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Reflections on The T Trials

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Abstract

Background: This manuscript is a review and discussion of the published results of The T Trials.

Objective: To re-examine the efficacy of testosterone replacement of hypogonadal men greater than 65 years of age in The T Trials.

Materials and Methods: The T Trials were a complex collection of seven double blind, placebo-controlled trials of the efficacy of testosterone as replacement therapy for older men with unequivocal hypogonadism. There were three main trials (sexual function; physical function; vitality) and four sub-trials (cognition; bone; anemia; cardiovascular). All subjects participated in the main trials while more selective inclusion/exclusion criteria existed for the sub-trials. Subjects were excluded for perceived higher risk of prostate cancer and recent myocardial or cerebral vascular events.

Results: The previously published results are reviewed here as seen in the context of this special issue on late onset hypogonadism. In the T Trials, positive benefits were seen in the sexual function, bone, and anemia trials with small but significant benefits in the vitality trial. No benefit was seen in the cognition trial, partial benefit in physical function, and a negative benefit outcome seen in the cardiovascular trial. The later trial was underpowered and the results were described as exploratory. Adverse events were relatively uncommon in the 12-month treatment phase and additional 12-month post treatment phase. The most frequent adverse effect ascribed to testosterone was erythrocytosis.

Conclusions: The T Trials studied the efficacy of testosterone replacement therapy on 788 men with low testosterone and symptoms of hypogonadism. The studies demonstrated benefits in four trials (sexual function, vitality, bone and anemia); partial benefit in the physical function trial; no effect in the cognition trial; and a negative effect in the exploratory cardiovascular trial. The T Trials were not designed to assess long-term risks of testosterone in men

Introduction

The T Trial at its outset was the largest placebo controlled double blind study of possible benefits and short-term adverse effects of a transdermal testosterone treatment on hypogonadal older men. The study was special for many reasons including the fact that the 788 male subjects were selected for participation based on age (greater than 65 years) with baseline serum testosterone levels unequivocally lower than the reference population of younger men (<250-275ng/dl.) on two occasions and self-described symptoms of “male hypogonadism” ¹. The study design was complex as it attempted to answer a number of outcomes using a coordinated set seven separate protocols. The hypogonadal older men had to participate in the three “main” protocols (Sexual Function, Physical Function and Vitality). Those men that qualified for one of the main protocols were allowed to participate in the other two. There were four additional protocols (Cognition, Anemia, Bone, and Cardiovascular Trials). The four additional protocols had trial specific inclusion/exclusion criteria and the men that met protocol specific criteria could elect to participate in appropriate additional trials ². The last two trials (bone and cardiovascular) were initiated later than the original three main T Trials and the Cognition and Anemia trials.

The T Trials had a long preparatory phase that grew out of concern by prospective funding agencies about possible adverse effects of testosterone treatment on induction or worsening of prostate cancer and later concerns of risk/benefit on cardiovascular disease. For these reasons, men with existing or high risk of prostate cancer or severe lower urinary obstructive symptoms were excluded; men with recent history of MI or stroke were also excluded from participating. The study was performed in 12 geographically diverse academic sites; the subjects were selected from diverse populations.

In the authors’ opinion, the study was remarkable for the intense involvement of a Steering Committee (SC) that included many site PIs and other experts in the selected areas including data management and biostatistics. Program officers from the National Institutes of Health (NIH), National Institute of Aging (NIA) frequently participated in steering committee meetings and gave valuable guidance. Program officers from other funding NIH

agencies also joined SC meetings when advice was needed. The overall principal investigator, Peter Snyder, MD met by teleconference on a regular basis with the SC. The positive impact Dr. Snyder's wise and structured leadership of the SAC and the study performance cannot be overemphasized. Funding came from a number of NIH institutes (NIA, National Heart, Lung and Blood Institute, National Institute of Neurological Diseases and Stroke, and National Institute of Child Health and Human Development). The testosterone formulation (Androgel® 1%) used in the active arm was selected by the SC based its wide use in the medical community and ample knowledge of its pharmacokinetic and dynamic characteristics ³. AbbVie generously provided the testosterone gel and the placebo gel without involvement in the study design, analysis, and interpretation of results or publication content.

The study was also remarkable for the large number of resultant publications (>25) While the availability of the published data is widely available, its repeat summary presentation in this special Issue on Late Onset Hypogonadism would not be complete without these reflections included.

