Testosterone Therapy and Bone Quality in Men with Diabetes and Hypogonadism

NCT03887936

December 19, 2023

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VA RESEARCH CONSENT FORM

H-45062 - TESTOSTERONE THERAPY AND BONE QUALITY IN MEN WITH DIABETES AND HYPOGONADISM

Study on the efficacy of testosterone therapy on bone quality of men with diabetes mellitus and low testosterone.

Concise and Focused Presentation

This is a placebo-controlled study comparing the effect of testosterone therapy to placebo (inactive substance that looks like study drug) in men with diabetes mellitus and low testosterone. We will be performing bone mineral density testing (testing for bone thickness), perform measures that reflect bone strength, and markers of bone function, The study will be conducted for 1 year. The benefits include improvement in bone mineral density and bone strength, improvement in symptoms such as low energy and low sex drive, and increase in muscle mass. Risk of testing includes possible pain, bleeding or infection from blood draws and from bone indentation, exposure to radiation and possible loss of confidentiality. Risks associated with the drug testosterone include but not limited to possible increase in red blood cell count, increase in prostate size and growth of prostate cancer, water retention, allergy, skin irritation, blood clots, stroke, heart attack and possible death.

Your participation in the study is purely voluntary. However, the testosterone gel is FDA-approved and if interested in being prescribed you can consult with your healthcare provider(s) outside of the study to discuss options.

Background

You are invited to take part in a research study that is conducted by Reina Villareal, MD who is the project Principal Investigator. Please read this information and feel free to ask any questions before you agree to take part in the study.

Diabetes mellitus is a risk factor for low testosterone resulting in a significant number of men with diabetes also diagnosed with low testosterone. Both conditions are associated with increase in the risk for fractures. Testosterone has been shown to improve the bones of men with low testosterone in addition to improving symptoms such as low sex drive and poor energy. This study will examine if testosterone will also improve the bones of men who have diabetes mellitus in addition to low testosterone.

One-hundred and sixty-six subjects will take part in this study. The study drug is testosterone gel and has been approved by the Food and Drug Administration (FDA) for the treatment of low testosterone. Please read the consent form and feel free to ask any questions before you agree to take part in the study. This form will explain the research study, the possible risks as well as any possible benefit to you. We encourage you to talk with your family and friends before you decide to take part in this research study. If you have any questions, please ask one of the

study investigators.

This research study is funded by the VA Merit Review.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Purpose

The purpose of this study is to evaluate the effect of testosterone treatment compared to placebo in men with diabetes mellitus and low testosterone on: 1) bone strength, 2) bone turnover markers or markers of bone function, and 3) an exploratory aim, to examine the mechanism for the improvement in bone metabolism in response to testosterone therapy

Procedures

The research will be conducted at the following location(s):
Baylor College of Medicine, Baylor College of Medicine -- Alkek Eye Center, and Michael E. DeBakey Veterans Affairs Medical Center.

How long will I be in this study?

The total duration of the study is 12 months. There is a total of 5 visits during the entire study. As best as we can, we will arrange that some of your study visits will be scheduled on the same day as your other clinic visits at the Michael E. DeBakey VA Medical Center.

Participation in this study will take you approximately at most a total of 20 hours for the whole study which mostly involves testing and answering questionnaires.

If you agree to participate, the following things will happen:

A. SCREENING TESTS - to determine whether you are eligible to participate you will undergo a medical history, physical examination, blood tests, DXA (bone scan, a machine that uses a low dose of x-ray).

B. BASELINE AND FOLLOW-UP TESTS - if you are eligible to participate and choose to do so, you will undergo a series of tests and procedures:

a. High resolution quantitative computed tomography (HR-pQCT). This machine is able to assess the 3-dimensional bone microarchitecture (amount of bone thickness and arrangement of bone that is too small to be seen by the unaided eye) and bone strength of your leg and forearm. During the examination, you will sit down on a chair in front of the machine . You will be asked to extend one of your legs (usually the left) and one of your forearm (usually the left) inside a cylindrical machine which uses X-rays to take special pictures. In order to obtain good pictures, it is important that you do not move during the procedure. The examination will last approximately 20 min.
DXA and HR-pQCT will be done at baseline, 6 months, and 12 months.

