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Original Article

Comparison of Bone Mineral Density by Dual-Energy X-Ray Absorptiometry and Bone Strength by Speed-of-Sound Ultrasonography in Adults With Gaucher Disease

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Abstract

Patients with the lysosomal disorder Gaucher disease (GD) are at risk of osteoporosis and/or avascular necrosis, but to date, no adequate biomarkers are available to ascertain individual predilections. Bone mineral density by dual-energy X-ray absorptiometry (DXA) has traditionally been used to monitor trends. With the availability of a speed-of-sound (SOS) ultrasonography to assess bone strength/elasticity, we aimed to ascertain whether these modalities are complimentary or comparable so SOS, with no radiation risk, might be used more routinely as a potential biomarker. A prospective comparative study in adult GD patients undergoing routine follow-up of bone mineral density *T*- and *Z*-scores at forearm (FA), femoral neck, and lumbar spine, and SOS *Z*-scores at FA was initiated. Interpretation was by qualitative categorization of *Z*-scores. The kappa measure of agreement beyond chance was calculated between pairs of measurements and the McNemar test was then applied. This noninterventional trial (ClinicalTrials.gov Identifier: NCT02067247) was approved by the institutional ethics committee. There were 89 patients (ages 21–78 years, 61% female, 62% common Ashkenazi genotype, 18% splenectomized, and 18% with avascular necrosis/fractures). When comparing *Z*-scores at FA by DXA and SOS, only 39.3% correlated, while the remaining results were in disagreement; no trend was noted. Similarly, when comparing *Z*-scores at the femoral neck by DXA with those at FA by SOS, 44.9% of the results were in agreement; no trend was noted; and *Z*-scores at the lumbar spine by DXA with FA by SOS, 46% were in agreement and no trend was noted. DXA at the 3 sites did not track in the same direction or the same magnitude of difference with SOS at FA in adult patients with GD. Due to the fundamental differences between the 2 measurements and their clinical correlates, plus the lack of long-term follow-up to assess outcome, the potential added value of the measurements at the FA by SOS in patients with GD awaits further studies.

Key Words: Avascular necrosis; bone mineral density; dual-energy X-ray absorptiometry; Gaucher disease; speed-of-sound ultrasonography.

Introduction

Dual-energy X-ray absorptiometry (DXA) is a current standard of practice for assessment of bone mineral density (BMD) and derivative values such as risk of osteoporosis based on *T*-scores *(1)*. Although DXA technology continues to evolve, new instruments and technologies have been introduced *(2)*, making it necessary to document how these advances compare with earlier equipment and prior

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densitometric evaluations. Among the newer technologies is the ultrasound-driven speed-of-sound (SOS) BeamMed system, which measures bone strength and elasticity *(3)* as distinct from BMD of the bony architecture.

Patients with Gaucher disease (GD), one of the more common lysosomal storage diseases *(4)*, have been shown to suffer from low BMD *(5)* with increased risk of osteonecrosis *(5)* and pathological fractures *(6)*, but to date, no biomarker or technology has been able to accurately predict which patients are imminently at risk. Predicting skeletal damage because of osteoporosis at any site but also osteonecrosis at the femoral neck (FN) due to osteopenia or osteoporosis because of Gaucher cell infiltration in the bone marrow *(4)* has clinically relevant ramifications *(7)*. Moreover, because the option of disease-specific treatment is very costly, whether with either intravenous enzyme replacement therapy (ERT) *(8)* or oral substrate reduction therapy (SRT) *(4)*, its use is often predicating on the estimated risk of severe disease, particularly skeletal involvement. DXA and SOS *(9)* putatively measure 2 different components of the bone, and may be either complimentary or comparable. If it can be shown that SOS is correlated with GD bone parameters and is sensitive to changes in elasticity/fragility and/or density over time because of ERT or SRT, then SOS would have a place in routine Gaucher evaluations. This is especially relevant because SOS does not involve radiation exposure and could be performed on an annual or semiannual basis in the clinic or medical office. SOS technology is based on the principle that ultrasound waves travel faster through bone than through soft tissue. The bone sonometer measures time elapsed between axially transmitted sound and its reception after traveling through the selected bone. With greater density and elasticity, speed of propagation is greater *(10)*. BMD measured by DXA has long been accepted as the most valid predictor of fracture risk in the future and consequently of all the attendant morbidity and mortality that that may entail. All recent clinical trials of new management options for GD have included DXA as an exploratory or tertiary endpoint; both current patient registries include DXA evaluations for treated and untreated patients. Moreover, low bone density has been associated with other Gaucher-specific parameters of disease severity *(5,6)*. Nonetheless, to date, no studies have proven whether BMD as reflective of calcium content and trabeculation and measured by DXA is the equivalent feature of bone that is evaluated in SOS measurements. Additionally, there have been no studies using the SOS modality in GD.

Thus, the present study is a comparison of 2 methodologies that as yet have not been applied in tandem in patients with GD with the underlying premise that, should there be any correlations in the findings that implicate risk of osteoporosis and/or avascular necrosis (AVN) in GD patients, one could envision using sonographic SOS on a routine basis in GD to assess what has heretofore been assessable with DXA, the latter only at biannual intervals because of the radiation involved.

Methods

The present study was planned as an observational prospective comparative study of modalities with a predefined cohort of adult GD patients comparing 2 methodologies not previously assessed in this manner in this population.

The population included nonpregnant adult (>18 years) patients with GD who undergo routine annual monitoring at the Gaucher Clinic, which also includes DXA evaluation of BMD approximately once every 1 to 2 years.

DXA was assessed using a standard Hologic DXA unit (Hologic, Bedford, MA). The routine DXA evaluation includes 3 sites: forearm (FA), FN, and lumbar spine (LS). In otherwise healthy populations, including postmenopausal women and the aged, LS is the standard site for assessment of *T*- and *Z*-scores of BMD and is the basis for recommendations for the prevention of osteoporosis and/or treatment options. The FN is also usually assessed in otherwise healthy populations but is especially of interest in GD because the hip joint is the site of the most frequent cases of AVN in GD. The FA is only rarely informative relative to the LS and FN in GD.

SOS was performed using a Sunlight machine (BeamMed Ltd., Sunlight Omnisense 8000 series, Petach Tikva, Israel). The SOS portion was described to the patients as a research study and that participation was optional; therefore, only those patients who volunteered for the SOS in addition to undergoing the routine requisite DXA evaluation on the same day were included in the study. The SOS site chosen was the FA only, although some other sites such as the tibia can be evaluated. The choice of FA only was to minimize the inconvenience to the patient with the rationale that, should this modality be incorporated as a routine evaluation, patient convenience would be an important consideration.

Each modality (DXA and SOS) was performed by a single technician (MT and TD, respectively) for all the patients to eliminate issues of reproducibility because of operator-dependent variables.

Daily calibration was performed for each modality; for DXA a standardized calibrating phantom was provided by the company. SOS was determined as the mean of 3 scans statistically similar as calculated by the software.

Institutional Ethical Review Board (Helsinki Committee) approval was received and the study was registered (January 28, 2014) as a clinical trial (NCT02067247).

Statistical Analysis

Raw data of BMD and *T*- and *Z*-scores are imputed by the respective modality software.

Direct comparison of the absolute measurements and/or of the *T*- and *Z*-scores using standard statistical approaches did not yield meaningful meta-analyses (not shown). This approach also disallowed division into subpopulations such as those with the common Ashkenazi Jewish genotype (N370S/N370S), which is predictive of