Cover page

Official title of the study:

Effect of testosterone on elderly frail men with testosterone deficiency - a double-blinded, randomized and placebo-controlled intervention study

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Protocol v. 7.8

Effect of testosterone on elderly frail men with testosterone deficiency

- a double-blinded, randomized and placebo-controlled intervention study

Mainly responsible for project initiation, finances, and progression:
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Karsten Overgaard, Senior Consultant, Specialist in Neurology, Neurological Department N, Herlev University Hospital.
Rune Skovgaard Rasmussen, PhD, neuropsychologist, associate professor in general pathology, Neurological Department N, Herlev University Hospital.
Note: Mette Midttun and Karsten Overgaard are the primary trial managers; it follows from the attached CVs for the above-mentioned persons that both are qualified to make treatment-related decisions and have extensive clinical experience.

Project participants:
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Purpose

The purpose of this study is to increase the functional level of the elderly to thereby reduce fall risk, improve motor skills, and increase psychological well-being, as well as to assess whether the restoration of a normal testosterone level contributes to a faster recovery. The effect of testosterone is investigated as measured by physical and mental functional capacity, including cognition, in hypogonadal elderly men with a significant loss of function. In this supplementary protocol, participants do not receive supplementation with protein, calcium, Vitamin D, and do not receive DXA scans or progressive strength training, unlike the main protocol v. 7.6. This supplementary protocol is aimed at participants who are too weak to participate in the progressive strength training included in the main protocol.

Background

Disability and mortality after falls in elderly people constitute an extensive health problem. Each year, about 40% of all elderly over 65 years fall, of which approx. 10% of these falls cause serious injury; thus, fall accidents are a significant source of increased mortality and disability in the elderly (1-3). Disability after a fall accident leads to an increased need for support and fall accidents among the elderly are associated with extensive societal costs, which are also expected to increase significantly in the future (4-6). In Denmark, more than 1000 people die annually from the consequences of falls, and more than 10,000 are hospitalized (6); the Danish Health Authority has published the following forecast (7):

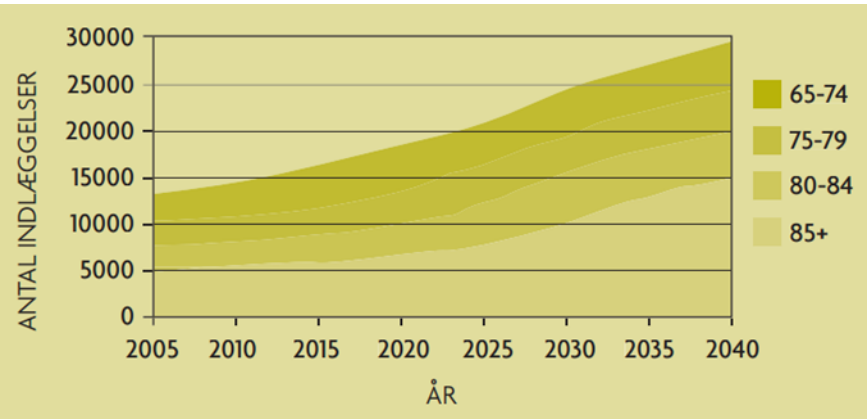


Figure 1: Projection to the year 2040 of admissions after falls, elderly over 65 years (7)

The cause of serious fall accidents is due to several factors but is primarily reduced muscle strength in the elderly, especially in the thigh musculature (8-9).