b. Blood tests: Blood (~4 tablespoons) for complete blood count, prostate-specific antigen and electrolytes, for measurements of blood sugar including hemoglobin A1C, cholesterol, vitamin

D, hormones (such as testosterone), insulin, markers of bone function and cells coming from the bone. These tests will be performed at baseline, 3, 6 months, and 12 months.

c. An optional Bone Microindentation Studies
We will measure the material strength of your bone using the osteoprobe microindentation device. . The microindentation procedure inserts a needle into the leg. To reduce the discomfort of the procedure, a local anesthetic (numbing drug to decrease the feeling of pain) will be used. This is an injectable drug which will temporarily numb the skin. The drug that will be used is 2% xylocaine. After the anesthetic has taken effect, a sterilized stainless needle will be inserted into contact with the bone surface of your lower leg. The bone microindentations are small (375 microns, about the size of the period at the end of this sentence) and are not harmful. The indentations will be obtained up to ten times during each of the two sessions. The insertion of the needle is done once through the skin but redirected ten times at different locations (about 2 mm apart) in the bone. Total time for the test is about 5 minutes. These tests will be done at baseline and at 12 months. This procedure is optional.

d. Questionnaires: The ADAM or Androgen Deficiency in Aging Male questionnaire asks about symptoms related to low testosterone including as sex drive, and energy, the IPSS or International Prostate Symptom Score questionnaire asks questions related to your prostate health including the number of times you go to the bathroom to urinate at night. The physical activity questionnaire will evaluate your level of physical activity. The 3-day food record will evaluate your food intake, collecting data about the foods and beverages consumed. It will take approximately 10 minutes each time to complete all questionnaires, hence a total of 40 minutes to finish the 4 questionnaires. These tests will be done at baseline, 3 months, 6 months, and 12 months.
The FFQ or Food Frequency Questionnaire will evaluate the frequency of the food consumption over the past year and will take 15-20 minutes to complete it. This test will be done at baseline and 12 months.

C. INTERVENTIONS

After the medical screening and baseline assessments are complete, you will be randomly assigned (like a flip of a coin) to receive either:

Testosterone gel or placebo gel which you apply on the skin of your upper arms once daily for 12 months. You will be given a detailed instruction on how to apply the gel by one of the members of the study team.

You may require an adjustment in dose if necessary depending on the results of the blood tests that monitor safety or adequacy of therapy. To monitor safety or any necessary adjustment in dose, one of the study doctors will know if you are on the drug or the placebo, but neither you nor the rest of the study team will know which medication you are taking as they are identical in appearance. However, this information is available in case of an emergency. You will continue to take this medication for up to 12 months.

Testosterone gel 1.62% is approved by the FDA for men with low testosterone and symptoms associated with low testosterone and is, therefore, available commercially. The placebo is an inactive gel that will be used a a control for this study.

You will be given calcium and vitamin D supplement to take daily by mouth

D. BIOLOGICAL SPECIMENS AND STORAGE OF TISSUE FOR FUTURE RESEARCH

Researchers from this study will collect samples of blood for analyses which we are requiring you to provide to be a participant in the study. Every result from the tests described above will be used in the current research and also in future research should the research team determine that these tests would be relevant in future studies. In addition, you can decide to allow the research staff to keep any leftover blood samples and use it in future research should new biomarkers relevant to the study of the effects of testosterone therapy on bone quality in men with diabetes and hypogonadism.
Any research study using your samples must also be approved by an Institutional Review Board. The research that is done with your blood is not designed to specifically help you. It might help researchers to collect more information about the response to testosterone therapy on bone quality in diabetic patients with low testosterone. These reports will not be put in your records. The research using your blood, will not affect your care.
In the future, people who do research with your blood samples and people who do other types of health-related research may need to know more about your health. These researchers may access only reports about your health, while your name, address, phone number social security number, or any other information that will let the researchers know who you are won't be provided. Even if your blood samples are used for this kind of research, the results will not be told to you and will not be put in your health records. You will not hear from us unless we find information that may be have an impact on your health.

