What are the benefits and harms of testosterone replacement therapy (TRT) in men with low testosterone?

EVIDENCE-BASED ANSWER

In men with low testosterone and type 2 diabetes mellitus (DM2) or metabolic syndrome, TRT improves glycemic control, triglyceride levels, and body composition (SOR: C, meta-analysis of disease-oriented outcomes from RCTs). In men with low testosterone and frailty or low mobility, TRT does not result in clinically relevant improvements in muscle strength, body composition, or quality of life (SOR: B, 2 RCTs, 1 stopped early due to an increase in adverse cardiovascular events in TRT users). TRT is associated with an increased risk of death, myocardial infarction (MI) or stroke after adjustment for baseline comorbidities (SOR: B, one retrospective cohort).

A 2013 systematic review and meta-analysis of 9 RCTs (N=627) studied the effects of TRT on men with late-onset hypogonadism (LOH) and metabolic syndrome or DM2.1 LOH is most commonly defined as a syndrome of total testosterone level of less than 11 nmol/L plus erectile dysfunction, decrease in morning erections, and decrease in sexual thoughts; however, the RCTs used total testosterone cutoff levels ranging from 8 to 15 nmol/L. One of the RCTs used a free testosterone level of less than 225 pmol/L as the cutoff. TRT was dosed orally in 4 trials, via transdermal gel in 3 trials, and via intramuscular injection in 2 trials. For men with metabolic syndrome, multiple metabolic measurement were followed for a mean of 57 weeks (range 30–104 weeks). Men with DM2 were followed for a mean of 28 weeks (range 12–52 weeks).

In the men with metabolic syndrome, TRT reduced fasting plasma glucose (FPG), triglyceride levels, and waist circumference (see TABLE 1). In the men with DM2, TRT reduced FPG, HbA1C, and triglyceride levels (see TABLE 2). No adverse effects of TRT were reported.¹

A 2010 RCT of elderly men (N=274) with LOH investigated the effects of TRT on physical frailty.² All patients were older than 65 years (mean age 73 years), and were diagnosed with LOH using a total testosterone level of less than 12 nmol/L or free testosterone level of less than 250 nmol/L. They exhibited at least 1 symptom of frailty defined as unintentional weight loss, self-reported exhaustion, low physical activity, slow walk time, or low handgrip strength. Patients applied 50 mg testosterone gel or matching placebo once a day for 6 months. After 10 days and again after 3 months of treatment testosterone levels were measured and the dose was adjusted to 25 or 75 mg as needed to target serum levels of 18 to 30 nmol/L. Muscle strength, body composition, overall physical functioning, and quality of life were measured at baseline and again after using TRT for 6 months. Because abnormal glucose metabolism was not an inclusion criterion, this RCT was excluded from the 2013 meta-analysis.

TRT increased isometric knee extension peak torque compared with placebo (mean difference [MD] 8.6 newton-meters; 95% CI, 1.3–16); however, all other measures of muscle strength and physical function were unchanged. TRT increased lean body mass (MD 1.1 kg; 95% CI, 0.6–1.5) and decreased fat mass (MD −0.6 kg; 95% CI, −1.1 to −0.1). The Aging Males Symptoms scale (range 17–85) showed minor improvement on the somatic subscale (MD −1.2; 95% CI, −2.4 to −0.04) and the sexual subscale (MD −1.3; 95% CI, −2.5 to −0.2).²

A 2010 RCT (N=209) investigated the rate of adverse events in men with limited mobility and low testosterone.³ Men (mean age 74 years) with LOH (total testosterone level 3.5–12 nmol/L or free testosterone <173 nmol/L) received TRT or placebo for 6 months. No significant differences were noted at baseline in age, BMI, race, total testosterone level, or strength testing. The investigators noted a higher incidence of hyperlipidemia (63% vs 50%; P=0.05) and statin therapy (62% vs 47%; P=0.03) in the TRT group at baseline. Patients applied 100 mg testosterone gel or matching placebo once a day for 6 months. After 2 weeks of treatment, testosterone levels were measured and the dose was adjusted to 50 or 150 mg to target serum levels of 17 to 35 nmol/L. This RCT was also excluded from the 2013 meta-analysis.

TRT increased leg-press force (129 newtons; 95% CI, 44–215) and chest-press force (35 newtons; 95% CI, 13–56) compared with placebo. No improvement occurred in grip strength, 50-meter walking speed, stair-climbing power, or repeated lifting and lowering. The trial was stopped before completing enrollment (N=252) when a safety analysis found significantly higher rates of cardiovascular adverse
events including chest pain, MI (1 fatal), atrial fibrillation with rapid ventricular response, heart failure exacerbation, new-onset heart failure, hypertension, stroke, new ischemic ECG changes, and syncope in the TRT group (relative risk 5.4; 95% CI, 2.0–15).³

A 2013 retrospective cohort study of Veterans Administration patients evaluated adverse outcomes associated with TRT.⁴ All men had an initial total testosterone level of less than 300 ng/mL and underwent coronary angiography between 2005 and 2011. TRT users who filled a prescription for gel, patch, or injection (n=1,233; mean age 61 years) were compared with TRT nonusers (n=7,486; mean age 64 years).