Muscle mass decreases by about 40% from age 20 to age 80 (9). The increased fall risk in the elderly (7) is especially associated with loss of muscle power (muscle strength x contraction speed), which falls by approx. 3.5% annually from age 65 because of sarcopenia (10). One week of immobilization can lead to a reduction in muscle strength of up to

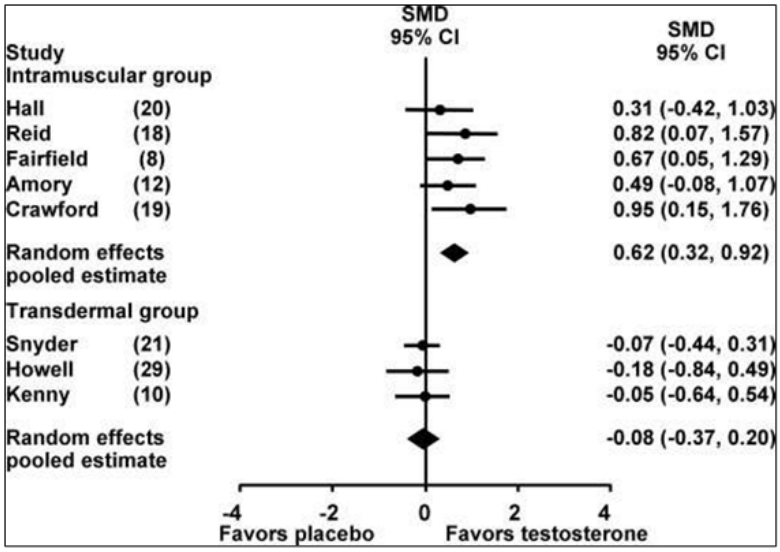
20% (11) and a bone loss of up to 1% of the maximal bone mass corresponding to the normal annual reduction (12). Especially for weak elderly, bed rest can cause muscle strength to fall below a critical threshold value where basic activities of daily living can no longer be performed. Fall accidents are a frequent cause of death and the most frequent cause of traumatic brain injury - and fall accidents among the elderly cause more bed days than all other accidents combined (6, 13).

The elderly can achieve an increased reserve capacity in both muscle strength and muscle power through strength training. In a Cochrane review from 2009 including 121 studies, it was found that 8-12 weeks of progressive strength training significantly increased the muscle strength of the elderly by 10-45% (9). Men's testosterone levels fall with age. 20% of men over 60 and 50% over 80 are hypogonadal with serum testosterone below 10 nmol/L or 300 ng/dl (14-15). The normal average is approx. 22 nmol/L (650 ng/dl) with an upper limit of 35 nmol/L (1000 ng/dl) (15). Statistics Denmark has calculated that there are 450,000 Danish men who are at least 65 years old, and of these approx. 85,000 are over 80 years old – hypogonadism can thus be estimated to occur among approx. 115,000 male Danes aged at least 65 years (16).

Hypogonadism is associated with reduced muscle mass, muscle strength, and bone mass (14, 17). In a meta-analysis of 17 studies, a significantly increased Lean Body Mass (corresponding to increased muscle mass) of 2.7% was found after 3-36 months of testosterone supplementation (17). Despite significantly increased muscle mass, two meta-analyses of 10 and 11 studies respectively found only a tendency towards increased muscle strength after 1-39 months of testosterone supplementation (17-18). A positive effect on bone mass has been found after 24-36 months of testosterone supplementation in elderly men with verified hypogonadism (19-20). A randomized controlled trial has shown that the increase in muscle mass, strength, and power with testosterone supplementation is dose-dependent (21). Testosterone supplementation for hypogonadal men has resulted in a highly significant improvement in balance (22).

Unlike previous studies, participants in this study will be older and have verified hypogonadism. In a controlled study of the effect of testosterone without simultaneous training in elderly men with low and slightly reduced testosterone levels, it was shown that testosterone prevents weakening of the leg muscles, improved body composition, quality of life, and physical performance (29). Further studies are required to verify these results.

