Skeletal Physiology Dysregulation in Obesity: The Role of Growth Hormone

NCT# 01724489

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PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
Karen K. Miller, MD

PROTOCOL TITLE
Skeletal Physiology Dysregulation in Obesity: The Role of Growth Hormone

FUNDING
[redacted]

VERSION DATE
10.16.19

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

Specific Aim 1: **Low-dose GH administration for 18 months to osteopenic obese men and women will increase bone mass, improve bone microarchitecture and increase bone strength.**
We will investigate in osteopenic men and women with obesity and relative IGF-1 deficiency, whether GH administration for 18 months to increase IGF-1 levels within the normal range results in:

- **A.** Increased BMD
- **B.** Improved bone microarchitecture, including trabecular and cortical thickness.
  - The increase in trabecular thickness will be mediated primarily by GH and the effect on cortical thickness by IGF-1
- **C.** An increase in bone strength, as determined by finite element analysis

Specific Aim 2: **We will investigate mechanisms responsible for the increase in bone strength due to GH administration.** *We hypothesize that the increase in strength will be mediated by:*

- **A.** A reduction in bone marrow fat mediated by a decrease in Pref-1 associated with an increase in osteoblast activity, assessed by markers of bone formation, including P1NP
- **B.** Increased insulin, in associations with an increase in undercarboxylated osteocalcin
- **C.** Improved body composition, including a decrease in abdominal adiposity and lipid deposits in muscle and liver, and an increase in muscle mass
- **D.** A reduction in inflammatory cytokines and improvement in the serum lipoprotein apoB
- **E.** An increase in circulating vitamin D.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Obesity is an important risk factor for osteoporosis and fractures. With the growing prevalence of obesity in the U.S., understanding the pathophysiology of bone loss in this population is of importance to public health. The etiopathology of obesity-associated bone loss is incompletely understood but includes reduced bone formation, deleterious effects of inflammatory cytokines, low levels of circulating vitamin D and elevated lipids and lipoproteins and ectopic lipid deposits. Growth hormone (GH) is a critical mediator of bone homeostasis and is markedly reduced in obesity. Obesity is a state of relative GH and IGF-1 deficiency. Our preliminary data suggest an important role for the GH/insulin-like growth factor 1 system in the pathogenesis of bone loss in obesity. The GH-IGF-1 system is also an important regulator of lipolysis, inflammation and vitamin D metabolism and decreases lipids and lipoprotein levels. Our preliminary data demonstrate that GH administration for 6 months increases markers of bone formation and GH administration for 12 months increases BMD of the lumbar spine in obese subjects. An 18-month study will be necessary to investigate the full effects of GH on skeletal physiology. The development of novel imaging techniques, including Xtreme CT and FEA, provides an opportunity to investigate the effects of GH on skeletal structure and strength, which will provide insights into the pathogenesis of obesity related bone loss. Understanding the pathophysiology of bone loss in obesity may help identify new treatment targets for this important complication.

An emerging area of intense interest is the role of the common mesenchymal stem cell bone marrow precursor of both osteoblasts and adipocytes. Increased bone marrow fat is seen in subjects with morphologic evidence of bone weakness including endplate depression and compression fractures. Therefore, an understanding of the factors that influence the development of bone marrow fat and stem cell differentiation is of clinical importance. This will be the first study on the effects of GH on stem cell differentiation and bone marrow fat in humans.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

Over the five years of this proposal, we expect to screen 300 patients in order to enroll 75 (38 healthy women and 37 healthy men) total men and women with obesity, osteopenia and relatively low IGF-1, adiposity for an evaluable 50 subjects. We will attempt to replace subjects who have dropped out of the study to ensure 50 completers at 18 months (for which the study is powered).

Eligibility:

Subjects will undergo a pre-study screening visit to determine eligibility for the study.

