Testosterone Therapy and Bone Quality in Men with Diabetes and Hypogonadism

NCT03887936

Statistical Analysis Plan

September 17, 2025

Statistical analyses.

Treatment associations with changes in the primary outcome, i.e. μFEA as represented stiffness and failure load, over time will be modeled using linear mixed models with treatment as the grouping factor and measurement times as the repeated factor and will be adjusted for covariates as age, and initial value. Additional covariates considered are race, pack-years smoking, body mass index, duration of diabetes, medications, presence of diabetes complications, the Charlson index; and changes in A1C, strength, lean mass, 25OHD hormonal levels, activity. Changes in CTX (aim 2) and circulating osteoblast precursors (aim 3) over time will be analyzed by linear mixed model adjusted for baseline values. Other secondary outcomes areal bone mineral density (BMD) by dual energy x-ray absorptiometry, bone microarchitecture by high-resolution peripheral quantitative computed tomography (HR-pQCT) such as volumetric BMD, bone area, cortical and trabecular thickness, trabecular number and separation, biomarkers (such as osteocalcin, sclerostin, N-terminal propeptide of type 1 collagen [P1NP] and runt-related protein 2 [RUNX2], hormonal levels and circulating osteoclasts will similarly be analyzed with adjustments as appropriate. We will perform follow up post hoc after the linear mixed model shows a significant omnibus test (i.e. $p<.05$). Log transformations will be considered when they will equalize variances. If we discover that the distributional assumptions required for the above analyses are not met by our data, even after standard data transformation, we will explore the use of more robust semi-parametric or non-parametric tests (e.g. rank tests.).

We will employ two powerful statistical methods to deal with the issues of non-compliance and missing values. These will be considered as alternative analyses unless the original analyses are not validated thereby; in which case these analyses will be promoted in importance in our results. ***First,*** if non-compliance in either arm results in missing values, we use multiple imputation (MI) to randomly generate 100 complete databases. Our statistical analyses will be repeated for these 100 databases, and the 100 estimates +/- SE will re-combined (MIANALYZE) into one, less biased answer/result. MI and MIANALYZE procedures are available in SAS statistical package. ***Second,*** if noncompliance results in biased values (not missing values), non-compliance measures; for example, # of prescription refills for testosterone, placebo and diabetic medications, as well as other measures such as age, will be used as predictors in a non-parsimonious propensity scoring in order to adjust for these biases. Typically, the propensity scores (PS, probabilities) are computed as residuals in a (non-parsimonious) logistic regression of two arms, as a binary outcome, on predictors. Weights for each record in the database are computed by a stabilized inverse probability method. Subsequently, our alternative analysis will be the weighted analyses using these weights.