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Original Article

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# Least significant changes and monitoring time intervals for high-resolution pQCT-derived bone outcomes in postmenopausal women

**C.E. Kawalilak[1], J.D. Johnston[2], W.P. Olszynski[3], S.A. Kontulainen[1]**

[1]College of Kinesiology, University of Saskatchewan; [2]Department of Mechanical Engineering, College of Engineering, University of Saskatchewan; [3]College of Medicine, University of Saskatchewan

**Abstract**

**Background:** Least Significant Change (LSC) assists in determining whether observed bone change is beyond measurement precision. Monitoring Time Interval (MTI) estimates time required to reliably detect skeletal changes. MTIs have not been defined for bone outcomes provided by high resolution peripheral quantitative computed tomography (HR-pQCT). The purpose of this study was to determine the LSCs and MTIs for HR-pQCT derived bone area, density and micro-architecture with postmenopausal women. **Methods:** Distal radius and tibia of 33 postmenopausal women (mean age: 77, SD: ±7 years), from the Saskatoon cohort of the Canadian Multicentre Osteoporosis Study (CaM*os*), were measured using HR-pQCT at baseline and 1-year later. We determined LSC from precision errors and divided them by the median annual percent changes to define MTIs for bone area, density, and micro-architecture. **Results:** Distal radius: HR-pQCT LSCs indicated a 1-8% observed change was needed for reliable monitoring of bone area and density while a 3-18% change was needed for micro-architectural measures. The longest MTIs (>3 years) pertained to cortical and trabecular area and density measures, cortical thickness and bone volume fraction; the shortest MTIs (~2 years) pertained to bone micro-architectural measures (trabecular number, thickness, separation and heterogeneity). Distal tibia: LSCs indicated a <1-5% observed change was needed for reliable monitoring of bone area and density, while a 3-19% change was needed for micro-architectural measures. The longest MTIs (>3 years) pertained to trabecular density, bone volume fraction, number, separation and heterogeneity; the shortest MTIs (~1 year) pertained to cortical and trabecular area, cortical density and thickness. **Conclusion:** MTIs suggest that performing HR-pQCT follow-up measures in postmenopausal women every 2 years at the distal radius and every 1 year at the distal tibia to monitor true skeletal changes as indicated by the LSCs.

**Keywords:** HR-pQCT, Least Significant Change, Monitoring Time Interval, Postmenopausal Women

## Introduction

Osteoporosis is characterized by low bone mass and the deterioration of bone micro-architecture, consequently leading to bone fragility and an increase in fracture risk[1]. The advent of high-resolution peripheral quantitative computed tomography (HR-pQCT) has enabled the measurement of 3D micro-architectural properties at the distal tibia and fracture-prone distal radius. Importantly, fragility fractures at the distal radius are a sentinel for future fragility fractures at other sites[2,3]. Further, because the tibia is a weight-bearing skeletal site, it may reflect bone strength at other weight-bearing sites, such as the hip and vertebrae[4]. As such, HR-pQCT is an important tool for advancing our understanding of osteoporosis-related bone deterioration and for providing new targets for investigations and strategies aiming to optimize osteoporotic fracture prevention.

Measuring and monitoring minute skeletal changes over time using any imaging modality requires a high degree of measurement precision or repeatability (i.e., low precision error) to ensure measurement sensitivity to capture changes and treatment effects[5]. There are several reports of HR-pQCT short-term precision in young adults[6-8], postmenopausal

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*Corresponding author: Chantal E Kawalilak, MSc*, College of Kinesiology, University of Saskatchewan, 87 Campus Drive, Saskatoon, SK, S7N 5B2, Canada*
*E-mail: chantal.kawalilak@usask.ca*

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**Table 1.** Literature reporting *in vivo* precision using high-resolution peripheral quantitative computed tomography (HR-pQCT), with breakdown of precision dependent components including: type of precision, participant number and degrees of freedom, age, follow-up criteria, method used in determining precision error, and reported precision results.

