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Title: Triple Phase CT May Replace Dual-energy X-ray Absorptiometry Scan For Evaluation of Osteoporosis in Liver Transplant Candidates

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List of Abbreviations (in order of appearance).

LT, liver transplantation

OP, osteoporosis

DXA, dual-energy X-ray absorptiometry

TPCT, triple phase abdominal computed tomography

BCT, biomechanical computed tomography

BMD, bone mineral density

BMI, body mass index

TVBMD, trabecular volumetric bone mineral density

Abstract (275 words)

Background: Assessment of bone density is an important part of liver transplant (LT) evaluation for early identification and treatment of osteoporosis (OP). Dual-energy X-ray absorptiometry (DXA) is currently the standard clinical test for osteoporosis; however, it may contribute to the appointment burden on LT candidates during the cumbersome evaluation process and there are limitations affecting its accuracy. In this study, we evaluate the utility of biomechanical analysis of vertebral images obtained during triple phase dual-energy abdominal CT (TPCT) in diagnosing osteoporosis among LT candidates.

Methods: Retrospective review of cases evaluated for liver transplant between 01/2017 and 03/2018. All patients who underwent dual-energy TPCT within 3 months of DXA were included.

The biomechanical CT (BCT) analysis was performed at a centralized lab (O.N. Diagnostics, Berkeley, CA, USA), blinded to the DXA data. DXA-based osteoporosis was defined as T-score ≤ -2.5 at the hip or spine. BCT-based osteoporosis was defined as vertebral strength ≤ 4,500 N women or ≤ 6,500 N men, or trabecular volumetric bone mineral density ≤ 80 mg/cm^3.
Results: Comparative data were available for 91 patients who had complete data for both DXA and BCT: (31 women, 60 men), mean (± SD) age 54 ± 11 years, mean body mass index 28 ± 6 kg/m^2. Using DXA as clinical reference, sensitivity of BCT to detect DXA-defined osteoporosis was 83.3% (20/24 patients) and negative predictive value was 91.7%; specificity and positive predictive value were 65.7%, 46.5%, respectively.
Conclusion: Biomechanical CT analysis of vertebral images on triple phase CT, routinely obtained during transplant evaluation, can reliably rule out osteoporosis in liver transplant candidates. Patients with suspicion of osteoporosis on TPCT may need further evaluation by DXA.

Background:

Osteoporosis is a common complication of chronic liver disease, particularly in patients with cirrhosis and cholestatic liver diseases (1). The pathophysiology of osteoporosis in the setting of chronic liver disease is multifactorial including but not limited to low serum levels of insulin-like growth factor 1 (IGF-1) (2), vitamin D deficiency (3), negative impact of bilirubin on osteoblast function (4), and uncoupling of bone resorption and bone formation (5). Therefore, among patients with cirrhotic-stage liver disease, the prevalence of osteoporosis can exceed 50% (5). In contrast to other complications of liver disease, osteoporosis is not cured with transplantation, and prior studies have identified acceleration of bone loss within the first few months of liver transplantation, possibly owing to corticosteroid use during this timeframe (6, 7). As a result, osteoporotic fractures can occur early after transplantation (8).

The American Association for the Study of Liver Diseases and American Society of Transplantation recommend testing for and treatment of osteoporosis prior to transplantation to prevent post-transplant decline of BMD and fractures (9). Dual energy x-ray absorptiometry (DXA) is currently the standard test used to diagnose osteoporosis (10). Despite its widespread use, there are several limitations to DXA, including only modest sensitivity in predicting fracture risk (11-14). In addition, DXA scanning lacks the ability to distinguish cortical from trabecular bone and can be further confounded by the presence of aortic calcification and certain bone

abnormalities, including arthritic changes and osteophytes (15). These limitations have led to interest in the possibility of a CT-based assessment of osteoporosis which studies thus far indicate that it can be comprehensive and reliable means of assessing osteoporosis and fracture risk (16). More particular to the context of liver transplantation, DXA scan is part of the appointment burden during the overwhelming transplant evaluation. To date, there have been no studies evaluating the possibility of utilizing triple phase CT (TPCT), routinely performed prior to transplantation, to assess osteoporosis. In this study, we evaluate the utility of TPCT in diagnosing osteoporosis among patients with cirrhosis undergoing evaluation for liver transplantation.

