

Version 5

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27<sup>TH</sup> of August 2018

Protocol

Testosterone in bariatric patients

Title

Muscle strength and -mass after bariatric surgery - a possible effect of testosterone replacement therapy?

Randomized, placebo-controlled and double-blinded study

### **Research group**

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## 1. General information

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The trial will be monitored in accordance with GCP, and the local GCP unit will help establish the extent of the monitoring to ensure that the trial comply with GCP and applicable law. The trial will be conducted according to this protocol. The study protocol will be submitted to The Danish Medicines Agency and the Regional Ethics Committee, notified to the Danish Data Protection Agency and registered at ClinicalTrials.gov. The investigations are conducted as part of a post.doc position at the University of Southern Denmark.

Collaborators:

KBA at SVS and OUH (biochemistry)

Institute of Regional Health Research/Centre of Southwest Jutland (muscle strength and VO<sub>2</sub>max)

Physical Therapy section (exercise counseling)

The GCP-section at Odense University Hospital

OPEN (randomization and eCRF)

Pharmacy at OUH (handling of study medicine)

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Time schedule:

Estimated August 2018 – January 2021

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Date            Signature

## 2. Introduction

Obesity, poor physical fitness and low muscular strength are associated with all-cause mortality [1-5]. Loss of bodyweight is commonly achieved by diet with or without exercise intervention. However, both diet and diet+exercise programs are often followed by weight regain and it is generally difficult to achieve long-term weight loss [6].

There are many challenges associated with the counselling of obese and sedentary individuals in order to increase their physical activity (PA), and there may be a need for a tight schematic counselling to achieve positive results [7]. Additionally, promoting PA among patients that have undergone bariatric surgery has also shown to be challenging [8, 9] even though PA may be of a great importance regarding several postoperative outcomes [9-12]. Lifestyle changes following bariatric surgery may be important for the overall effect of the BS in the long term. Therefore, it is vital to find an appropriate and well-suited setting to improve PA among these patients. When structuring PA counselling, the five A's (Assess, Advise, Agree, Assist, Arrange) might be a helpful tool and it is considered important to engage the patients in PA counselling both before and after the surgery [9, 13].

Loss of bodyweight reduces morbidity and mortality [14]. Bariatric surgery is the most effective method to treat severe obesity and type 2 diabetes mellitus achieving high remission rates [15]. However, weight loss also decreases skeletal muscle mass [16, 17] which might counterbalance the positive effects of a bariatric surgery since low lean body mass is linked to increased mortality under various circumstances (i.e., heart disease, cancer, burn injuries) [18]. Furthermore, a substantial loss of bone mass is seen after bariatric surgery [19, 20] despite weight stability in the second-year post-operative [19], which could have important clinical implications for long-term skeletal health with increased fracture risk [19, 21]. On the other hand, the loss of muscle and bone mass could merely be a natural adaptation to a lower weight after bariatric surgery. Studies trying to establish whether the loss of muscle mass is disproportionately in patients following bariatric surgery compared to BMI-matched controls are conflicting, showing lower muscle mass in both sexes after surgery compared with their respective matched controls assessed by magnetic resonance imaging in one study [22] whereas another study has shown comparable fat-free mass 24 months post-operative assessed by bioelectric impedance [23]. Currently, there are no effective approaches to prevent the immense loss of muscle and bone mass following bariatric surgery [18] although several approaches can be considered, e.g. exercise and dietary intervention [24].

Low testosterone levels have been associated with sarcopenia, insulin resistance, increased body fat, reduced quality of life and loss of libido and sexual function. Testosterone therapy increases lean body mass (i.e. muscle mass), improves bone density and decreases fat mass [25]. As up to 78.8% of patients undergoing bariatric surgery suffer from low testosterone levels [26-28], testosterone therapy prior to and after bariatric surgery may prevent or reduce the considerable loss of muscle mass during the weight loss period [29]. So far, no studies have evaluated the effect of testosterone therapy combined with exercise and diet counselling on body composition and quality of life in men undergoing bariatric surgery.

#### Testosterone therapy and cardiovascular risk

Studies on cardiovascular risk during testosterone therapy are conflicting. A study in old men with limitations in mobility showed significantly more cardiovascular events during testosterone therapy compared to placebo and the study was ended prematurely [30]. Low HDL levels are linked to an increased morbidity and mortality of cardiovascular disease. A significant small decrease in HDL cholesterol levels in men treated with testosterone was reported in a meta-analysis [31] and a systematic review [32]. However, a large observational study on pooled data in obese, hypogonadal diabetic men during six years of testosterone therapy reported a favorable change in lipid profile along with reduced pulse pressure and reduced arterial stiffness, which are independent risk factors for cardiovascular disease [33]. Another approach in clarifying the effect of testosterone therapy on cardiovascular disease risk is the evaluation of biomarkers for cardiovascular disease during therapy, i.e. soluble Klotho, a protein, which may function as a hormone [34]. Higher levels of soluble Klotho are independently associated with a lower likelihood of having cardiovascular disease [35]. To date, no reports on Klotho have been published in obese patients undergoing bariatric surgery during testosterone therapy.

