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Diagnosis and Treatment of Low Testosterone among patients with End-Stage Renal Disease

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Abstract

The prevalence of low testosterone level is particularly high among patients with end-stage renal disease (ESRD) and has been associated with mortality. In populations without ESRD, low testosterone level has also been associated with a number of morbidities including cardiovascular disease, diabetes mellitus, low muscle mass, low bone mass, low physical performance, and frailty. However, there is controversy regarding what constitutes low testosterone level in the aging population and at what level replacement therapy with testosterone is indicated. There are no randomized controlled trials investigating long-term outcomes of testosterone replacement therapy in populations with or without ESRD. Available trial results suggest equivocal improvements in sexual function. Muscle mass and bone mineral density appear to improve but results in physical function and performance are mixed and there are no data on fracture prevention. Some recent data suggest harm when testosterone was given to men with limited mobility. Finally, there is little evidence that testosterone adds to existing erythropoietin agents in the treatment of anemia in ESRD. Due to lack of evidence supporting long-term use of testosterone, the authors recommend against the routine use of testosterone in ESRD patients with low testosterone levels. Testosterone treatment can be considered in those with low bone mass and total testosterone level less than 200 ng/dL, or in younger patients with sexual complaints with total testosterone level lower than the reference range. It is important to engage patients in discussion of risks and benefits before initiating testosterone therapy; testosterone therapy should be discontinued if the intended treatment effect is not observed after short-term use.

The prevalence of low testosterone levels is particularly high among patients with end-stage renal disease (ESRD) (1). Recent studies have reported association of low testosterone levels with higher mortality in patients on dialysis (2,3). This has led to renewed interest in testosterone as a potential therapy to improve outcomes in ESRD. However, in spite of advances in our knowledge in the area of testosterone replacement in the non-ESRD population, there are still few data on testosterone therapy in patients with ESRD. On the other hand, for the aging male population, who share many similarities with patients on dialysis such as the burden of comorbidities and functional limitations, the issue of

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testosterone replacement therapy is at best controversial. Therefore, this review will focus on the controversies surrounding testosterone replacement in older men and expand on their relevance to the ESRD population whenever possible.

Clinical signs and symptoms of low testosterone level

Signs and symptoms suggestive of testosterone deficiency include sexual dysfunction such as low libido and erectile dysfunction. Other manifestations may include loss of muscle mass and strength, increased body fat, obesity, gynecomastia, fatigue, depression, and diminished physical and work performance. Such sexual, physical and psychological signs and symptoms, however, are non-specific and are common among aging men with comorbidities as well as patients with ESRD. For this reason, diagnosis of testosterone deficiency should never be based on clinical signs and symptoms alone. Rather, laboratory evaluation is an integral part of the diagnosis.

Pitfalls in laboratory evaluations

Most commercial laboratories use antibody-based immunoassays to measure serum total testosterone, the accuracy of which has been a source of considerable concern when compared against measurement by mass spectrometry (4-6). Taieb *et al* (4) compared ten immunoassays against gas chromatography – mass spectrometry (GC-MS) in measuring serum total testosterone and found that the ten immunoassays differed by a factor of five when the serum testosterone concentrations were below 230 ng/dL, levels commonly seen in hygonadal men!

The Endocrine Society (TES) has convened a task force to standardize testosterone measurement and improve its accuracy (7). For the present, recommendations from several bodies including TES, the International Society of Andrology (ISA), International Society for the Study of Aging Male (ISSAM), European Association of Urology (EAU), European Academy of Andrology (EAA), and American Society of Andrology (ASA) agree that the clinician be familiar with the method, its performance and its reference range in the performing laboratory rather than using a universal cutoff value in evaluating testosterone levels cited in textbooks or clinical guidelines (8). Because testosterone levels exhibit circadian rhythm with peak values in the morning, it is also recommended by the above professional societies that serum testosterone values be checked in the morning and repeated at least once before making a diagnosis of testosterone deficiency.