Methods

Study design and population

This is a retrospective review of charts of adult patients who underwent evaluation for liver transplant (LT) at Mayo Clinic, in Rochester, MN between January 1st, 2017 and March 15th, 2018. The standard transplant evaluation at our center includes a dual-energy, triple-phase contrast-enhanced computed tomography scan (TPCT) to assess vascular anatomy and for screening for hepatocellular carcinoma and dual-energy X-ray absorptiometry (DXA) for evaluation of osteoporosis. Our study included patients who underwent TPCT within 3 months of DXA. Patents were excluded if their TPCT and DXA were more than 90 days apart, their DXA exams were missing either hip or spine measurements, or if they had abnormal spine morphology. The patients' charts were also excluded from the review if there was no state-required research authorization on file. The patients selection process is depicted in Figure 1. Osteoporosis was defined as BMD T-score ≤ 2.5 on DXA at either hip or spine. The study was approved by the institutional review board.

Data Collection

The list of patients evaluated for liver transplant during the observation period was obtained from our prospectively collected transplant center database. Clinical data such as age, sex, and body mass index (BMI) were collected by manual chart review. DXA reports were individually reviewed and the following information were manually collected: a) femoral neck bone mineral density (BMD), femoral neck bone T-score, total hip T-score, and total hip BMD on each side b) vertebral BMD at L1, L2, L3, and L4 individually as well as total spine BMD and total spine T-score. De-identified, coded TPCT images were exported to the analysis team at ON diagnostics after establishing an inter-institution data transfer agreement.

DXA: DXA was performed on GE Healthcare Lunar iDXA scanners for both hip and spine.

TPCT: CT exams were acquired on dual-energy Siemens SOMATOM Definition Flash and SOMATOM Force scanners using a contrast-enhanced triple phase protocol (late arterial to visualize tumor arterial enhancement, venous to look for complications of portal hypertension [such as portosystemic shunts and short gastric and esophageal varices], and delayed to visualize tumor washout), with dual energy acquisitions acquired during the late arterial and delayed phases of enhancement. For these exams, intravenous iodinated contrast is administered using a weight-based table, with a similar patient size-based table used for selecting the x-ray tube energies.. Prior work in the enteric phase of enhancement has shown BCT-based osteoporosis estimation is highly accurate at contrast-enhanced CT (17). We selected the delayed phase for BCT analysis as we felt marrow enhancement would be minimized compared to the late arterial and portal phases. Mixed kV images were chosen for BCT analysis as opposed to other dual energy reconstructions owing to their CT number accuracy and no need for additional post-processing. Images were reconstructed at 3 mm slice thickness, using the Q30 (Flash) and Br44 (Force) kernels and a linear blend ratio of 0.6 (i.e., 60 % of the image coming from the low energy x-ray tube, and 40% from the high energy x-ray tube). Reconstruction FOV was adjusted according to patient size (380 mm on average).

Biomechanical computed tomography (BCT) analysis

Finite element analyses and trabecular volumetric density (mg/cm^3) measurements were performed on the CT scans by two trained analysts at OND, blinded to the DXA data, using VirtuOst software (O.N. Diagnostics, Berkeley, CA, USA). The repeatability precision between two analysts analyzing the same scan (inter-operator) for spine strength and trabecular density is 0.5 %CV as illustrated in prior study by Lee et al (18). In that study, 25 women and 15 men (mean ± SD age of 67 ± 9 years, range 41–86 years) were analyzed, one scan per anatomic site per patient, and the scans were analyzed independently by two analysts using the VirtuOst software (O.N. Diagnostics, Berkeley, CA) — as in the current study. The scans were acquired at 120 kVp, with a slice thickness/increment of 3 mm or less, on nine different CT scanner models across 24 different scanners. The precision for the same analyst analyzing the same scan (intra-operator) was not measured in that study, but is expected to be at least as good as the inter-operator precision. With regard to additional contribution of OND affiliates to the study, T.K. assisted with

the clinical interpretation which was led by the clinicians on the study team and D.L. assisted with the technical interpretation of BCT.

Briefly, the L1 vertebra was segmented and voxel intensity values were converted to BMD using a phantomless calibration (Figure 2). The bone volume was then resampled into isotropic voxels (1 × 1 × 1 mm), and each voxel was then converted into a hexahedral finite element and assigned material properties based on empirical relationships with BMD. Displacement boundary conditions simulated uniform axial compression applied through a virtual layer of bone cement. Vertebral strength (N) was defined as the compressive force at 2% deformation. Trabecular volumetric bone density (TVBMD) was determined using the same software, which was defined as the average density of an ellipsoidal volume placed inside the trabecular compartment in the central 10 mm section of the vertebral body.

