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Validation of a CT-Derived Method for Osteoporosis Screening in IBD Patients Undergoing Contrast-Enhanced CT Enterography

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Abstract

OBJECTIVES—Osteoporosis and bone fractures are of particular concern in patients with inflammatory bowel disease (IBD). Biomechanical computed tomography (BCT) is an image-analysis technique that can measure bone strength and dual-energy X-ray absorptiometry (DXA)-equivalent bone mineral density (BMD) from noncontrast CT images. This study seeks to determine whether this advanced technology can be applied to patients with IBD undergoing CT enterography (CTE) with IV contrast.

METHODS—Patients with IBD who underwent a CTE and DXA scan between 2007 and 2011 were retrospectively identified. Femoral neck BMD (g/cm^2) and *T*-scores were measured and compared between DXA and BCT analysis of the CTE images. Femoral strength (Newtons) was also determined from BCT analysis.

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CONFLICT OF INTEREST

Guarantor of the article: David H. Bruining, MD.

Potential competing interests: D.H. Bruining has served as a consultant for Bracco. J.L. Fidler serves on the Medical Advisory board for Bracco. T.M. Keaveny has equity in and consults for O.N. Diagnostics, and D.C. Lee is a full-time employee of O.N. Diagnostics.

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RESULTS—DXA- and CTE-generated BMD *T*-score values were highly correlated ($R^2 = 0.84$, $P < 0.0001$) in this patient cohort ($n = 136$). CTE identified patients with both osteoporosis (sensitivity, 85.7%; 95% confidence interval (CI), 48.7–97.4 and specificity, 98.5%; 95% CI, 94.5–99.6) and osteopenia (sensitivity, 85.1%; 95% CI, 72.3–92.6 and specificity, 85.4%; 95% CI, 76.6 –91.3). Of the 16 patients who had "fragile" bone strength by BCT (placing them at the equivalent high risk of fracture as for osteoporosis), 6 had osteoporosis and 10 had osteopenia by DXA.

CONCLUSIONS—CTE scans can provide hip BMD, *T*-scores, and clinical classifications that are comparable to those obtained from DXA; when combined with BCT analysis, CTE can identify a subset of patients with osteopenia who have clinically relevant fragile bone strength. This technique could markedly increase bone health assessments in IBD patients already undergoing CTE to evaluate small bowel disease.

INTRODUCTION

Osteoporosis and bone fractures have an increased prevalence in patients with inflammatory bowel disease (IBD). In this patient population, the prevalence of osteoporosis ranges from 18 to 42% (1,2), and the relative risk of fractures is estimated to be 40% greater than that in the general population (3–7). This increased risk may be due to bone weakening associated with active bowel inflammation, malnutrition, chronic steroid use, and/or hypogonadism (4,8). Other risk factors that are not directly associated with bowel inflammation include advanced age, previous fragility fracture, a family member with a hip fracture, cigarette smoking, and low body mass index (BMI) (4,9–11). Therefore, the American Gastroenterology Association has recommended dual-energy X-ray absorptiometry (DXA) screening for evaluation of bone in patients with IBD who have one or more of the following risk factors: corticosteroid use for greater than 3 months or a recurrent need of steroids, hypogonadism, fragility fracture, male >50 years old, or postmenopausal patients (1). If the initial DXA result is within normal limits, then a repeat evaluation should be performed in 2–3 years as per guidelines (4). Despite these recommendations and known risk factors, screening rates remain low for evaluation of bone in the IBD population (12). Etzel *et al*. (13) found that in a cohort of more than 2,000 patients with IBD, only 23% of the recommended group was tested for osteoporosis as per societal guidelines. Th ese suboptimal screening rates may be due to patient inconvenience associated with the already high number of tests required in this population. To further complicate the issue, even if the above guidelines are followed, many IBD patients with osteoporosis may not be identified owing to suboptimal screening performance of societal guidelines.

Addressing these challenges, a new image-analysis technique, biomechanical computed tomography (BCT) (14), may provide an opportunity to improve screening rates in the IBD population and at no inconvenience to the patient. This technique provides a virtual stress test of the bone by combining medical image processing, bone biomechanics, and the engineering "finite element (structural) analysis" technique to noninvasively assess bone strength from clinical CT scans (14). In addition to providing an estimate of the strength of the proximal femur, which is highly associated with fracture risk (15–18), two other important aspects of BCT are its ability to also provide DXA-equivalent measures of bone

mineral density (BMD) and to be used without the need for an external calibration phantom. The latter enables the technique to be performed as an “add-on” ancillary analysis to a previously taken CT. Although review of anatomical images (axial and coronal images) with bone window settings is a routine part of CT enterography (CTE) interpretation and can identify avascular necrosis of the femoral head, vertebral body compression fractures, and sacral and other pelvic insuffi ciency fractures in patients with Crohn’s disease, meaningful evaluation of BMD before fracture identification is usually not possible. BCT analysis via post processing of CT enterography data can address this void. This ancillary BCT technique has been validated clinically in a previous study in which the BMD scores obtained from DXA and CT colonography had a high degree of agreement ($R^2 = 0.84$) (19). In fracture-outcome studies, BCT has also been shown to identify a subset of individuals with-out osteoporosis based on BMD but who have clinically relevant low levels of “fragile bone strength” , placing them at a high risk of fracture (18).