Over 95% of the circulating testosterone is tightly bound to sex hormone binding globulin (SHBG), and a small percentage is loosely bound to albumin. Only about 0.5 to 3% of circulating testosterone is unbound; this so called free testosterone is deemed to have access to cells and be able to exert biological effects at the tissue level. Under most circumstances, measurement of total testosterone is considered adequate unless there is significant disturbance in the production of SHBG and albumin. However, in patients with ESRD, circulating SHBG concentration could be variable for a number of reasons: it could be low in nephrotic syndrome, moderate obesity, or diabetes mellitus, whereas it could be high with aging, hepatic cirrhosis, or HIV disease. The gold standard of measurement for free testosterone is by equilibrium dialysis, which is not readily available in most commercial

laboratories. TES recommends against the use of analog method for measurement, but rather suggests calculation of free testosterone from total testosterone and SHBG concentrations using algorithms based on the law of mass action, which correlates well with measurements by equilibrium dialysis (8), although we are aware of no data addressing the extent to which uremia might affect formulas established in individuals with normal kidney function.

Controversies in the definition of hypogonadism

Major professional societies (TES, ISA, ISSAM, EAU, EAA, ASA) agree that the diagnosis of hypogonadism requires both the presence of clinical signs and symptoms and a low testosterone level (8,9). In other words, hypogonadism is defined as a syndrome with both clinical and biochemical criteria. However, what constitutes a low testosterone level, especially in the aging male and in those with chronic illnesses such as ESRD, is where substantial controversies arise.

By convention, values below the 2.5th percentile for most laboratory tests are deemed below normal. However, the testosterone reference ranges of commercial assays are based on small convenience samples, which could partly explain the wide variations in the limits of normal encountered in clinical practice. Bhasin *et al* (10) recently measured serum total testosterone levels by liquid chromatography tandem mass spectrometry (LC-MS/MS) in a cohort of 456 young healthy men from the Framingham Heart Study Generation 3 and determined that the 2.5th percentile of total testosterone was 348 ng/dL.

Because serum testosterone levels decline with age, some argue that the reference range for testosterone should be age specific. In a cohort of 890 relatively healthy men from the Baltimore Longitudinal Studying of Aging (BLSA) followed longitudinally for a mean of 10 years, serum total testosterone levels, as measured by radioimmunoassay (RIA), decreased on average 3.2 ng/dL per year, and the rate of decline did not vary significantly from the third to the ninth decade of life and was independent of smoking, alcohol use, and medication use (11). Using GC-MS, Yeap *et al* (12) found that in a cohort of 394 men with a mean age of 76 years reporting excellent and very good health and without significant comorbidity, the 2.5th percentile of serum total testosterone value was 184 ng/dL. Thus, it is clear that if we use age specific reference ranges, the cutoff for low serum testosterone would be substantially lower in the elderly population than that for young healthy individuals.

Still others argue that the lower limit of normal for serum testosterone values should be based on the threshold below which men are more likely to develop symptoms. In the European Male Aging Study (EMAS), Wu *et al* (13) found that three sexual symptoms (decreased frequency of morning erections, erectile dysfunction, and decreased frequency of sexual thoughts), but not physical or psychological symptoms, were consistently associated with a low serum total testosterone level (below 320 ng/dL), and the probability of these sexual symptoms was much lower above this concentration.

Benefits and risks of testosterone therapy

Regardless of how we define “normal” for serum testosterone levels, the ultimate clinical question is to designate a threshold level below which the benefits of testosterone therapy outweigh its attendant risks. Epidemiological studies have shown association of low serum testosterone levels with a number of adverse outcomes including low bone mineral density (14), diabetes mellitus (15), cardiovascular events (16-18), poor physical performance (19), frailty (20) and mortality (16-18). The association of low testosterone level and mortality has also been shown in patients on dialysis (2,3).

To date, however, no randomized controlled trial (RCT) of sufficient power has addressed whether testosterone therapy will improve any of these outcomes or the risks and benefits of long-term testosterone therapy. Most RCTs were small in size, of short duration, and addressed only a few outcomes of interest. In addition, trials differed widely in inclusion criteria in terms of testosterone levels and patient age and health, testosterone replacement regimen (route of delivery and dose), and target testosterone levels on treatment. Altogether, this variability makes it difficult to generalize results, and findings from meta-analyses should also be interpreted cautiously.