Things to think about: It is your choice whether you will allow the study investigators to keep your blood samples for future research. No matter what you decide to do, it will not affect your care. If you decide now that your blood samples can be kept for research, you can change your mind at any time. Just contact a study investigator and let her know that you do not want the investigators to use your blood samples, and they will no longer be used for research. Otherwise, they may be stored for up to 10 years, or until they are used up. If you decide to revoke your authorization samples and data will be destroyed or discarded.
Your blood samples will not be sold. The research done with your samples may help to develop new products in the future, but there are no plans to pay you. You may or may not benefit but the investigators will gain new information.
The greatest risk in storing your blood samples is related to the release of information from your health records. The investigators will protect your records so that your name, address, phone number, or any other information that may easily identify you will be kept private. The chance that this information will be given to someone else is very small. There will be no cost to you for any blood samples and stored by the investigators.
By initialing below you allow the investigators within this study to use your blood samples for a better understanding of the mechanism underlying the effect of testosterone therapy on bone quality in men with diabetes and hypogonadism.

The research team will make every possible effort to keep the information collected during the study confidential. Data will be kept in a locked cabinet, in a restricted area where access is restricted to the study personnel only.

Making your choices:
Please read each question below and think about your choice. After reading each question, circle "yes" or "no". If you have questions, please talk to a member of the research team. Remember that no matter what you decide about the collection and use of your blood samples in this research study, you may still take part in the study.

1) Investigators outside this study may be allowed to use my blood samples for future research

YES NO Subject's Initials _____

2) Investigators within this study may use my blood to obtain more information regarding the response to testosterone therapy on bone quality in diabetic patients with low testosterone levels or for other unspecified future research.

YES NO Subject's Initials _____

3) If I fail the initial screening test, I can be contacted again by the study team for re-screening.

YES NO Subject's Initials _____

4) Participate in the optional bone microindentation studies
YES NO Subject's Initials_____

Clinically Relevant Research Results

The results generated from this research study are not expected to have any clinical relevance to you.

Sharing and Future Research Studies with Identifiable Private Information

Information that identifies you may be removed from your identifiable private information collected as part of this research, and after such removal, your information may be used for future research studies or distributed to another investigator for future research studies without additional consent/authorization from you.

Sharing and Future Research Studies with Identifiable Biospecimens

Information that identifies you may be removed from your identifiable biospecimens collected as part of this research, and after such removal, your biospecimens may be used for future research studies or distributed to another investigator for future research studies without additional consent/authorization from you.

Confidentiality

The health information that we may use or disclose (release) for this research includes:

- Information from health records such as diagnoses, progress notes, medications, lab or radiology findings, etc.
- Demographic information (name, D.O.B., age, gender, race, etc.)
- Full Social Security #
- Partial Social Security # (Last four digits)
- Identifiable biospecimens

Use or Disclosure Required by Law

Your health information will be used or disclosed when required by law.

Your health information may be shared with a public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability and conducting public health surveillance, investigations or interventions.

No publication or public presentation about the research described above will reveal your identity without another authorization from you.

Potential Risks and Discomforts

You may have side effects while on the study. Everyone taking part in the study will be followed carefully for any side effects. However, doctors do not know all the side effects that may happen. Side effects may be mild or very serious. Your study doctor may give you medicines to help lessen the side effects. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death. Many side effects go away soon after you stop taking testosterone.

You should report to your study doctor any side effects you experience while taking part in the study.

Risks associated with testosterone treatment:
o Frequent (Greater than 20%) Side Effects: Increase in red blood cell count which may result in your blood being thicker than normal. As a result, you may need to provide blood (phlebotomy) and may adjust the dose of testosterone or even suspend the use of this medication for a period of time. Increased blood thickness may cause headaches, visual disturbances, dizziness, ringing in ears, high blood pressure, heart failure and blood clots. Testosterone may also result testicular shrinkage or decrease in the size of your testicles, or infertility (common in young men, usually reversible).