Analysis of CTE images for quantitative BMD analysis is complicated by the presence of IV contrast in the CTE images, which can infiltrate both the porous bone and the adjacent soft tissues (20). We aimed to test the hypothesis that this novel technique could produce BMD measures and *T*-scores from CTE that correlated highly with those values obtained from DXA imaging. We also sought to determine whether the BCT-derived measures of femoral strength in this cohort can identify additional patients at high risk of fracture, and we assessed the relationship between femoral strength and age as very little is known about how strength depends on the age of IBD patients . As CTE scans are widely used for IBD small bowel assessments, if validated, this new ancillary image-analysis technique may provide an avenue to better define the burden of osteoporosis and osteopenia in IBD patients, develop new screening guidelines, provide feedback to patients and clinicians about medical intervention for osteopenia or osteoporosis, and identify patients at high risk for fracture who require medical intervention.

METHODS

Patient identification and inclusion criteria

Medical records were analyzed retrospectively to identify all patients who were 18 years or older with an established diagnosis of IBD (after an evaluation by a gastroenterologist or a colorectal surgeon) who underwent a CTE and DXA scan within 30 days of each other between 1 January 2007 and 31 December 2011 at Mayo Clinic in Rochester, Minnesota. The sample size was based on the total number of patients with dual studies available who met all other inclusion criteria. Baseline characteristics including gender, IBD subtype, age at imaging, and BMI were collected for each patient. CTE scans were all single-phase imaging studies with IV contrast acquired during the enteric phase (50s delay) and using eight different CT models (either Siemens, Milwaukee, WI or GE Healthcare, Malvern, PA). DXA scans included an analyzable left hip, considered the nondominant hip in most patients, and were acquired using three different DXA models (all by GE Lunar). All patients had signed a research authorization consent form at the time of their clinical assessment. The institutional review board at Mayo Clinic approved this study.

Exclusion criteria

Patients with a BMI ≥3 30 kg/m^2 were excluded, as were patients who did not have a BMI recorded within 30 days of both CTE and DXA. Individuals with insuffi cient femur coverage on CTE or image artifact due to metallic implants, a tumor, or other proximal femur abnormality were excluded. Patients who did not have analyzable left hip data on DXA were excluded as well. As noted earlier, patients without IBD or CTE and DXA performed >30 days apart were excluded.

Study outcomes

As it is the preferred site for clinical fracture risk and osteoporosis assessment (21,22), femoral neck *T*-score from areal BMD (g/cm^2) was the primary outcome. Secondary outcomes included femoral strength (in Newtons, N) and bone health classifications.

Image and data analysis

After patient identification and before sending images to O.N. Diagnostics (Berkeley, CA), all CTE scans, including both axial and coronal slices, were de-identified. Each scan was then submitted to O.N. Diagnostics in Digital Imaging and Communications in Medicine format for analysis. In addition to the images, O.N. Diagnostics was provided with de-identified baseline patient characteristics and CTE specifics (including X-ray tube energy (kVp), X-ray tube current (mAs), field of view, reconstruction kernel, and slice thickness). All analyses of CTE images were performed blinded to the DXA data. Each CTE scan, which spanned from approximately the T12 vertebra to the proximal femur, was first calibrated using a previously developed phantomless technique based on the analysis of the visceral fat surrounding the L1 vertebra and the external air.

Areal BMD is the standard outcome from a DXA test and is expressed for osteoporosis classification as a "*T*-score", namely, the number of s.d. that the patient's BMD measure is below the mean BMD of a reference population of young women. As the BMD is measured from a two-dimensional projectional image, it has units of gm/cm^2 and is not a true (volumetric) measure of density. To measure areal BMD from the CTE scans, the femur was segmented using a local threshold scheme that is independent of the calibration, virtually removed from the surrounding tissue, rotated into a standardized coordinate system at a DXA-like degree of internal rotation, and then projected into a frontal plane. Femoral neck areal BMD was then calculated from each projected image using the same regions of interest as used in DXA (Figure 1), and the respective *T*-scores were calculated using the Third National Health and Nutrition Examination Survey database as per World Health Organization and Fracture Risk Assessment Tool guidelines; young female reference values were used for both sexes (21).

To measure biomechanical femoral strength, the calibrated segmented images were converted into three-dimensional finite element models (Figure 1), using techniques described previously (15,23–25). The calibrated segmented image was resampled and rotated into a standardized coordinate system for a sideways fall and converted into a voxel-type mesh, using 1.5 mm-sized cube-shaped elements. Isotropic material properties for elements were then calculated using empirical relations based on the BMD information in

the underlying calibrated CT scan. Virtual loads were applied to simulate a sideways fall with impact on the lateral aspect of the greater trochanter and with the femur rotated at 15 ° to the horizontal and with 15 ° of internal rotation. The femoral strength was then obtained from the resulting force-deformation curve, as the force at 4% deformation. This technique has been well validated in both cadaver strength and prospective fracture-outcome clinical studies (15,18).

Statistical analysis

The primary assessment of agreement between the *T*-scores as measured by the two modalities was determined by linear correlation (26). General linear regression was used to determine whether the difference in *T*-scores between the two imaging modalities, on a per-patient basis, was associated with various patient factors (age, sex, BMI, and time between DXA and CT scans). Contingency analysis and the κ-statistic were used to quantify the agreement in classification, in which osteoporosis was defined as a femoral neck *T*-score ≤ −2.5 (by either DXA or CTE) (27), osteopenia was defined as a femoral neck *T*-score between −1 and −2.5 (27), and “fragile bone strength” was defined as a femoral strength of less than 3,000 N for women and less than 3,500 N for men (18). These FDA-cleared diagnostic thresholds were all predetermined in advance. We used the Wilson score method to calculate a 95% confidence interval (CI) for sensitivity and specificity (28). All statistical analyses were performed in JMP (version 5.0, SAS Institute, Cary, NC).