Benefits of testosterone therapy

Sexual function—In general, more trials have reported improvement in libido than in erectile dysfunction, and there appears to be a threshold value above which testosterone replacement is unlikely to produce improvement (8,21). One meta-analysis showed that among trials that enrolled men with total testosterone levels < 300 ng/dL, there was a large improvement in libido (1.3 SD units; 95% CI, 0.4, 2.2), although only 5 trials were included and 3 of the 5 trials were cross over studies using oral testosterone un decanoate, which is not available in the United States (22). The remaining 2 trials used transdermal testosterone application in the elderly, and the effect size on libido was much smaller compared to trials using oral testosterone (0.2 SD units; 95% CI, -0.02, 0.57). The same meta-analysis did not show a statistically significant improvement in erectile function.

Body composition, muscle strength, and physical function—Systematic reviews show consistent increases in lean body mass and decreases in fat mass with testosterone replacement therapy regardless of baseline serum testosterone levels (23). However, improvement in muscle strength and physical function is less consistent. Since muscle strength and physical function are two important clinical outcomes to target in the ESRD population, we will describe RCTs that were specifically designed to evaluate these outcomes in the elderly with significant comorbidities or functional limitations, cohorts which otherwise share many characteristics with patients on dialysis.

To the best of our knowledge, there has been only one RCT that specifically targeted older men with mobility limitation: the Testosterone in Older Men with Mobility Limitations (TOM) trial (24). The TOM trial enrolled men who were 65 years of age or older, had serum total testosterone between 100 and 350 ng/dL or a calculated free serum testosterone level of less than 50 pg/mL, and had evidence of limitations in mobility, defined as difficulty walking two blocks on a level surface or climbing 10 steps and had a score between 4 and 9

on the Short Physical Performance Battery. Among 138 men who received at least one post-randomization assessment, testosterone treatment with 100 mg of a transdermal gel daily (adjusted to target serum total testosterone of at least 500 ng/dL) for 6 months significantly increased lean body mass and appendicular lean soft tissue mass and decreased total body fat mass. Testosterone treatment also significantly increased leg press strength, chest press strength and power, and loaded stair-climbing power. There was a trend toward increased loaded walking speed, but it did not reach statistical significance. Testosterone treatment did not significantly improve unloaded walking speed or self-reported functional disability or physical activity. The favorable changes in body composition, muscle strength and physical performance were associated with increases in total and free testosterone. The TOM trial was terminated early due to increased cardiovascular events in the treatment arm (25), which we shall elaborate on later in this manuscript.

Another RCT by Srinivas-Shankar *et al* (26) published in the same year as the TOM trial enrolled men who were 65 years of age and older and who had serum total testosterone level of 345 ng/dL or lower or calculated free testosterone of ≤7.2 ng/dL (72 pg/mL). Men also met at least one of the five criteria of frailty as defined by Fried *et al*. (27), which include unintentional weight loss, self-reported exhaustion, low physical activity, slow walk time, and low handgrip strength. A total of 274 men were randomized, and treatment consisted of daily 50 mg transdermal testosterone gel (half the dose of that used in the TOM trial) for 6 months, adjusted to target serum testosterone in the laboratory reference range (518 to 864 ng/dL). At the end of the 6 months, lean body mass increased significantly and fat mass decreased significantly among men who received testosterone. Isometric knee extension peak torque improved significantly in the treatment group, but isokinetic knee extension peak torque, isometric knee flexion peak torque, isokinetic knee flexion peak torque, and grip strength did not. There was no significant difference between the groups for physical function as measured by Tinnetti gait and balance, aggregate locomotor function (ALF) test, physical performance test (PPT), or 6 minute walk test. In subgroup analyses, those who met at least two criteria of frailty at baseline and received testosterone had significant improvements in ALF and PPT. There was also significant improvement in PPT in those older than 75 year of age who received testosterone. There was a correlation between change in muscle strength and change in physical function. A follow up at 12 months showed that none of the gains in body composition, muscle strength or physical function persisted 6 months after treatment ended (28).

