The Effect of Testosterone Therapy on the Mortality Rate in Men Suffering From Diabetes Mellitus

Deion Tran

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Abstract

Background: Low testosterone level is common with aging men and is associated with many adverse outcomes like diabetes mellitus (DM). In addition, men with low testosterone and DM have increased mortality risk. This review looks at the effect of testosterone therapy on mortality in men suffering from DM.

Methods: An exhaustive literature search of available databases using Medline-OVID, CINAHL and Web of Science was conducted using the following keywords: testosterone, diabetes mellitus, and mortality.

Results: The initial search of the databases yielded 58 articles. A total of two articles, both observation studies, met the inclusion criteria. The articles demonstrated decreased mortality rate in treated men with low testosterone suffering from DM.

Conclusion: In both observation studies, testosterone therapy is associated with decreased mortality rate in men with DM. However, due to the studies’ limitations, further studies are needed to confirm the data.

Keywords: Testosterone, mortality, diabetes mellitus, therapy.

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Saje Davis-Risen, PA-C, MS

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Deion Tran

A Clinical Graduate Project Submitted to the Faculty of the
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Faculty Advisor: Saje Davis-Risen, PA-C, MS
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
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# Table of Contents

Cover Page .................................................................................................................................. 1  
Biography .................................................................................................................................. 2  
Abstract .................................................................................................................................... 3  
Table of Contents ................................................................................................................... 4  
List of Tables ........................................................................................................................... 5  
List of Abbreviations ............................................................................................................... 5  
BACKGROUND ......................................................................................................................... 6  
METHODS .................................................................................................................................. 7  
RESULTS .................................................................................................................................... 7  
DISCUSSION ............................................................................................................................. 10  
CONCLUSION ........................................................................................................................... 12  
References ................................................................................................................................. 13  
Tables ...................................................................................................................................... 16
List of Tables

Table I: Characteristics of Reviewed Studies and Summary of Finding

List of Abbreviations

CI……………………………………………………………………………Confidential Interval
DM………………………………………………………………………………Diabetes Mellitus
DM type 2………………………………………………………………Diabetes Mellitus Type 2
HR……………………………………………………………………………Hazard Ratio
IM……………………………………………………………………………………Intramuscular
S.D………………………………………………………………………………Standard Deviation
VA…………………………………………………………………………………Veterans Affairs
The Effect of Testosterone Therapy on the Mortality Rate in Men Suffering From Diabetes Mellitus

BACKGROUND

Testosterone is one of the important hormones in the body. It maintains bone density, fat distribution, muscle strength and mass, red blood cells production, sex drive, and sperm production. A decline in testosterone level is common with aging men. As a result, diabetes, obesity, cardiovascular events, sarcopenia, osteoporosis, or a decreased libido occurs. A study had noted mortality rate in men with low testosterone levels is double compared to men with normal testosterone levels. A low testosterone level in men is defined as total testosterone < 300 ng/dl (10.4 nmol/L). Several studies have noted that low testosterone levels are associated with increase mortality risk in men with diabetes mellitus (DM). In addition, there is evidence demonstrating an increased occurrence of low testosterone in men with DM type 2, and a longitudinal cohort study found there is an increase in mortality associated with low testosterone in men with DM type 2. However, the direct link between low testosterone and DM is unknown.

Since 2000, testosterone therapy prescriptions have increased astronomically from 700,000 per year to 2,700,000 in 2008. Some studies have shown the benefit of testosterone therapy such as increasing strength, muscle mass, bone mineral density, insulin sensitivity, and libido. In a large, multi-centre, randomized, double-blind, placebo-controlled study testosterone therapy was shown to improve insulin resistance, cholesterol, lipoprotein, body fat composition, sexual dysfunction in men with DM type 2. A meta-analysis of testosterone therapy trial on men with DM showed no increase of cardiovascular events in the treatment group; however, they
METHODS

An exhaustive literature search of available databases using Medline-OVID, CINAHL and Web of Science was performed using the following keywords: testosterone, DM, and mortality. In both Medline-OVID and CINAHL, no further eligibility criteria were used. In Web of Science, the result was narrowed down using years 2000 to 2014, articles only, English-language only, and endocrinology. The bibliographies of the articles were then screened by relevance. All articles that contained discussion of testosterone therapy and mortality were included. Relevant studies were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) criteria.20

