INTRODUCTION
The ability to monitor in vivo mechanical changes of human trabecular bone in osteoporosis is important during longitudinal clinical studies in evaluating the progression of diseases and the efficacy of their treatments [1]. Severely hypogonadal men due to pituitary or testicular disease have lower bone density than eugonadal men, and testosterone replacement of severely hypogonadal men increases their bone density [2]. It has recently been shown that men who are severely hypogonadal also have deteriorated trabecular bone architecture and impaired mechanical competence [3, 4]. The purpose of this study was to determine if testosterone replacement these severely hypogonadal men could reverse the deterioration of mechanical properties of trabecular bone.

MATERIALS AND METHODS
Micro magnetic resonance imaging (µMRI) based virtual bone biopsy data were obtained from the Laboratory of Structural NMR Imaging at University of Pennsylvania Medical Center. These data are part of a previously published study on hypogonadal men (N=10) with low serum testosterone levels, matched individually with eugonadal control subjects (N=10) studied for the purpose of assessing the structural manifestations of long-term testosterone deficiency, as described in [5]. These subjects were µMRI assessed at 0, 6, 12 and 24 months. Patients in the hypogonadal group received testosterone (50-100 mg) treatment daily. Cylindrical subvolumes (7.54 mm in diameter and 5.12 mm in length) of subvoxel processed and binarized in vivo µMRI images were extracted around the mass central axis of the trabecular bone in distal tibiae at a 68.5x68.5x102.5μm spatial resolution (Fig 1). A rectangular volume of interest (VOI) of 57x57x50 voxels, corresponding to 5.14x5.14x5.12 mm, was isolated from inside each cylinder. The isolated voxels or voxel-clusters in the images were removed using cluster analysis.

The images were converted to micro finite element (µFE) models by converting the voxels that represent bone tissue to 8-node brick elements. The bone tissue properties were chosen as isotropic, linear elastic with a Young’s modulus of 15 GPa and a Poisson’s ratio of 0.3 for all models. Using an element-by element pre-condition conjugate gradient solver, six FE-analyses were performed for each specimen, representing three compression tests and three shear tests [6]. The anisotropic stiffness tensor of the VOI was calculated in the coordinate system aligned with the anatomical positions (xyz) (Fig 1). Based on the stiffness tensor, elastic material constants (three Young’s moduli, Eyy, Eex and Exx, shear moduli Gxy, Gxz, Gyz) were calculated [6]. The bone volume fraction (BV/TV) was also calculated for all VOIs.

RESULTS
There is no significant change in either BV/TV or elastic properties in 6 and 12 month and therefore only comparisons between 0 and 24 month are reported here. Fig 2 shows representative virtual µMRI bone biopsies from one hypogonadal subject before (left) and after 24 months of treatment (right), indicating visibly improved trabecular bone architecture and density. BV/TV of the hypogonadal trabecular bone between the eugonadal group and the hypogonadal group at month 0 (left) and month 24 (right). At month 0, all elastic constants of the hypogonadal group were significantly different from those of the eugonadal group. At month 24, there were significant increases in Eyy, Gyz and Gxy of the hypogonadal group such that they were not significantly different from those of the eugonadal group. Between month 0 and 24 in the hypogonadal group, there were significant increases in Exx, Eyy, and Gyz (p = 0.013, 0.005, and 0.007) (Fig 4). Interestingly, these are the mechanical constants that remained different from those of eugonadal group.

DISCUSSION
Using in vivo µMRI based µFE analyses, significant differences in anisotropic elastic material constants were detected between the eugonadal and hypogonadal men and improvements in elastic properties of trabecular bone in treated patients were found. These results are the first in vivo data showing that testosterone replacement of severely hypogonadal men can reverse the deterioration in mechanical properties of trabecular bone. It is further noted in the current study that the restoration in anisotropic elastic properties is not uniform along different anatomic directions. The elastic moduli increased most following 24 months of treatment are still lower than those of the eugonadal control group. Those elastic moduli showed bigger differences with those of eugonadal group before treatment. The analyses of morphological changes of trabecular bone microstructure are in progress and it would be of interest to correlate changes in morphology to changes in mechanical properties observed in these patients.

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