Kenny *et al* (29) recruited men 60 years and older who met at least one of the five criteria of frailty by Fried *et al* (27) and who had a bone mineral density t score at the hip of -2.0 or less or had had a non-traumatic fracture within the past 5 years. Baseline serum testosterone level was ≤350 ng/dL. One hundred thirty-one men were randomized, and the treatment arm received daily 50 mg transdermal gel (Androgel 1%) for 12-24 months. There was an increase in lean mass and a decrease in fat mass in the testosterone group but no significant differences in strength or physical performance were observed. The adherence in this study was only 54% at the end of 12 months, but the authors commented that outcomes were not different from intention-to-treat analysis when only those with higher adherence rate or those who reached the highest tertile of bioavailable testosterone were included in the

analysis. There was a non-significant trend for higher dropout rates in those who were more frail.

Although direct comparisons across these trials are not possible, it is worth noting that the mean serum total testosterone levels achieved with therapy appeared different among the three trials: 328 ng/dL for the TOM trial (25), 210ng/dL for the trial by Srinivas-Shanker *et al* (26), and 187 ng/dL for the trial by Kenny *et al* (29). The TOM trial showed the most positive results in the domains of muscle strength and physical performance, and the results in the trial by Kenny *et al* were essentially negative. Bhasin *et al* (30) have previously shown that older men are as responsive as young men to the anabolic effects of testosterone on muscle, and the response is dose dependent. Since all three trials showed improvement in body composition with testosterone treatment, it appears that frail men with functional limitations are also responsive to the anabolic effects of testosterone on muscle mass, but improvements in muscle strength and physical function may need higher doses of testosterone, or longer duration of treatment, or concurrent physical and functional training, or a combination of all of the above.

There have been few trials that evaluated the anabolic effects of testosterone in the ESRD population. Johansen *et al* (31) in a RCT showed that nandrolone decanoate 100 mg once weekly significantly increased lean body mass, serum creatinine level, and improved time to complete the walking and stair-climbing tests compared to placebo in patients with ESRD on dialysis. The trial was small in size (N=29), and participants were relatively young (mean age 44 years, SD 15 years). However, it is reasonable to expect that testosterone is capable of inducing anabolic changes in patients with ESRD to a similar extent as in patients without chronic kidney disease.

Bone health—Another anabolic effect of testosterone that may be of particular interest to patients on dialysis is its effect on bone health. There are no RCTs reporting fragility fractures as an outcome, but there have been several RCTs that evaluated bone mineral density (BMD) after testosterone treatment in the general elderly population (32-34). Meta-analyses showed a moderate increase in lumbar BMD in men and inconclusive results on femoral neck BMD (35). The effect of testosterone on BMD appears to be limited to those with baseline values in the low to low normal range, while testosterone fails to improve BMD when baseline values are normal.

In a RCT of healthy men 65 years of age and older with baseline serum total testosterone level below 475 ng/dL, treatment with 6 mg testosterone daily delivered by a transdermal patch did not significantly improve BMD at either lumbar spine or femoral neck (33). However, in linear regression analysis, the lower the pretreatment testosterone level, the greater the increase in bone mineral density over 36 months in the men treated with testosterone compared to those who received placebo ($p = 0.02$).

In the Osteoporosis Fractures in Men study, there appeared to be a threshold association between serum testosterone level and prevalence of osteoporosis and rapid bone loss at the hip: the odds of having osteoporosis at the hip tripled, as did the odds of experiencing rapid hip bone loss, with baseline testosterone levels below 200 ng/dL (14). For fracture

prevention, TES currently recommends testosterone therapy only in men whose serum testosterone levels are below 200 ng/dL who have contraindications to approved “bone” agents for fracture prevention or who meet criteria for androgen deficiency syndrome and are otherwise appropriate candidates for testosterone treatments for non-bone related outcomes (8). TES acknowledges that this conservative approach largely stems from the unknown long-term safety of testosterone therapy. While patients on dialysis are at higher risk for fractures, their underlying bone diseases are often more complicated than senile osteoporosis. The review of kidney disease related bone mineral disorders is beyond the scope of this review, but one should bear in mind the possibility of a dynamic bone disease in patients on dialysis. In dialysis patients, application of transdermal testosterone increased serum estradiol level into the normal range for healthy men (36). If the effects of testosterone on bone are at least partially mediated through aromatization to estrogen, an anti-resorptive agent, then its use could potentially have deleterious effects in the setting of low turnover bone disease.