Few studies have addressed the influence of testosterone therapy on the haemostatic system. Thrombin generation (TG) measures are risk markers of cardiovascular disease and address the composite of multiple factors that influence blood coagulation [36]. One intervention study showed that i.m. testosterone treatment for one year in elderly men with low testosterone levels had no impact on thrombin generation measured at one year [37]. A significant number of patients sustaining venous thrombotic events after initiation of testosterone therapy often had inherited cardiovascular risk factors such as Factor V Leiden [38], and thrombotic events were primarily

observed within the first months of testosterone treatment, suggesting that testosterone therapy triggers cardiovascular events in thrombosis prone individuals. Thus, studies on both the short term and the long term impact of testosterone treatment on the haemostatic system are warranted [38, 39].

### Pseudo-Cushing's syndrome

Central obesity results in a cluster of metabolic abnormalities contributing to premature death, so-called Pseudo-Cushing's syndrome [40]. Glucocorticoids regulate adipose-tissue differentiation, function and distribution, and in excess, cause central obesity. To our knowledge, no studies have reported results on levels of cortisol and testosterone before and after bariatric surgery.

## **3. Trial plan and design**

### **General aim**

To investigate the effect and clinical relevance of testosterone therapy combined with exercise and diet counselling in hypogonadal men undergoing bariatric surgery.

### **Objectives**

To evaluate the effect of testosterone therapy combined with exercise and diet counselling on muscle strength, body composition, hormones, components of the metabolic syndrome, inflammation, sexual function, and quality of life after weight loss in obese, hypogonadal men undergoing bariatric surgery.

### **Perspective**

The study will investigate whether testosterone therapy can stabilize muscle function, prevent the substantial decrease in muscle mass (lean body mass), and improve components of the metabolic syndrome, inflammation and quality of life in patients after bariatric surgery.

### **Study design**

A two centre, randomized, double-blind, placebo-controlled study on testosterone therapy combined with lifestyle intervention, in men eligible for bariatric surgery with low testosterone levels. Routine

bariatric procedure will be conducted between 3 and 6 months after inclusion. The end of the study is 52 weeks postoperatively.

## Study endpoints

### Primary outcome:

- Maximal isometric muscle strength (N) in shoulder muscles (shoulder elevation).

### Secondary outcomes:

- Regional body composition (DXA scan, BMI, Waist/hip-ratio)
- Physical strength: maximal isometric muscle strength in lower extremities (hip extension, hip abduction), muscle strength in upper-extremities (shoulder abduction, shoulder adduction)
- Physical function: performance-based measures of physical function (stair climb test) and maximal oxygen uptake (VO<sub>2</sub>max).
- Glucose metabolism (HOMA-R, HbA1c, Fasting-P-Blood glucose)
- Coagulation/fibrinolysis status (thrombin generation measures)
- Adipokines and inflammation markers (leptin, adiponectin, hsCRP, IL-6, suPAR, lipid profile (HDL, LDL, triglycerides))
- Hormones and binding proteins (testosterone, SHBG, LH, FSH, prolactin, CBG, growth hormone-axis (IGF-I and IGF-II, IGFBPs, bioactive IGF-I), cortisol, aldosterone, Cortisol and cortisol metabolites)
- Vascular markers (soluble Klotho, fibulin-1)
- Bone markers and calcitropic hormones (osteocalcin, PINP, ICTP, CTX, PTH, 25OH-vitaminD, 1.25(OH)<sub>2</sub>-Vitamin-D)
- Quality of life and sexual function (International Index of Erectile Function (IIEF-5), Major Depression Inventory (MDI), World Health Organization Well Being Index (WHO-5), Physical function component of Vitality scale of Short Form 36 (SF36))



## **Method**

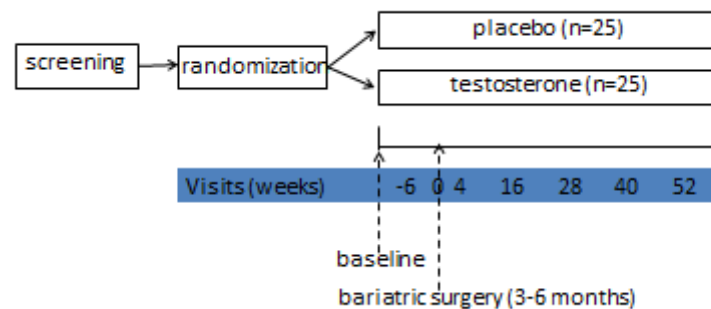
A randomized, double-blind, placebo-controlled intervention study in men eligible for bariatric surgery and low testosterone levels (total testosterone < 12.0 nmol/l [41]). Routine bariatric procedure will be conducted between 3 and 6 months after inclusion.