TRT users were more likely to be obese, but had significantly lower rates of obstructive coronary artery disease, hypertension, hyperlipidemia, heart failure, prior MI, COPD, peripheral vascular disease, and cerebrovascular disease. Compliance with TRT and dose-response were not evaluated. Patients were followed for an average of 28 months. Although adverse outcomes (death, MI, or stroke) were more common in TRT users, the differences did not reach statistical significance (see TABLE 3). After adjusting

### TABLE 1

<table>
<thead>
<tr>
<th>Measurement</th>
<th>No. of trials</th>
<th>N</th>
<th>Mean difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>5</td>
<td>471</td>
<td>−8.6</td>
<td>−14 to −3.4</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>6</td>
<td>483</td>
<td>−7.2</td>
<td>−12 to −2.5</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>6</td>
<td>483</td>
<td>−4.1</td>
<td>−7.8 to −0.30</td>
</tr>
</tbody>
</table>

LOH=late-onset hypogonadism; TRT=testosterone replacement therapy.

### TABLE 2

<table>
<thead>
<tr>
<th>Measurement</th>
<th>No. of trials</th>
<th>N</th>
<th>Mean difference</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>5</td>
<td>263</td>
<td>−20</td>
<td>−32 to −6.3</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>5</td>
<td>263</td>
<td>−0.62</td>
<td>−1.0 to −0.24</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>5</td>
<td>263</td>
<td>−11</td>
<td>−15 to −6.7</td>
</tr>
</tbody>
</table>

HbA1C=glycosylated hemoglobin; LOH=late-onset hypogonadism; TRT=testosterone replacement therapy.

### TABLE 3

<table>
<thead>
<tr>
<th>Years of follow-up</th>
<th>Cumulative rate of adverse events (%)</th>
<th>Risk difference (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TRT nonusers</td>
<td>TRT users</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>11</td>
<td>1.3</td>
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<tr>
<td>2</td>
<td>15</td>
<td>19</td>
<td>3.1</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>26</td>
<td>5.8</td>
</tr>
</tbody>
</table>

MI=myocardial infarction; TRT=testosterone replacement therapy.
for the differences in baseline comorbidities, TRT use was associated with an increased risk of adverse outcomes compared with nonuse (hazard ratio 1.3; 95% CI, 1.1–1.6).⁴

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What is the role of helminth therapy for inflammatory bowel disease?

EVIDENCE-BASED ANSWER
Evidence is insufficient to recommend helminth therapy for inflammatory bowel disease (IBD) (SOR: B, systematic review of 2 small RCTs and a single RCT).

Helminth therapy—administering the ova of parasites to stimulate an immune reaction—is an increasingly studied intervention for IBD.

A 2014 Cochrane review assessed studies comparing the helminth Trichuris suis ova (TSO, porcine whipworm, which is not considered a human pathogen) with placebo treatment in patients with IBD.¹ Studies commonly used as an outcome measure the Ulcerative Colitis Disease Activity Index (UCDAI), full range 0–12 points, in which a total score of 0–2 was remission; 3–6, mild disease; 7–10, moderate disease; and >10, severe disease). One RCT in this review (n=54; age range 18–72 years) compared treatment with 2,500 TSO every 2 weeks for 12 weeks with a placebo in patients with ulcerative colitis and an UCDAI of at least 4. Although UCDAI symptom scores improved in the treatment group (mean difference [MD] −1.4; 95% CI, −1.8 to −1.1), clinical improvement and remission rates did not reach statistical significance (relative risk [RR] 2.6; 95% CI, 0.97–7.0 and RR 2.4; 95% CI, 0.27–22, respectively). The second RCT in the review (n=36; age range 18–55 years) compared the safety and tolerability of TSO at various single-dose regimens (500, 2,500, and 7,500 ova) with placebo in patients with symptoms of Crohn’s disease of at least 3 months’ duration. No significant differences were noted in adverse events between the groups (RR 0.83; 95% CI, 0.35–2.01).

A study of TSO in Crohn’s disease reported only in a 2013 press release (double-blinded RCT, N=250) compared the Crohn Disease Activity Index score (CDAI, a self-reported scale of 8 weighted factors, scored from 0 to 600) in patients with moderate-to-severe Crohn’s disease who were treated with 7,500 TSO every 2 weeks for 12 weeks with the CDAI of similar patients given placebo.² The treatment group did not demonstrate a significant response (100-point decrease in CDAI) or evidence of remission (CDAI ≤150) compared with the placebo group.

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