o Occasional (Between 2-20%) Side Effects Include: induction or worsening of sleep apnea, mood disorder (disturbance in a person's feelings or emotions), acne or oily skin, enlargement of the prostate AbbVier. Because of the potential for testosterone to cause enlargement of the prostate, you may need to undergo a biopsy of the prostate to make sure you don¿t have prostate cancer, a procedure that would not otherwise be required if you are not taking testosterone. Mild pain, bruising or skin irritation at the site of application.
o Rare (Less than 2%) Side Effects Include: edema or fluid retention, breast enlargement (usually reversible), skin reactions, change in cholesterol levels increased risk of blood clots, (deep venous thrombosis and pulmonary embolism), myocardial infarction and cerebrovascular events especially in those who had these conditions previously or those who are at risk for these conditions which could be serious and may lead to death..

Allergic reaction: Symptoms may include but not be limited to trouble breathing, fast heart rate, rash, dizziness, and swelling.

If you experience any of the above symptoms, you should contact your study doctor immediately.

If you are randomized to the placebo you may not experience the potential beneficial effects of testosterone therapy in improving energy, sexual function, muscle mass, muscle strength, bone density and bone strength.

Randomization risks:
You will be assigned to a treatment program by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatment (s) or other available treatments.

Risks associated with testing procedures
Frequent (Greater than 20% of patients)
- Your participation in this research study involves exposure to radiation. We are exposed to radiation every day of our lives from both natural and manmade sources. The average, whole body radiation dose to a member of the U.S. from these sources is about 360 millirem per year. Individuals who use radiation in their work (for example x-ray technologists, radiologists, etc.) may legally receive up to 5000 millirem per year. The total radiation dose that you will receive over the one year period of this study is 1205 millirem. This is greater than the average radiation dose to a member of the U.S. from natural and manmade radioactive sources (360 millirem per year), but less than the limit for radiation workers (5000 millirem per year). The risk any potential harmful effects from the radiation is considered to be minimal. There is a very slight chance of causing cancer.
- Possible side effects of blood drawing and inserting a thin tube through your vein are discomfort, bruising, and /or bleeding at the site of the needle.
Rare (Less than 2% of patients)
- An infection can occur at the site of the needle insertion for drawing blood samples; however, careful sterile technique is used to decrease this risk. Occasionally, some people may experience dizziness after blood drawing.
-The risks of bone microindentation include discomfort, bleeding, bruising, and scarring. Occasionally some people experience dizziness or feel faint. Risks associated with the injection of the local anesthesia are an allergic reaction (redness and swelling of the skin in the area of the injection, red bumps on the body, and in very rare instances, difficulty in breathing, low blood pressure, and death). The anesthesia is the same as the local anesthesia used by most dentists. If you have not experienced an adverse reaction from anesthesia received at the dentist' s office, it is unlikely for you to have allergic reaction. An infection can occur at the sites. Careful, sterile techniques are used during the tests to decrease the risk of infection.

There are risks of stress, emotional distress, and inconvenience associated with participating in a research study. You may experience emotional discomfort when answering some questions in the questionnaires. You will be encouraged to discuss the importance and the need to answer these questions with a member of the research team. If you remain uncomfortable in answering these questions despite the above efforts, you will be given the option not to answer them.

There are risks related to the loss of confidentiality of your health information. We may use, disclose or release for this research is past and present medical and mental health information, alcoholism or alcohol abuse information, medications, tests including diagnostic laboratory, pathology results, imaging such as x-rays, MRIs scans, dates of tests, demographic information such as name, date of birth, age, home address, phone number, last four SSN, race, dates of tests and test results, completed research questionnaires and records of study drug received. These sensitive information may be disclosed unintentionally in the course of the study. However, study personnel will make every effort to minimize the risk.

Unknown risks: The experimental treatment may have side effects that no one knows about yet including potential death. They may also have unknown risks to a fetus or embryo. Since the effect of the medication on a developing fetus or embryo is unknown, we suggest avoiding pregnancy in your wife or partner by using birth control methods throughout the duration of the study and to continue for 6 months after stopping the medication.

Study staff will update you in a timely way on any new information that may affect your decision to stay in the study. There is a small risk for the loss of confidentiality. However, the study personnel will make every effort to minimize these risks.