Statistical analysis

After the BCT testing was performed on all scans received, the BCT results were sent to Mayo Clinic for data lock, and the DXA results were released for statistical comparisons with the BCT results. DXA-based osteoporosis was defined in two ways: T-score ≤ -2.5 at either the hip or the spine and at the hip only. BCT-based osteoporosis was defined in three ways: using only trabecular volumetric bone mineral density measurement (≤ 80 mg/cm^3), using only strength measurement (≤ 4,500 N for men, ≤ 6,500 N for men), and using both (*either* TVBMD ≤ 80 mg/cm^3 *or* strength ≤ 4,500 N for men, ≤ 6,500 N for men). The two types of DXA-based osteoporosis classifications were compared against the three types of BCT-based classifications. The reclassification analysis, using DXA as a standard, values of agreement, sensitivity, specificity, positive and negative predictive values, the Kappa statistic, and prevalence of osteoporosis were calculated. T-test was used to compare difference between means in patients with and without osteoporosis categories (nonparametric tests were used to confirm t-tests with small sample sizes). All statistical analyses were performed using JMP (v.9, SAS, Cary, NC).

Results

Among all patients who underwent liver transplant evaluation during the study period, 91 patients met inclusion and exclusion criteria (Table 1); 31 of those included were women. Mean age for women and men was 56 and 53 years of age, respectively. Mean BMI of participants was comparable for women and men (27 vs 28 kg/m^2) (Table 1).

Osteoporosis by DXA was present in present in 24 out of 91 patients with a prevalence of 26.4% . The prevalence was 18.7% when CT vertebral images were analyzed with trabecular volumetric bone mineral density measurements with the threshold value of 80 mg/cm^3, and 47.3% with fragile bone strength assessment (FBS) with the threshold value of 100% (percentage of the fragile bone strength value (4,500 N for women, 6,500 N for men)). Figure 3 depicts the performance of these two analyses as compared to DXA in a scattered plot format for men and woman subjects. In case of DXA, the prevalence of osteoporosis was 29% in women and 25% in men while for BCT, it was 48.4% in women and 46.7% for men.

Separate analyses were performed for spine osteoporosis by TVBMD and by FBS, and either TVBMD or FBS using the same 91 subjects with both hip and spine DXA and spine BCT. There was 79.1% agreement of DXA with TVBMD, and 70.3% agreement with FBS, kappa score being 0.4 (± 0.1) and 0.4 (± 0.09), respectively.

Sensitivity of analyzed vertebral CT images was better with FBS at 83.3% (20/24 patients) compared to TVBMD at 45.5 %. Three of those four patients had borderline negative testing by BCT. The specificity was better with TVBMD at 91.0% compared to FBS at 65.7%. Negative predictive value to exclude osteoporosis with either TVBMD or FBS was 91.7% (Table 2).

Discussion

The present study reveals novel observations that expand our diagnostic toolbox for osteoporosis in patients with cirrhosis. In particular, this study demonstrates the utility of using post-processing of CT images obtained during triple phase abdominal CT (TPCT) for hepatocellular carcinoma screening, in evaluating osteoporosis. This additional analysis of vertebral images (also known as biomechanical computed tomography, BCT) on TPCT evaluated for osteoporosis in liver transplant candidates with a negative predictive value exceeding 90% and a sensitivity exceeding 80%.

These findings suggest that BCT can eliminate the need for pre-transplant DXA in a large proportion of liver transplant candidates in whom osteoporosis was ruled out by this technique. In patients whose BCT suggests osteoporosis, further evaluation using DXA would be needed to further evaluate these findings and to establish baseline DXA measurements, which would be used to assess response to treatment with osteoporosis therapy. A major advantage of this step-wise approach is the convenience to the patient and reduction in testing burden since TPCT is already a part of standard of care testing for LT candidates; therefore, incorporating these CT assessments requires no additional burden during the cumbersome transplant evaluation

process. While DXA per se is a simple and relatively quick test, the cumulative time assigned to the test during the evaluation process after accounting for registration, waiting, test performance, and check out is about an hour, which is the time window reserved for DXA on the patients' schedule in our institution. If the patient is a working individual, such additional appointment and/or visit, particularly when not combined with other tests at the same day, can have further financial implications reflecting losing a day or half day from work. Consequently, if another test that is already routinely done (i.e., triple phase CT) during the transplant evaluation can provide the information that is to be provided by DXA (i.e., diagnosis of osteoporosis), it will be in the best interest of patient's convenience to eliminate DXA in this case. Additionally, given that TPCT is frequently performed in non-transplant patients with chronic liver disease, measuring bone density at TPCT can increase the number of patients who are appropriately screened for osteoporosis potentially preventing the morbidity associated with osteoporotic fractures.

