Blue Cross and Blue Shield of New Mexico

Testosterone Therapy in the Elderly: potential benefits and risks

Introduction

The pharmaceutical industry has recently caught the attention of the public through its widespread "LOW-T" advertising campaigns. What's most interesting is how they have been convincing us that treating a number (i.e., low testosterone serum level) will magically turn back the hands of time and correct all of our ills.

The benefits of testosterone therapy for hypogonadism in younger and middle aged males appear to be diverse and wide-ranging. From improving libido, vitality, mood, cognition and anemia to increasing bone mineral density, and lean muscle mass, testosterone may appear to be a panacea. There are even studies indicating that testosterone therapy may decrease hemoglobin A1C, glucose intolerance and inflammatory markers [1, 2].

The Controversy

The controversy surrounding the use of testosterone in our senior population stems from the fact that there are very few large, double-blind, multiple-endpoint, high quality randomized trials on which to base expected benefits or risks of testosterone therapy. It is a controversy that revolves around multiple issues including defining normal testosterone levels in the elderly and possible benefits and potential risks in the elderly[1]. Over the last couple decades, it has become evident that after peaking in the 20s, testosterone levels decline with age. The exact amount of decline varies, but the annual decrease has been reported from less than 1% up to 2%[3]. Since many individuals with below normal testosterone remain asymptomatic, the issue as to whether the decrease in testosterone is pathological or a physiological phenomenon remains to be fully clarified[3]. Without clearly defined normal/abnormal testosterone serum levels in both the healthy and unhealthy elderly male it raises the question as to what is the appropriate goal of testosterone therapy. Whereas, serum levels for other conditions (e.g., A1C, TSH, etc.) have well known target ranges with direct correlations to positive outcomes the same cannot be said for testosterone serum levels.

Potential Risks

Although many of the known and suspected risks and benefits of testosterone therapy in older men are debatable and cannot be accurately assessed with current data, the possible risks include worsening sleep apnea, decreased HDL, and polycythemia [1, 2, 3]. Testosterone may also increase the risk of developing prostate cancers and cardiovascular events [1, 2, 3]. Although two meta-analyses found no increase in cardiovascular events, the Testosterone in Older Men with Mobility Limitations (TOM) trial, which was not included in either meta-analysis, was discontinued early due to an increase in the cardiovascular-related events in the group receiving relatively high doses of testosterone therapy[3]. Of the 209 subjects enrolled in the study, 23 men receiving testosterone therapy versus 5 men receiving placebo experienced a cardiovascular-related event. We also know that testosterone therapy appears to accelerate metastatic prostate cancer[1]. In regards to a possible increase in the incidence of prostate cancer, we know that appropriate testosterone therapy in younger men has increased the volume of the prostate but only to normal levels[1]. Although it is plausible that testosterone therapy in older men might lead to an increase in prostate cancer in this population, there is currently no evidence to support this conclusion. On the contrary, Cunningham and Toma point out that there is also evidence that prostate cancer incidence and BPH prevalence increases in older men when serum testosterone levels are falling[1]. However, since these studies are epidemiological studies, they should not be used to imply cause-effect relationships. It is also important to remember that since androgens can cause fluid and sodium retention, extreme caution should be used in patients with cardiac disease, severe hepatic disease or severe kidney disease[2].

Conclusion

Health plans are seeing increased utilization of testosterone products in the older male population with the usual treatment goal of increasing low testosterone serum levels. However, there is a need for more data to clarify the benefits and risks of long term testosterone therapy. The testosterone trial in older men is a one year randomized trial designed in response to the recommendation of the Institute of Medicine panel to better evaluate the benefits of testosterone therapy in males over 60 years of age[1]. Although the data from this trial will no doubt increase our understanding of the medical benefits of testosterone in the older generation, as of January 2013, it was still in the process of recruitment (http://www.clinicaltrials.gov/ct2/show/NCT00799617). However, as Cunningham and Toma point out in their clinical review on the topic, that even though we will be gaining great information on the benefits, it is important to remember that the results will not be powered to assess long term potential risks of testosterone therapy in the elderly[1].

In order to mitigate some of the side effects and risks of androgen replacement therapy, careful monitoring of a patient's therapy should be conducted.[1] Testosterone levels should be evaluated three to six months after the start of therapy and appropriate dose adjustments should be made to maintain desired serum testosterone levels. As part of the patient's monitoring program a hematocrit should be checked prior to the start of therapy, at three to six months, and then annually. If the hematocrit is >54%, testosterone therapy should be stopped until the hematocrit returns to normal.

In the interim, it is of vital importance to consider chronic medications that may lead to hypogonadism (corticosteroids, metoclopramide, opioids, psychoactives, and high doses of cimetidine, spironolactone, ketoconazole, flutamide, cyproterone) [4] and weigh potential benefits and potential risks of testosterone therapy. It is also important to keep in mind the advantages and disadvantages of current therapies. Long acting parenteral preparations (testosterone cypionate and testosterone enanthate) may lead to fluctuations in the level of testosterone[2]. The ANDRODERM patch mimics the diurnal pattern of testosterone seen in younger males but introduces the risk of skin irritation and possible transfer to other family members, etc.[2]. Gels and solutions provide less fluctuation in the level of testosterone but also bear the potential for transfer[2]. The Striant buccal system also does away with large fluctuations in testosterone levels but safety data is limited, and it may cause changes in taste as well as gum and mouth irritation[2]. With all topical testosterone applications, it is very important to communicate exactly how and where they should be used as well as how to avoid transfer to other family members, etc.

A recent 2013 research letter published in the Journal of American Medical Association (JAMA) showed that from 2001 through 2011 there was a 3-fold increase in androgen use among men 40 years or older.[5] The findings reported that almost 20% of all new users received ART (androgen replacement therapy) for 30 days or less and that most men did not have clear evidence for an appropriate clinical indication for ART. This suggests that the clinical reasons for starting therapy are complex. More research is needed to determine the extent to which normal men with normal testosterone levels and ambiguous symptoms seek and are prescribed ART, particularly given the concerns about cardiovascular and other potential toxic effects from ART.

A few counseling points to remember:[2]

- ANDROGEL's (1.62%) bioavailability is reduced when applied to the abdomen.
- Topicals should never be applied to the genitals.
- Since the buccal system does not dissolve completely, it needs to be removed before replacing it.
- Many individuals with below normal testosterone remain asymptomatic.
- Side effects of testosterone include worsening of sleep apnea, decreased HDL, and polycythemia.
- TOM trial was discontinued early because of increased rate of CV events.
- Careful monitoring of testosterone levels should occur every 3-6 months.
- Hematocrit should be checked prior to starting, at 3 & 6 months, then annually.
    - If hematocrit >54% testosterone therapy should be stopped.
- Review for other medications that may cause hypogonadism.

This information is not intended to replace your clinical judgment. Only you, in direct consultation with your patient, may determine if drug therapy benefits outweigh the potential risk. If a change is warranted please advise your patient directly.

References

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