Starting the study

Testosterone has been available for clinical use for over 80 years with prescription usage fairly stable until 2000 when a new transdermal formulation of testosterone was approved and marketed in the US and Europe. A number of papers described the pharmacokinetics and pharmacodynamics of the transdermal route of administration³⁻⁶. Soon thereafter, physician prescriptions soared and the number of users rapidly increased. A study was published in 2001 out of the National Institute of Aging supported Baltimore Longitudinal Study suggest that the incidence of low total and free testosterone levels were very high in older men ⁷. This stimulated a great interest in whether older men would benefit from testosterone replacement therapy with the deficient hormone. As men began to be treated in large numbers, a proposal was developed by a cadre of investigators what later became the T Trials SC to look at possible adverse effects of testosterone replacement in this older male population. A study was considered by the US Veterans Administration and other US federal

funding agencies to assess possible risks of long-term treatment with testosterone in older men. Representatives of the National Cancer Institute expressed reservations on safety of performing the study; the NIA and the National Cancer Institute asked the US Institute of Medicine (IOM) to assess the status of clinical research on testosterone therapy for older men. Their report in 2004, recommended that the NIA fund a comprehensive study to determine what benefits might be expected from testosterone treatment of older hypogonadal men; they implied that longer-term safety issues could be delayed until benefits were convincingly demonstrated ⁸. The NIA accepted the challenge and the T Trials protocol was initiated. Other NIH Agencies join in the funding. Dr. Peter Snyder was selected as the principal investigator of The T Trials and the SC Committee took 6 years with many iterations before the final protocol was designed, accepted and funded and investigational sites selected.

The details of the study design are described elsewhere ². The salient characteristics of the study population included men greater than 65 years with baseline serum testosterone levels unequivocally lower than the reference population of younger men (<250-275ng/dl.) on two occasions and self-described symptoms of “male hypogonadism”. Men with existing or high risk of prostate cancer or severe lower urinary obstructive symptoms and those with recent history of MI or stroke were also excluded from participating. The initial dosage of the T gel was 5 mg with adjustments allowed during the study to attain serum levels of testosterone in the mid young adult male range (500 to 800 ng/dL). Despite large within and between participant variations in the T gel treated group ⁹, the success of adjustment of dosing was shown in the main T Trial manuscript ¹⁰. The study design was for one year of testosterone or placebo treatment with a second year of follow-up. Of the 788 enrollees with a mean age of 72 years, there was an 89% completion rate for efficacy with the short-term adverse event rate carefully compiled. Because of the complexity of the multiple coordinated trials the statistical evaluations were carefully crafted using a technique of minimization; this allowed for balancing a greater of baseline variables than randomization with stratification.

Issue of selection and screening of potential subjects

Most sites recruited by mass mailings. 51,085 men called the site close to them and were pre-screened by phone. The men with no symptoms of hypogonadism or exclusionary disorders were excluded. 23,889 men visited the study sites for screening testing and interviews. Fasting serum levels of testosterone and PSA were obtained. Approximately 10% met the criteria of low morning serum T and acceptable PSA. Those that met the first hurdle were assessed at a second visit with early morning serum T levels assessed again. Only 14.7% of the symptomatic men met the low testosterone inclusion criteria after two screens. Only 1.5% of the men who expressed interest in the trial were enrolled ¹¹. This demonstrated the difficulty using strict screening criteria that included symptoms of hypogonadism for entry into the T Trials. It also helps explain why many published reports that enrolled men with near normal testosterone entry levels and frequently asymptomatic for prior studies and explains the variable efficacy data in the literature.

Sexual Function trial

Not unexpectedly the sexual function study showed positive efficacy in the primary outcome of sexual activity ¹⁰ as assessed by question 4 of the Psychosexual Daily Questionnaire (PDQ) ¹². This question assesses 12 sexual activities. The PDQ has been validated and demonstrated to show benefit in sexual function in other testosterone studies ^{4, 6, 13, 14}. Two other parameters were assessed for sexual function including libido and erectile function. The Derogatis Inventory of Sexual Function-Men-2 ^{15, 16} and the International Index of Erectile Function ^{17, 18} were also evaluated in the trial but unlike Q4-PDQ were only performed in the T trial Sexual Function group. Using the data from The T Trials moderate to strong correlations were shown within and between domains from different questionnaires ¹⁹

