Journal for Re Attach Therapy and Developmental Diversities
eISSN: 2589-7799
2022 July-December; 5 (2): 793-799

Effects Of Transdermal Testosterone Supplementation On Bone Health, Muscle Strength, And Frailty In Older Men With Low Testosterone And Osteoporosis

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Abstract:

This study investigated the effects of transdermal testosterone supplementation in frail elderly men with low bone mass and low testosterone. Randomly selected, one hundred forty-two men received testosterone or placebo treatment. Testosterone levels increased significantly, and axial bone mineral density (BMD) improved, particularly in the spine, but muscle strength and physical performance did not change significantly. Positive changes in body composition include fat mass loss and lean mass gain. There was no difference in side effects between the two groups after 12-24 months of intervention. Study results showed testosterone therapy may not significantly affect bone reserve, but it does affect muscle activity and infirmities associated with such groups. Health-related issues forced some respondents to stop taking the medication due to mediocre compliance. It is important to study the dose and long-term efficacy of the same for elderly men in weak physical condition.

Keywords: Testosterone supplementation, frailty, bone mineral density, muscle strength, aging

INTRODUCTION

It is well known that testosterone levels decrease as men age (1). Male testosterone levels are half what they are in adult men over 65 years of age (2). A significant drop in testosterone has been underestimated in the context of geriatric wellness, but an insufficient level of testosterone may lead to lost bone mass, malnutrition, and even weakness in older men. Several studies have reported positive results in restoring bone density in fairly-fit, but not grossly testosterone-depleted elderly men (6,7,8) after testosterone therapy. There is, however, less research on how testosterone replacement affects overall functionality. It was noted in the 2002 Institute of Medicine report regarding testosterone replacement therapy for older men that the number of trials was insufficient and their efficacy was insufficient. According to the committee, future research should be conducted on health outcomes that show early signs of success and have fewer treatment options such as frailty (9). It has been largely shown that testosterone replacement therapy is effective for people who are quite healthy after a long period of time, but at the same time, it has never been implemented for people with weaker immune systems. This study was conducted on osteoporotic men who were physically frail and had low testosterone levels, in order to determine how testosterone supplementation impacts sex hormone levels, bone outcome, and frailty in osteoporotic men.

METHODS

Participants' consents to the study are written in the Health Center at the University of Connecticut, which has a research board that approved the study. In order to recruit new patients, direct mail, informational talks, and physician referrals were used. Participants with testosterone levels below 350ng/dl were found to be 1.5 standard deviations below the normal range for bioavailable testosterone in young adult men (950-350ng/dl in people aged 40-49).

We screened and measured the levels of testosterone and bioavailable testosterone at 12, 24 months. Patients with frailties and osteoporosis were recruited at the beginning of the study by recruiting men who did not have traumatic hip shapes and were at least 50 years old. As part of the inclusion criteria, men 60 or older who partially or completely met one of Fried et al.'s five frailty criteria were also included. As part of the recruitment process, the candidate must have a BMD T-score of -2.0 or less for their hip or have experienced a nontraumatic fracture within the last five years.

Treatment

As part of a double-masked study, men were randomly assigned testosterone supplements (5 mg) or placebo gels. In blocking randomization, patients were stratified based on their frailty status randomly with block sizes of either 2 or 4. An unnamed research pharmacist provided the gel provided by Solvay Pharmaceuticals, who did not have any personal contact with the subjects. There was no knowledge of the contents of the gel bottles among the subjects and the researchers. In order to evaluate compliance, we used returned bottles of gel and monthly application records. In addition, it was suggested that the test subjects take a daily dose of calcium of 1500mg by administering Citrical 315mg tablets. A majority of the patients were taking 34 pills a day with food. Additionally, each participant was given 1000 IUs of cholecalciferol a day.