| ***In vivo* Precision** | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Reference** | **Type of Precision** | **Participant Number (Degrees of Freedom)[1]** | **Age (years)** | **Follow-up Criteria** | **Method of Determining Precision Error** | **Precision Results** | |
| Boutroy et al (2005)[6] | Short-term Precision | 15 F Radii and Tibiae (30) | 21-47 | 3 Scans within 1 month[2] | Gluer et al (1995)[5]: $CV\%_{RMS}$ | *Radius:*<br>Densities: 0.9-1.5%<br>Micro-architecture: 0.9-4.4% | *Tibia:*<br>Densities: 0.9-1.5%<br>Micro-architecture: 0.9-4.4% |
| Kazakia et al (2008)[10] | Short-term Precision | 8 Radii[3] (16)<br>7 Tibiae[3] (14) | 25-65<br>29-73 | 3 Scans[2] | Not Specified: CV% | BV/TV: 1.2%<br>Micro-architecture: 1.0-5.8% | |
| MacNeil & Boyd (2008)[7] | Short-term Precision | 14 M (14)<br>15 F (15) | 20-37<br>20-40 | 2 Scans within 1 week | Not Specified: $CV\%_{RMS}$ | *M-Radius*:<br>Densities: 0.3-0.7%<br>Micro-architecture: 0.6-4.4%<br>*F-Radius*:<br>Densities: 0.4-0.5%<br>Micro-architecture: 0.5-3.4% | *M-Tibia*:<br>Densities: 0.2-0.5%<br>Micro-architecture: 0.5-3.6%<br>*F-Tibia*:<br>Densities: 0.6-1.0%<br>Micro-architecture: 0.8-4.0% |
| Kawalilak et al (2013)[8] | Short-term Precision | *Young Adult*:<br>28 F Radii (28)<br>32 F Tibiae (32)<br>*Postmenopausal Women*:<br>29 M and F Radii (29)<br>30 M and F Tibiae (30) | 19-48<br>19-48<br>62-88<br>62-88 | 2 Scans on 2 separate days within 24 hours<br>2 Scans within 1 week | Gluer et al (1995)[5]: $CV\%_{RMS}$ | *Young Adult Radius*:<br>Area: 0.6-3.1%<br>Densities: 0.8-1.6%<br>Micro-architecture: 0.9-8.0%<br>*Postmenopausal Radius*:<br>Area: 0.4-2.9%<br>Densities: 1.1-2.1%<br>Micro-architecture: 1.2-6.5% | *Young Adult Tibia:*<br>Area: 0.2-0.9%<br>Densities: 0.4-1.4%<br>Micro-architecture: 0.9-5.0%<br>Postmenopausal Tibia:<br>Area: 0.1-1.1%<br>Densities: 0.3-1.9%<br>Micro-architecture: 1.3-6.8% |
| Wong et al (2014) (Part I)[9] | Short-term Precision | 31 M and F Radii and Tibiae (31) | 20-69 | 2 Scans repeated within same day | Gluer et al (1995)[5]: $CV\%_{RMS}$ | *Radius*:<br>Densities: 0.5-0.7%<br>Micro-architecture: 0.7-4.8% | *Tibia*:<br>Densities: 0.2-0.4%<br>Micro-architecture: 0.4-4.1% |
| MacNeil & Boyd (2008)[7] | Long-Term Precision | 14 M (14)<br>15 F (15) | 20-37<br>20-40 | 2 Scans within 4 months | Langton & Njeh (2004)[17]: SEE | *M-Radius*:<br>Densities: 0.3-0.7%<br>Micro-architecture: 0.6-3.9%<br>*F-Radius*:<br>Densities: 0.3-0.5%<br>Micro-architecture: 0.5-3.2% | *M-Tibia*:<br>Densities: 0.3-0.5%<br>Micro-architecture: 0.4-3.4%<br>*F-Tibia*:<br>Densities: 0.5-1.0%<br>Micro-architecture: 0.8-3.8% |
| Wong et al (2014) (Part II)[11] | Long-term Precision | *All Participants*:<br>38 F Radii (38)<br>38 F Tibiae (38)<br>*Non-fracture, Non-medicated:*<br>13 F Radii (13)<br>13 F Tibiae (13) | 61-89<br>63-81 | 2 Scans repeated within 1 year | Gluer et al (1995)[5]: SEE | *All Participants Radius*:<br>Densities: 1.9-2.5%<br>Micro-architecture: 2.6-6.2%<br>*Non-fracture, Non-medicated Radius:*<br>Densities: 1.7-2.5%<br>Micro-architecture: 1.7-6.8% | *All Participants Tibia*:<br>Densities: 1.1-1.9%<br>Micro-architecture: 2.0-7.7%<br>*Non-fracture, Non-medicated Tibia*:<br>Densities: 0.7-0.9%<br>Micro-architecture: 1.0-8.1% |

*Abbreviations: M = Male; F = Female; $CV\%_{RMS}$ = Root-mean-squared percent coefficient of variation; SEE = Standard Error of the Estimates.*

*[1] Degrees of Freedom = m·(n-1) where m=number of subjects, n = repeat measures; equation from Gluer et al. (1995)[5].*

