Men with low T when diagnosed with prostate cancer have a lower GS?

•

• 1. True
• 2. False
• 3. Unsure
ARS: Testosterone replacement therapy (TRT) has been shown to flair prostate cancer in men on Active Surveillance?

• 1. Yes
• 2. No
• 3. Not sure
### Potential Benefits
- Increase sexual interest
- Improve erectile function
- Increase muscle mass/strength
- Decrease central fat
- Increase bone density
- Improve cognition
- Improve mood/well-being
- Improve physical performance/activity
- Decrease fractures
- Improve QOL
- Increase life expectancy

### Potential Risks
- Increase risk and severity of prostate cancer
- Exacerbate benign prostatic hyperplasia
- Polycythemia
- Exacerbate sleep apnea
- Fluid retention
- Coronary artery disease
- Gynecomastia
- Priapism
- Acne
<table>
<thead>
<tr>
<th>Potential Benefits</th>
<th>Potential Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase sexual interest</td>
<td>Increase risk and severity of prostate cancer</td>
</tr>
<tr>
<td>Improve erectile function</td>
<td>Exacerbate benign prostatic hyperplasia</td>
</tr>
<tr>
<td>Increase muscle mass/strength</td>
<td>Increase sleep apnea</td>
</tr>
<tr>
<td>Decrease central fat</td>
<td>Fluid retention</td>
</tr>
<tr>
<td>Increase bone mass</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Improve mood/well-being</td>
<td>Gynecomastia</td>
</tr>
<tr>
<td>Improve physical performance/activity</td>
<td>Priapism</td>
</tr>
<tr>
<td>Decrease fractures</td>
<td>Acne</td>
</tr>
<tr>
<td>Improve QOL</td>
<td></td>
</tr>
<tr>
<td>Increase life expectancy</td>
<td></td>
</tr>
</tbody>
</table>
Prostate Disease

Low Testosterone

Metabolic Syndrome

Obesity, hyperinsulinemia, hyperlipidemia, hyperleptinemia

Testosterone Treatment

Prostate Disease

Low Testosterone

Metabolic Syndrome

Obesity, hyperinsulinemia, hyperlipidemia, hyperleptinemia
Testosterone Substitution and Possible Prostate Changes

- Increases in PSA levels?
- Increases in prostate volume?
- Stimulation of growth in previously undiagnosed tumors?

- *No data to support testosterone substitution as a cause of prostate cancer*

Testosterone and the Prostate

• Prostate development, differentiation, and maintenance are known to be closely linked to the bioavailability of testosterone and other related sex hormones

• Huggins, 1941
  • Deprivation of testosterone slowed the progression of prostate cancer
Testosterone and the Prostate

Clinical concern:

Testosterone risk of converting an occult cancer into a clinical cancer?
Testosterone and the Prostate

If castration makes PCa cells die, then shouldn’t raising testosterone (T) make cancer cells grow?
Testosterone and the Prostate

BUT...
Men dying from prostate cancer are all castrated!
Testosterone and Prostate Cancer

Time for reevaluation based on evidence!
- One of the principles of Evidence-based Medicine is that concepts that fail to withstand scientific scrutiny are to be discarded.

- Such a time has come for the belief that T causes enhanced growth of prostate cancer (PCa).
A. Morgentaler, MD
Beth Israel Deaconess Medical Center
Harvard Medical School
Boston, Massachusetts

Testerone and Prostate Cancer: An Historical Perspective on a Modern Myth

Morgentaler A. Eur Urol. 2006;50(5);935-939.
Huggins’ Heritage From a 1967 Review Article:

“Orchiectomy or the administration of estrogens resulted in regression of PCa

“Whereas, in untreated prostates, testosterone enhanced the rate of growth of cancer”

There is no dispute that castration causes PCa to regress. However... Proof for the second part of Huggins' assertion—“T causes PCa to grow”—has been elusive!!
The logic: “testosterone favors PCa growth” is completely inconsistent.

There is robust data supporting this view.
Huggins and Hodges reported that daily injections of testosterone propionate caused **acid phosphatase** levels to increase. LHRH Flair!!!

Although 3 men were injected, results were provided for only 2 of them.

One of these 2 had already been castrated.

In the remaining patient, acid phosphatase levels rose during 18 days of T treatment, but fluctuated widely before and afterward, reaching the same peak levels 3 weeks after T discontinuation.