Hypogonadism is a risk factor for obesity, type 2 diabetes, atherosclerosis, myocardial infarction, chronic heart failure, and erectile dysfunction (30-32). Furthermore, it has been found that testosterone supplementation for hypogonadal men can reduce depression and improve cognitive functional level (33-35). Testosterone supplementation for men with testosterone deficiency significantly counteracts erectile dysfunction, i.e., impotence and erection problems (36). Dosages of approx. 100 mg testosterone weekly are associated with the best cognitive results, unlike significantly higher or lower dosages (37). Trials with particularly positive effects of testosterone supplementation used weekly intramuscular injections with approx. 100 mg slow-acting testosterone esters, while the effect of transdermal applications was not correspondingly positive (38). Intramuscular injections are additionally found in a meta-analysis to be associated with improved bone mass, while transdermal testosterone did not cause this effect (39), cf. the following figure:



Intramuscular injections thus appeared more effective than transdermal applications. The findings in this study may have fundamental significance for future recommendations for the elderly male population and for efforts related to improving quality of life by reducing muscle weakness, loss of function, osteoporosis, falls, and bone fractures in this population group.

Design

Double-blinded randomized placebo-controlled intervention study.

Material

Recruitment

Suitable patients are included consecutively from the Geriatric Outpatient Clinic at Holbæk Hospital. There is thus only one and not several trial sites. A screening log is maintained. In addition, records from the Geriatric Department are screened. Information from patient records may be passed on in the project, and this information will always be anonymized. Participation is voluntary. Informed written consent must be given.

The first contact with a possible participant takes place in connection with a referral to the Geriatric Outpatient Clinic at Holbæk Hospital. Contact is made via the outpatient clinic's nurses, Senior Consultant Mette Midttun, or Maja Sparre, who hand out written information and orally describe the project. A subsequent conversation takes place with Senior Consultant Mette Midttun or Maja Sparre, undisturbed, in an outpatient clinic office. The patient will be informed of the right to have an observer, and relatives will also be informed of this if deemed necessary.

Demented and cognitively impaired persons will not be included, cf. the exclusion criteria below. Up to one week of reflection time is given to provide consent. Note that the present study is not time-critical such that patients must be included a few days after any symptom onset. There is therefore no significant time pressure regarding obtaining consent.

Power Calculation

The primary endpoint is the chair-stand test for 30 seconds (39). As a basis, $\alpha = 0.05$ and $\beta = 0.2$ were used. SD = 4.6. Miredif = 3. Sample size is calculated to be 38 participants in each group. Due to high age and time-consuming intervention, up to 25% dropout is expected (9), thus 48 participants must be included in each group to ensure that 38 people complete in each group.

Target Group

96 hypogonadal elderly men with physical functional loss. Inclusion and exclusion criteria follow the National Treatment Guidelines for male testosterone deficiency prepared by the Danish Endocrine Society; http://www.endocrinology.dk/index.php/nbvhovedmenu/5-gonadelidelser/1-mandlig-testosteronmangel.

Inclusion Criteria: Men aged 70 or over. Living at home in their own home or in sheltered housing. Independent walking function, possibly with a walking aid. Able to perform the chair-stand test a maximum of 8 times in 30 seconds or Timed Up and Go (TUG) of at least 30 seconds. There must be at least 3 symptoms or objective findings. Serum testosterone < 10 nmol/L (16) as an average of 2 independent measurements at the Center for Growth and Reproduction, Rigshospitalet.