RESULTS

The initial search of Medline-OVID, CINAHL, and Web of Science yield 4, 18, and 36 articles, respectively. After screening for relevance, a total of two articles met the inclusion criteria. These articles included one prospective cohort study5 and one retrospective cohort study.11

Muraleedharan et al

In this prospective cohort study,5 the authors compared the mortality rate associated with testosterone therapy in men with DM type 2 to men that did not receive testosterone therapy with the same conditions. This study included patients that were recruited by district-wide diabetic retinopathy screening, in a hospital diabetic clinic, through the general community, or through a hospital database identifying DM type 2 patients. Of the 591 patients with DM type 2 who had
testosterone screened from 2002 to 2005, 238 patients were identified to have low testosterone. Low testosterone level is defined as total testosterone < 10.4 nmol/L. Of the 238 patients with low testosterone, 64 received testosterone therapy and 174 did not. The 174 patients did not receive testosterone therapy for following reasons: patient choice, declined to attend for further clinical assessment, did not response to invitation, or declined treatment. The authors noted that testosterone therapy is mainly administered to patient with total testosterone level < 8.4 nmol/L, without prostate cancer or other contraindication for testosterone therapy.5

The treatment group received either testosterone gel or testosterone intramuscularly (IM). Of the 64 patients, 55 received testosterone gel and 9 received testosterone IM. Doses were adjusted to achieve testosterone levels within the mid to upper normal range. The average duration of treatments was 41.6±20.7 (S.D.) months with 60 patients receiving testosterone therapy for ≥ 12 months and 51 patients receiving testosterone therapy ≥ 2 years. There was no significant differences in baseline characteristics between the normal testosterone group and low testosterone group. A follow-up was performed on average, 5.8±1.3 (S.D.) years later.5

The mortality rate was significantly higher in the untreated group (20.11%) compared to the treated group (9.38%). The authors used the Kaplan-Meier curves which showed improved survival rate in the treated group compared with the untreated group. The authors also used the multivariate-adjusted survival curves in the Cox regression model, which showed the hazard ratio (HR) for decreased survival for the untreated group was 2.3; 95% CI 1.3-3.9; P=0.004.5

The authors noted that several meta-analyses have not found any increase in cardiovascular events with testosterone therapy.19,21-23 They concluded that long-term testosterone therapy is safe and there was a decreased mortality rate in men with low testosterone and DM type 2. In addition, the authors encouraged careful monitoring of testosterone levels
also hematocrit and prostate specific antigen) when administering testosterone therapy with cautious dosing while achieving normal healthy range.\textsuperscript{5}

**Shores et al**

In this observational, retrospective cohort study,\textsuperscript{11} the authors examine the influence of testosterone therapy on mortality in men with low testosterone and whether results were modified by other factors such as DM. This study used the Veterans Affairs (VA) medical database, Consumer Health Information and Performance Set, to identify veteran men age > 40 years old who had received treatment at the seven VA medical centers in the Northwest states and had total testosterone ≤ 250 ng/d (8.7 nmol/L) between January 1, 2001 to December 31, 2002. Of the 5714 patients who had testosterone levels checked, 1090 patients were included in the final study. Of these final group, 393 patients with DM received testosterone therapy and 638 patients did not received treatment.\textsuperscript{11}

The primary focus of this study was mortality. The number of patients who died was obtained from the VA Beneficiary Identification records Locator Subsystem-Death File and the Social Security Administration-Death Master File. The Kaplan-Meier survival curves were used to show unadjusted survival times for the treated group compared to the untreated group. The HR and CI were calculated based on multivariate-adjusted survival curves in the Cox regression model.\textsuperscript{11}

In the treatment group, 88.6% received testosterone IM, 9.1% used the testosterone patch, and 2.3% received testosterone gel which resulted in 398 patients who were treated with testosterone. The average duration of treatment was 20.2 months. The patients in this group were younger, had lower testosterone levels, and higher BMI compared to the untreated group;
otherwise, both groups are similar in the baseline characteristics. The average follow-up was 42.8 months with 51 patients lost to follow-up.\(^\text{11}\)