*[2] Time between scans not specified.*

*[3] Sex not specified.*

*[4] Least Significant Change (LSC) determined using equation from Bonnick et al. (2001)[18].*

women[8,9], and mixed age cohort[10] (Table 1). Two studies reported long-term precision in young adults and postmenopausal women[7,11] (Table 1). The International Society for Clinical Densitometry (ISCD) recommends estimating the least significant change (LSC) to determine if true skeletal change has occurred[12]. LSC is estimated based upon measurement error (estimated via root-mean-squared coefficient of variation ($CV\%_{RMS}$) precision errors) and an adjusting Z-score derived from the selected level of statistical confidence (typically two-tailed 95% confidence, with a Z-score of 2.77 used in the relation $LSC=2.77 \times CV\%_{RMS}$). LSC essentially serves as a quantitative metric for ensuring (with a certain level of statistical confidence) that observed differences or changes are sufficiently larger than precision errors associated with a technique. Currently, the only available LSC data for HR-pQCT reports estimated LSC values which ranged from 1-40% for bone micro-architectural outcomes at the distal radius and tibia[11]. These estimates, however, need to be interpreted with caution as the LSCs were calculated using long-term precision estimates from postmenopausal women with and without fractures and osteoporosis medication[5,13]. Long-term precision estimates determined using follow-up data 1 year from baseline incorporate both precision error and non-linear skeletal changes, thereby obfuscating the measurement's actual precision[5]. Further, measurement precision should be applicable to the group being studied, such as postmenopausal women without fracture history[5].

To facilitate the design of therapeutic interventions and longitudinal follow-up studies in postmenopausal women[14-16], information of the LSC, together with the information of median annual changes, can be used to estimate a monitoring time interval (MTI) between HR-pQCT measurement occasions[12,17]. MTIs provide a time estimate (in years) to reliably measure bone change[17-19], thereby allowing follow-up measures to be performed within the optimal window for capturing true skeletal change, as well as minimizing patient radiation exposure and costs associated with repeated scanning in prospective studies. To our knowledge, there have been no reported MTIs for bone parameters using HR-pQCT in postmenopausal women.

The first objective of our study was to define the LSC using short-term precision data in postmenopausal women. Our second objective was to define MTIs for HR-pQCT derived bone area, density, and micro-architecture in postmenopausal women.

## Methods

### *Participants*

In 2011, 104 community-dwelling postmenopausal women (mean age ± standard deviation: 75±8 years), who were a part of the Saskatoon cohort of the Canadian Multi-centre Osteoporosis (CaM*os*) Study, enrolled to receive HR-pQCT measurements. Approximately 1 year later (410±54 days; 2012-2013), fifty-one women (78±7 years) returned for follow-up HR-pQCT measurements. There were no differences in osteoporosis status or HR-pQCT outcomes at baseline between the women who returned and those who did not return for follow-up measures *(data not shown)*. We excluded 18 women who were using hormone replacement therapy or bisphosphonates. Thirty-three women (77±7 years) were included in this study. Postmenopausal status was determined by a questionnaire and defined as not menstruating for at least 12 months[20]. Osteoporosis status was based on DXA-derived femoral neck (FN) T-scores obtained from the Saskatoon CaM*os* database (Table 2)[21]. Of the participants not using bone altering medication, 33% had normal FN T-Scores, 52% were osteopenic, and 15% had osteoporosis (Table 2). Participant consent was obtained prior to the study. This study was approved by the University of Saskatchewan Biomedical Research Ethics Board.

| (n = 33) | Minimum | Maximum | Mean ± SD |
|---|---|---|---|
| **Age** (*years*) | 62 | 88 | 77±7 |
| **Height** (*cm*) | 147.9 | 177.6 | 160.3±5.9 |
| **Weight** (*kg*) | 54.5 | 101.5 | 73.5±12.8 |
| **DXA Measures** | | | |
| FN aBMD ($g/cm^2$) | 0.4 | 1.1 | 0.7±0.1 |
| FN T-score | -3.5 | 2.0 | -1.2±1.1 |
| **Osteoporosis Status** | **n (%)** | | |
| Normal | 11 (33%) | | |
| Osteopenia | 17 (52%) | | |
| Osteoporosis | 5 (15%) | | |

**Table 2.** Participant demographics (minimum, maximum, and mean ± SD), including the number (n) and proportion (%) of participants with osteopenia or osteoporosis at the baseline.

### *HR-pQCT imaging*

The non-dominant arm and ipsilateral leg of all participants were immobilized in the standard carbon fiber cast prior to imaging, as per the manufacturer's standard *in vivo* protocol. A scout view scan was used to set the reference line and define the volume of interest for each scan, further defined elsewhere[8]. Using HR-pQCT (XtremeCT; Scanco Medical AG, Brüttisellen, Switzerland) we obtained a 9.02 mm region of interest (110 parallel CT slices) located 9.5 mm (radius) and 22.5 mm (tibia) proximal to the reference line. Using the standard *in vivo* imaging protocol, an isotropic voxel size of 82 μm was used to collect our data. The effective dose was <4 μSv[8]. Measurement time was approximately 2.8 minutes for each scan[8].