RESULTS

Of the 234 adult patients considered for inclusion into the study, 98 were excluded (Table 1), leaving a total of 136 study patients (Table 2). Left hips were analyzed with both CTE and DXA for 71 women and 65 men, with a median pooled age of 43.5 years (range, 18–85 years) at the time of imaging, and a median BMI of 23.0 kg/m^2 (range, 14.4–28.7). Of these 136 patients, 88 (64.7%) had Crohn’s disease and 45 (33.1%) had ulcerative colitis; 3 patients were classified as having indeterminate colitis. Additional demographic data including disease activity, disease phenotype, current medications, and prior history of bowel resections are shown in Table 2 . Eighty percent of the CTE and DXA exams were taken within 5 days of each other (range 0–27 days). The median slice thickness was 2.5 mm (range, 0.625–3.0), median tube energy was 120.0 kVp (100–120), median tube current at femoral neck was 310 mAs (range, 160–644), and the median CT dose index volume was 17.2 mGy (range, 4.4–28.6).

Overall, there was excellent agreement between the BMD measurements by the two modalities, both in terms of correlation and absolute values. DXA- and CTE-generated *T*-scores for femoral neck BMD were highly correlated (R^2 = 0.84, P <0.0001), with a $Y = X$ type of agreement (i.e., the data fell close to a line with a slope of 1.0 and a zero intercept), particularly close to region of the osteoporosis diagnostic threshold (Figure 2).

The mean *T*-score was slightly higher for DXA than CTE (on average, T = −0.88 for CTE vs. T = −0.70 for DXA; mean (±s.e.) difference of 0.18 ±0.04, P <0.001 paired *t*-test). The general linear regression analysis indicated some significant — but always weak — effects between this difference in *T*-score (DXA vs. CTE) and various patient factors. The

difference was weakly but positively associated with BMI (R^2 = 0.03, P = 0.03), meaning that the DXA *T*-score tended to be slightly higher at higher values of BMI. There was no significant effect associated with age (P = 0.06), sex (P = 0.91), or the time lapse between the DXA and CTE scan (P = 0.66).

Six of the seven patients who were classified as having osteoporosis by DXA were also classified as having osteoporosis by CTE, yielding a sensitivity of 85.7%; 95% CI, 48.7–97.4, and a specificity of 98.5%; 95% CI, 94.5–99.6. Of the 47 patients who were classified as having low bone mass (i.e., osteopenia) by DXA, 40 were also classified as having low bone mass by CTE (sensitivity, 85.1%; 95% CI, 72.3–92.6, and specificity of 85.4%; 95% CI, 76.6–91.3).

Of the 16 patients who had “fragile” bone strength (femoral strength ≤3,000 N for women or ≤3,500 N for men) as estimated by the finite element analysis, 6 had osteoporosis as defined by DXA and 10 had low bone mass (osteopenia; Figure 3); the same classifications were obtained when the CTE *T*-score was combined with the finite element results. Overall, DXA identified 7 patients at high risk of hip fracture compared with 16 patients as identified by combined BMD and bone strength analysis from CTE. There was one patient with osteoporosis by DXA that was not identified by CTE analysis.

The relationships between femoral strength and age (Figures 4a and b) revealed some unique characteristics for this IBD population. Nearly 15% of the patients in our cohort (10/71 women and 9/65 men) who were under the age of 50 years and who had normal BMD by DXA also had low femoral bone strength — corresponding to osteopenia — by BCT. Of those patients under the age of 50 years who had osteopenia by DXA, three women and three men had fragile bone strength, placing them at high risk of fracture (should they fall). In general, there was a weak but statistically significant negative correlation between femoral bone strength and the age for the women (R^2 = 0.20, n = 71, P = 0.0001), as would be expected from the general population, but no significant relation for the men (R^2 <0.01, n = 65, P = 0.60).

DISCUSSION

Despite the presence of IV contrast with CTE, there was excellent agreement in the femoral neck BMD and subsequent *T*-scores between CTE and DXA, the latter being the current clinical standard for assessment of osteoporosis. The high degree of correlation (R^2 = 0.84) reported here is the same as that (R^2 = 0.84) reported previously between DXA and CT colonography, which uses only oral contrast (19). CTE also demonstrated a high degree of sensitivity and specificity for confirming osteoporosis (85.7% and 98.5% , respectively) or osteopenia (85.1% and 85.4% , respectively). The excellent agreement observed for this analysis is extremely important as many gastroenterologists use CTE to evaluate the small bowel in patients with IBD. Th ese results, obtained on a typical series of IBD patients using typical clinical CTE scans, indicates that this type for “add-on” ancillary analysis can provide a comprehensive assessment of the bone in IBD patients without any inconvenience to the patient. Finally and importantly, DXA failed to identify a substantial cohort of

younger IBD patients <50 who had either low or fragile levels of femoral bone strength by BCT.

Although there are prior reports of high correlation for measurements of hip areal BMD between DXA scores and CT (17,30) to our knowledge, there is no existing study to report such high correlations specifically for CTE, which uses IV contrast for cross-sectional imaging for all study patients or when assessing within a specific IBD population. Part of the success of this study is related to the technical details of how the scans were analyzed. One such detail was our method of quantitative phantomless calibration. Although phantomless technology generally uses two internal surrounding tissues — typically muscle and fat (31,32) — to calibrate the Hounsfield unit values of the scan into equivalent-BMD values, the incorporation of IV contrast complicates this process as muscle is highly perfused, preventing its use as an internal reference tissue (blood cannot be used for the same reason). Visceral fat does not appear to be perfused to any appreciable extent, and we used external air as the second reference for calibration. In addition, as our bone segmentation algorithm was independent of any calibration, it was not affected by the presence of contrast in any muscle adjacent to the bone. Segmentation artifacts associated with the presence of contrast in the musculature have been suggested as a reason for why measurements of cortical bone density in the proximal femur can be altered by IV contrast, whereas trabecular measurements cannot. Further, although we found the trabecular bone in the vertebral bodies to be highly perfused, it appears that the trabecular bone in the proximal femur was not, consistent with other reports in the literature (20).

