# Testosterone Replacement Therapy is Associated with Increased Incidence Rate of Vertebral Fractures: A Matched Retrospective Analysis

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INTRODUCTION:
Testosterone replacement therapy (TRT) is frequently pursued in patients with low levels of serum sex hormones to combat low energy or sexual drive and decreased muscle mass. However, whether TRT use can mitigate the associated increase in the rate of fragility fractures has not been well-studied.
METHODS: The PearlDiver Mariner165 dataset was queried to identify and randomly select 150,000 patients ages 35 to 75 years who filled a prescription for exogenous TRT for a minimum period of 3 consecutive months. A control group of 150,000 patients ages 35 to 75 years who had no prior history of TRT prescription were similarly selected. Groups were subsequently matched 1:1 by age, sex, and Charlson Comorbidity Index (CCI), tobacco use, and history of diabetes. Vertebral fracture incidence rate over a two-year follow-up period was determined using ICD coding and compared across age and sex groups. Multivariate logistic regression was performed to identify the independent predictors of vertebral fractures.
RESULTS: Among the 77,491 matched TRT and Control patients, mean age was 54.7 ± 10.4 years, 74.3% were males, mean CCI was 0.17 ± 0.54, 34.5% reported tobacco use, and 36.2% had a diagnosis of diabetes. TRT patients had higher rates of vertebral fractures than the Control patients (0.31% vs 0.04%, p<0.001). After stratifying by sex, both males alone (0.36% vs 0.04%, p<0.001) and females alone (0.16% vs 0.03%, p<0.001) on TRT had higher rates of vertebral fractures than the matched Control patients. After stratifying by age, the incidence rate was observed to increase with age. After accounting for other confounding variables, multivariate logistic regression analysis revealed that TRT for 3 consecutive months (OR=7.7, 95%CI=5.1–11.7, p<0.001), as well as chronic kidney disease (OR=1.4, 95%CI=1.1–2.0, p=0.026), alcohol abuse (OR=2.5, 95%CI=1.8–3.5, p<0.001), and bisphosphonate use (OR=2.2, 95%CI=1.4–3.5, p<0.001) significantly increased the likelihood of vertebral fractures.
DISCUSSION AND CONCLUSION:
In this retrospective matched-cohort study, exogenous testosterone use was associated with increased two-year incidence rate of vertebral fractures. Future research should further investigate the impact of testosterone on bone mineral density, as well as the mechanism of injury that subsequently led to the development of vertebral fractures.

**Table 1**. Demographic and baseline characteristics of the matched and non-matched cohorts.

| | Non-Matched | | | Matched | | |
|---|---|---|---|---|---|---|
| | TRT | Control | P-value | TRT | Control | P-value |
| Count | 150,000 | 150,000 | | 77,491 | 77,491 | |
| Age (years) | 55.17 (10.5) | 56.07 (11.69) | **<0.001** | 54.68 (10.38) | 54.68 (10.38) | 1.000 |
| CCI | 0.80 (1.44) | 0.12 (0.46) | **<0.001** | 0.17 (0.54) | 0.17 (0.54) | 1.000 |
| Male Sex | 128,457 (85.64) | 64,118 (42.75) | **<0.001** | 57,554 (74.27) | 57,554 (74.27) | 1.000 |
| Tobacco Use | 49,695 (33.13) | 46,090 (30.73) | **<0.001** | 26,723 (34.49) | 26,723 (34.49) | 1.000 |
| Diabetes | 60,663 (40.44) | 56,697 (37.80) | **<0.001** | 28,026 (36.17) | 28,026 (36.17) | 1.000 |

Abbreviations: TRT = Testosterone Replacement Therapy, CCI = Charlson Comorbidity Index.

**Table 2**. Incidence of vertebral fractures at two years

| Variable | Count | TRT | Control | P-value |
|---|---|---|---|---|
| Total | 77,491 | 237 (0.31) | 31 (0.04) | **<0.001** |
| 35-45 years | 17,027 | 42 (0.25) | 8 (0.05) | **<0.001** |
| 46-55 years | 23,728 | 69 (0.29) | 10 (0.04) | **<0.001** |
| 56-65 years | 22,488 | 78 (0.35) | 3 (0.01) | **<0.001** |
| 66-75 years | 14,248 | 48 (0.34) | 10 (0.08) | **<0.001** |
| Males | 57,554 | 206 (0.36) | 25 (0.04) | **<0.001** |
| 35-45 years | 14,180 | 40 (0.28) | 8 (0.06) | **<0.001** |
| 46-55 years | 16,575 | 59 (0.36) | 10 (0.06) | **<0.001** |
| 56-65 years | 15,467 | 65 (0.42) | 1 (0.01) | **<0.001** |
| 66-75 years | 11,332 | 42 (0.37) | 6 (0.05) | **<0.001** |
| Females | 19,937 | 31 (0.16) | 6 (0.03) | **<0.001** |
| 35-45 years | 2,847 | 2 (0.07) | 0 (0.00) | 0.480 |
| 46-55 years | 7,153 | 10 (0.14) | 0 (0.00) | **0.003** |
| 56-65 years | 7,021 | 13 (0.19) | 2 (0.03) | **0.005** |
| 66-75 years | 2,916 | 6 (0.21) | 4 (0.14) | 0.290 |

Abbreviations: TRT = Testosterone Replacement Therapy.

**Table 3**. Logistic regression predicting the risk of vertebral fractures

| Variable | OR (95% CI) | P-value |
|---|---|---|
| Hypogonadism | 1.14 (0.87-1.49) | 0.346 |
| TRT | 7.70 (5.09-11.65) | **<0.001** |
| Obesity | 1.02 (0.76-1.36) | 0.787 |
| Morbid obesity | 1.35 (0.92-1.97) | 0.121 |
| Chronic kidney disease | 1.44 (1.05-1.98) | **0.026** |
| Alcohol abuse | 2.51 (1.79-3.52) | **<0.001** |
| Osteoporosis | 1.54 (0.89-2.67) | 0.123 |
| Bisphosphonate Use | 2.20 (1.38-3.50) | **<0.001** |

Abbreviations: TRT = Testosterone Replacement Therapy.