Validation of asynchronous quantitative bone densitometry of the spine: Accuracy, short-term reproducibility, and a comparison with conventional quantitative computed tomography

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Asynchronous calibration quantitative computed tomography (QCT) is a new tool that allows the quantification of bone mineral density (BMD) without the use of a calibration phantom during scanning; however, this tool is not fully validated for clinical use. We used the European spine phantom (ESP) with repositioning during scanning and assessed the accuracy and short-term reproducibility of asynchronous QCT. Intra-scanner and intra-observer precision were each calculated as the root mean square of the standard deviation (RMSSD) and the coefficient of variation (CV-RMSSD). We also compared asynchronous and conventional QCT results in 50 clinical subjects. The accuracy of asynchronous QCT for three ESP vertebrae ranged from 1.4–6.7%, whereas intra-scanner precision for these vertebrae ranged from 0.53–0.91 mg/cc. Asynchronous QCT was most precise for a trabecular BMD of 100 mg/cc (CV-RMSSD = 0.2%). For intra-observer variability, overall precision error was smaller than 3%. In clinical subjects there was excellent agreement between the two calibration methods with correlation coefficients ranging from 0.96–0.99. A Bland–Altman analysis demonstrated that methodological differences depended on the magnitude of the BMD variable. Our findings indicate that the asynchronous QCT has good accuracy and precision for assessing trabecular BMD in the spine.

Bone mineral density is a surrogate indicator of bone strength that plays an important role in the management of osteoporosis and related fractures1,2. Different from areal bone mineral density computed by dual-energy X-ray absorptiometry (DXA), bone mineral density (BMD) derived from quantitative computed tomography (QCT) is a volumetric measure of the vertebral trabecular bone. Given the high turnover rate of trabecular bone compared to cortical bone, BMD calculated from QCT offers substantially higher sensitivity. Yet, radiation doses associated with CT limit the application of QCT in osteoporosis screening.

Recently, asynchronous calibration QCT was described as a new tool for quantifying BMD3. Asynchronous calibration means that a calibration phantom is not necessary during QCT scanning. Rather, asynchronous QCT utilizes phantom data obtained separately from CT scans to calibrate data in Hounsfield units for the measurement of BMD. This approach is convenient for the assessment of BMD during routine abdominal and/or lung CT scans, and for the identification of patients who have an increased risk of fracture with diagnostic CT scanning. The 2015 International Society for Clinical Densitometry (ISCD) official position states that the in-scan

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A calibration phantom for density-based QCT measurement can be replaced with asynchronous calibration if scanner stability is maintained. Opportunistic screening enabled by the use of asynchronous calibration may therefore improve the current understanding of bone health status and decrease the number of undiagnosed or overlooked cases of osteoporosis.

Few studies to date have compared conventional QCT, asynchronous QCT, and DXA. Moreover, asynchronous QCT has not yet been fully validated for the clinical measurement of spinal BMD. Although an early study by Brown et al. reported the precision of asynchronous QCT using the Mindways QA phantom, this study did not perform an accuracy assessment using the European spine phantom (ESP), which is a standard evaluation tool for bone densitometry. Thus, we performed 10 ESP scans with repositioning in order to assess the accuracy and short-term reproducibility of asynchronous quantitative bone densitometry, and to compare spine BMD results of asynchronous and conventional QCT in 50 clinical subjects.