The original assertion that testosterone caused prostate cancer in untreated patients was thus based on equivocal acid phosphatase results in a single individual!!
The US Institute of Medicine:

“In summary, the influence of T on prostate carcinogenesis and other prostate outcomes remains poorly defined”

Prostate Saturation Model

Saturation Model of Physiologic Testosterone Replacement

“Normal Physiologic Range”

Virtually Castrate

Unsaturated

Serum testosterone level (ng/dL)

Saturation Effect

Incidence Of Prostate Cancer

Testosterone

PCa – Incidence per 100,000

Years of Age

Testosterone [pg/mL]

Occult Cancer in Men With Low Testosterone

- 77 men with low total or free serum testosterone, normal DRE, and PSA <4 ng/mL
- All underwent sextant ultrasound-guided prostate biopsy
- 11 (14%) had biopsies positive for prostate cancer
- Expected (published) prevalence of positive biopsies in men with normal DRE and PSA <4 ng/mL is 1.8% to 4.5%
- Decreased androgen status may mask prostate cancer
- Is low testosterone a risk for men treated with testosterone substitution?
## Low T Increases Prostate Cancer Risk

<table>
<thead>
<tr>
<th>References</th>
<th>Number of Pts</th>
<th>Study Type</th>
<th>Endogenous TTh Level</th>
<th>CaP Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morgentaler et al. [29]</td>
<td>77</td>
<td>Retrospective</td>
<td>T &lt;300 ng/dl or free T &lt;1.6 ng/dl</td>
<td>CaP incidence of 14% (11/77)</td>
</tr>
<tr>
<td>Mearini et al. [31]</td>
<td>206</td>
<td>Prospective</td>
<td>≤2.4 ng/ml ≤0.5 ng/ml</td>
<td>14.2% of patients had clinically locally advanced or metastatic CAP, and 57.1% have a pathological locally advanced CaP</td>
</tr>
<tr>
<td>Shin et al. [32]</td>
<td>568</td>
<td>Prospective</td>
<td>&lt;3.85 ng/ml</td>
<td>CaP incidence 38.0% (vs. 29.5% high testosterone)</td>
</tr>
<tr>
<td>Karamanolakis et al. [39]</td>
<td>718</td>
<td>Prospective</td>
<td>≤2.4 ng/ml ≤0.5 ng/ml</td>
<td>CaP incidence 30% (29/97)</td>
</tr>
<tr>
<td>Morgantaler et al. [30]</td>
<td>345</td>
<td>Retrospective</td>
<td>&lt;250 ng/dl</td>
<td>CaP incidence 21% (vs. 12% in men with T &gt;250 ng/dl)</td>
</tr>
<tr>
<td>Hoffman et al. [33]</td>
<td>117</td>
<td>Retrospective</td>
<td>T &lt;300 ng/dl or free T &lt;1.5 ng/dl</td>
<td>CaP incidence 43% (vs. 22%)</td>
</tr>
<tr>
<td>Garcia-Cruz et al. [34]</td>
<td>137</td>
<td>Prospective</td>
<td>&lt;346 ng/dl</td>
<td>Tumor burden 53% (vs. 32% in men with T &gt;346 ng/dl); tumor bilaterality 50% (vs. 25.5% in men with T &gt;346 ng/dl)</td>
</tr>
<tr>
<td>Isom-Batz et al. [35]</td>
<td>326</td>
<td>Retrospective</td>
<td>&lt;385 ng/dl</td>
<td>Associated with advanced pathological stage (OR 2.3, 95% CI 1.1-5.0; p = 0.03)</td>
</tr>
<tr>
<td>Lane et al. [36]</td>
<td>455</td>
<td>Prospective</td>
<td>&lt;220 ng/dl</td>
<td>Higher frequency of Gleason 4-5 disease (OR 2.4, 95% CI 1.01-5.7; p = 0.48)</td>
</tr>
<tr>
<td>Botto et al. [40]</td>
<td>431</td>
<td>Prospective</td>
<td>&lt;3 ng/ml</td>
<td>Higher frequency of Gleason 4 disease (47% vs. 28%)</td>
</tr>
<tr>
<td>Salonia et al. [37]</td>
<td>673</td>
<td>Prospective</td>
<td>Total T &lt;1 ng</td>
<td>Higher incidence of seminal vesicle invasion (OR 3.11)</td>
</tr>
<tr>
<td>Teloken et al. [38]</td>
<td>64</td>
<td>Retrospective</td>
<td>&lt;2.7 ng/ml</td>
<td>Increased positive surgical margins (p = 0.026)</td>
</tr>
</tbody>
</table>

Hypogonadism

A Marker for More Aggressive Prostate Cancer?

• Patients with a biopsy Gleason score of 8 or greater had low testosterone.\(^1,2\)

• Pretreatment testosterone level is an independent predictor of extraprostatic disease in patients with localized prostate cancer.\(^3\)

Final Thought.....

• After a radical prostatectomy, if you do not replace testosterone levels in hypogonadal men to make them eugonadal, then how can you justify not lowering testosterone levels in eugonadal men to make them hypogonadal?
T- Replacement and PCa – Risk Follow-up

- No promotion of cancer
- Statement is not final

Baseline - quarterly - 1 Year - Yearly

DRE / PSA - DRE/PSA
- No Biopsy
- Prior to Onset
Testosterone Treatment
Summary

• Testosterone treatment: beneficial effects for multiple systems

• Safe, with appropriate medical monitoring

• Need for more evidenced-based studies
The great enemy of the truth is very often not the lie . . . but the myth, persistent, persuasive and unrealistic

John F. Kennedy
IT TAKES A LONG TIME TO BECOME YOUNG

Pablo PICASSO