In addition to patient convenience, this approach is safe since this special vertebral analysis of TPCT does not require additional radiation exposure or any alteration to the TPCT protocol. For patients whose BCT is suggestive of osteoporosis prompting referral to DXA for further evaluation, this combination of modalities (BCT and DXA) may be of benefit given the resultant comprehensive evaluation of bone density (by DXA and BCT) and bone strength (by BCT). Agten and colleagues demonstrated that a screening interval of every 5 years can suffice with combining BCT and DXA. The combination was more cost-effective in relation to preventing future fractures compared with DXA alone or BCT alone. However, this simulation-based study was limited to post-menopausal women (19). These findings will need to be evaluated in LT recipients.

Prior studies evaluating BCT in comparison with DXA and showed high performance of BCT in predicting future fractures. Adam and colleagues showed that BCT assessment of hip and vertebral strength and density has higher sensitivity and specificity for predicting hip fracture compared with DXA — 64% of the exams in this study were contrast-enhanced (20). Furthermore, Weber et al showed in patients with Inflammatory Bowel Disease that hip BCT based on contrast enhanced CT enterography exams reliably identified patients with osteoporosis, using DXA as the reference modality (sensitivity 85.7% and specificity 98.5%)(17). CT colonography, in another study, showed a negative predictive value of 85.2% in ruling out osteoporosis compared with DXA(21). It is noteworthy that CT done for evaluation of hepatocellular carcinoma is performed under a special protocol consisting of three phases; arterial, venous, as well as delayed phase--hence the name triple phase CT. This difference in the timing and phases of administering contrast between TPCT and CT assessments used in

the aforementioned studies warranted validation of BCT utility in TPCT used for screening for HCC in patients with cirrhosis. Additionally, this study is the first study to our knowledge to use contrast-enhanced dual energy images for BCT analysis. Dual energy CT is used at many institutions for HCC screening as dual energy images can increase iodine signal at contrast-enhanced CT, thereby increasing the conspicuity of key imaging features of HCC such as arterial enhancement and tumor washout (22-25). The current study was able to demonstrate this validation especially with regard to sensitivity and negative predictive value and suggests little impact on test performance when delayed phase images are used.

With regard to post LT monitoring of bone health, this approach can also be of benefit to a subset of patients. In 2015, more than 27% of liver transplant recipients were transplanted for hepatocellular carcinoma (26). In these patients, post-transplant surveillance for HCC is indicated and most centers follow them with serial TPCT up to 5 years post LT. Over the span of 5 years, some of these scans can be utilized for evaluation of osteoporosis depending on the clinical scenario of the individual patients (e.g., an HCC patient who had negative BCT for osteoporosis pre-LT may have a repeat analysis on TPCT 3 years later).

The relatively limited agreement between BCT and DXA in our study merits further discussion of potential explanations. First is the heterogeneity across vertebrae as spine DXA is a composite result for all of L1-L4, whereas BCT analysis covers just one vertebral level (typically L1). As a result, there can be discrepancies if the lumbar vertebrae are not homogeneous in density or size. Second is the artifact(s) since DXA spine BMD can be influenced by artifacts such as aortic calcification and other degenerative features, deformities or fractures, all of which are projected into the 2D DXA measurement. With the 3D CT-based measurement, only the bone of interest is segmented; therefore, aortic calcifications or bony features from adjacent vertebrae are excluded. Plus, we avoid making measurements in fractured/deformed vertebrae, which can have artificially high BMD. In this study, 7 patients had deformed/abnormal vertebra in L1; thus, we analyzed an alternate level. It is possible that some patients had a normal L1 (which we analyzed) but had deformities in L2, L3 and/or L4. We did not evaluate L2, L3 or L4 as in many cases, the CT exam covers only L1-L2. Third is that agreement is expectedly lower when osteoporosis is defined by both with strength and density (as opposed to density only). This is because density by DXA and BCT does not take into account the bone's overall morphology and spatial distribution of bone density. By accounting for these 3D features, strength can better distinguish bones at risk of fracture -- at the cost of disagreeing with the simpler density measurement. This point emphasizes the fact that DXA is not a “gold standard” but rather a “clinical practice standard”; therefore, disagreement with BCT

in terms of properly classifying patients for osteoporosis and fracture risk may in fact reflect shortcomings of DXA rather than a problem with the BCT classification.