## **4. Study population**

### **Recruitment**

Patients will be recruited among bariatric patients at Hospital of Southwest Jutland and at Odense University Hospital. As part of a review of existing clinical practice in the Region of Southern Denmark, patients who are entitled to bariatric surgery are currently subject to an audit with the establishment of a quality and research database. As part of the audit, patients have had their testosterone levels in the blood measured. MD Line Velling Magnussen (LVM) may obtain these results from the journal, if there is a signed consent statement during the audit, where the patients also have agreed to be contacted for future projects, where their participation will be relevant. MD LVM may phone those patients with low testosterone levels and send the written information regarding the trial along with the booklets "Før du beslutter dig" and "Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt", if agreed by the patients. Patients are informed that they are entitled to bring a bystander for the oral information. Those who may wish to participate, are contacted on the first day of the participation of the patient school at the Southwest Hospital of Jutland, Esbjerg (as part of the standard treatment procedure prior to bariatric surgery), where a MD from the research team, all of whom have experience within the field of bariatric and GCP experience, will provide oral information regarding the trial. The information is given in a suitable room, ensuring that the conversation can take place without interference. After the oral information, the patient has minimum 24 hours to think about participation. Upon acceptance, time is given for visits, screening blood samples and obtaining written informed consent. Inclusion will be in the beginning of the mandatory 8% weight loss period lasting 3-6 months.

## Overview:

**Randomization**

After the baseline assessment, the patients will be randomly assigned to either testosterone or placebo. The randomization sequence will be created using OPEN Randomise, stratifying patients with a 1:1 allocation using random block sizes of 2, 4 and 6. The allocation sequence will be concealed from the researcher enrolling and OPEN Randomise will send an e-mail to an email address each time a randomization is performed.

**Inclusion criteria**

- Eligible for bariatric surgery according to the Danish national criteria (i.e. aged 18–60 years, BMI >35 kg/m<sup>2</sup> with specific secondary disease or BMI >40 kg/m<sup>2</sup> with significant health issues assessed by the multidisciplinary bariatric team) [42]
- Caucasian men
- Total testosterone < 12.0 nmol/l
- No contraindications for testosterone treatment

**Exclusion criteria**

- Previously diagnosed with prostate, mammae or liver cancer. Any other cancer within the last 5 years.
- Hypersensitivity to the active substance or to any of the excipients in Nebido<sup>®</sup>
- Symptomatic heart disease NYHA >2
- Recently thromboembolic disease <3 months
- PSA >4.0 ug/l or PSA >3.0 ug/l and lower urinary tract symptoms
- Disability that severely affect the ability to perform exercise training
- EVF > 52%

The following treatments are not allowed in the study

- 5- $\alpha$ -reductase inhibitors
- Prednisolone >5mg/day

## **5. Treatment of patients**

### **Treatment regimen**

- Inj. Testosterone undecanoat (Nebido®), 1000 mg im or placebo preoperative (baseline, weeks 6, 18 and 30 depending on time to surgery) and postoperative (weeks 4, 16, 28, 40) (Table 1).
- Administration: deep and slow (over two minutes) intragluteal injection
- Due to the risk of anaphylaxis, patients are observed at least 30 minutes on the test site after the first two injections

### **Non-pharmacological intervention**

- Routine bariatric procedure (Roux en Y gastric bypass or sleeve gastrectomy). Surgery will be conducted between 3 and 6 months after inclusion.
- Lifestyle intervention program: Routine instructions on diet and dietary precautions after surgery [43] and individual exercise counseling three times after surgery.

Contraindications Testosteron undecanoate (ATC-code G03BA03)

- previously diagnosed with prostate, mammae or liver cancer. Any other cancer within the last 5 years.
- hypersensitivity to the active substance or to any of the excipients

Caution in

- cardiac insufficiency, especially known ischemic heart disease and hypertension
- hepatic or renal insufficiency
- clotting disorders / anti-coagulant treatment
- known epilepsy and migraine
- pre-existing sleep apnoea

Adverse reactions (see Appendix).

Study medicine is administered at the departments of endocrinology at SVS or OUH. Study medicine is handled according to annex 13.

Patients are treated with Testosterone Undecanoate 1000 mg/4 ml, intramuscular (i.m.) or placebo. Study medicine and placebo have been produced by Bayer Health Care. Packing, blinding, labeling and randomization of study medicine are done by the pharmacy of Odense University Hospital according to annex 13: Name of sponsor, route of administration, batch number, trial reference code, user manual for study medicine, storage of study medicine expiration date (a copy of the label is placed in the trial master file).