Inclusion criteria:

- Ages 18-65 and generally healthy
- BMI $\geq$ 25 kg/m^2

- BMD T or Z-score ≤ -1.0 (as measured by DXA)
- IGF-I within or below the mean (plus 10% above the mean) for age and gender

Exclusion criteria

- For women: amenorrhea for 3 months or more if premenopausal, pregnancy or breastfeeding, polycystic ovary syndrome
- Elevated creatinine or TSH levels; alanine amino transferase levels greater than 2 times the upper limit of normal
- History of diabetes mellitus, cancer or other serious chronic disease
- Use of osteoporosis medications
- Medication that could affect bone metabolism within the past three months, such as chronic oral glucocorticoids, gonadal steroids, or anticonvulsants
- Hct > 5 units below the lower limit of normal
- Routine MRI exclusion criteria including the presence of pacemaker or cerebral aneurysm clips
- Osteoporosis, that, according to WHO classification (BMD T score less than or equal to -2.5 at the AP spine, total hip or femoral neck), would warrant treatment consideration.
- [redacted]

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Screening Visit: (n=300: 150 healthy obese women and 150 healthy obese men)

- A complete medical history, physical examination, height, weight, waist and hip circumferences. Calculation of BMI, waist:hip ratio.
- Fasting glucose, HbA1c, IGF-1, TSH, creatinine, SGPT, urine pregnancy test, HCT, Ghrelin
- DXA scan to evaluate for osteopenia and body composition
- Measurement of bone age for males 18 or 19 years old
- [redacted]

Study Visits:

1. Baseline: (n=75: 38 healthy obese women and 37 healthy obese men)

The baseline visit will occur within 8 weeks after the screening visit. The following assessments will be made during the baseline visit days and will occur within a 30-day period.

- Assessment of potential factors affecting BMD: family history of osteoporosis, alcohol, free testosterone, estradiol, exercise (Paffenbarger Physical Activity Questionnaire and Modified Activity Questionnaire (MAQ)), Calcium & Vitamin D Intake (Calcium & Vitamin D Frequency Questionnaire), and food diary log
- Waist circumference, weight, and BMI
- 2-hour GHRH-arginine GH stimulation testing

- CT
- DXA scan (only if baseline occurs more than 6 weeks after screening visit)
- Xtreme CT
- Head x-ray if subject reports possibility of metal in face or head
- MRI/MRS
- Blood drawn to determine levels of hormones and other chemicals
- Oral glucose tolerance test (OGTT)
- Functional Strength Test
- [redacted]

2. Follow-up visits:
The following assessments will be made during the 6 week, 3 month, 4.5 month, 6 month, 9 month, 12 month, 15 month, 18 month and 24 month visits. The 3 week, 9 week, and 4 month visits will be performed during a +/- 2 week interval around the indicated return time to allow for potential scheduling conflicts. The 6 month, 9 month, 12 month, 15 month, 18 month and 24 month visits will be performed during a +/- 1 month interval around the indicated return time. Subjects who drop out or are discontinued from the study after participating for at least 9 months will be asked to come in for a final study visit that will be identical to the 18-month study visit. The follow-up visits involve:

- Medical history, physical examination, weight, waist and hip. Return menses (for women), growth hormone dosing records, and all study medication vials.
- DXA scan (12 month, 18 month, and 24 month visits)
- CT scan (18 month visit)
- Low-dose CT for body composition only (6 month visit)*
- Xtreme CT scan (12 month, 18 month, and 24 month visits)
- MRI/MRS (6 month visit* and 18 month visit)
- Blood drawn to determine levels of hormones and other chemicals (3 week, 9 week, 4 month, 6 month, 9 month 12 month, 15 month, 18 month and 24 month visits).
- OGTT (6 month, 12 month, and 18 month and 24 month visits)
- Paffenbarger Physical Activity Questionnaire and Calcium & Vitamin D Frequency Questionnaire (6-month, 12-month, 18-month, 24-month visits)
- Functional Strength Test (6-month, 12-month, 18-month and 24-month visits)
- Food diary log (18-month visit)
- [redacted]

*discontinued performing starting in August 2017

Study endpoints

Aim 1:

Primary Endpoint: Change in BMD over 18 months in the GH vs placebo group.