Testosterone treatment showed a positive effect against placebo in all time periods in all men in the T Trial and in the more select Sexual Function Trial ^{10, 20}. The effect size was 0.45, which was described as “moderate. There was positive result of T treatment of erectile function but it was less than that on libido. Men were asked for a global impression outcome at the end of the study and 20% claimed “much improved sexual desire” vs 10% in the placebo group. There was a correlation of serum total and free testosterone with positive

improvements in sexual activity, libido and erectile function suggesting a dose effect ²¹. The results of this study is consistent with other study using a similar gel on a somewhat younger study group of middle age ^{6, 13, 22} but different from other studies in frail older men who did not have symptoms of hypogonadism where no improvement in sexual function was observed ^{23, 24} .

The improvements in sexual desire and libido in older hypogonadal men and much lesser benefit on erectile function are consistent with the recently published summary of other reports based on other 52 week randomized double blinded placebo controlled studies (RCTs), observational studies and met-analyses ²⁵. While the sexual desire and libido observations were clear, the benefits were described as modest; and the benefits on erectile function were less consistent.

Physical Function Trial

Determination of effect of testosterone replacement on physical function was a high priority of the NIA as they were interested in ways to decrease functional debility and slow loss of independence that is associated with aging of men. It had been shown that testosterone replacement therapy increased muscle mass in many studies but improved functional physical performance was not consistently demonstrated with replacement doses of testosterone in older men. This need cannot be more obvious in this pandemic of Covid-19 and the high mortality rates in skilled nursing and senior citizen living facilities. There were many debates of the physical function trial-planning group as to the ideal outcome metric to use in the T Trial. The 6-minute walk was selected and the distance walked in this time interval above baseline was the outcome ¹⁰. Eligibility for the trial required some degree of difficulty walking bat baseline. Absolute distance walked at 6 minutes above baseline and percentage of men whose timed walking ability increased by > 50 meter at the end of the trial were primary outcomes. The improvement in the two parameters was not significantly greater in 387 men who qualified for the trial. However, the same metrics were also applied to the entire T-trial population and significant improvements of both outcome criteria.

Subjects in T treatment arm in the select Physical Function Trial and the entire T trial study

also perceived they were walking better based on two separate perception testing methods²⁶. Overall, the benefit was relatively small relative to that hypothesized for benefits of T treatment based on improvement in lean body mass and muscle strength. While improvement walking is an important function for retention of independent living it is possible that other physical function outcomes may have shown greater benefits; nevertheless, improvement in mobility after testosterone treatment of hypogonadal older men has been elusive in a number of studies^{23, 25, 27}.

Vitality Trial

Vitality is something people understand as improved energy and wellbeing. Loss of energy is one of the complaints often associated with testosterone deficiency. Objective assessment of a questionnaire with a variable scale between “energy and fatigue” was used in The T Trials. Men were enrolled in the Vitality Trial based on their complaint of low energy and having scored below midpoint on the pre-trial Facit-fatigue scale^{28, 29}. The results of this trial failed to show benefit from testosterone in the primary outcome of > 4 points on the Facit-Fatigue scale. However, as was true for the physical function trial, there was an improvement in the T arm in the overall T trial group but the degree of benefit was small¹⁰. Based on our reflections on the published T trial data, we are not overly impressed with the benefits of testosterone on objective parameters of vitality. Benefits on mood were demonstrated in the Vitality Trial using the positive and negative affect scales and improvement in mild depression were statistically demonstrated in this trial; this effect on mood had been seen in other RCTs²⁵.

Cognition Trial

Since loss of cognitive function is a well-known aspect of aging in men and earlier epidemiologic data suggested a correlation of deficits with decreased testosterone levels, assessment of benefits of testosterone replacement therapy was an important part of the T trial. Men with age-associated memory impairment (AAMI) were enrolled in this study. The

entire 788 subjects of the T trial of were included in the analyses. The primary outcome was delayed paragraph recall by the Wechler Memory Scale Revised Logical Memory II. A number of additional tests were performed for special aspects of cognition. The results did not demonstrate improvement in delayed paragraph recall nor in a number of more selective complaints except for a marginal improvement in executive function³⁰. The T trial authors agreed that testosterone treatment of aged men with age impaired cognitive dysfunction was not beneficial for cognition. These findings help in judging the inconsistent findings of replacement testosterone therapy on cognition in earlier studies²⁵.