The medicine (active and placebo) is delivered to the pharmacy from Bayer with no labels. Identical labels will be put on the ampules, with the exception of the randomization number.

Study medicine can be used only in clinical trials.

Sponsor is responsible for the destruction of surplus medicine.

### **Medicine records**

All medicine is accounted for in total and for every patient. The records are kept in the trial master file. The randomization code is kept according to law. The procedure for code breakage: In case of a medical emergency an investigator is allowed to break code and inform whether testosterone or placebo is administered. Other members of the study group will remain blinded. The patient will be excluded from the study if the code is broken. Testosterone treatment is a registered treatment. It is not of clinical significance for further acute treatment to know within 24 hours if a patient is in active treatment or not. All the investigators who are medical doctors are affiliated with one the departments of endocrinology at SVS or OUH. At least one of these investigators has their cell phone open 24 hours a day, also during vacations.

### **Discontinuation of study treatment**

Treatments stop:

- Confirmed increase in serum PSA > 3 ug/l and clinical symptoms and at least 20% increase since baseline is followed by referral to urological evaluation
- Suspicion of prostate cancer

- Hematocrit (EVF) > 0.52 and at least 20% increase since baseline
- Serum ALAT >3 times upper normal limit and at least 20% increase since baseline
- Patients can leave the study prior to end of study, due to safety issues (increased safety parameters), fulfillment of exclusion criterion, at own request or due to lack of compliance including failure to achieve 8% weight loss prior to operation.

### **Pharmacokinetics**

Nebido® slowly releases testosterone after intramuscular injection with no first-pass effect.

Testosterone is metabolized in the liver (CYP3A4) to active metabolites estradiol and dihydrotestosterone. An increase in serum levels of testosterone above basal values may be seen one day after administration, and has an average half-life time of 50-130 days. Steady-state conditions are expected to be achieved between the 3rd and the 5th administration with constant dosing interval of 10 weeks during the following administrations. The median intra- and inter-individual variability (coefficient of variation, %) of C<sub>min</sub> values was 22 % (range: 9-28%) and 34% (range: 25-48%), respectively.

## 6. Evaluation of effect

Assessments according to visits:

	Pre-operative				Per/Post-operative					
	Baseline	W 6	W 18	W 30	W 0	W 4	W 16	W 28	W 40	W 52
Testosterone injection*	X	X	X	X		X**	X	X	X	
Safety	X	X	X		X		X	X		X
Exercise and diet counseling	X				X			X		X
Muscle strength and VO <sub>2</sub> max test	X				X			X		X
Physical examination	X				X			X		X
Blood samples	X				X			X		X
Urine samples	X				X					X
Body composition (DEXA scan)	X				X			X		X
Questionnaires	X				X			X		X
Dexamethasone suppression test	X				X					X

W=weeks, W0= from one to seven days before operation.

\* Number of injections depends on time to achieve the mandatory 8% preoperative weight loss. The testosterone injection needs to be applied in the preoperative period at Weeks 6 and hereafter every 12 weeks, correspondingly Weeks 18 and Weeks 30 if necessary.

\*\* The first time for injection in the postoperative period will be 12 weeks after the last injection during the preoperative period. Injection within 4 weeks before planned surgery is postponed to week 4 +/- 2 weeks postoperatively.

### Blood samples

1) Hormones and binding proteins: Total testosterone, SHBG, LH, FSH, prolactin, CBG, growth hormone-axis (IGF-I and IGF-II, IGFBPs, bioactive IGF-I), cortisol, ACTH

2) Adipokines and inflammation markers (leptin, adiponectin, hsCRP, IL-6, suPAR, YKL40, GDF15, sCD36, FGF23, phosphate, total-calcium, lipids)

- 3) Vascular markers (aldosterone, fibulin-1, soluble Klotho)
- 4) Bone markers and calcitropic hormones (osteocalcin, PINP, 1CTP, CTX, PTH, 25OH-vitaminD)
- 5) Glucose metabolism: s-insulin, HbA1c, Fasting-P-Blood glucose
- 6) Safety parameters (hemoglobin, hematocrit, PSA, ALAT)
- 7) Coagulation/fibrinolysis status (thrombin generation measures)

### **Urine samples**

Diurnal U-Cortisol and cortisol metabolites

### **Body composition**

Whole body composition, lumbar and hip bone mineral density and will be assessed using Dual x-ray absorptiometry (DEXA) on Hologic Discovery devices (Waltham, MA, US). DXA scans will be performed at the Department of Endocrinology, SVS.