Secondary Endpoints:

1. Bone microarchitectural parameters
2. Bone strength by FEA

Aim 2:

Primary Endpoint: Change in bone marrow fat in the GH vs placebo group.

Secondary Endpoints:

1. Pref-1.
1. Bone formation markers P1NP, ucOC.
2. Fasting and 2-hour OGTT insulin.
3. Inflammatory markers hsCRP, TNF1 receptor, and IL-6.
4. Serum lipoproteins.
5. 25-OH vitamin D.

Dual-energy X-ray-absorptiometry (DXA): DXA will be used to measure BMD of the AP and lateral spine (L1-L4), distal radius, total hip, femoral neck and total body. Total fat and fat-free mass measurements will also be obtained.

Quantitative computed tomography (QCT): As DXA may overestimate BMD in obesity,[107] we will perform volumetric QCT of L1 and L2 and of the proximal femur (GE LightSpeed Pro CT scanner, GEHealthcare, Waukesha, WI or Somatom Definition, Siemens Healthcare, Forchheim Germany) and low-dose single slice CT of the abdomen and thigh for body composition.

High-resolution CT: High resolution peripheral QCT will be used to measure volumetric density, morphology and microarchitecture at the distal radius and distal tibia (XtremeCT, Scanco Medical AG®, Bassersdorf, Switzerland). The outcome variables computed by automated analysis will include volumetric BMD (g hydroxyapatite/cm^3) for total, trabecular, and cortical regions; cortical thickness (μm) and porosity measures and trabecular number (mm-1), thickness (mm), and separation (mm). HR-pQCT measurements will be performed at the non-dominant wrist and leg in the absence of a history of fracture.

Bone Strength: Finite element (FE) models will be generated and analyzed as published[93] using software provided by Scanco Medical AG (Bassersdorf, Switzerland) by converting each voxel to an equally-sized brick element,[111] resulting in FE models with approximately 2 million elements.

MR spectroscopy: Proton MR Spectroscopy of lumbar vertebral and femoral bone marrow (for lipid content), muscle and liver (for lipid content) will be performed with a 3.0 Tesla MR scanner (Siemens Trio, Siemens Medical Systems, Erlangen, Germany) as previously described by our group.[97, 105, 106, 114-116]

Functional strength testing: Functional strength of the hand and forearm will be determined. Additionally, functional strength of the lower and upper extremities will also be determined.

Endocrine testing:

- fasting GHRH-arginine stimulation test
- GH
- IGF-1
- Bioactive IGF-1
- P1NP and CTX
- Osteocalcin
- Pref-1
- hsCRP and apoB
- IL-6 and TNF-)-α receptors I and II
- Testosterone
- Estradiol and SHBG
- 75-g oral glucose tolerance test (OGTT)

- Glucose, insulin, hemoglobin A1c, 25(OH) vit D, 1,25 $(OH)_2$ vitamin D, ionized calcium, phosphorous, iPTH, total cholesterol, LDL, HDL, and triglycerides

[redacted]

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

Understanding the pathophysiology of bone loss in obesity may help identify new treatment targets for this important complication. We have excluded potential study subjects with severe bone loss and will refer them for treatment. Mild bone loss, such as we are studying, is not typically treated in young patients, but rather monitored. We will share BMD results with study participants and their physicians (with participants' permission).

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

A number of procedures will be instituted to protect against potential risk involved in this protocol. The potential effects of growth hormone on a fetus are not known and therefore precautions against administration to pregnant patients will be instituted. All patients will have pregnancy tests on admission prior to receiving radiation or study medication. Subjects will also have serial pregnancy tests – one at every study visit – and study participation will be discontinued if a subject becomes pregnant. DXA scans and cross-sectional CT scans will be performed during the length of the protocol. The combined radiation from these procedures is approximately 9% of the amount of radiation to which a person who works with radiation can be exposed each year. [redacted] Because of the potential importance of insulin resistance to cardiovascular risk, we will investigate with validated techniques, including oral glucose tolerance test, the effects of GH on insulin resistance in our population. Because glucose tolerance may deteriorate with GH administration, especially acutely, we will not allow patients with DM to participate and we will discontinue study participation if a subject develops fasting plasma glucose >=126 mg/dl or 2-hour post OGTT glucose >= 200 mg/dl while they are taking the study medication (between the baseline visit and the day before the 18 month visit).