Risks of testosterone therapy

The adverse effects of testosterone replacement include acne, worsening of male pattern balding, gynecomastia, breast tenderness, worsening lower urinary tract symptoms, and precipitation or worsening of sleep apnea. Potential serious risks of testosterone replacement include increase in prostate specific antigen (PSA), accelerating the growth of prostate cancer and breast cancer, and increased cardiovascular events. A recent meta-analysis showed that testosterone treatment of variable duration (3 months to 3 years) was associated with a decrease in high-density lipoprotein cholesterol (weighted mean difference, -0.49 mg/dL; 95% CI, -0.85 to -0.13), but there was no significant effect on mortality, prostate, or cardiovascular outcomes (37).

However, this meta-analysis did not include the results of the previously mentioned TOM trial, which was prematurely terminated due to a significantly higher rate of cardiovascular events in the treatment group: 23 events vs .5 events in the placebo group (25). To our knowledge, this is the only trial that has shown a higher rate of cardiovascular events with testosterone treatment, although no other trials have been designed and sufficiently powered to evaluate cardiovascular outcomes. While it remains possible that the cardiovascular events were more frequent in the treatment group from the TOM trial by chance, it certainly deserves further investigation; a causal link between testosterone treatment and cardiovascular events cannot be excluded. Mechanistically, testosterone stimulates human platelet aggregation by increasing thromboxane A2 receptor density (38). Additionally, testosterone can be aromatized to estrogen, a steroid known to promote thrombosis and increase risks for venous thromboembolism, coronary events and cerebrovascular events.

Upon further analysis of the TOM trial, the increase in free testosterone level at the end of treatment, but not the change in circulating concentrations of IL-6, CRP and fibrinogen levels, was associated with greater risk for cardiovascular events in multivariable regression (39). The increase in serum total and free estradiol and estrone levels were approximately twice as high in those who experienced cardiovascular events compared to those who did not, although the difference was not statistically significant. It is important to bear in mind

that the trial was not designed to assess cardiovascular outcomes, and the relatively small number of events should give us pause in our confidence in the observed difference. Another important observation about the TOM trial is that the testosterone dose was rather high, and although the mean testosterone level on treatment was comparable to that achieved in most other trials, significant variations existed, and several participants had levels above the upper limit of normal (1000 ng/dL). Cardiovascular events were reported in 4 of 14 (28.6%) participants with testosterone levels higher than 1000 ng/dL, in 5 of 21 (23.8%) with levels of 500 to 1000 ng/dL and in 7 of 46 (15.2%) participants with levels less than 500 ng/dL.

Since the publication of the TOM trial, several epidemiological studies have attempted to address the potential relationship between testosterone therapy and cardiovascular disease. Vigen *et al* (40) conducted a retrospective cohort study of men with low total testosterone levels (<300 ng/dL) who underwent coronary angiography in the Veterans Affairs (VA) system. After adjusting for the presence of pre-existing coronary artery disease, testosterone therapy was associated with higher risk of the composite of all-cause mortality, myocardial infarction (MI) and stroke (hazard ratio, 1.29; 95% CI, 1.04 to 1.58). In contrast, another retrospective cohort study from the VA (41) found that among 1031 male veterans with low total testosterone levels (≤250 ng/dL) and age older than 40 years, testosterone treatment was associated with lower risk of death (hazard ratio 0.61; 95% CI, 0.42 to 0.88; P=0.008). In subgroup analysis, there was no significant effect modification by age or coronary heart disease (CHD), although a greater mortality reduction was observed among younger veterans (age < 60 years) and among those without CHD. It should be noted that the prevalence of CHD in the study by Vigen *et al* was >50% while that in the latter study was 20%, which could have accounted for the discrepancy in results.