**Methods**

**Evaluation of accuracy and short-term reproducibility with ESP.** The ESP (QRM, Erlangen, Germany) was recommended by the International DXA Standardization Committee as a possible standard for use in DXA as well as QCT. The ESP consists of three simulated vertebrae that are designed to give trabecular density values of 50, 100, and 200 mg/cm³ of hydroxyapatite, respectively. To simulate slight differences seen on daily quality control (QC) charts due to repositioning of the phantom, we performed each phantom scan with repositioning of the ESP. This method was recommended in the 2005 ISCD Official Position and reported to improve the estimate of the mean measure by a factor of nearly three. Briefly, the ESP was placed on the scanner table on top of the table pad and aligned along the long axis of the table. CT scanning parameters were summarized in Table 1. Images were transferred to a QCT workstation and analysed using the 3D spine function version 5.10 of Mindways QCT pro software (Mindways Software Inc., Austin, TX, USA). This novel version includes a conventional QCT module and an asynchronous calibration module. For asynchronous QCT measurements, a new Model 4 asynchronous calibration phantom (Mindways Software Inc.) (Fig. 1) was scanned for quality assurance (QA) calibration. A Model 3 conventional calibration phantom (Mindways Software Inc.) was used to validate QA calibration for conventional QCT analysis. To evaluate short-term intra-scanner precision, a ten-scan series was performed in duplicate over two sessions, with one month between each scanning session. For the evaluation and comparison of asynchronous and conventional QCT, a Toshiba Aquilion 80-slices CT scanner (Toshiba Medical Systems Corp., Tokyo, Japan) was used to scan the ESP (no. 145) in the presence and absence of a Mindways calibration phantom, ten times each. Each group of ten scans was analysed individually and the average of each parameter was used to compute accuracy. To further compare the effect of inter-scanner differences,

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| European spine phantom | Patient spine |
|-------------------------|---------------|
| Scanner type            | 80-slice Toshiba Aquilion | 16-slice Toshiba Aquilion |
| Voltage (kV)            | 120            | 120            |
| Exposure (mAs)          | 100            | Auto exposure  |
| Reconstruction kernel   | Standard       | Standard       |
| DFOV (mm)               | 400            | 400            |
| Slice thickness (mm)    | 1.0            | 1.0            |
| Table height (cm)       | 120            | 90             |

Table 1. Computed tomography (CT) scan parameters for phantom and patient image acquisition. DFOV, display field of view.

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Figure 1. Quality assurance (QA) for asynchronous quantitative computed tomography using the Model 4 asynchronous QA phantom.
Results

Accuracy. The results of the accuracy analysis based on 10 ESP scans with repositioning are summarized in Table 2. The accuracies of conventional and asynchronous QCT were different, ranging from 3.7–5.9% for conventional QCT and from 1.4–6.7% for asynchronous QCT. Asynchronous QCT had higher accuracy than conventional QCT for measuring trabecular BMD in 50 and 100 mg/cc ESP (L1 and L2, respectively) vertebrae, whereas conventional QCT showed better accuracy for measuring the 200 mg/cc ESP L3 vertebra. Conventional QCT tended to overestimate ESP trabecular bone, whereas asynchronous QCT underestimated the BMD of the ESP L3 vertebra. The mean trabecular volumetric BMD (vBMD) for all three ESP vertebrae using conventional QCT tended to overestimate ESP trabecular bone, whereas asynchronous QCT underestimated the BMD of the vertebrae.

Intra-scanner short-term reproducibility. The intra-scanner precision of synchronous QCT for vBMD across all three vertebrae ranged from 0.53–0.91 mg/cc. Asynchronous QCT was most precise (in terms of the

| Site | ESP BMD (mg/cm^2) | Conv. values | Asyc. values | Conv. – Asyc. | P-value | Conv. values on 16-slice scanner (mg/cm^2) | Diff. (mg/cm^2) | P-value |
|------|------------------|--------------|--------------|--------------|---------|------------------------------------------|----------------|---------|
| L1   | 50               | 52.94 ± 0.99 | 51.89 ± 0.53 | 3.8%         | 1.05    | <0.0001                                 | 52.14 ± 1.45   | 0.80    | 0.66   |
| L2   | 100              | 104.18 ± 0.85| 101.40 ± 0.61| 4.2%         | 2.78    | <0.0001                                 | 105.00 ± 0.37   | 0.82    | 0.37   |
| L3   | 200              | 207.40 ± 0.97| 186.70 ± 0.53| 7.7%         | 20.71   | 0.0029                                  | 204.85 ± 1.35   | 2.55    | 0.023  |

Table 2. The accuracies of asynchronous and conventional quantitative computed tomography (QCT) and comparisons of inter-scanner differences. Asyc., asynchronous QCT method; BMD, bone mineral density; Conv., conventional QCT; ESP, European spine phantom; RE, Relative error; Diff. difference defined as 80-slice scanner – 16-slice scanner. Data represent the mean ± standard deviation.
root mean square of the standard deviation [RMSSD]) for the 100 mg/cc ESP L2 vertebra with a coefficient of variance (CV)-RMSSD value of 0.2%.