It is noteworthy that as we used clinical DXA and CTE scans, the results reflect more real-world actual clinical precision than what might be expected in a controlled, prospective comparison that would permit little variation in the CT or DXA scanner model. In particular, there was one patient who had DXA-assessed osteoporosis (of the left femoral neck) but who did not have osteoporosis by CTE analysis. Retrospective analysis of that patient revealed that their DXA-based *T*-score was particularly low for their left hip (compared with their right hip and their lumbar spine *T*-scores) and, on their left hip only, a lower *T*-score for their femoral neck region than for the total hip region (we based our overall analysis only on the left femurs). Further, analysis of the CT scans revealed no appreciable difference between the left and right hips. We speculate for this case, on the basis of these observations, that indeed the CTE *T*-score is more reliable than the DXA *T*-score. Part of the reason for this may be related to the three-dimensional nature of the CT scan, which enables a more standardized (virtual) orientation of the bone, which sometimes can be diffi cult to achieve (physically) in patients during a DXA exam.

The use of finite element analysis of clinical CT scans is a well-established research technique for noninvasive assessment of whole-bone strength and is now widely used in various clinical research studies (14). This technique uses advanced engineering structural “finite element” analysis — the same type of analyses used by engineers to design and assess the strength of bridges, cars, buildings, aircraft , and various structural components — to virtually load the bone to failure and in that way provides a noninvasive estimate of overall bone strength. Well supported by cadaver studies, the technique has provided substantial new insight into drug treatment effects for osteoporosis (14,33–36) and is more

highly associated with fracture risk than is DXA (15,17,18,37–39). The technique can also identify a subset of individuals who have low bone density (but not in the osteoporosis category) and whose femoral strength is so low as to place them at high risk of hip fracture ("fragile" levels of bone strength). Because of this, when we combined the BMD and femoral strength assessments from CTE, the number of patients identified as being at high risk for hip fracture was more than double that identified from the DXA results alone.

Owing to larger effects of IV contrast on the vertebrae, CTE was not used for lumbar spine assessments in this analysis. Bauer *et al*. (20) demonstrated that, although there is a good correlation between BMD (volumetric) for trabecular bone in the spine with vs. without IV contrast, the absolute numbers are highly divergent because of the presence of the contrast in the vertebral bone marrow. It is not yet clear whether retrospective correction via regression analysis is suffi ciently general to provide corrected values of BMD to be used clinically; thus, this warrants further study. Interestingly, Pickhardt *et al*. (40) recently reported on using ancillary analysis of any abdominal CT exams — with or without contrast — to identify patients at risk of having vertebral osteoporosis, and who would then be recommended for follow-up DXA imaging. However, these investigators did not calibrate their scans for a quantitative analysis as we did, and they did not appear to treat the contrast-enhanced scans differently from the unenhanced scans (~ 45% of their scans were unenhanced). Given our and other's (20) experience with the effects of the presence of the contrast in the vertebral bone marrow, it is not clear that their approach would be appropriate for contrast-enhanced CTE exams. Further, whereas their approach seeks to identify patients at risk of having osteoporosis (potentially missing an appreciable proportion of the patients unless sensitivity is very high and requiring a DXA to confirm in all patients who test positive), our approach provides a more comprehensive assessment than a DXA exam.

There are several limitations worth discussing. Although this was a retrospective study at a single medical center, all analyses were performed in a blinded manner according to a prespecified analysis plan. Despite the relatively large sample size, nearly half of the total potential study population was excluded. Over half of the excluded patients had high BMI (>30 kg/m^2). As high BMI is associated with imaging artifacts (41), which compromise DXA much more than CT (42), DXA was considered to be unreliable as a standard of comparison in high-BMI patients. Indeed, clinically, bone analysis of high-BMI patients would be more appropriately performed using CT rather than DXA, and thus high-BMI patients can be analyzed clinically. Similarly, most other exclusion criteria would not disqualify patients clinically, although patients with metal implants at the hip or those with motion artifacts (altogether, 11 of the total 234 patients) cannot be analyzed. Because of the large time range for patient inclusion, there were variations in the type of DXA and CT scanners used in this study and also slight variations in the CT acquisition and contrast protocols — challenging for a controlled comparison study but more realistic for a clinical setting. In addition, we used routine dose CTE exams at 120 kVp tube energy. We would anticipate similar performance for lower dose studies, given prior results with CT colonography (19), but adaptation to lower X-ray tube energies (which reduce radiation dose) will require further validation. Future adaptation to this and other low-dose CT

acquisition techniques is possible, but it may be necessary to adapt or refine existing methods depending on what imaging parameters are changed. Finally, we noted wide CIs for identifying DXA-defined osteoporosis (sensitivity, 85.7%; 95% CI, 48.7–97.4) and osteopenia (sensitivity, 85.1%; 95% CI, 72.3–92.6). This primarily reflects the small number of patients with poor bone health in our study. Our findings would therefore be strengthened by including a larger cohort with significant bone disease and/or fractures. Finally, as DXA-defined osteoporosis misses identifying the majority of patients who go on to a hip fracture (43), and as the association with hip fracture is at least as high for bone strength as it is for hip BMD (15,18), future studies might also explore outcomes such as fracture occurrence when comparing these modalities.