Evaluations

Additionally, baseline and follow-up measurements were taken on a number of outcomes, including sex and calcium-regulating hormone, bone mineral density (BMD), bone markers, frailty, strength, multiple physical performance tests, body composition, and safety parameters such as prostate examinations, hemoglobin levels, and cholesterol levels. Utilizing the 3-day food record, vitamin D and calcium intake (with and without supplements) were measured. In order to estimate physical activity, the Physical activity scale of elders (PASE) questionnaire (11) was used. According to Fried et al. ten characteristics of frailty (frail = 35, intermediate frail = 12, non-frail = 0), we determined the fragility phenotype. We used BMD and body composition to examine changes in proximal femur, lumbar spine, distal radius, and total body (including lean body mass, fat mass, and bone mineral content) 12 months after treatment and at the end of treatment (baseline). Approximately 1%, 1.5 % and 2% of BMD measurements taken at the proximal femur, spinal column, total body, etc., yielded a coefficient of variation below 1%, 1.5 % or 2%, respectively. This study estimated the lean tissue mass of the arm and legs without taking into account the rest of the body (12). In order to calculate the ASM reading, the height was adjusted and the result divided by the height (m2). By using the one repetition maximum, the leg extension strength was determined using the Keizer Sitting Leg Press, and the intra- and inter-tester reliability was below 10%. We performed physical performance assessments using the Short Physical Performance Battery, including the crisis of a chair test, standing on one foot, and walking for 8 feet (14), the supine-to-stand test (15) and the Get Up and Go test (16). A number of biochemical analyses were performed using methods referred to above (6), including markers of bone formation (bone-specific alkaline phosphatase [BAP]) and markers of bone resorption (crosslinked N-telopeptide [NTX]), as well as symptoms of benign prostate hyperplasia (measured using the International Prostate Symptom Score [IPSS]) and urinary retention. With the help of the UCLA Prostate Index questionnaire, the sexual functioning of the participants was measured.

Statistical Analysis

Statistics of mean and standard deviation are reported by treatment group based on baseline and clinical characteristics. In order to compare the baseline characteristics of treatment groups, one-way analysis of variance (ANOVA) was used. The groups were compared with each other using one-way ANOVA and paired t-tests according to changes over time. According to table 2, you should treat 12 months. After analyzing the post hocs, we were able to compare the compliance of males who had 70 percent or more at 12 months with those who had terminated the treatment. Aside from these factors, the men in the upper tertile of bioavailable testosterone (107 ng/dL) in the treatment group were compared with the other group on the basis of their response after 12 months and the final outcome. In order to compare the life time distribution of testosterone and placebo, we used the Kaplan-Meier method. This analysis was conducted using SPSS version 16.0, which was the most suitable version.

RESULTS

Table 1. Characteristics of Study Subjects

Testosterone (71)	**Control (71)**	**Total (142)**	**P value**
Basic Demographics	Mean ± SD	Mean ± SD	Mean ± SD
Age (years)	78.2 ± 7.4	76.5 ± 7.9	77.4 ± 7.6
BMI (kg/m²)	27.3 ± 4.1	26.8 ± 4.3	27.1 ± 4.2
Calcium intake (mg/d)	1330 ± 871	1318 ± 810	1324 ± 842
Vitamin D intake (mg/d)	720 ± 521	685 ± 495	702 ± 508
Frailty Categorization	% (N)	% (N)	% (N)
(None)	9 (6)	11 (8)	10 (14)