Despite the new insight provided by our results, there remain limitations to our study. It is a retrospective single center study with a small sample size. The latter can potentially explain the difference in positive predictive value between our study and prior ones. The relatively low positive predictive value does not support the use of TPCT as a stand-alone osteoporosis test, therefore we suggest the aforementioned step-wise approach where positive BCT-based testing is followed by DXA. We note that most of our population were men, which reflects the nature of our cohort being liver transplant candidates (27), while osteoporosis affects mostly women (28). Another limitation is that since TPCT is an abdominal imaging modality that is not inclusive of the pelvis, we were not able to evaluate the femoral bone density and strength. Though, our study still showed remarkable negative predictive value using vertebral BCT to predict osteoporosis of hip or vertebra on DXA. This is not unexpected in view of prior data showing the evolution of osteoporotic changes starting at the vertebra before involving the hip and leading to hip fractures (29). In fact, in the prior CT colonography-based study there was no patient with isolated hip osteoporosis (i.e., without concurrent vertebral osteoporosis). Furthermore, L1 trabecular attenuation on CT has been shown in a prior study to be predictive of hip fracture (30).

In summary, the routinely performed triple phase CT done for HCC screening in liver transplant candidates is a reliable modality in ruling out osteoporosis in this patient population, even when images are performed to maximize HCC detection using dual energy CT technique. However, patients with suspicion of osteoporosis on TPCT can be further evaluated with DXA. Larger studies are needed to validate these findings and to evaluate the predictability of BCT of future fracture risk and BCT utility during osteoporosis treatment in these patients.

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Figure Legend

Figure 1. Sample selection

Figure 2. L1 vertebral body of a 67-year-old male. Left panel shows a cut-out view of the finite element model after virtual stress testing for a compression overload; the colors depict regions of failure. Center panel shows a transverse cross-section of the vertebral body and trabecular measurement region outlined in yellow. Right panel shows a sagittal section with the analyzed vertebral body highlighted in red.

Figure 3. Scatter plot of vertebral strength versus trabecular density. Strength is shown as a percentage of the fragile bone strength value (i.e., 4,500 N for women, 6,500 N for men). The horizontal line through 100% indicates the threshold in which the patient has fragile bone strength. Similarly, the vertical line through 80 mg/cm^3 indicates the threshold in which the patient has BMD-defined osteoporosis. “X” points indicate patients with BMD-defined osteoporosis by DXA (T-score ≤ -2.5 in either the hip or spine), while solid circles indicate all others.

Tables

Table 1: Baseline characteristics (mean ± SD), with and without DXA-defined osteoporosis.

Table 2: Diagnostic equivalence of Dual energy x-ray absorptiometry (DXA) vs Biomechanical CT analysis (BCT) for identifying patients with osteoporosis

For DXA, osteoporosis was defined as bone mineral density (BMD) T-score ≤ -2.5 at the hip or spine. For BCT, only the spine was analyzed, and separate analyses were performed for defining osteoporosis by trabecular volumetric bone mineral density bone mineral density (TVBMD), fragile bone strength (FBS), and either.

Table 1: Baseline characteristics (mean ± SD), with and without DXA-defined osteoporosis.