Although the finite element analyses are complex and challenging to perform in a local clinical environment, clinical implementation is still highly feasible. For example, to incorporate this test into our medical practice, we plan to use a cloud model to provide such measurements clinically, in which the CT exam is sent to a central facility (O.N. Diagnostics) for analysis, and a medical report is sent back to the hospital. This approach, similar to any lab test, moves the burden of technical training, specialized infrastructure, and quality assurance from the hospital to a central facility, although it should be possible in the future to perform the analyses locally if so desired.

In summary, we have demonstrated that clinical contrast-enhanced CT enterography exams can provide synchronous hip BMD, *T*-scores, and clinical classifications that are comparable to those obtained from DXA, and when combined with BCT analysis, CTE can further identify a subset of patients with osteopenia who have clinically relevant low levels of femoral strength, placing them at high risk of hip fracture. In a changing healthcare environment where cost containment and practice effi ciency continue to become even more paramount, our relatively large validation study may be quite applicable for daily medical practice. Many gastroenterologists are increasingly using cross-sectional imaging to evaluate the small bowel in patients with IBD. The ability to calculate BMD and femoral strength measurements without a phantom on routine CTE as part of post processing prevents the need for an additional DXA scan in patients requiring osteoporosis screening, or for patients desiring to track the effi cacy of medical intervention. In addition, these measurements can be obtained from archived CT data even aft er the patient has left the medical facility. For these reasons, ancillary analysis of CTE exams for BMD and bone strength could potentially improve osteoporosis screening rates in IBD patients and alter management plans.

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REFERENCES

1. Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. Gastroenterology. 2003; 124:795. [PubMed: 12612917]
2. Van Hogezand RA, Hamdy NA. Skeletal morbidity in inflammatory bowel disease. Scand J Gastroenterol Suppl. 2006:59–64. [PubMed: 16782623]
3. Compston JE, Judd D, Crawley EO, et al. Osteoporosis in patients with inflammatory bowel disease. Gut. 1987; 28:410–5. [PubMed: 3583068]

4. Ali T, Lam D, Bronze MS, et al. Osteoporosis in inflammatory bowel disease. Am J Med. 2009; 122:599. [PubMed: 19559158]
5. Bernstein CN, Blanchard JF, Leslie W, et al. The incidence of fracture among patients with inflammatory bowel disease. A population-based cohort study. Ann Intern Med. 2000; 133:795–9. [PubMed: 11085842]
6. Loftus EV Jr, Crowson CS, Sandborn WJ, et al. Long-term fracture risk in patients with Crohn's disease: a population-based study in Olmsted County, Minnesota. Gastroenterology. 2002; 123:468–75. [PubMed: 12145800]
7. Loftus EV Jr, Achenbach SJ, Sandborn WJ, et al. Risk of fracture in ulcerative colitis: a population-based study from Olmsted County, Minnesota. Clin Gastroenterol Hepatol. 2003; 1:465–73. [PubMed: 15017646]
8. Compston J. Osteoporosis in inflammatory bowel disease. Gut. 2003; 52:63. [PubMed: 12477761]
9. Shen B, Remzi FH, Oikonomou IK, et al. Risk factors for low bone mass in patients with ulcerative colitis following ileal pouch-anal anastomosis. Am J Gastroenterol. 2009; 104:639. [PubMed: 19262520]
10. Johansson H, Oden A, Johnell O, et al. Optimization of BMD measurements to identify high risk groups for treatment: a test analysis. J Bone Miner Res. 2004; 19:906. [PubMed: 15190881]
11. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in White women. Study of Osteoporotic Fractures Research Group. N Engl J Med. 1995; 332:767. [PubMed: 7862179]
12. Kaufman L, Loftus E, Sandborn W, et al. Osteoporosis screening in a tertiary referral: inflammatory bowel disease. Am J Gastroenterol. 2010; 105(Suppl 1):S476.
13. Etzel JP, Larson MF, Anawalt BD, et al. Assessment and management of low bone density in inflammatory bowel disease and performance of professional society guidelines. Inflamm Bowel Dis. 2011; 17:2122–9. [PubMed: 21910174]
14. Keaveny TM. Biomechanical computed tomography-noninvasive bone strength analysis using clinical computed tomography scans. Ann NY Acad Sci. 2010; 1192:57–65. [PubMed: 20392218]
15. Orwoll ES, Marshall LM, Nielson CM, et al. Finite element analysis of the proximal femur and hip fracture risk in older men. J Bone Miner Res. 2009; 24:475–83. [PubMed: 19049327]
16. Amin S, Kopperdhal DL, Melton LJ III, et al. Association of hip strength estimates by finite-element analysis with fractures in women and men. J Bone Miner Res. 2011; 26:1593–600. [PubMed: 21305605]
17. Keyak JH, Sigurdsson S, Karlsdottir G, et al. Male-female differences in the association between incident hip fracture and proximal femoral strength: a finite element analysis study. Bone. 2011; 48:1239–45. [PubMed: 21419886]
18. Kopperdahl DL, Aspelund T, Hoffmann PF, et al. Assessment of incident spine and hip fractures in women and men using finite element analysis of CT scans. J Bone Miner Res. Aug 16.2013 advance online publication. doi: 10.1002/jbmr.2069. (e-pub ahead of print).
19. Murthy NS, Keaveny TM, Lee DC, et al. Comprehensive osteoporosis assessment for the hip using ancillary CTC . Abstract. RSNA. 2012
20. Bauer JS, Henning TD, Müeller D, et al. Volumetric quantitative CT of the spine and hip derived from contrast-enhanced MDCT: conversion factors. Am J Roentgenol. 2007; 188:1294–301. [PubMed: 17449773]
21. Kanis JA, McCloskey EV, Johansson H, et al. A reference standard for the description of osteoporosis. Bone. 2008; 42:467–75. [PubMed: 18180210]
22. Kanis JA, Johnell O, Oden A, et al. The use of multiple sites for the diagnosis of osteoporosis. Osteoporos Int. 2006; 17:527–34. [PubMed: 16402164]
23. Keaveny TM, Hoffmann PF, Singh M, et al. Femoral bone strength and its relation to cortical and trabecular changes aft er treatment with PTH, alendronate, and their combination as assessed by finite element analysis of quantitative CT scans. J Bone Miner Res. 2008; 23:1974–82. [PubMed: 18684084]
24. Keaveny TM, McClung MR, Wan X, et al. Femoral strength in osteoporotic women treated with teriparatide or alendronate. Bone. 2012; 50:165–70. [PubMed: 22015818]