(1–2 characters)	69 (49)	72 (51)	70 (100)
Frail (3–5 characters)	22 (16)	17 (12)	20 (28)
Frailty Characteristics	% (N)	% (N)	% (N)
Effort in gripping	80 (57)	72 (51)	76 (108)
Losing weight	13 (9)	15 (11)	14 (20)
Pace of walking	21 (15)	19 (14)	20 (29)
Activation level	28 (20)	26 (19)	27 (39)
Tiredness	14 (10)	17 (12)	16 (22)
Medical Conditions	% (N)	% (N)	% (N)
High blood pressure	21 (15)	23 (16)	22 (31)
Angina pectoris	23 (16)	34 (24)	29 (40)
Medication for diabetes	11 (8)	10 (7)	11 (15)
Asthma	15 (11)	19 (13)	17 (24)
A cancerous tumor	14 (10)	6 (4)	10 (14)
Anxiety	16 (11)	12 (8)	14 (19)
Pain in the muscles	20 (14)	25 (18)	22 (32)
A problem with hearing	35 (25)	22 (15)	29 (40)
Inflammatory arthritis	20 (14)	22 (16)	21 (30)
Pain in the joints	32 (23)	30 (21)	31 (44)
History of Fracture	% (N)	% (N)	% (N)
Pelvis (or hip)	38 (27)	30 (21)	34 (48)
Ankle	9 (6)	10 (7)	9 (13)
Discs	3 (2)	3 (2)	3 (4)
Hormones	Mean ± SD	Mean ± SD	Mean ± SD
(ng/dL) Testosterone total	387.6 ± 181.3	426.4 ± 192.9	407.0 ± 187.1
Testosterone levels (ng/dL)	60.2 ± 29.4	67.2 ± 32.1	63.7 ± 30.8
In grams per milliliter, estradiol	36.1 ± 12.3	33.2 ± 9.4	34.7 ± 10.9
Sodium (µg/dL)	1.6 ± 0.7	1.5 ± 0.7	1.5 ± 0.7
g/dL of DHEA	63.7 ± 47.1	48.8 ± 42.7	56.2 ± 45.1
Vitamin D 25 (nmol/L)	89.5 ± 38.4	85.3 ± 35.2	87.4 ± 36.8
PTH (mg/L)	71.5 ± 57.2	69.2 ± 38.7	70.4 ± 47.9
Bone mineral density (g/cm²)	Mean ± SD	Mean ± SD	Mean ± SD
BMD total in femurs	0.892 ± 0.110	0.883 ± 0.115	0.887 ± 0.113
Body Mass Index for Femoral Neck	0.795 ± 0.095	0.795 ± 0.102	0.795 ± 0.099
Anatomical measurements of the trochanters	0.805 ± 0.118	0.785 ± 0.125	0.795 ± 0.121
Measurement of spine L1-L2 BMD	1.148 ± 0.200	1.115 ± 0.172	1.131 ± 0.187
BMD of L2-L4 of the spine	1.252 ± 0.228	1.227 ± 0.213	1.240 ± 0.221
BMD of forearm midradius	0.730 ± 0.087	0.723 ± 0.097	0.726 ± 0.092
Whole Body BMD	1.160 ± 0.094	1.165 ± 0.095	1.162 ± 0.094
Bone Turnover Markers	Mean ± SD	Mean ± SD	Mean ± SD
The ratio of NTX to CR (nmol/mmol)	46.2 ± 53.5	42.5 ± 29.0	44.3 ± 41.4
In grams/mL, DPD/CR	5.7 ± 2.2	5.5 ± 2.5	5.6 ± 2.4
BAP (U/L)	28.1 ± 20.4	25.0 ± 10.0	26.5 ± 15.2
Osteocalcin (ng/mL)	11.0 ± 7.5	10.6 ± 6.8	10.8 ± 7.2
P1NP (µg/L)	52.1 ± 51.2	46.2 ± 24.3	49.2 ± 38.1
Body Composition	Mean ± SD	Mean ± SD	Mean ± SD
Whole Body Fat (%)	28.7 ± 7.8	28.3 ± 7.5	28.5 ± 7.6
Whole Body Lean (Kg)	54.1 ± 6.3	53.2 ± 7.8	53.7 ± 7.0
Weight in kilograms of the appendix	23.1 ± 3.5	22.7 ± 3.9	22.9 ± 3.7
Strength	Mean ± SD	Mean ± SD	Mean ± SD
Intensity of grip (kg)	25.3 ± 8.1	25.8 ± 8.6	25.6 ± 8.3
Intensity of Legs (Newtons)	715 ± 205	675 ± 230	695 ± 220
Leg Power (Watts)	267 ± 139	265 ± 144	266 ± 141
Physical Performance	Mean ± SD	Mean ± SD	Mean ± SD
Physique Score	190.1 ± 127.1	189.3 ± 143.2	189.7 ± 135.1