Exclusion Criteria: Known or previous prostate cancer. Abnormally elevated serum PSA (PSA = prostate-specific antigen) corresponding to PSA > 5 ng/ml or PSA > 0.15 ng/ml/cc (relative to prostate size in cubic centimeters (cc)). Hemochromatosis. Heart diseases in the form of: Peri-, myo-, or endocarditis, angina pectoris, severe heart failure (NYHA class III and IV), severe hypertension (systolic BP > 180 or diastolic BP > 105 mmHg after possible antihypertensive treatment). Resting dyspnea. Liver (ASAT > 2 x upper normal limit) or renal insufficiency (serum creatinine > 200 micromol/l). Severe intractable epilepsy or migraine. Insulin treatment. Previous or current bisphosphonate, fluoride, HRT, SERM, strontium, teriparatide, or more than 3 weeks of prednisolone treatment. Joint disease with acute inflammation. Active cancer disease, in chemo- or radiotherapy. Bone metabolic disease except for age-related osteoporosis. Autoimmune diseases, chronic systemic diseases (cirrhosis, AIDS, chronic renal failure). Primary testosterone deficiency in the form of testicular dysgenesis, Klinefelter syndrome (47,XXY), 46,XX males, LH resistance, Y chromosome deletions, other sex chromosome abnormalities. Significant abuse, mental illness, dementia, physical handicaps with inability to complete the intervention or tests, or to give informed consent. Contraindications for testosterone undecanoate are thus included in exclusion criteria, such as the presence of liver tumors, breast carcinoma, and prostate cancer, for which trial participants will be examined before the start of the trial.

Method

Randomization and Blinding

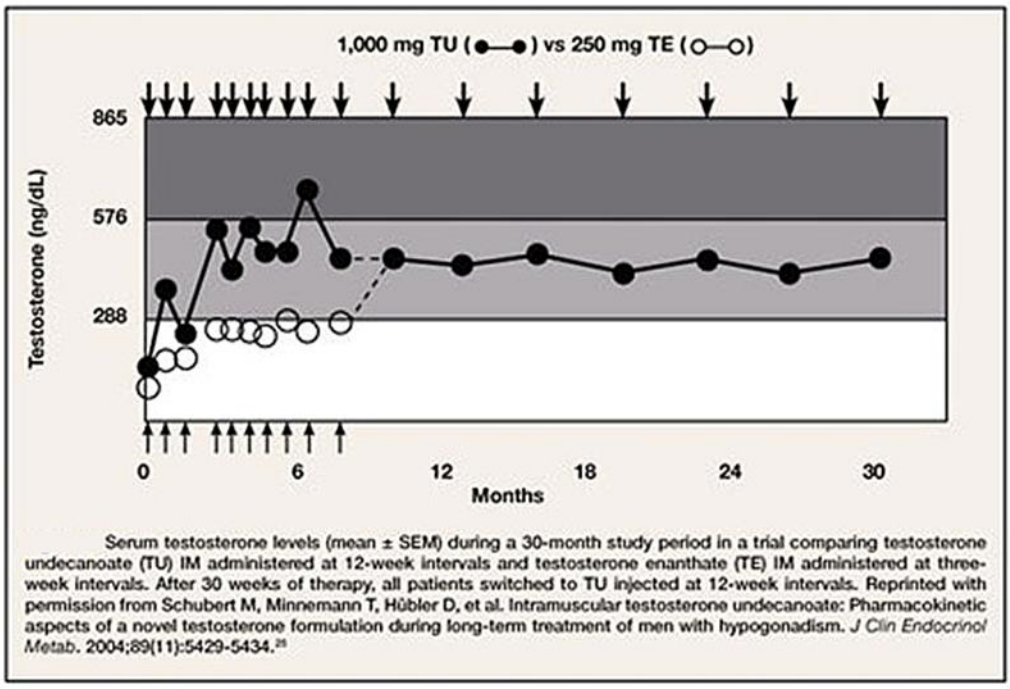
Participants are randomized equally into 2 different treatment groups with 48 participants each:

1. A control group given 3 placebo injections

2. A testosterone group given 3 testosterone injections.

Randomization is thus into two arms so that the effect of testosterone can be evaluated against placebo. Treatment with testosterone is made double-blind. We will ensure that the persons evaluating a patient do not have knowledge of the patient's treatment group.