Clinical study. Table 3 shows that among 25 male subjects and 25 female subjects, the mean age was 62 ± 9 years (range, 33–85 years), the mean height was 165.9 ± 7.9 cm (range, 150.0–181.0 cm), the mean weight was 70.7 ± 9.8 kg (range, 50.0–89.5 kg), and the mean BMI was 25.6 ± 2.7 kg/m² (range, 20.4–32.8 kg/m²). Of the 50 subjects, twelve female subjects and 10 male subjects had osteoporosis, and two patients had other vertebral compressive fractures.

Relationships between conventional and asynchronous QCT scanning results. Figure 3 shows correlations between the results of conventional and asynchronous QCT for each vertebra (L1–L3) and the average of all 3 vertebrae of the clinical subjects. The analysis demonstrated excellent agreement between the two methods, with correlation coefficients (R²) ranging from 0.96–0.99. A Bland–Altman analysis (small upper panel inserts in Fig. 3) showed differences between conventional and asynchronous QCT for different vertebrae with respect to a linear correlation. Methodological differences (expressed as absolute differences) depended on the magnitude of the BMD variable.

Intra-observer variability. Table 4 summarizes the RMMS and CV-RMSS values for repeated measures with the asynchronous calibration method. The intra-observer precision for asynchronous QCT measured across all three ESP vertebrae ranged from 2.68–3.80 mg/cc. Overall precision error for BMD was smaller than 3%, consistent with the known precision of QCT technology.

Discussion
In this study, we determined the accuracy and intra-operator precision of asynchronous QCT using an ESP vertebra dataset and data retrospectively collected from clinical subjects. In both datasets, the precision of BMD measurement was around 3%. Our results suggest that vertebral trabecular BMD measurements can be conveniently obtained by asynchronous QCT with good accuracy and precision.

The results of an analysis based on ten ESP scans demonstrated that asynchronous QCT had excellent accuracy for measuring trabecular BMD and agreed well with conventional QCT. Asynchronous QCT had slightly higher accuracy than conventional QCT for measuring trabecular BMD in 50 and 100 mg/cc ESP vertebrae; however, the differences between the two methods for 50 and 100 mg/cc vertebrae were relatively small (1.05 mg/cc and 2.78 mg/cc, respectively). In contrast, conventional QCT was more accurate for measuring the 200 mg/cc ESP vertebra, suggesting that the asynchronous QCT method may underestimate the BMD of high-density bone. While traditional QCT utilizes a calibration equation obtained from each individual slice, asynchronous QCT uses the same calibration equation for all data. This may result in lower variability in high-BMD bone for asynchronously calibrated results. Inconsistent with our finding, Brown et al. showed excellent agreement between conventional and asynchronous QCT using high-BMD Mindways QA phantom scan data5. The reason for this
The discrepancy is unclear; however, one explanation may be related to the fact that peak histogram values used in the calibration procedure depend on noise and thus exposure settings, the reconstruction kernel, and slice thickness5.

True in vivo precision measurements were obtained by measuring subjects twice at a one-month interval with repositioning. Repositioning has a lower impact on precision in three-dimensional QCT than in traditional two-dimensional slice-based imaging, where the location of the slice relative to the vertebral body is determined at the time of acquisition using the scout view taken before the actual CT scan. In an earlier study, Brown et al.3 investigated inter-observer variability for the asynchronous method using data from 43 patients aged 63.8 ± 8.6 years and reported RMSSD and CV-RMSSD values of 4.34 mg/cc and 3.67%, respectively; bias was not considered to be clinically important in the context of osteoporosis screening. In our study, we assessed the intra-observer reproducibility for asynchronous QCT and calculated RMSSD values of 3.12, 3.73, and 2.68 mg/cc and CV-RMSSD values of 2.5%, 2.6%, and 2.2% for the ESP L1–L3 vertebrae, respectively. Inter-observer reproducibility for asynchronous QCT reported by Brown et al. is therefore similar to the calculated intra-observer variability in our study.