A physician will be available at all times during the study by pager to answer any questions a patient might have. The physician will arrange to immediately see every patient with a concern. All efforts will be made to protect the confidentiality rights of the study subjects who will be referred to by code numbers only. Confidentiality of the patients will always be of paramount importance to study investigators. No data on patients will be shared with persons other than those directly involved in the study, except at the documented request of the patient. Samples that are sent to laboratories outside of [redacted] will be labeled with a non-identifying numeric code.

All adverse events will be reported to the IRB in a timely manner according to the guidelines provided by Partner's Human Subjects Research Committee.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Safety assessments

1. IGF-I levels:
    a. Must have IGF-I within or below the lowest 2 quartiles for age and gender
    b. Measurements at screening, baseline, 6week, 3 month, 4.5 month, 6 month, 9 month, 12 month, 15 month, 18 month and 24 month
    c. Dose decrease for IGF-I levels above the upper limit of normal
2. Glucose: 2 hour 75 g OGTT: baseline, 6, 12, 18 and 24 months. Fasting glucose at screening, 6 week, 3 month, 4.5 month visits.
3. Pregnancy testing: screening, baseline, 6 week, and 3, 4.5, 6, 9, 12, 15, 18 and 24 months (Additional testing will be arranged if lengthened menstrual cycle)
4. HbA1c: screening, 6 month, 12 month, 18 month and 24 month

Subjects will be discontinued from the study if they develop

a. Glucose: fasting $\geq$ 126 mg/dl or 2h GTT $\geq$ 200 mg/dl while they are taking the study medication (between the baseline visit and the day before the 18 month visit)
b. Diabetes: HbA1c $\geq$ 6.5%
c. Positive pregnancy test
d. Severe / intolerable side effects of GH
e. Development of malignancy
f. Initiation of the following medications: OCPs

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Subjects will have DXAs of the total body, PA and lateral spine, hip and radius at up to 5 visits. Also, QCT scans of L1 and L2 and of the proximal femur at 2 visits. Subjects will also have an XtremeCT of the ultradistal radius and distal tibia at 4 visits. They will also undergo low dose CTs of the thigh and abdomen at three visits. Some subjects may undergo a wrist X-ray at the screening visit and a head X-ray prior to the baseline MRI. The combined radiation from all these aforementioned procedures for the entire study is approximately 4.757 mSv – this amount of radiation is equal to approximately 19 months of natural background radiation. Blood drawing may result in bruising or infection at the venipuncture site.

[redacted]

[redacted]

MRS and MRI will be performed using FDA approved devices and pulse sequences. There are no known foreseeable risks associated with exposure to MRI, provided there are no metallic implants (i.e., vascular clamps or pacemakers). All potential subjects will be screened for the presence of such prior to the exam. Some subjects do report some claustrophobia during the scan. If a patient expresses any discomfort during the scan, the procedure will be aborted and not repeated without his/her full consent. Subjects will be required to lie in a magnet for about 1 hr. The 3.0T MR device is FDA-approved for clinical use. No serious or lasting side effects associated with the use of MRI have been reported. Rarely, subjects report sensations such as vertigo and a metallic taste when exposed to magnetic fields. Minor theoretical hazards arise from rapid gradient switching and RF transmission. All parameters used for conventional and spectroscopic imaging fall within FDA limits for specific absorption rates (SAR) of RF transmission and rapid gradient switching (dB/dt). Experiments properly conducted in compliance with FDA, OSHA and standard safety practices of the MGH-NMR Center pose no significant risk to research subjects. MR examinations will be performed by a Radiological Technologist certified by the Commonwealth of Massachusetts. Any adverse events will be reported immediately to the MGH Human Research Committee.

[redacted]

[redacted]