25. Keaveny TM, Kopperdahl DL, Melton LJ III, et al. Age-dependence of femoral strength in white women and men. J Bone Miner Res. 2010; 25:994–1001. [PubMed: 19874201]
26. Lin L, Hedayat AS, Sinha B, et al. Statistical methods in assessing agreement: models, issues, and tools. JASA. 2002; 97:257–70.
27. Assessment of fracture risk and its application to screening for postmeno-pausal osteoporosis: report of a WHO Study Group. World Health Organ Tech Rep Ser. 1994; 843:1–129. [PubMed: 7941614]
28. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med. 1998; 17:857–72. [PubMed: 9595616]
29. Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implication. Gut. 2006; 55:749–53. [PubMed: 16698746]
30. Khoo BC, Brown K, Cann C, et al. Comparison of QCT-derived and DXA-derived areal bone mineral density and T scores. Osteoporos Int. 2009; 20:1539–45. [PubMed: 19107384]
31. Pickhardt PJ, Lee LJ, del Rio AM, et al. Simultaneous screening for osteoporosis at CT colonography: bone mineral density assessment using MDCT attenuation techniques compared with the DXA reference standard. J Bone Miner Res. 2011; 26:2194–203. [PubMed: 21590738]
32. Gudmundsdottir H, Jonsdottir B, Kristinsson S, et al. Vertebral bone density in Icelandic women using quantitative computed tomography without an external reference phantom. Osteoporos Int. 1993; 3:84–9. [PubMed: 8453195]
33. Keyak JH. Improved prediction of proximal femoral fracture load using nonlinear finite element models. Med Eng Phys. 2001; 23:165–73. [PubMed: 11410381]
34. Bessho M, Ohnishi I, Matsuyama J, et al. Prediction of strength and strain of the proximal femur by a CT-based finite element method. J Biomech. 2007; 40:1745–53. [PubMed: 17034798]
35. Crawford RP, Cann CE, Keaveny TM. Finite element models predict in vitro vertebral body compressive strength better than quantitative computed tomography. Bone. 2003; 33:744–50. [PubMed: 14555280]
36. Imai K, Ohnishi I, Yamamoto S, et al. In vivo assessment of lumbar vertebral strength in elderly women using computed tomography-based nonlinear finite element model. Spine (Phila Pa 1976). 2008; 33:2732.
37. Wang X, Sanyal A, Cawthon PM, et al. Prediction of new clinical vertebral fractures in elderly men using finite element analysis of CT scans. J Bone Miner Res. 2012; 27:808–16. [PubMed: 22190331]
38. Melton LJ III, Riggs BL, Keaveny TM, et al. Structural determinants of vertebral fracture risk. J Bone Miner Res. 2007; 22:1885–92. [PubMed: 17680721]
39. Melton LJ III, Riggs BL, Keaveny TM, et al. Relation of vertebral deformities to bone density, structure, and strength. J Bone Miner Res. 2010; 25:1922–30. [PubMed: 20533526]
40. Pickhardt PJ, Pooler BD, Lauder T, et al. Opportunistic screening for osteoporosis using abdominal computed tomography scans obtained for other indications. Ann Intern Med. 2013; 158:588–95. [PubMed: 23588747]
41. Bolotin HH, Sievänen H. Inaccuracies inherent in dual-energy X-ray absorptiometry in vivo bone mineral density can seriously mislead diagnostic/prognostic interpretations of patient-specific bone fragility. J Bone Miner Res. 2001; 16:799–805. [PubMed: 11341324]
42. Yu EW, Thomas BJ, Brown JK, et al. Simulated increases in body fat and errors in bone mineral density measurements by DXA and QCT. J Bone Miner Res. 2012; 27:119–24. [PubMed: 21915902]
43. Schuit SC, van der Klift M, Weel AE, et al. Fracture incidence and association with bone mineral density in elderly men and women: the Rotterdam Study. Bone. 2004; 34:195–202. [PubMed: 14751578]

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Patients with inflammatory bowel disease (IBD) are at an increased risk for osteoporosis and subsequently for fractures.
- Screening for osteoporosis in this patient population generally remains suboptimal.
- Current data demonstrate that bone mineral density (BMD) may be calculated from routine noncontrast computed tomograpghy (CT) images.