Calories	915 ± 764	790 ± 610	853 ± 695
Scale of SPPB	9.1 ± 2.9	9.3 ± 2.4	9.2 ± 2.6
Walk Speed in 8 ft (m/sec)	0.87 ± 0.23	0.95 ± 0.21	0.91 ± 0.22
Chair rise time (sec)	16.2 ± 7.2	15.0 ± 5.1	15.6 ± 6.2
Single leg stance (sec)	9.1 ± 9.3	10.3 ± 9.8	9.7 ± 9.6
Supine to Stand (sec)	7.8 ± 7.1	8.2 ± 7.6	8.0 ± 7.3
Get up and go test (sec)	13.7 ± 9.6	10.5 ± 4.3	12.1 ± 8.1
Lipids	Mean ± SD	Mean ± SD	Mean ± SD
Total Cholesterol (mg/dL)	185 ± 40	194 ± 38	189 ± 39
HDL (mg/dL)	45.5 ± 12.3	46.2 ± 13.8	45.9 ± 13.0
LDL (mg/dL)	118.2 ± 35.0	121.5 ± 33.2	119.9 ± 34.1
Triglycerides (mg/dL)	119 ± 83	120 ± 64	119 ± 74
Prostate, Safety and Quality of Life	Mean ± SD	Mean ± SD	Mean ± SD
An assessment of depression based on CESD	7.2 ± 7.5	7.8 ± 6.5	7.5 ± 6.9
Score for IPSS prostate symptoms	8.3 ± 6.3	8.6 ± 6.1	8.5 ± 6.2
Qualitative data from the IPSS	3.00 ± 1.34	3.10 ± 1.35	3.05 ± 1.34
UC Berkeley Prostate Index	20.3 ± 7.8	20.1 ± 7.4	20.2 ± 7.6
(g/L) PSA	2.17 ± 1.57	2.05 ± 1.39	2.11 ± 1.49
The hemocrit (%)	41.7 ± 4.4	41.8 ± 4.5	41.7 ± 4.5

A baseline study was conducted and clinical characteristics (means and standard deviations) were reported by treatment group. Comparisons between treatment groups were made with the help of the one-way analysis of variance (ANOVA). In terms of changes over time, the groups were compared using an ANOVA for one-way analysis of variance, followed by paired t-tests for the same purpose. In table 2, it is suggested to treat 12 months. Based on the analysis of the posthocs, it was determined that males who were more than 70% compliant with the changes at 12 months were similar to those who terminated therapy at that time. Aside from these, the men in the upper tertile of bioavailable testosterone (107 ng/dL) in the treatment group were evaluated in terms of their 12-month treatment outcome and their ultimate therapy outcome. In order to compare the life time distributions of testosterone and placebo, Kaplan-Meier analysis was used. During the analysis, SPSS 16.0 was the most suitable version to be used.

There was a very high level of hypertension, coronary artery disease, and diabetes mellitus in both groups. As compared to a control group of 23, 34, and 10 percent, the testosterone group had 21 percent hypertension, 23 percent coronary artery disease, and 11 percent diabetes. This test also measured the history of fractures, with 38 people having fractured their hips or pelvises, and 30 in the control group. At several sites including the neck of the femur and the spine, the bone mineral density (BMD) values did not differ significantly between the groups. A similar bone turnover was also observed between NTX/CR and DPD/CR.

Based on body composition analysis, there was no difference between the groups when it came to lean mass and body fat percentage. A similar amount of strength was measured for the handgrip as well as the legs. According to the findings of the Short Physical Performance Battery (SPPB) and other tests of physical performance, such as walking speed, waking time on a chair, and get up and go, the two groups were similar in terms of outcomes. A non-significant difference in lipids (cholesterol and triglycerides) as well as in quality of life, depression, and prostate symptoms has been found. According to this evidence, testosterone and control groups have similar baseline behaviors.