Potential Benefits

The benefits of participating in this study may be: There may or may not be benefit to you form participating in this study. Possible benefits to taking part in the study include potential health improvement form the study intervention. You may experience benefits from the study drug such as improvement in the following: bone mineral density or the thickness of your bones, bone strength, mood or well-being, strength and muscle mass and sexual function. It is hoped that results of this study will provide information if testosterone will help the bones of men who have both diabetes mellitus and low testosterone.. However, you may receive no benefit from participating.

Alternatives

The following alternative procedures or treatments are available if you choose not to participate in this study: The testosterone gel is FDA-approved and available commercially. If interested in being prescribed you can consult with your healthcare provider(s) outside of the study to discuss options..

Investigator Withdrawal of Subject from a Study

The investigator or sponsor may decide to stop you from taking part in this study at any time. You could be removed from the study for reasons related only to you (for example, if you move to another city, if you do not take your study medication, or if you have a serious reaction to your study medication) or because the entire study is stopped. The sponsor, investigator, Food and Drug Administration, or Institutional Review Board may stop the study at any time.

Subject Costs and Payments

You will not be asked to pay any costs related to this research.

You will be compensated for your time as follows:
$40 at the time of randomization, $20 at 3 months and $40 at 6 months and at 12 months for a total of $140 for the entire 12 months of study participation.

If you choose to participate in the optional microindentation studies, you will be compensated a separate $40 at baseline and another $40 at the end of the study at 12 months.

Research Related Injury

There is an emergency department at the Michael E. DeBakey VA Medical Canter that can treat any research-related injury. In the event of illness or injury, you may also contact Dr. Reina Villareal, the principal investigator, during the day at (713) 578-4300 (phone) or (713) 485-5687 (phone) or 281-567-0745 (beeper) after office hours. You may also contact the Michael DeBakey VA Medical Center Emergency Department at (713) 791-1414 ext 27440 or ext 23748 for emergencies only.

Research personnel will try to reduce, control, and treat any complications from this research. If you are injured because of this study, you will receive medical care that you or your insurance will have to pay for just like any other medical care.

Subject's Rights

Your signature on this consent form means that you have received the information about this study and that you agree to volunteer for this research study.

You will be given a copy of this signed form to keep. You are not giving up any of your rights by signing this form. Even after you have signed this form, you may change your mind at any time. Please contact the study staff if you decide to stop taking part in this study.

If you choose not to take part in the research or if you decide to stop taking part later, your benefits and services will stay the same as before this study was discussed with you. You will not lose these benefits, services, or rights.

The investigator, REINA VILLAREAL, and/or someone he/she appoints in his/her place will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury related to the research, you may speak with a member of the study staff: REINA VILLAREAL at 713-794-7534, 713-578-4300 or x 23644 during the day and Reina Villareal at beeper 281-567-0745 after hours.

Members of the Institutional Review Board for Baylor College of Medicine and Affiliated Hospitals (IRB) can also answer your questions and concerns about your rights as a research subject. The IRB office number is (713) 798-6970. Call the IRB office if you would like to speak to a person independent of the investigator and research staff for complaints about the research, if you cannot reach the research staff, or if you wish to talk to someone other than the research staff.

Under Federal Regulations, the VA Medical facility shall provide necessary medical treatment to you as a research subject injured as a result by participation in a research project approved by a VA Research and Development Committee and conducted under the supervision of one or more VA employees. This requirement does not apply to treatment for injuries that result from non-compliance by a research subject with study procedures. If you sustain an injury as a direct result of your study participation, medical care will be provided by the Michael E. DeBakey VA Medical Center. The Department of Veterans Affairs does not normally provide any other form of compensation for injury. You do not waive any liability rights for personal injury by signing this form.

You may withdraw from this study at any time without penalty or loss of VA or other benefits to which you are entitled. Your participation will not affect the way you now pay for medical care at the VAMC. If you would like to verify the validity of the study and authorized contacts, you may speak with the Michael E. DeBakey Veterans Affairs Medical Center Research Office at 713-794-7918 or 713-794-7566.