Testosterone Supplementation
Testosterone supplementation is given intramuscularly with 1000 mg testosterone undecanoate, which has an effect for approx. 12 weeks (41-44), but which can be repeated more frequently between the 1st and 2nd administration. The injection is thus repeated in week 6. 3 injections per trial subject are expected, i.e., in weeks 1, 6, and 16. Trials have shown that injections with 1000 mg testosterone undecanoate resulted in normalization of testosterone levels in hypogonadal men without significant fluctuations.:



Serum testosterone levels (mean ± SEM) during a 30-month study period in a trial comparing testosterone undecanoate (TU) IM administered at 12-week intervals and testosterone enanthate (TE) IM administered at three-week intervals. After 30 weeks of therapy, all patients switched to TU injected at 12-week intervals. Reprinted with permission from Schubert M, Minnemann T, Hübler D, et al. Intramuscular testosterone undecanoate: Pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. *J Clin Endocrinol Metab*. 2004;89(11):5429-5434.[25]

The placebo group is treated with placebo, which is identical to the trial drug, just without testosterone.

If the participants are motivated to continue so that long-term effects can be measured, the participants will be asked in week 12 whether they wish to continue to week 52. Upon acceptance of continuation to week 52, testosterone and placebo injections are offered according to original groups in weeks 26, 36, and 46, after which testing of primary and secondary endpoints is not only performed in week 20 but also in week 52.

Data Collection

Data collection sheets and a database are prepared for registration and data processing. Information at baseline for data collection sheets: Age, living alone/living together, home help, mobility aid, social network, height, weight, waist/hip measurement, smoking, alcohol. The following measurements and data collection are performed at baseline, after 1 month at the start of training, and at the end of the study.

Primary Endpoint
Chair-stand test: A measure of general strength in extremities. Number of times the participant can stand up and sit down from a chair in 30 seconds. A good correlation (r=0.78) has been found with leg press (46) and acceptable test-retest reliability (ICC=0.86) (47). It has recently been scientifically documented that the ability among elderly persons to perform this simple test correlates with the risk of serious fall accidents (48).

Secondary Endpoints
Measurement of fall frequency and severity – this is registered via a questionnaire for each trial subject and is also included in the monitoring of adverse events.
Balance ability, which is linked to fall risk, is tested via the Tandem test, which contains three starting positions: 1) Standing with feet together, standing in semi-tandem stance, and standing in tandem stance (49).
Avlund's mobility scale: Questions about experiencing fatigue and need for support in common activities of daily living. Avlund's mobility scale is correlated with isometric muscle strength, simple functional tests (50), increased risk of hospitalizations (51), and mortality (52). Good inter- and intra-reliability (kappa 0.72-1.00) has been shown (53).

Geriatric Depression Scale (GDS): Questionnaire about depression and psychological well-being.
Montreal Cognitive Assessment (MoCA): Cognitive screening test that provides an estimate of the intellectual functional level; this test is also sensitive to mild cognitive problems and dementia.
Mini Mental State Examination (MMSE): Cognitive screening test that provides an estimate of the intellectual functional level. This test is included as it is performed as standard at the Geriatric Outpatient Clinic. Combined, MMSE and MoCA provide a broader assessment of cognitive functional level.
Quality of life EQ-5D: Questionnaire about perceived quality of life.
Clinical Frailty Scale (CFS): General assessment of health and functional level in the elderly.
Falls Efficacy Scale – International (FES-I, Fear of falling): Assessment of fall risk in the elderly.

Safety parameters - measured at each injection
Blood pressure. Blood samples: Serum testosterone, hemoglobin, PSA, and 25-OH Vitamin D are measured. If 25-OH Vitamin D < 25 nmol/L is found, treatment according to the department's usual guidelines is recommended. In addition, side effects and unintended events are registered very carefully, e.g., in the form of ischemic episodes and the like. Blood samples are not stored for more than one week and are not included in a research biobank. The biological material is analyzed immediately and subsequently destroyed. No parts of the blood samples will be used in person-identifiable ways.