![Figure 3.](image)

**Figure 3.** Correlation scatter plots for conventional and asynchronous quantitative computed tomography (QCT) outcomes of clinical subjects and Bland–Altman plots (small upper panel inserts) for conventional and asynchronous QCT BMD measurements of clinical subjects. Small upper inserts: Y-axis (Diff) is defined as (Asyc. – Conv.); X-axis is defined as the mean value of (Asyc. + Conv.).

| Intra-observer variability | Intra-scanner variability |
|----------------------------|---------------------------|
| Subjects (n = 50) | Obs. 1 | Obs. 2 | RMSSD | CV-RMSSD |
| L1 vBMD | 93.04 ± 34.58 | 94.02 ± 35.14 | 3.12 | 2.5 |
| L2 vBMD | 86.76 ± 34.01 | 87.64 ± 34.43 | 3.73 | 2.6 |
| L3 vBMD | 81.44 ± 33.42 | 81.39 ± 33.51 | 2.68 | 2.2 |

| | ESP scans (n = 10) | Scan 1 | Scan 2 | RMSSD | CV-RMSSD |
| | L1 vBMD | 51.89 ± 0.53 | 51.79 ± 0.20 | 0.56 | 0.7 |
| | L2 vBMD | 101.40 ± 0.61 | 101.67 ± 0.40 | 0.91 | 0.6 |
| | L3 vBMD | 186.70 ± 0.53 | 186.55 ± 0.46 | 0.53 | 0.2 |

Table 4. Intra-observer and intra-scanner reproducibility of asynchronous quantitative computed tomography (QCT). CV, coefficient of variation; Obs., observation; RRMSD, root mean square of the standard deviation; vBMD, volumetric bone mineral density. Data represent the mean ± standard deviation.
In one phantomless QCT BMD study, inter-observer variability was 3.1 mg/cc and CV-RMSSD was 4.0%\textsuperscript{11}, which are high compared to the results of our study. Although previous reports have indicated that non-calibrated Hounsfield unit values from CT scanners may be used for the opportunistic screening of low bone mass\textsuperscript{12–13}, the use of a phantom calibration standard guarantees that the derived BMD computations will be consistent across CT scanners from different manufacturers and consistent across different scanning X-ray energy levels.

Lastly, we found that asynchronous and synchronous QCT results were highly correlated; regression lines for each method were not significantly different. Accordingly, it appears that bias (expressed as the absolute difference between method results) depends on the magnitude of the BMD variable. Different from conventional QCT utilizing a calibration equation obtained from each individual slice, the asynchronous QCT uses the same calibration equation for all slices and could have such calibration before or after CT images acquisition. The different calibration methods might be one of important causes of the bias. Further, there might be a phantom-induced bias between asynchronous and conventional QCT. Brown et al. had investigated the phantom-induced bias on clinical individuals and found that the bias induced by the presence of the phantom was 2.3 mg/cm\textsuperscript{3} when asynchronous calibration was applied\textsuperscript{15}.

The present study had several limitations that most notably affected our precision assessments. First, due to concerns about radiation doses, it was not appropriate to scan patients twice in one session, so we performed ESP scans to investigate intra-scaner bias; however, this approach does not meet conservative recommendations (>27 degree of freedom, DOF) and may have underestimated precision error\textsuperscript{16}. Second, we did not analyse the long-term precision of asynchronous QCT; this should be investigated in future studies. Lastly, the BMD of volunteers recruited in precision studies is often normal. In this study, we selected patients from a population with low-to-normal BMD. Given that BMD typically decreases with age, precision errors are typically larger in elderly individuals\textsuperscript{17}. Additionally, precision errors are typically underestimated\textsuperscript{18} when scanning a subject twice on the same day with repositioning in between scans and all scans performed by the same operator. Instead, we report precision using repeat scans taken at a one-month interval. We believe these aspects of our study provide a more accurate reflection of the real precision of asynchronous QCT measurement. Further studies are necessary to confirm and extend our results.

In conclusion, we demonstrate that asynchronous QCT could be used for spine BMD screening based on the results of accuracy assessment for volumetric trabecular BMD in the spine and good short-term precision; however, even when the asynchronous and synchronous methods are highly correlated, the presence of bias was observed.

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Additional Information
Competing Interests: The authors declare that they have no competing interests.

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