		With DXA-defined Osteoporosis (N = 24)	Without DXA-defined Osteoporosis (N = 67)	Pooled (N = 91)
Sex		F = 9 M = 15	F = 22 M = 45	F = 31 M = 60
Age (yrs)		59.1 ± 13.1 54.3 ± 8.6	54.5 ± 11.9 52.4 ± 11.8	55.8 ± 12.3 52.9 ± 11.0
BMI (kg/m^2)		23.6 ± 5.2 25.8 ± 4.0	27.7 ± 7.8 29.0 ± 5.2*	26.5 ± 7.3 28.2 ± 5.1
Time between DXA and CT (days)		4.3 ± 6.4 7.3 ± 15.9	8.0 ± 17.2 13.1 ± 23.6	6.9 ± 14.9 11.6 ± 21.9
DXA Hip T-score		-2.6 ± 0.4 -2.5 ± 0.6	-1.2 ± 1.1† -0.6 ± 0.9†	-1.6 ± 1.1 -1.1 ± 1.1
DXA Spine T-score		-2.8 ± 1.1 -2.7 ± 0.8	-0.8 ± 1.5† -0.1 ± 1.4†	-1.4 ± 1.6 -0.8 ± 1.7
BCT Spine Strength (N)		4350 ± 1240 4980 ± 1110	5440 ± 1960 7650 ± 2520†	5130 ± 1830 6980 ± 2520
BCT Trabecular volumetric bone mineral density (mg/cm^3)		95 ± 34 79 ± 30	111 ± 35 115 ± 32†	106 ± 35 106 ± 35

*p 0.002, †p < 0.001

Abbreviations: DXA, Dual-energy X-ray absorptiometry; BMI, Body Mass Index; CT, Computed Tomography; BCT, Biomechanical computed tomography

Table 2: Diagnostic equivalence of Dual energy x-ray absorptiometry (DXA) vs Biomechanical CT analysis (BCT) for identifying patients with osteoporosis

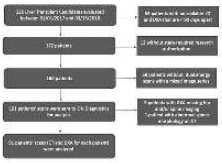
For DXA, osteoporosis was defined as bone mineral density (BMD) T-score ≤ -2.5 at the hip or spine. For BCT, only the spine was analyzed, and separate analyses were performed for defining osteoporosis by trabecular volumetric bone mineral density bone mineral density (TVBMD), fragile bone strength (FBS), and either.

	Patients with DXA BMD T-score ≤ -2.5 (at either hip or spine)		
	TVBMD	**FBS**	**TVBMD or FBS**
Accuracy* (%)	79.1	70.3	70.3
Sensitivity (%)	45.8	83.3	83.3
Specificity (%)	91.0	65.7	65.7
PPV (%)	64.7	46.5	46.5
NPV (%)	82.4	91.7	91.7
Kappa Score (± S.E.)	0.4 ± 0.1	0.4 ± 0.09	0.4 ± 0.09
BCT Prevalence (%)	18.7	47.3	47.3
DXA Prevalence (%)	26.4		

Patients with DXA BMD T-score ≤ -2.5 (at the hip only)	TVBMD	FBS	TVBMD or FBS
Accuracy* (%)	80.2	64.8	64.8
Sensitivity (%)	46.7	86.7	86.7
Specificity (%)	86.8	60.5	60.5
PPV (%)	41.2	30.2	30.2
NPV (%)	89.2	95.8	95.8
Kappa Score (± S.E.)	0.3 ± 0.1	0.3 ± 0.08	0.3 ± 0.08
BCT Prevalence (%)	18.7	47.3	47.3
DXA Prevalence (%)	16.5		

*Accuracy = (number of true positives + number of true negatives)/total number of patients

PPV = positive predictive value; NPV = negative predictive value.



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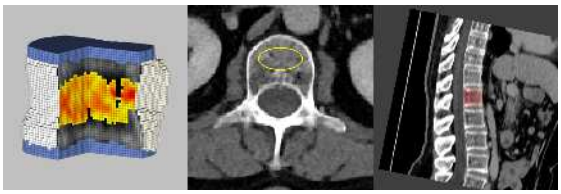

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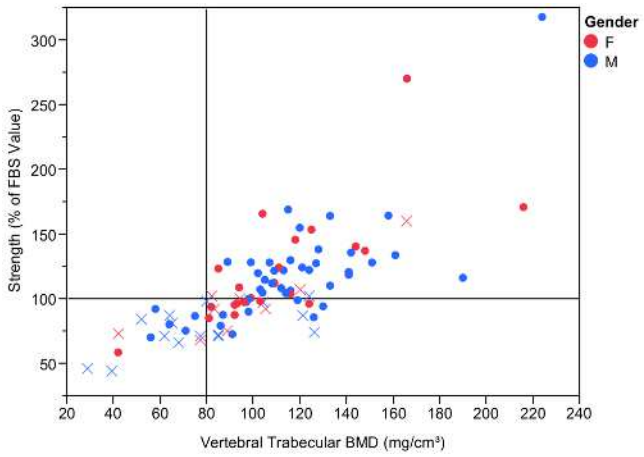

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