WHAT IS NEW HERE

- BMD can be calculated from contrast-enhanced CT enterography (CTE) in IBD patients.
- Our validated technique with CTE and in patients with IBD has multiple potential benefits.
- Some patients may not require an additional dual-energy X-ray absorptiometry (DXA) scan, which may reduce costs.
- This post-processing technique may reduce the high burden of necessary testing in this patient population.
- This post-processing technique can provide BMD values for patients after they have left the clinic.

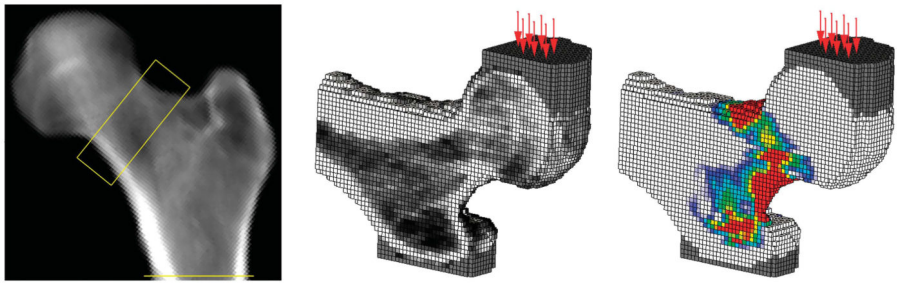


Figure 1.

Left: projectional image of the femur from the CT enterography (CTE) scan, used for areal bone mineral density (BMD) measurement. Yellow lines show subregions for BMD analysis. Middle: three-dimensional finite element model for biomechanical computed tomography (BCT) analysis, sectioned for viewing purposes, showing density distributions of the bone. Right: same model showing regions of failure (red being most severe) after virtual stress testing. Arrows denote schematically how the bone was virtually loaded.

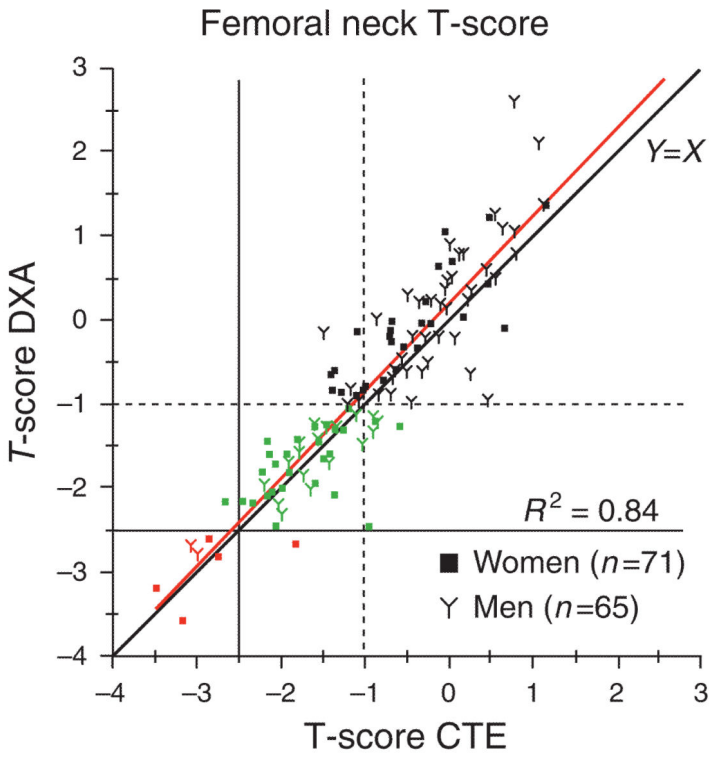
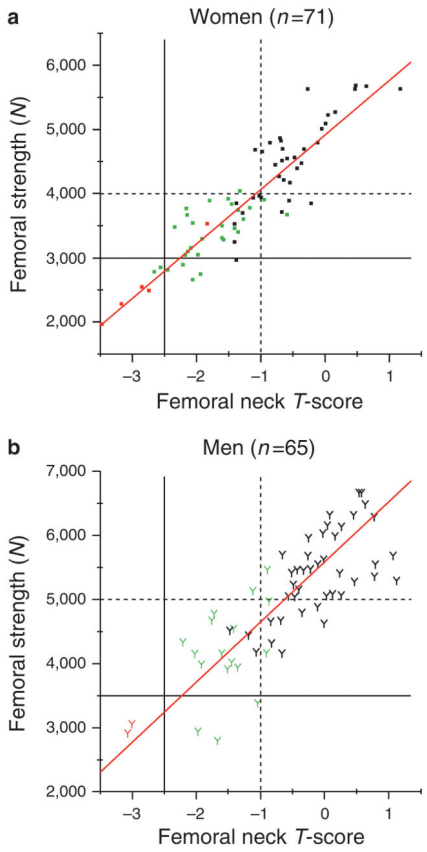


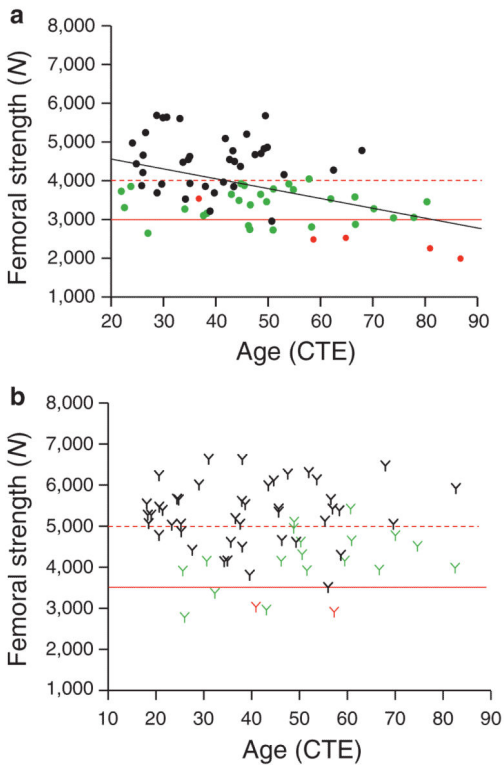
Figure 2.