### **Questionnaires**

The participants will be asked to fill in standardized and validated questionnaires regarding quality of life and sexuality:

- Short Form 36 (SF-36) from Qualimetrics ([qualimetrics.com](http://qualimetrics.com))
- IIEF5 –International Index of Erectile Function, copyright of Pfizer Danmark, Lautrupvang 8, 2750 Ballerup
- Major Depression Inventory (MDI)
- World Health Organization Well Being Index (WHO-5)

### **Dexamethasone suppression test**

The test is used in diagnosing Cushing's syndrome by measuring how cortisol levels change in response to 1 mg dexamethasone overnight.

**Physical examination**

- 1) Body weight: will be measured on calibrated scales with patients only wearing their underwear (no shoes)
- 2) Height: will be measured without shoes
- 3) BMI will be calculated by the formula  $\text{weight}/\text{height}^2$  (kg/m<sup>2</sup>)
- 4) Waist: will be measured in the middle of the distance between the 12th rib and antero-superior iliac spine, while keeping the measuring tape parallel with the floor
- 5) Hip: will be measured across the widest part of the hips while keeping the tape parallel to the floor
- 5) Waist/hip ratio will be computed
- 6) Blood pressure measures thrice while sitting (the participants are to be seated at least 5 minutes prior to the measurements). The mean of the last two measurements is registered
- 7) Testicular volume will be assessed by using Prader orchid meter
- 8) Changes in primary and secondary sex characteristics (breast size / gynecomastia and pubic hair) will be assessed by using the Tanner scale

**Muscle strength testing**

- 1) Muscle strength: Maximal isometric muscle strength will be measured with a Bofors MODEL dynamometer (Bofors Elektronik, Karlskoga, Sweden). Three maximal voluntary contractions (MVC) with 30 seconds of recovery between attempts will be conducted, and the highest value will be recorded. Maximal force and the corresponding moment arm will be registered [44].
- 2) VO<sub>2</sub> max and functional capacity: Maximal oxygen uptake will be estimated from the relation between sub-maximal workload and stable heart rate obtained in Åstrand one-point sub-max test [45]. The bike test will be conducted by using Monark 939E electronic ergometer work test bike (939E) which is digitally controlled and has embedded protocol and calculation of max VO<sub>2</sub> (Åstrand formula). The pedaling frequency will be adjusted at 60 rounds per minute and the initial workload is 450 kilopond meter/minute (corresponding to ~ 75 watt).
- 3) Functional capacity will be estimated using stair-climb test. The outcome is the number of times the subjects are able to reach the stairs up and down for a period of one minute.



## 7. Safety evaluation

### Monitoring:

- Physical examination (baseline, per/postoperative weeks 0, 28 and 52) (Table 1)
- Biochemical examinations: 1. testosterone levels (baseline) 2. PSA, EVF, ALAT (baseline, preoperative weeks 6 and 18, postoperative weeks 0, 16, 28 and 52)
- Clinical relevant abnormal measurements are repeated

### Safety parameters:

- Measurements of hematocrit: testosterone therapy increases the hematocrit level and high levels of hematocrit leads to higher risks of venous thrombosis (Danish Urological Society (DUS) 2013).
- In order to take into account the Danish Urology Cancer Group (DUCG) 2013 report on prostate cancer, and the Danish Urological Society report on androgen substitution (2013) the exclusion criterion for PSA in the study is based on the above level.

### Registration and reporting of adverse events:

An adverse event: Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

A serious adverse event: Any untoward medical occurrence or effect that at any dose results in death is life threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect. All serious adverse events are reported from investigator to sponsor within 24 hours of becoming aware.

Adverse events are reported to Danish health and medicines authority and regional ethics committee according to current guidelines. Other investigators are informed.

The sponsor ensures that all relevant information about suspected unexpected serious adverse reactions (SUSARs) that are fatal or life threatening is recorded and reported as soon as possible to the competent authorities and to the Ethics Committee no later than seven days after knowledge by the sponsor of such a case. Relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected serious unexpected adverse reactions will be reported to the Danish health and medicines authority (DKMA) and to the Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the sponsor. The sponsor is obliged to inform all investigators.

A definition of a suspected unexpected serious adverse reaction (SAR) is as follows: An adverse reaction, the nature or severity of which is not consistent with the applicable product information as not being according to the summary of product characteristics of Nebido®. The reference document used is the specified product summary for Nebido® (section 4.8 of the summary), when assessing whether a SAR is unexpected/expected, thus possibly becoming a SUSAR.

SUSARs are reported electronically (e-blanket) to DKMA.

All adverse events are registered. Sponsor is obliged to report a list of serious adverse events to DKMA and the regional ethics committee annually.

Sponsor will forward serious adverse events and suspected unexpected serious adverse reaction to Bayer within 24 hours of becoming aware.

Treatment of complications and follow-up:

- Patients will be referred to the relevant specialist department for further control and possible treatment.