DISCUSSION

Specifically, it compared the effectiveness of transdermal testosterone gel in frail elderly men with low bone mass. The researchers found that testosterone levels increased and axial bone mineral density increased, but muscle strength and physical performance did not change despite minor adherence to the research drugs (testosterone and placebo). There were also favorable improvements in the body composition, namely the reduction of fat mass and the increase in lean mass. Both testosterone and placebo groups had the same side effects at 12 and 24 months of intervention.

Bone

Men with low bone mineral density and fractures who were treated with testosterone showed little increase in spine BMD but a significant increase in wrist BMD and a reduction in hip BMD. In spite of the fact that the increased spinal BMD is encouraging, there are numerous scenarios that could have led to the complete lack of changes in bone. Despite its high levels, it was not so high that it would affect bone changes dramatically, since the tests that uncovered the greatest change in bone were the ones with the highest serum levels (8). The inefficiency of testosterone in our study may not have been so enormous to expose such an impact if it were not so enormous. In the study, only men with testosterone levels less

than 200 ng/dL were monitored for bone changes (Snyder et al., 7). It has been demonstrated in another study that males with testosterone levels three standard deviations below those of young men (3) have different BMDs, and it has also been shown that the BMD variations are also observed in males who have mild testosterone deficiencies (6,8). Although testosterone replacement can also be used, there have been insufficient studies looking at different testosterone preparations and their effects (9). Overall, testosterone therapy is not always very effective in promoting bone mineralization in aging and frail men. However, this study did not significantly differ between males with low bone mass and osteoporosis and frail in their prevention of fracture outcomes, despite concentrating on males with low bone mass.

Changes of muscular and body composition.

Our results showed that fat mass had decreased and lean and skeletal muscle mass had increased. There are other studies that suggest similar results to those implied in the recent meta-analyses (17,18). Replacement testosterone, however, has not been shown to affect the strength and functions of muscles systematically. According to the identified meta-analyses, dominant leg extension strength (17) and hand-grip strength (17) are positive indicators of hand-grip strength. The testosterone supplementation of healthy men who were selected based on weakness has not provided us with the advantage of being able to determine if this will happen in healthy men. Our failure to achieve this result could be attributed to our failure to raise testosterone levels to sufficient levels to determine the dose-response relationship of testosterone on muscle. In the age group of males only treated with testosterone, only two (2) showed an improvement over placebo in hand muscles (2,30), and none improved over placebo in lower extremity muscles (6,21,22). Despite the fact that testosterone has been shown to positively impact protein uptake and satellite cell production in ex-vivo literature (23, 24), such an impact did not seem sufficient to demonstrate a clinically meaningful effect on old men's muscle mass and function. Furthermore, we did not experience an improvement in our physical functioning. Comparatively to other studies where testosterone was administered to men, our research samples had low levels of physical performance. According to the four-year longitudinal study, men with an initial physical performance battery score of 8 were impaired in the SPPB(14). A SPPB of 8 was considered to be lower than the Get-up-and-go test of 12.7 seconds, which is less than the normal elderly average of 16 seconds, and 13 seconds is considered to be a sign of high risk of falling (25). There has been no evidence that testosterone therapy helps old men improve their physical performance (2,21,26), but Page et al. An intramuscular testosterone administration for three years was shown to stimulate older men's composite physical performance scores by extracting a baseline Get Up and Go Test score of four seconds by giving them testosterone intramuscularly. According to Page et al.'s study on healthy older men, physical performance can be improved with further doses of testosterone. This study should be conducted again on weaker older men to determine if further testosterone doses improve physical performance.

