IRB Submission

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Impact of HbA1c on Trabecular Bone Score to Better Understand Fracture Risk

A. Study Purpose and Rationale

Osteoporosis is a major risk factor for fragility (low trauma) fractures with tremendous public health effects including pain, loss of function, decreased quality of life, death, and increased healthcare costs (1,2). Bone mineral density (BMD), as measured by dual x-ray absorptiometry (DXA), is currently the gold standard used for screening osteoporosis (3). However there are limitations to the accuracy of this test due to overlap in BMD between individuals who develop fractures and those who not (4-6). This discrepancy is further highlighted in type 2 diabetes (T2D) which is associated with increased fracture risk despite greater BMD (7-9).

BMD is only one major determinant of bone strength and fracture risk. Other determinants include microarchitecture of trabecular bone, bone turnover, and macrogeometry of cortical bone (10-12). It was recently shown that skeletal fragility in T2D can be measured and better predicted using trabecular bone score (TBS) (13). TBS is a novel measurement that examines the pixel gray-level variations in DXA images which is independent of BMD and is related to bone microarchitecture (14-17). Bone with denser trabecular network should have greater strength, produce an image with higher gray-level texture variations, and a higher TBS score. TBS have been shown to predict fracture risk prior studies (18-22).

It is the goal of this study to confirm this relationship between TBS and T2D and analyze the effect of worsening T2D as measured by higher hemoglobin A1C (HbA1C) levels on TBS scores.

B. Study Design and Statistical Analysis

This study will be a case control study comparing T2D patients with varying hemoglobin A1Cs and age-matched controls. There will be five study groups which are subjects with normal hemoglobin A1C < 6.5% (controls), HbA1Cs 6.6-7.5%, HbA1Cs 7.6-8.5%, HbA1Cs 8.6-9.5%, and HbA1C >9.6%.

In order to achieve 80% power with an alpha-error rate of 0.01 for two-tailed t-test, 62 subjects are needed in each study group based on the difference in lumbar TBS scores by Leslie et al (13). A p-value of 0.01 was chosen due to the multiple study groups and repeated testing. Two sample t-testing will be used to compare TBS/DXA ratios.

The primary outcome of this study will be the ratio of TBS to DXA score among subjects within the different groups.

Secondary outcomes will include correlating TBS scores to serum markers including calcium, parathyroid hormone, vitamin D levels, and bone turnover markers (pro-collagen terminal peptide [p1np], bone alkaline phosphotase [bap], osteocalcin [OC], C-terminal telopeptide [ctx], sclerostin [Scl]). Pearson correlation testing will be used to analyze any potential relationships between TBS and bone markers.

C. Study Procedure

Each person recruited will undergo DXA imaging (Hologic, Waltham, MA, USA) to obtain BMD of femoral neck, lumbar spine, and distal one third of the radius. TBS data can then be extracted from the DXA images using TBS iNsight software (TBS iNsight Software, version 1.8; Med-Imaps, Pessac, France). Serum samples will also be collected at time of imaging for calcium, parathyroid hormone, vitamin D levels, and bone turnover markers (p1np, bap, osteocalcin, ctx, sclerostin) analysis.

D. Study Drugs*
N/A

E. Medical Device.*
Each subject will undergo DXA imaging using Hololgic DXA imaging (Waltham, MA, USA) which is used on all patients on CUMC for osteoporosis screening.

F. Study Questionnaires
N/A

G. Study Subjects
Inclusion Criteria: Post-menopausal T2D females and aged match controls
Exclusion Criteria: Black race, subjects taking bone active medications such as bisphosphonates or thiazolidinediones, decreased renal function as defined as GFR < 30 mL/min/1.73 m^2

Only one gender is included in this study to simplify data analysis and reduce confounders as female gender is a known risk factor for osteoporosis. Further subjects of black race will be excluded as this characteristic is protective against osteoporosis.

H. Recruitment of Subjects

Subjects who come to New York Presbyterian Hospital for their primary and diabetes care who meet inclusion criteria will be approached about enrollment. In addition, the investigators will attempt to contact their primary physician to make them aware of the trial.

I. Confidentiality of Study Data
All study data will be de-identified and personal identifiers will be unavailable. All subjects will be given a unique alphanumeric code known only to investigators and all data will be stored in a secure location.

J. Potential Conflict of Interest
None of the study investigators have any conflicts of interest to disclose or stand to benefit financially or in any other way from the results of this investigation.

K. Location of the Study
All aspects of the study including recruitment, imaging, serum collection, serum analysis, and image analysis will be done at NYP-CUMC.

L. Potential Risks
There are no potential risks associated with this study.

M. Potential Benefits

The potential benefits of this study to society is a better understanding of bone health through trabecular bone score which may determine fracture risk better in diabetics. There is no immediate benefit to subjects participating in this study as TBS.

N. Alternative Therapies
N/A

O. Compensation to Subjects
Study subjects will undergo DXA imaging testing and serum collection and so will be compensated $50 for their time and effort.

P. Costs to Subjects
There will be no costs to the subjects or their insurance companies for participation in this study.

Q. Minors as Research Subjects
N/A

R. Radiation or Radioactive Substances
Since the DXA imaging involves exposure to radiation, though very minimal, an application for approval from the Joint Radiation Safety Committee (JRSC) will be sent along with this IRB application.

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