Criteria for end of study:

- The study will end after 52 weeks of testosterone therapy postoperatively. The patients will be offered a visit in the clinic six months after end of study.
- Patients can leave the study prior to this due to safety issues (increased safety parameters), fulfillment of exclusion criterion, at own request or due to lack of compliance including failure to achieve 8% weight loss prior to operation.

## 8. Statistics

Sample size: The power and sample size calculation is based on the primary outcome maximal voluntary isometric contraction in shoulder muscles (shoulder elevation) after the intervention. To detect a minimal relevant difference between (MIREDIF) of 14% [46] the groups with a two-sided significance level of 0.05 assuming a SD of 34 N [46], and to obtain a power 80%, it is required to

enroll 18 patients in the ITT-population. We will include 25 participants in each group to account for drop outs.

Statistical analyses: All data being collected, primary and secondary outcomes will be analyzed according to the ITT principle. Missing data were handled by multiple imputations, assuming missing values were randomly distributed. Baseline demographic and clinical characteristics will be reported descriptively for all patients in the full analysis set. For assessments of change from baseline, analyses of covariance (ANCOVA) will be applied, with treatment assignment serving as the main factor and the baseline value as covariate. Unless stated otherwise, results will be expressed as the difference between the group means with 95% confidence interval. P values will be reported if appropriate. Significance level: 5%. Additionally to the ITT analyses per protocol analyses will be conducted.

## **9. Source data**

Source data includes patient journals and laboratory/scan reports using eCRF in REDCap through OPEN. Direct access to source data is allowed in monitoring of the study, audit and inspection from ethics committee, Danish health and medicines authority, the Danish data protection agency and other relevant health authorities. This is accepted by participants in a written authorization.

## **10. Quality control and quality assurance**

Quality control and securing of quality is done according to §§ 3 and 4 in the GCP–guidelines, annex 3 and GCP guidelines section 1.46 and 1.47.

## **11. Ethical questions**

An increasing number of patients become obese. Bariatric surgery is an effective method in the treatment of severe obesity and T2D achieving high remission rates. However, weight loss also decreases skeletal muscle mass. Obesity together with poor physical fitness and low muscular strength is associated to all-cause mortality. As many patients undergoing bariatric surgery suffer from low testosterone levels, testosterone therapy may prevent the immense loss of muscle mass together with physical and diet counselling in these patients. So far, no other treatment has prevented this loss of muscle mass. Hence a study like this is needed to investigate if testosterone therapy in these patients will be beneficial.

Nebido® is registered in Denmark. Injection with testosterone or placebo can be uncomfortable for some. The drug is administered in the gluteal muscle and local swelling and redness of the skin can be observed. This is temporary and safe. The study is in accordance with the Helsinki II declaration and is reported to the regional ethics committee and the Danish health and medicines authority. Individuals found eligible to bariatric surgery and who accept to undergo the operation will be included in the study at the beginning of the mandatory 8% preoperative 6 month's weight loss period. Individuals will be recruited among patients referred to bariatric surgery at Hospital of Southwest Jutland and at Odense University Hospital. Patients will be asked at their first attendance at the clinic if they would like to consider participation in the study and if so they will receive written information regarding the study and they will be contacted by MD Line Velling Magnussen. It will be emphasized that participation is voluntary and that the consent can be withdrawn at any time and that this will not have any relevance further treatment. The written information concerning the trial will follow guidelines regarding information and consent requirements. All patients will be provided written information material (see appendix). For oral information, this will include an explanation of the written information and a further description of the study. Information relating to patients is protected by the law on the processing of personal data and the law on patients' legal status.

In this trial, half of the patients are treated with Nebido®, which is an approved and marketed testosterone product. The other half will receive injection with placebo. Placebo is necessary during this double-blinded study for methodological reasons. It could affect the results of the trial, if the patients or healthcare staff know in advance whether active treatment is given or not. As always, in clinical trials, unknown effects or complications might occur. Patients cannot be guaranteed effect of treatment, but it is highly probable that: The patients randomized to Nebido® experience an improvement in their muscle mass and muscle strength, as well as improved quality of life and reduced symptoms associated with low testosterone levels. The patients randomized to placebo will receive counseling in relation to exercise before and after bariatric surgery compared to standard procedure. As standard treatment is used as comparative treatment, no one is treated differently or worse compared to the normal treatment procedure, including standard follow-up by physician, dietitians and nurses in the clinic. The knowledge gained through the experiment will contribute with significant scientific information of importance to the future treatment of men undergoing bariatric surgery. Thus, it is the opinion of the investigators that the trial is relevant and ethical.

The DXA scans in the study program give rise to a radiation dose of 1 mSV, which corresponds to 1/7 of the background radiation per year in Denmark. Exposure for 1 mSv increases the risk of dying of cancer by 0.005%. The background risk of dying of cancer in Denmark is 25%.

Participation in the project will mean exposure to ionizing radiation for patients, which will give rise to a risk increase from 25% to 25.00125%. This does not affect current or future health.

