Q/ How should we monitor men receiving testosterone replacement therapy?

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EVIDENCE-BASED ANSWER

A/ **MONITOR HEMATOCRIT AND BONE MINERAL DENSITY** (BMD) (strength of recommendation [SOR]: **B,** meta-analysis of non–patient-oriented outcomes). Monitoring prostate-specific antigen (PSA), performing prostate digital rectal examination, and observing symptom response to testosterone are also recommended, although direct evidence is lacking (SOR: **C,** consensus opinion).

Monitoring lipid levels is unnecessary (SOR: **A,** based on several meta-analyses), as is monitoring testosterone levels (SOR **C,** consensus opinion). Unless the patient is taking oral testosterone, no evidence exists for or against monitoring liver function (SOR: **C,** consensus opinion).

Clinicians who prescribe testosterone therapy should monitor hematocrit and bone mineral density.

Evidence summary

A hematocrit >50% is the most frequent testosterone-related adverse event in clinical trials. In a meta-analysis of 19 randomized controlled trials (RCTs)—with a total of 1084 subjects, 651 on testosterone, 433 on placebo—testosterone-treated men were nearly 4 times as likely as placebo-treated men to have a hematocrit >50% (odds ratio [OR]=3.67; 95% confidence interval [CI], 1.82-7.51; number needed to harm [NNH]=14).[1] The clinical significance of the increase is unclear.

Increased BMD at lumbar spine

A meta-analysis of 5 RCTs with a total of 264 subjects (135 on testosterone, 129 on placebo) demonstrated a 3.7% (95% CI, 1.0%-6.4%) absolute increase over baseline in lumbar spine BMD after ≥12 to 36 months of treatment.[2] However, pooled effects on lumbar spine BMD across all studies failed to reach statistical significance because of differences in baseline bone density among subjects (BMD increase=0.03 g/cm^2; 95% CI, 0-0.07).

No studies in this meta-analysis showed statistically significant improvement in BMD at the femoral neck. We found no studies that demonstrated reduced fracture risk in patients taking testosterone replacement.

No correlation between testosterone therapy and cancer

Although testosterone can stimulate the growth of locally advanced and metastatic prostate cancer,[3] at least 16 longitudinal studies have failed to show any correlation between testosterone replacement and the development of malignancy.[4] In the previously mentioned meta-analysis of 19 RCTs, rates of prostate cancer, PSA >4 ng/mL, increase in International Prostate Symptom Score (IPSS) >4, and prostate biopsies were all numerically higher in testosterone-treated men, but the differences between the testosterone and placebo groups weren't statistically significant.[1] Moreover, the average serum PSA level in the testosterone-treated men increased only 0.3 ng/mL from a baseline of 1.3 ng/mL.

Testosterone lowers total cholesterol

A meta-analysis of 30 RCTs (1642 men, 808 on testosterone therapy, 834 on placebo) that assessed testosterone's effect on lipid levels found that testosterone reduced total cholesterol levels by 16 mg/dL (95% CI, 6-26 mg/dL); effects on all other lipid fractions weren't significant.[5]

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TABLE

Monitoring testosterone therapy: What the consensus guidelines say

Organization	First follow-up	DRE	PSA test	Testosterone levels	Hematocrit	BMD	Lipids
American Association of Clinical Endocrinologists[9]	q 3-4 mo in first year	q 6-12 mo	Annually		q 6 mo x 3, then annually	q 1-2 y	At 6-12 wk, then annually
American Society for Reproductive Medicine[6]	At 2-3 mo	In first 2-3 mo	At 3 and 6 mo, then annually	At 3 and 6 mo, then annually	At 3 and 6 mo, then annually	At 2 y	
The Endocrine Society[10]	At 3 mo, then annually	At 3 mo, then per routine guidelines	At 3 mo, then per routine guidelines	At 3 mo	At 3 mo, then annually	At 1-2 y	
European Association of Urology[3]	At 3 mo	At 3 and 6 mo, then annually	At 3 and 6 mo, then annually		At 3 mo, then annually	q 1-2 y	

BMD, bone mineral density; DRE, digital rectal exam; PSA, prostate-specific antigen.

A second meta-analysis of 16 RCTs (578 men, 320 on testosterone therapy, 258 on placebo) similarly showed that testosterone lowered total cholesterol levels by 8 mg/dL (95% CI, 4-14 mg/dL) and that its effects on other lipid fractions weren't significant.[2] The previously mentioned meta-analyses of 19 and 30 RCTs found no significant difference in cardiovascular events between testosterone- and placebo-treated groups.[1,5]

Optimal testosterone level is unknown

Data are inadequate to determine the optimal serum level of testosterone for efficacy and safety.[3] Expert opinion suggests that because therapy is empiric, monitoring clinical response may help guide treatment more than testosterone level.[6]

What about the liver?

Oral testosterone can be associated with hepatotoxicity; it is seldom used in the United States. Liver monitoring is unnecessary for patients receiving testosterone by injection, patch, or transbuccal tablet.[7,8]

Recommendations

Consensus guidelines for monitoring men on testosterone therapy overlap considerably with regard to monitoring clinical effectiveness, prostate measures, hematocrit, and BMD (**TABLE**).[3,6,9,10] Assessing testosterone level is recommended, with the aim of achieving levels in the mid-normal range.[10] **JFP**

References

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