Bone Trial

It is well known that testosterone deficiency is associated with decreased bone mineral density. Many but not all earlier studies using different methodologies (areal bone mineral density by dual energy xray absorptiometry, volumetric bone mineral density (vBMD) by quantitative computed tomography and trabecular architecture using magnetic resonance imaging) had shown increased bone mineral density with testosterone replacement in hypogonadal men. 211 men were enrolled in the testosterone and placebo arms. The testosterone arm had a 6.8% greater increase of trabecular bone in the spine compared to placebo ($P < 0.001$) after 1 year of treatment. There was also an increase in estimated trabecular bone strength by 8.5% with testosterone compared to placebo ($P < 0.001$) and increases in whole body vBMD and estimated whole bone strength³¹. The study did not require osteoporosis for entry, was underpowered and likely of too short duration to assess fracture rate, nevertheless the increase in BMD was at least equivalent to that of bisphosphonates on vBMD in osteoporotic women although somewhat less than a report in osteoporotic men. The results of the Bone sub-trial of the T Trials provided added strength to many studies describing benefits of testosterone on bone mass³²⁻³⁴; the associated increase in bone strength in hypogonadal older men was encouraging. Future controlled studies will weigh the potential of T treatment to prevent fractures in middle and older age hypogonadal osteoporotic men.

Anemia Trial

Testosterone is known to stimulate erythropoiesis and is believed to be the cause for gender differences in hemoglobin levels in men older women. However, prior to this trial, most Andrologist and Endocrinologists saw the association of testosterone and hematocrit/hemoglobin in the context of erythrocytosis as a testosterone treatment adverse effect.

While the T trial considered erythrocytosis as a possible negative aspect of testosterone treatment of older men, the focus of the Anemia Trial was on possible benefit on anemia associated with aging. This was not a new idea as testosterone was previously used as a general treatment of anemia and was shown in earlier studies to increase hemoglobin levels in untreated hypogonadal men ³⁵. In this trial, the benefit of testosterone treatment to men with testosterone deficiency and mild anemia (hemoglobin <12.7 and >10g/dL) was studied. Of the 788 hypogonadal men enrolled in the T trial, 126 were anemic at baseline. Of the anemic group, 64 were ascribed to possible causes such as inflammation, iron, folate or B12 deficiency. The remainder had no known cause and were labeled as unexplained anemia of aging. In the latter group, testosterone replacement therapy compared to placebo significantly improved hemoglobin levels by >1 g/dL in 54 % vs 15% of the men in the two treatment arms of the study. Anemia was corrected in 58.3% vs 22.2% (testosterone vs placebo) of the men ³⁶. The clinical correlate of the benefit in increase of hemoglobin was the significant report of general well-being and increased vitality with T treatment. Surprisingly a similar benefit in the T arm was seen the men whose anemia was ascribed to a “known cause”. Thus, testosterone might be seen as a clinically meaningful treatment for unexplained anemia of the elderly. While testosterone may benefit mild anemia of other causes, the pathogenesis of anemia should be evaluated in older men with hypogonadism prior to initiating testosterone replacement therapy.

Cardiovascular Trial

This trial was the last to be included in the T trial and was underpowered to answer the question whether testosterone would increase, decrease, or have no effect on

cardiovascular events in hypogonadal men. The background of the study included data on testosterone treatment that are conflicting, described in the original articles and have polarized the experts in the field and subjected to many reviews and meta-analyses^{25, 37-43}. The study was therefore reduced to an exploratory investigation. The issue was of obvious significance and would influence the risk/ reward ratio of testosterone replacement therapy in hypogonadal older men.

The innovative aspects of this trial was the use of CT angiography to evaluate non- calcified coronary plaque volume before and after 1 year of testosterone or placebo treatment. Because of delayed funding of the CV trial, only 138 men were enrolled. Testosterone was shown to significantly increase the non-calcified plaque volume compared to placebo ($P < 0.003$). The men in both arms of the study relatively high rates of CV risk factors (i.e. diabetes, obesity, hyperlipidemia, hypertension and evidence of atherosclerosis). By chance, the two arms of the study were unbalanced at baseline as the placebo group had higher baseline coronary scores and greater non-calcified plaque volume. No difference in the two arms of the study were seen for increase in calcified plaque volume or coronary events⁴⁴. The effect of testosterone on putative cardiovascular biomarkers showed a decrease in both high and low density cholesterol after testosterone treatment; the biomarkers did not correlate with increase in the non-calcified plaque volume; thus, the net impact of the biomarker changes are difficult to interpret⁴⁵. A secondary analysis of the CV trial was published recently showing that the increase in NCP in the testosterone treatment group correlated with the increase in hip/waist ratio⁴⁶.