The patients will be offered a visit in the clinic six months after end of study including a physical examination and control of androgen status.

## **12. Handling and archiving data**

Data is handled and filed according to EMEA guidelines for Good Clinical Practice section 5.5.

Data is collected and analyzed electronically (OPEN) and no unauthorized access to data is allowed.

Original data is filed according to one participant number.

The study is reported to the Danish Data Protection Agency (joint report from the Region of Southern Denmark) and will be handled according to the regulations of the Act on Processing of Personal Data. Data will be stored for 10 years.

This is a privately initiated trial and hence sponsor is responsible for data. Information on concomitant medication and patient history from the medical journal will be given to the investigator as part of the inclusion procedure to secure that the exclusion criteria are met and later on for the evaluation of the effect of testosterone therapy in patients undergoing bariatric surgery. In the latter case referring to data observed during the study: physical examination (weight, height, hip goal, waist circumference, breast development, blood pressure), blood tests and urine tests.

## **13. Bio bank**

A research bio bank will be established for blood (approximately 200 ml) and urine (approximately 300 ml) per participant. The purpose is to analyze blood and urine according to section 6 as part of this trial. Some of the analyses will be conducted during the trial due to evaluation of "safety", lack of resistance to freezing or as part of everyday analyses, whereas other analyses will be performed after end of trial due to economic and/or methodological reasons. If the research group wishes to carry out other analyzes than those approved in the current project material, the Regional Ethics Committee must be requested for permission. After the study is finished, the remaining material will be fully anonymized and kept for 10 years and then destroyed.

## 14. Financing and insurance

Investigator initiated research project. Funding is obtained from Hospital of Southwest Jutland, Odense University Hospital and Region of Southern Denmark. The investigators and the departments of endocrinology have no financial gain regarding the study and no conflict of interest that could be perceived as prejudicing the impartiality of this study. The patients will not receive payment. The placebo and Nebido have been donated by Bayer. There will be applied for additional research grants.

The study is conducted under the insurance of the department of endocrinology, SVS.

The grant from the Region of Southern Denmark has been placed on a project account by Deputy Head in "økonomi og planlægning" Morten Lyhne Jørgensen at the Hospital of Southwest Jutland. Sted no. 101 123 190 123. Account 138 61 633 04.

## Budget

	Støtte opnået fra bevilling fra Region Syddanmarks Forskningspuljer	Medfinansiering fra ansættelsessted i ansøgte periode	Opnået støtte fra anden steds til brug i perioden	Beløb der ansøges andet steds	Total budget i perioden
<b>LØN</b>					
<b>Videnskabeligt personale</b>					
Postdoc (20%)			402.000		402.000
Videnskabelige medarbejdere SVS		402.000			402.000
Videnskabelige medarbejdere OUH		201.000			201.000
<b>Teknisk administrativt personale</b>					
Forskningssygeplejersker	200.000			70.000	270.000
<b>DRIFT</b>					
Dexa-skanning, blodprøver, urinprøver	800.000			250.000	1.050.000
<b>UDSTYR -APPARATUR</b>					
<b>Andet</b>					
Medicin			375.000		375.000
Overhead (3,1% ) af totale omkostninger					
<b>TOTAL</b>	<b>1.000.000</b>	<b>603.000</b>	<b>777.000</b>	<b>320.000</b>	
<b>Total budget</b>					<b>2.700.000</b>
<b>Forklarende tekst til budget og de enkelte budgetposter:</b>					
<b>Blodprøver:</b> Hormones and binding proteins, Adipokines and inflammation markers, Vascular markers, Bone markers and calcitropic hormones, Glucose metabolism, Safety parameters , Coagulation/fibrinolysis status. <b>Se venligst ansøgning for nærmere specifikation.</b>					
<b>Urinprøver:</b> diurnal U-Cortisol and cortisol metabolites					
<b>Medicin:</b> Dexametason, Nebido/placebo					

## 15. Guidelines for publication

The study is registered at clinicaltrials.gov and publication is according to the Vancouver regulation.

The study group is obliged to publish positive, inconclusive as well as negative results. Sponsor will inform the Danish medicines agency no later than 90 days after study end and 1 year after study end report study outcomes to the Danish medicines agency (lov om lægemidler § 89, stk. 2, nr. 4). In summarized form: number of treated patients, used doses, results and adverse events. The Danish medicines agency can ask for the full study report.