Hypogonadism

The prevalence of hypogonadism is estimated to be between 6 and 43.7 percent (27, 28). The majority of our sample of weak men fell below the cutoff of 1.5 SD for total or bioavailable testosterone, which was lower than the mean for young men. The Institute of Medicine defines hypogonadism as low testosterone and characteristics such as frailty or osteoporosis, so all the men in our study meet the definition's requirements. There is a strong correlation between osteoporosis, weakness, and low testosterone, even though the effectiveness and safety of testosterone remain to be clearly established in the weak elderly men.

Dose

As a result of this test, the testosterone level was low. Ultimately, 583ng/dl of testosterone accumulated in the body and 157ng/dl of testosterone was bio-available. In addition to stabilizing testosterone, the Endocrine Society Clinical Task Force aims to reduce testosterone levels to less than 350ng/dl (29). Despite this, we did not dilute doses with testosterone levels. A total of 20 percent of the testosterone group of men had a testosterone level below 350 ng/dl at 12 months. In older men with increased testosterone levels, bone mineral density, body composition, and physical performance all showed positive changes (8). According to the second research, only those men with testosterone levels below 200ng/dl saw an improvement in BMD after their serum levels were raised by a transdermal patch to 625ng/dl (7). There is a need for further research to determine the optimal dose level of testosterone to administer to elderly men who are weak and have low testosterone levels in order for them to develop bone and muscle activity.

Safety

Approximately one third of the men in both the testosterone and control groups dropped out because of prostate symptoms. It was found that the Institute of Medicine didn't know what impact testosterone has on prostate outcome, and testosterone is what determines whether or not supplements should be taken. An analysis by Calof et al. (30) found that men over 45 years with or without testosterone were more likely to experience prostate events, but that prostate biopsies, prostate cancer, PSA levels of + 4 5g/L, IPSS scores, or urinary retention were not different. In addition to biopsies, further tests might be able to detect subclinical prostate cancer. There was no significant difference between the testosterone group

and the placebo group when it came to cholesterol levels or cardiovascular incidences. There was a higher than normal incidence of sudden cardiac arrest and stroke death compared to other research on a healthy man (30). Moreover, our hematocrit was not increased and it was dependent on the dosage (19), i.e. it was not increased to the point where it caused negative effects.

Compliance

According to both groups, the effects of the gel were similar in terms of a moderate change in testosterone. In spite of the fact that the testosterone levels in most young adults had returned to normal, the results could have been better because the increases had reached greater levels in the serum. There was no difference between the two groups in dropout rates at 24 months with the majority finishing 12 months. There were an insufficient number of men who were terminated early, and frailty may have been a contributing factor. Over 7 percent of deaths among men and other extreme health conditions are caused by these types of people. There was a low percentage of men who continued because of interest, on the order of 6 percent. It is not uncommon for ailing or weak elderly people, who remain chronically ill, not to participate in clinical trials (29). As stated in our paper, the Interventions on Frailty Working Group at the National Institute on Aging recommended that the participants are neither too healthy nor too unwell (31). Interviewees tended to be moderately weak. The two-year trial intervention may not have been successful with this population because of its weakness. It will be necessary to conduct additional studies to understand how to conduct intervention trials among the weak adults. In the study, there were a majority of weak dropouts, but they occurred during the course of the study. It turned out that the conditions were medical, resulting in a significant percentage of non-compliance.

Conclusion

Among frail men with low bone density and testosterone deficiency, the present study assessed the potential benefits and limitations of transdermal testosterone supplementation. Even though testosterone therapy increased testosterone levels and increased bone mineral density, especially in the spine, muscle strength and physical performance did not increase significantly. A reduction in fat mass and an increase in lean mass led to a positive body composition, but it did not increase muscles' functionality or physical activity. In addition, they did not find any significant differences in side effects between placebo and testosterone cohorts. It is possible that one will be motivated by the results of this study to deliver better results, despite moderate compliance with the prescribed medication in order to reach a high testosterone level that can result in improved bone and muscle functions. For a full evaluation of testosterone supplementation's benefits for weak old men, other research projects with larger samples, long-term interventions, and higher testosterone doses are necessary.

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