In the unadjusted analyses, the mortality rate is significantly higher in the untreated group - 20.7% compared to 10.3% in the treated group. In the unadjusted Kaplan-Meier survival curves shown, survival rate in the treated group was better compared to the untreated group (\(p = 0.029\)). In the time-varying Cox-adjusted regression model, there was a 39% reduction in mortality risk (HR 0.61, 95% CI 0.42-0.88, \(p = 0.008\)) in the treated group compared to untreated group. When analyzing the mortality rate in the treated group compared to untreated group by DM, there is an association with improve survival in men with DM received testosterone therapy. The HR for treated group with DM was 0.44; 95% CI 0.23-0.84; \(p=0.013\) compared to the untreated with DM, HR 0.72; 95% CI 0.46-1.13; \(p=0.155\).\(^\text{11}\)

As a result of a lower HR in the treated group with DM compared to untreated men with DM, the authors concluded that testosterone therapy is associated with improved survival in men with low testosterone and DM. However, because this is the first study to examining the association between testosterone therapy and mortality in men with low testosterone levels, and this is an observational study, the authors caution readers to interpret the results cautiously.\(^\text{11}\)

**DISCUSSION**

In men, low testosterone is commonly associated with many adverse outcomes such as DM. In addition, men with DM has significant lower testosterone levels than those without DM.\(^\text{24}\) The link between those two conditions are unknown, but these men are at increasing risk of mortality when they are combined. There has been increased use of testosterone therapy since 2000 which has shown to improve strength, muscle mass, bone mineral density, insulin
sensitivity, and libido.\textsuperscript{14-17} However, there have been no studies on mortality until two studies in the Muraleedharan et al\textsuperscript{5} and Shores et al\textsuperscript{11} demonstrated increase survival rate in low testosterone men suffering from DM compared to men who did not received treatment.

Reviewing the two studies\textsuperscript{5,11} that compared testosterone treatment and mortality risk in men with DM it is clear that there is some correlation. In the Shores et al study,\textsuperscript{11} the authors demonstrated a decreased in mortality rate of men with DM who received testosterone therapy compared to men with the same condition and did not received treatment. The result can be seen in Table 1.\textsuperscript{11} In the Muraleedharan et al study,\textsuperscript{5} the authors demonstrated an increase in survival rate of low testosterone men with DM type 2 who received testosterone therapy compared to men with the same condition and did not received treatment.\textsuperscript{5} Furthermore, testosterone therapy has been shown to be safe when a patient has low levels.\textsuperscript{19}

Although these two studies showed the benefit of testosterone therapy in men with low testosterone and DM, there are limitations in both studies. These two studies were evaluated using the GRADE method and the results can be seen in Table 1. Both studies\textsuperscript{5,11} were of observational study design. Moreover, both used a lower testosterone thresholds in treated patients. In the Shores et al study,\textsuperscript{11} treated patients had total testosterone levels of 8.7 nmol/L compared to the treated patient in the Muraleedharan et al study\textsuperscript{5} who had an average total testosterone level of $6.8\pm2.3$ nmol/L. This could lead to overestimating the treatment effects, thus, limiting the interpretation of the results.

Another limitation, mainly from the Shores et al study,\textsuperscript{11} is that patients were initiated into testosterone therapy based on one testosterone level check instead of the recommended two testosterone level checks from the clinical guideline. It is recommended to recheck the testosterone level because lower testosterone level can be due to serious conditions like
cardiovascular diseases or DM.\textsuperscript{25} Lastly, the study\textsuperscript{11} contains patients with history of high risk of chronic medical morbidity including coronary heart disease and diabetes. The generalizability of the results are, therefore, limited.

Because of these limitations, larger and longer studies with double-blind, placebo-controlled design will increase confidence of whether or not mortality risk is improved in men with DM who also have low testosterone.

**CONCLUSION**

Testosterone therapy has shown to decrease mortality rate in men suffering from DM in two observation studies. However, due to these studies’ limitations, the results should be cautiously interpreted but testosterone therapy may be beneficial in the long-term in improving survival rate in men with low testosterone and DM. A further long-term and large randomized controlled trial is needed to confirm this data.
References


<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Treatment Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>RR</td>
</tr>
<tr>
<td>Design Limitations</td>
<td>Indirectness</td>
<td>Imprecision</td>
</tr>
<tr>
<td>Muraleedharan et al</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shores et al</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Studies were upgraded due to large treatment effect*