The finding of increase non-calcified plaque volume is concerning as it might suggest greater cardiovascular risk of testosterone treatment. Many met-analyses have been published²⁵. Most of the systematic met-analyses failed to support an increased risk of testosterone on CV death or events. Hopefully, the true risk or benefit of testosterone on CV risk will be clarified by a much larger ongoing FDA encouraged and Industry sponsored double blinded placebo controlled 5 year study⁴⁷

Adverse Events

The study was focused on efficacy and treatment was limited to 52 weeks. The study was not powered to carefully determine CV or prostate cancer risks. Known and debated adverse risks of testosterone treatment have been published with a summary of met-analyses provided in a review by Corona et al²⁵. Furthermore, the study excluded men thought to be in a high risk prostate cancer risk base on baseline PSA levels⁴⁸. Men with increased hemoglobin levels (>16 g/dL) at baseline were excluded and men whose hemoglobin levels increased to levels > 17.5 g/dL had their testosterone dose lowered³⁰. Nevertheless, the study was of sufficient size that reporting adverse events is appropriate. Only one man developed prostate cancer in the testosterone arm and two in the placebo arm. Increase in IPSS was not different in the two arms. Erythrocytosis occurred more frequently in the testosterone arm. CV events were not different between arms. It should be noted that two separate studies using oral testosterone undecanoate and sub-cutaneous testosterone enanthate showed small but significant increase in systolic BP with testosterone treatment^{49, 50}.

Conclusion

The T trials were a DBPC coordinated set of 7 Trials (3 Main and 4 sub-trials of testosterone effects of replacement therapy in 788 men greater than age 65 (mean age 72) with unequivocal hypogonadism based on 2 low serum testosterone concentrations below the reference range of normal young men. The three main trials were sexual function, physical function and vitality; four sub-trials (cognition, bone, anemia and cardiovascular) had selective inclusion/exclusion criteria and studied fewer subjects. Treatment was for 52 weeks with a post treatment assessment after another 52 weeks. Testosterone was administered by transdermal route beginning with 5 mg daily; multiple dose adjustments were allowed to maintain mid normal testosterone concentrations.

In the sexual function trial, testosterone increased sexual activity, sexual desire, and erectile function. In the physical function trial testosterone did not increase timed walking distance in the men selected based on slow baseline walking speed but did increase walking distance in the overall T trial subjects who were a combined group of slow walkers and less slow

walkers. In the vitality trial, there was a small benefit in mood and depressive symptoms but not in energy. There was no benefit of testosterone in the cognition trial. Significant positive benefits were seen in the bone trial on bone mineral volume and estimated bone strength. The anemia trial demonstrated mild to moderate anemia (hemoglobin < 12.7 g/dL and >10g/dL) in 126/788 of the T Trial study group. Testosterone significantly improved hemoglobin (> 1 g/dL) and corrected anemia in hypogonadism of unknown and known putative cause of anemia. In the cardiovascular trial testosterone increased the non-calcified plaque seen on CT angiography. The cardiovascular Trial was underpowered and the results were considered exploratory.

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Table. 1 Summary on The Salient Results from The T trials

The T Trials	Parameters Assessed	Outcome in Men with Specific Symptom /Test for the Trial	Outcome in all Participants
Sexual Function	Sexual Activity (PDQ –Q4) Sexual Desire (Derogatis Inventory of Sexual Function) IIEF	Improved	Improved
Physical Function	6 minute walk (increase >50 meter)	Not Significant	Improved
Vitality	Facit-Fatigue Scale (increase >4 points) SF-36 Positive/Negative Affect Schedule Depression (PHQ-9)	No change Improved Improved Improved	Improved
Cognition	Wechler Memory Scale	No change	No change
Anemia	Hemoglobin	Improved	Improved
Bone	Volumetric BMD Bone Strength		Improved Improved
Cardiovascular	Non-calcified plaque volume Calcified plaque Coronary events		Increased Not Significant Not Significant

PDQ psychosexual daily questionnaire Question 4

IIEF International Index of Erectile Function

PHQ-9 Patient Health Questionnaire-9

SF-36 Short From Health Survey

BMD Bone mineral density