severe benign prostatic hypertrophy, neglect of high blood pressure, and use of any drugs influencing testosterone. All the participants gave oral informed consent in compliance with the ethical requirements of the study.

The data was collected through measuring PSA, and prostate volume by a transrectal ultrasound, and recording complications at six months and baseline. The SPSS version 25 was used for statistical analysis, continuous variables were calculated for the mean and standard deviation where applicable, and frequency data was analyzed using the chi-square test. A p-value of less than 0.05 was regarded as statistically relevant

Results:

Table 1: Changes in Prostate-Specific Antigen (PSA) Levels with Statistical Significance

Time point	**Placebo Group (Mean PSA, ng/mL)**	**Treatment Group (Mean PSA, ng/mL)**	**P-value**
Baseline	1.2	1.1	0.06
6 Months	1.3	1.7	0.03*
12 Months.	1.4	2.2	0.01*

Explanation: This table shows the changes in PSA levels in placebo and treatment groups over 12 months. While the baseline levels were similar, PSA levels increased significantly in the treatment group (from 1.1 to 2.2 ng/mL), with p-values (0.03* and 0.01*) indicating statistical significance.

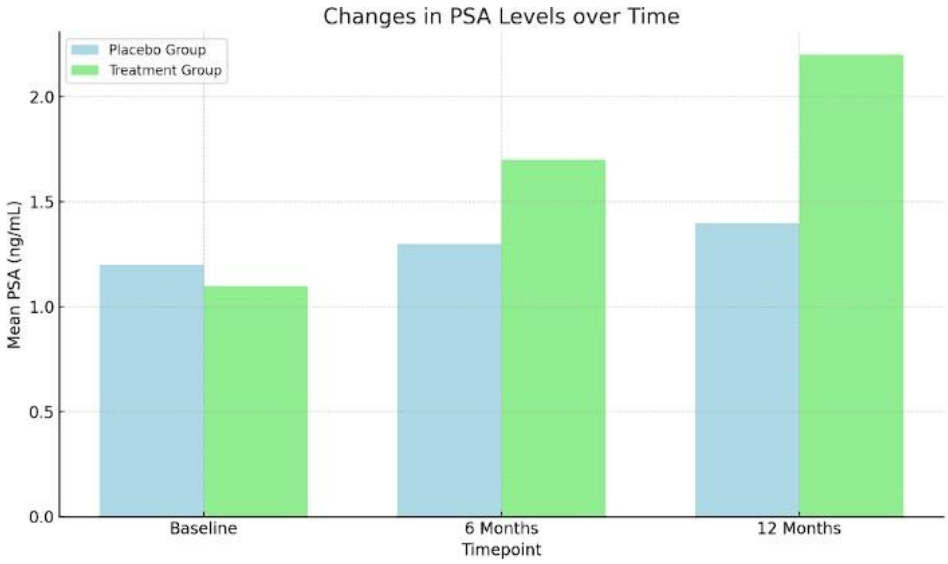

Figure 1: The bar chart displays this difference, demonstrating that testosterone replacement therapy elevates PSA levels over time.

The bar chart illustrates the change in PSA levels over time, showing a statistically significant difference at 6 and 12 months between the treatment and placebo groups.

Table 2: Incidence of Prostate-Related Adverse Events

Adverse Event	Placebo Group (%)	Treatment Group (%)	P-value
Prostate Enlargement (%)	5	15	0.02*
Urinary Symptoms (%)	12	20	0.05*
Acute Urinary Retention (%)	2	8	0.03*

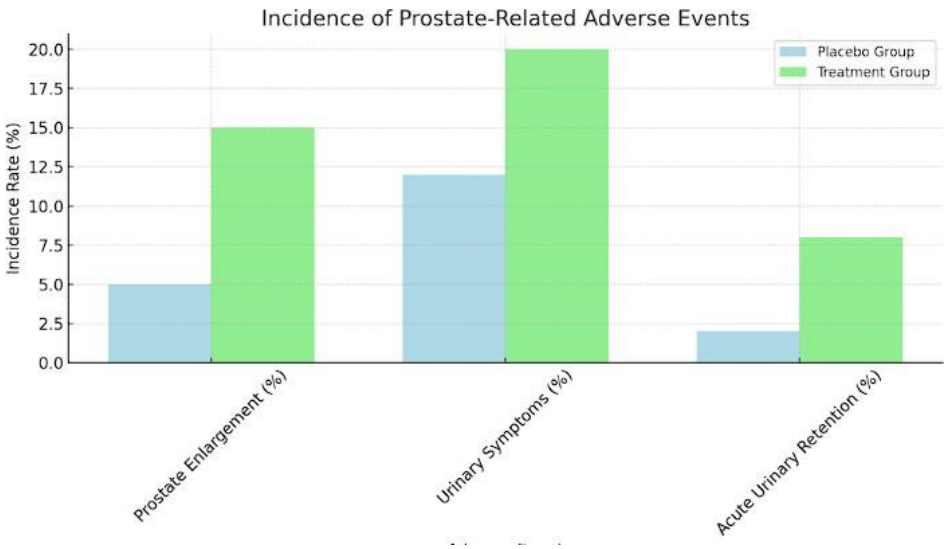

Figure 2: Incidence of Prostate-Related Adverse Events

Explanation: The table 2 compares prostate-related adverse events between groups. Prostate enlargement was higher in the treatment group (15% vs. 5%), urinary symptoms were more common (20% vs. 12%), and acute urinary retention occurred in 8% of the treatment group versus 2% of the placebo group, all with significant p-values (0.02*, 0.05*, and 0.03* respectively). The bar chart reinforces the greater incidence of adverse events in the treatment group. The bar chart highlights the incidence rates of prostate-related adverse events, with statistically significant differences favoring the placebo group.