## 16. Summary and appendices.

### Resume

Bariatric surgery is an effective method in the treatment of severe obesity and type 2 diabetes mellitus achieving high remission rates. However, weight loss also causes loss of skeletal muscle and bone mass which at least partly could be prevented by exercise and dietary intervention although the counselling of obese and sedentary individuals in order to increase their physical activity presents a challenge. As up to 78.8% of men undergoing bariatric surgery have low levels of testosterone, testosterone therapy could be considered an attractive alternative or supplement to prevent the immense loss of muscle mass during weight loss. Furthermore, low testosterone levels are associated with sarcopenia, insulin resistance, increased body fat, reduced quality of life, loss of libido and reduced sexual function. The study is a long-term randomized, placebo-controlled trial investigating the effects of testosterone therapy combined with exercise and diet counselling on body composition, components of the metabolic syndrome, hormones, inflammation, sexual function and quality of life before and after weight loss in obese, hypogonadal men undergoing bariatric surgery.

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## APPENDIX

### Adverse reactions/side effects, testosterone.

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to <1/100)	Rare (≥ 1/10,000 to < 1/1,000)

Blood and lymphatic system disorders	Polycythaemia	
	Haematocrit increased	
	Red blood cell count increased	
	Haemoglobin increased	
Immune system disorders		Hypersensibility
Metabolism and nutrition disorders	Weight increased	Increased appetite
		Glycosylated haemoglobin increased
		Hypercholesterolaemia
		Blood triglycerides increased
		Blood cholesterol increased
Psychiatric disorders		Depression
		Emotional disorder
		Insomnia
		Restlessness
		Aggression
		Irritability
Nervous system disorders		Headache
		Migraine
		Tremor
Vascular disorders	Hot flush	Cardiovascular disorder
		Hypertension
		Dizziness
Respiratory, thoracic and mediastinal disorders		Bronchitis
		Sinusitis
		Cough
		Dyspnoea

		Snoring
		Dysphonia
Gastrointestinal disorders		Diarrhoea
		Nausea
Hepatobiliary disorders		Liver function test abnormal
		Aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	Acne	Alopecia
		Erythema
		Rash
		Pruritus
		Dry skin
Musculoskeletal and connective tissue disorders		Arthralgia
		Myalgia
		Pain in extremity
		Musculoskeletal stiffness
		Blood creatine phosphokinase increased
Renal and urinary disorders		Urine flow decreased
		Urinary retention
		Urinary tract disorder
		Nocturia
		Dysuria
Reproductive system and breast disorders	Prostate specific antigen increased	Prostatic intraepithelial neoplasia

	Prostate examination abnormal	Prostate induration Prostatitis
	Benign prostate hyperplasia	Prostatic disorder Libido changes Testicular pain Breast induration Breast pain Gynaecomastia Oestradiol increased Testosterone increased
General disorders and administration site conditions	Various kinds of injection site reactions <sup>1</sup>	Fatigue Asthenia Hyperhidrosis Night sweats
Injury, poisoning and procedural complications		Pulmonary oil microembolism <sup>2</sup>

<sup>1</sup> - Various kinds of injection site reaction: Injection site pain, Injection site discomfort, Injection site pruritus, Injection site erythema, Injection site haematoma, Injection site irritation, Injection site reaction

<sup>2</sup> - can in rare cases lead to signs and symptoms such as cough, dyspnoea, malaise, hyperhidrosis, chest pain, dizziness, paraesthesia, or syncope. These reactions may occur during or immediately after the injections and are reversible.

Other: nervousness, hostility, sleep apnoea, various skin reactions including seborrhea, increased hair growth, increased frequency of erections and in very rare cases jaundice have been reported under treatment with testosterone containing preparations.

Therapy with high doses of testosterone preparations commonly reversibly interrupts or reduces spermatogenesis, thereby reducing the size of the testicles; testosterone replacement therapy of hypogonadism can in rare cases cause persistent, painful erections (priapism). High-dosed or long-

Version 5

EudraCT: 2018-002365-19

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term administration of testosterone occasionally increases the occurrences of water retention and edema.

See SPC for complete safety reference information

(<https://www.medicines.org.uk/emc/product/3873/smpc>)

## **Counselling intervention**

The overall aim with the counselling is to prevent significant decrease in muscle strength as a consequence of Bariatric surgery. The partial aims are, through counselling, to make the patients aware of the importance of maintaining physical function to increase motivation and PA levels.

The Counselling:

The patients will be offered counselling four times during the study period; one exercise counselling before the surgery and three times exercise counselling post-surgery (Table 1).

The structure of the counselling will be based on the five A's (Assess, Advise, Agree, Assist, Arrange) however, specific emphasis will be on motivational interviewing, goal setting, individual tailored PA programs, and instructions in the provided programs.

**Test manual - The effect of testosterone on bodyweight and muscle strength in obese, hypogonadal men undergoing bariatric surgery**

**Ankomst:**

- Har forsøgspersonen underskrevet samtykkeerklæring?
- Kort introduktion om hvad der skal foregå.
- Montering af accelerometer

Cand.Scient i Idræt og Sundhed, Ph.d. Bibi Gram

PDF with test protocol (double-click to open)