Results reporting

Results will be analyzed according to intention-to-treat and per protocol; that is, those who have followed 60% of the testosterone treatment and training. Regarding statistical data processing, data will be ranked and group comparisons performed using non-parametric tests (Kruskal-Wallis, Mann-Whitney), comparisons of ranked before and after performances are performed using Wilcoxon non-parametric test and possibly categorical variables with chi-2 test. Non-linear correlations will be assessed via Spearman's Rank correlation coefficient. Spurious and unused data are not included in the statistical evaluation and are treated as missing data, i.e., no calculations are performed via these data. Missing data are acceptable as long as they do not make an assessment of the primary endpoint impossible. In case of deviation from the original statistical plan, trial managers will discuss possibilities and apply to the necessary authorities for permission for an associated protocol change. Data from trial subjects that make it possible to perform an assessment of the primary endpoint will be used as a minimum; the hope is, however, that data from all randomized patients can be used so that assessment of secondary endpoints can also be performed.

Ethics

The project is in accordance with the Helsinki Declaration and is approved by the Research Ethics Committee. Written patient information and informed consent have been prepared. The trial is notified to the Data Protection Agency, and the Act on Processing of Personal Data will be complied with. In the trial, records from the Geriatric Department at Holbæk Hospital are examined. This is solely as a part of being able to find and offer suitable persons the opportunity to participate in the trial. No data is extracted from records that can be attributed to persons, and such information is assigned solely to trial manager Senior Consultant Karsten Overgaard or Senior Consultant and investigator Mette Midttun. To the extent that the trial can include data from records, this will always be anonymized. In the trial, only patients who have testosterone deficiency are treated, thus testosterone undecanoate is only used according to indication and in full accordance with the criteria approved by the Danish Medicines Agency for use of the product (incl. dosage). In the section below, possible side effects and risks are described, but we do not expect significant side effects in the trial subjects, and as written in the introduction, the treatment can lead to better motor skills, reduced fall risk, increased cognitive skills, lower risk of cardiovascular disease, increased quality of life, better sexual function, and lower risk of developing depression. The project is focused on normalizing and increasing both health and quality of life; it is our conviction that the benefits of the trial for the individual trial subject far outweigh the risks and side effects.

Side effects/risks

Side effects of testosterone undecanoate (59): Common (1-10%): Diarrhea, snoring, worsening of hypertension, elevated hemoglobin, arthralgia, myalgia, dizziness, headache, mood disturbances, acne, pruritus, dry skin, alopecia, increased sweating, prostate hypertrophy, elevated PSA. Rare (0.01-0.1%): Polycythemia, priapism. Very rare (< 0.01%): Liver impact. Testosterone supplementation has previously been suspected of being able to contribute to cardiovascular disorders, but a newer study published in spring 2015 and based on more than 7000 trial participants found no connection between testosterone supplementation and cardiovascular disorders (60), and a larger meta-analysis based on almost 130,000 trial subjects found correspondingly (61). Previously, it has also been found that testosterone deficiency is a risk factor for atherosclerosis, myocardial infarction, and chronic heart failure (30-32), so the trial participants' general health can be improved significantly via the present project.

Timeline and feasibility of practical implementation

The project is performed over 2.5 years in the Geriatric Outpatient Clinic at Holbæk Hospital, where the necessary expertise, experience, and equipment are present. Expected project period May 1, 2026, to July 31, 2029. Primary investigator is Mette Midttun, Senior Consultant, DMSc, who performs the study – in collaboration with Senior Consultant, Clinical Associate Professor Maja Sparre. Other project management and continuous monitoring are performed by Senior Consultant Karsten Overgaard and neuropsychologist, PhD Rune Skovgaard Rasmussen. All financing of the project is via private foundations and the workplace.

Other information about the project and finances

There is no connection between trial managers and supporters; the project is fully funded by private foundations and the workplace. No compensation is paid to trial subjects.

Dissemination

The results, whether negative, positive, or inconclusive, will be sought for publication in national and international journals, as well as presented at national and international conferences.

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