Linear fi t for comparative *T*-scores between CT enterography (CTE) and dual-energy X-ray absorptiometry (DXA). The red points are subjects who have osteoporosis, by DXA femoral neck T ≤ −2.5. The green points are subjects who have osteopenia, by DXA femoral neck −2.5 <T <−1.0. The red line shows the best-fit line for the sexes combined (n = 136), which is almost identical to the line of $Y = X$, particularly in the vicinity of the osteoporosis threshold (T = −2.5). For viewing purposes, data are not shown for one man who had a very high *T*-score by both measures (DXA T = 4.4; CTE T = 3.2).



Figures 3.

(**a** , **b**) Linear fit for bone classification when combining femoral strength and *T*-scores from CT enterography (CTE). This plot shows how both femoral strength and femoral neck *T*-scores, both from CTE, identify subjects who have osteoporosis by dual-energy X-ray absorptiometry (DXA; red points) and osteopenia by DXA (green points). The red line shows the best-fit line for each sex. The sexes were not pooled because the relationship between strength and femoral neck *T*-score is slightly different between the sexes; the men tending to have a higher strength for any given *T*-score. The horizontal solid line denotes the threshold for “fragile bone strength” , which corresponds approximately to the *T*-score osteoporosis threshold; the horizontal dashed line denotes the threshold for “low bone strength” , which corresponds approximately to the *T*-score osteopenia (aka low bone mass) threshold. For viewing purposes, data are not shown for two men who had very high strengths (>8,000 N).



Figures 4.

(**a** , **b**). Femoral strength vs. age for women (circles) and men (Y marks). Red points signify patients who had osteoporosis by dual-energy X-ray absorptiometry (DXA), green points signify patients who had osteopenia by DXA, and black marks signify patients with normal bone mineral density (BMD) by DXA. The thresholds for femoral bone strength equivalent to osteoporosis and osteopenia are defi ned by the solid and dashed lines (“fragile bone strength” and “low bone strength” , respectively). Note that for under age 50, many women and men had low bone strength but normal DXA, and three women and three men had fragile bone strength but osteopenia by DXA.

Table 1

Reasons for study exclusion (*n*=98)

BMI≥30 kg/m^2, *n* (%)	70 (71.4)
IBD diagnosis in question, *n* (%)	9 (9.2)
Insufficient coverage or motion artifact, *n* (%)	7 (7.1)
BMI not within 30 days of CTE/DXA, *n* (%)	4 (4.1)
Metallic implant causing artifact, *n* (%)	4 (4.1)
Only right hip accessible on CTE, *n* (%)	3 (3.1)
No axial image available, *n* (%)	1 (1.0)

BMI, body mass index; CTE, computed tomography enterography; DXA, dual-energy X-ray absorptiometry; IBD, inflammatory bowel disease.

Table 2
Demographic data for patients with inflammatory bowel disease

Gender (M:F), *n*	**65:71**
Median BMI, kg/m^2	23.0 (range, 14.4–28.7)
Median age at imaging, years	43.5 (range, 18–85)
IBD subtype, n (%)	
Crohn's disease	88 (64.7)
Ulcerative colitis	45 (33.1)
Indeterminate colitis	3 (2.2)
Disease activity for Crohn's disease[a], n	88
No activity	19 (21.6)
L1, *n* (%)	3 5 (39.8)
L2, *n* (%)	1 1 (12.5)
L3, *n* (%)	23 (26.1)
L4, *n* (%)	0
Crohn's disease phenotype, n[b]	88
B1, *n* (%)	4 6 (52.3)
B2, *n* (%)	3 5 (39.8)
B3, *n* (%)	22 (13.6)
Perianal modifier, *n* (%)	2 (6.8)
Disease activity for ulcerative colitis, n	45
No activity, *n* (%)	2 (20.0)
Proctitis, *n* (%)	2 (2.2)
Proctosigmoiditis, *n* (%)	8 (17.8)
Left-sided, *n* (%)	2 (15.6)
Pancolitis, *n* (%)[c]	20 (44.4)
Current medications for entire cohort, n[d]	136
None, *n* (%)	25 (18.4)
5-ASA, *n* (%)	25 (33.1)
Oral corticosteroids, *n* (%)	56 (41.2)
Anti-TNF, *n* (%)	4 4 (32.4)
Immunomodulator, *n* (%)	45 (33.1)
Prior bowel resection	
Crohn's disease, *n* (%)	59 (43.4)
Ulcerative colitis, *n* (%)	2 (1.5)
Indeterminate colitis, *n* (%)	1 (0.7)

5-ASA, 5-aminosalicylic acid; BMI, body mass index; B1, non-stricturing, non penetrating; B2, structuring; B3, penetrating; IBD, inflammatory bowel disease; L1, ileal; L2, colonic; L3, ileocolonic; L4, isolated upper gut disease (29); TNF, tumor necrosis factor.

Some patients met criteria of more than one phenotype (29).

[a] Montreal classification for assessing Crohn's disease activity.

[b] Montreal classification for Crohn's disease phenotype.

[c] Disease noted beyond splenic flexure.

[d] Summation of percentages are greater than 100 as many patients were taking more than one of the listed medications.