Until results become available from RCTs that address long-term outcomes of testosterone therapy, clinicians should be particularly cautious in considering the risks and benefits of testosterone replacement therapy in ESRD patients with their high burden of vascular disease; certainly supraphysiological levels of testosterone should be avoided.

Testosterone therapy and erythrocytosis

It has been well described that testosterone stimulates erythropoiesis. Erythrocytosis is a known risk of testosterone replacement in populations without chronic kidney disease. Before the introduction of recombinant human EPO (rHuEPO) into clinical use in 1989, androgens were the mainstay of pharmacological therapy for anemia in patients with ESRD on dialysis. Hendler *et al* (42) conducted a double-blind crossover study in 21 patients on maintenance hemodialysis and found that nandrolone decanoate 100 mg intramuscularly per week for five months increased mean hematrocrit from 23 to 27 percent (P< 0.005). When androgen therapy was discontinued, the hematrocrit fell slowly toward previous levels over a period of one to three months. In an interview at study completion, four patients mentioned increased strength during treatment; only one participant reported improvement in feelings of well-being and libido. Testosterone enanthate was also to treat anemia used and appeared to be comparable to nandrolonein a randomized trial by Neff *et al* that compared four androgens (nandrolone at 3 mg per kilogram of body weight per week intramuscularly, testosterone enanthate 4 mg per kilogram per week given intramuscularly, fluoxymesterone

0.4 mg per kilogram per day by mouth, oxymetholone 1 mg per kilogram per day by mouth) (43). Patients were randomly assigned to receive one of the four agents for six months (except that women did not receive testosterone enanthate). The response to the two injectable testosterone formulations over 6 to 8 months (4.7% increase in hematocrit) was superior to the response to the oral agents (1.8% increase). No specific side effects were reported, but authors commented that almost a quarter of patients withdrew because of side effects or refusal to take androgens.

With the widespread use of rHuEPO as an effective treatment for anemia, the use of androgens as an erythropoietic agent has become obsolete. However, there remains a continued interest in using androgen as an adjunctive therapy to rHuEPO to augment the effect of rHuEPO, to decrease the dose of rHuEPO, or in situations when patients are not reaching target hemoglobin even on maximum dose of rHuEPO. Some small trials showed that combination treatment with nandrolone and rHuEPO increased hemoglobin more than rHuEPO alone (44,45), but no trials have examined whether nandrolone allowed for a decrease in rHuEPO dose. In a small (n=40) RCT, the addition of 100 mg 1% testosterone gel daily for 6 months did not diminish the rHuEPO dose required to maintain a stable hemoglobin level (46). However, there was a high attrition rate in that trial, and the increase in serum testosterone level in the treatment group was not statistically significant compared to the placebo group.

The recently published Clinical Guidelines from the Kidney Disease Improving Global Outcome (KDIGO) for Anemia in Chronic Kidney Disease recommend against the use of androgens as an adjuvant to erythropoiesis-stimulating agents (ESAs) (47). The rationale behind this recommendation is the lack of evidence from large RCTs to show the benefits of androgen in patients who are hyporesponsive to ESAs and the uncertain long-term risks of androgen use.

In summary, the field of testosterone therapy in ESRD is filled with controversies, which calls for well-designed RCTs to elucidate the benefits and risks of long-term testosterone use in this population. Given the recently published results of the TOM trial, the authors recommend against offering testosterone therapy to all ESRD patients with low testosterone levels. Testosterone therapy can be considered in patients at high risk for fractures and whose serum testosterone level is below 200 ng/dL. In the younger patients with sexual complaints, testosterone therapy can be considered if their serum testosterone level is below 300 ng/dL or the lower limit of normal of the local laboratory. However, testosterone should be discontinued if there are no improvements in sexual dysfunction. Before evidence from high quality RCTs becomes available, clinicians are advised to make individualized decisions in each clinical situation and to engage patients in the discussion of the uncertainties of the risks and benefits of testosterone therapy.

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