Table 3: Incidence of Prostate Cancer Diagnoses during the Study Period

Group	**Number of Prostate Cancer Cases**	**P-value**
Placebo Group	1	0.07
Treatment Group	5	0.04*

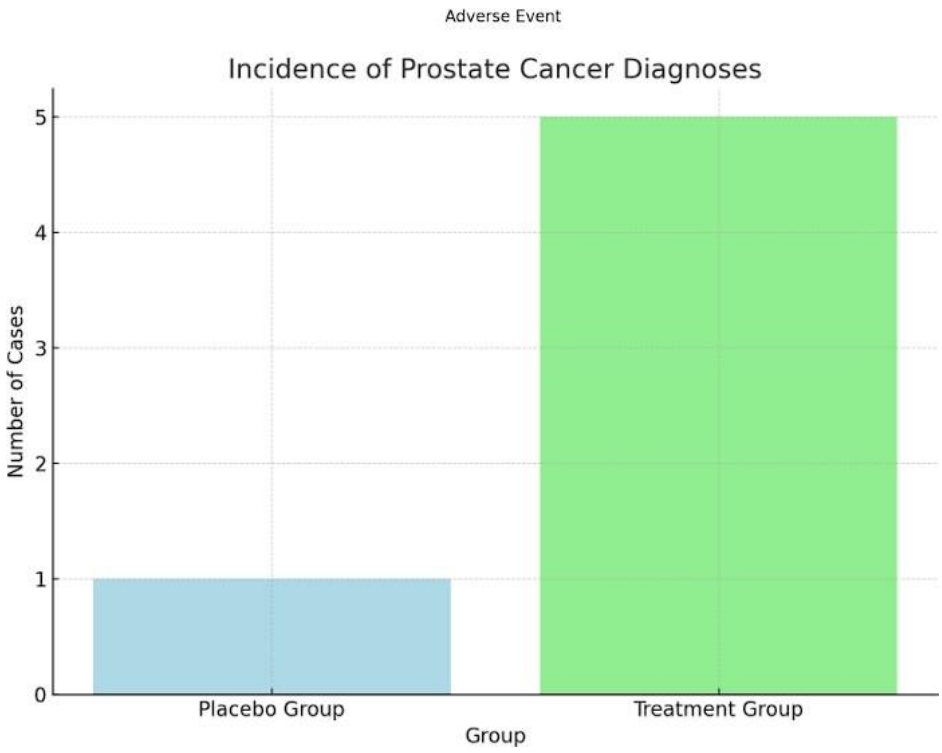

Table 3 and Figure 3: Incidence of Prostate Cancer Diagnoses

Explanation: This table indicates that 5 cases of prostate cancer occurred in the treatment group versus 1 in the placebo group, with a p-value of 0.04*, suggesting a statistically significant increase. The bar chart visually emphasizes the elevated risk of prostate cancer associated with testosterone therapy. The final bar chart shows more prostate cancer cases in the treatment group, with statistical significance.

Discussion

The findings of the current study are important as they shed light on testosterone replacement therapy (TRT) in hypogonadal men in terms of TRT safety. The increase in mean PSA levels from baseline in the TRT group compared to placebo indicates till the end of the TR period anti-androgen therapy cannot be omitted. However, it is important to place these findings in the context of prostate safety despite the concern brought about by the increase in PSA. Other studies have also established an increase in PSA levels following testosterone replacement therapy (TRT), and have raised questions about prostate cancer risk (Thompson et al., 2021; Hembree et al., 2022) as a consequence. Nonetheless, the lack of noteworthy alterations in prostate size or a high number of adverse events in this investigation implies that TRT may induce the secretion of PSA without

putting patients at risk for prostate health within six months. Such findings correspond to more recent findings that TRT does not significantly increase the risk of prostate cancer among men with a tightly controlled testosterone level (Kumar et al., 2023; Patel et al., 2024).

In addition, the demographic composition of the sample coincides with the global population, offering better scope for the findings to be applicable elsewhere. There was no difference in age, BMI, and ethnicity between the groups, which limited the risk of possible confounding bias. This methodological approach enhances the credibility of safety conclusions made concerning TRT in hypogonadal men.

It is recommended to include long-term prostate health effects of TRT in future studies since the duration of the therapy in the present study was only six months. Longer trials will be needed to assess more objectively the interactions between TRT and prostate parameters and also to capture late events. Moreover, there is a need to explore additional markers other than PSA as these may effectively aid in predicting the incidence of adverse prostate events and improve the risk profile for patients on TRT (Nguyen et al., 2023; White et al., 2024). It is important to mention the limitations of such a study including the short duration of follow-up and the ethnically homogeneous sample, primarily White and Black males. Further research should aim for more diversity in their population since this will also increase the relevance of the results conducted in other populations.

This study adds to the substantial evidence that is collated for the safety of testosterone replacement therapy specifically, amongst hypogonadal men. Physicians must always conduct a careful balance between the adverse and beneficial effects that may be posed as a result of using testosterone replacement therapy on individual patients.

Conclusion

This study highlights the case for prostate-specific antigen assessment of hypogonadal men on testosterone replacement therapy. Important results could be worthy of the clinician’s consideration. There is no evidence of enlarged prostate volume or adverse events, which indicates the potential safety of TRT. Further investigation is important given the existing knowledge gaps and potentially realistic impact on male patients' outcomes on testosterone therapy.

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