### *HR-pQCT image analysis*

One operator (CK) scanned, graded, and analyzed all images. Based on the 5 point image grading scale, all images with a quality of 4 and 5 were deemed unacceptable and removed from the study without further analysis[22,23]. At the radius, we included scans of grade quality 1-3. At the tibia there were only grades 1 and 2, therefore all tibia measurements were included in the study.

Image analysis was completed according to the manufacturer's standard *in vivo* evaluation protocol, described in detail elsewhere[8]. Briefly, we outlined the periosteal surface of the bone of interest (i.e., radius or tibia) to separate the bone from the surrounding soft tissue. A semi-automatic edge-finding algorithm was used to detect the periosteal bone surface and facilitated the contour iteration process from the first slice through the subsequent 109 slices in a slice-by-slice manner. For every slice the contour line was examined and adjustments were manually made to correct the line when it strayed from the periosteal surface of the bone. Bone area outcomes were: cortical and trabecular area. Bone density outcomes were: total, cortical, and trabecular bone densities (including: meta and inner densities). Bone micro-architecture outcomes were: cortical thickness (*Ct.Th*), bone volume fraction (*BV/TV*), trabecular number (*Tb.N*), trabecular thickness (*Tb.Th*), trabecular separation (*Tb.Sp*), and trabecular heterogeneity (*Tb.SpSD*). The methods to define these outcome variables are described elsewhere[24-28].

*Statistical analysis*

We determined the LSC, median annual percent change, and MTI. As the LSC calculation requires $CV\%_{RMS}$, short-term $CV\%_{RMS}$ precision errors were first obtained from repeated measures of the 32 postmenopausal women, reported earlier[8]. This sample size provided 32 degrees of freedom (DOF), which exceeded Gluer's recommendation of 27 DOF required to establish reliable precision errors with an upper 90% confidence limit less than 30% (e.g., if the precision error is 2%, we are 90% confident that the true precision error is less than 2.6%)[5]. $CV\%_{RMS}$ was calculated using the following equations:

$$CV\%_j = \left(\frac{SD_j}{\bar{x}_j}\right) x\ 100\% \quad (1)$$

$$CV\%_{RMS} = \sqrt{\frac{\sum_{j=1}^{m} CV_j^2}{m}} \quad (2)$$

Where $j$ refers to an individual participant, $SD_j$ is the standard deviation between the baseline and follow-up measurements (for that individual participant), $\bar{x}_j$ is the mean of these two measurements, and $m$ is the total number of participants in the analysis[5].

LSC was then calculated as follows:

$$LSC_{(1x1)} = Z \times CV\%_{RMS} \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} = 2.77 \times CV\%_{RMS} \quad (3)$$

Where (*1x1*) indicates that we performed 1 measurement at each visit (i.e., baseline and follow-up); Z-score corresponds a two-tailed 95% confidence level (Z=1.96), while $n_1$ and $n_2$ are the number of measures performed at baseline ($n_1$=1) and follow-up ($n_2$=1), respectively[18].

The median annual percent change was determined using the median difference in bone measures between baseline and 1 year follow-up, expressed in relation to the baseline measurement.

MTI was defined as the ratio of LSC to median annual percent change, and specifies the period after which half the participants demonstrate a measured change exceeding the LSC[17-19]. We calculated MTI using the following equation, defined by Glüer[17]:

$$MTI = \frac{LSC}{Median\ Annual\ Percent\ Change} \quad (4)$$

## Results

*Least significant change (LSC)*

At the distal radius, trabecular area, bone volume fraction, and all density measures had LSC values that were <6.0% (range: 1.1-5.9%; Table 3). LSCs for distal radius cortical area and micro-architecture (excluding bone volume fraction) were >8.0% (range: 8.1-18.2%; Table 3). At the distal tibia, all area and density measures, as well as cortical thickness and bone volume fraction had LSC values that were <5.5% (range: 0.3-5.3%; Table 3). Distal tibia micro-architecture measures (excluding bone volume fraction) had LSC values that were >17% (range: 17.4-19.0%; Table 3).

*Monitoring time interval (MTI)*

At the distal radius, all area and density measures exhibited MTIs >3.7 years (Table 3). MTIs for density measures ranged from 3.9 years (total density) to 29.5 years (inner trabecular density) (Table 3). MTIs for micro-architectural measures were ~2 years for trabecular number (Tb.N), thickness (Tb.Th), separation (Tb.Sp) and heterogeneity (Tb.SpSD) (Table 3). The MTI for distal radius cortical thickness was 4.4 years.

At the distal tibia, all area measures exhibited MTIs of ~1 year (Table 3). MTIs for density measures ranged from 0.5 years (cortical density) to >7.8 years (all trabecular density variables) (Table 3). MTIs for micro-architectural measures were >6 years for trabecular number (Tb.N), thickness (Tb.Th), separation (Tb.Sp) and heterogeneity (Tb.SpSD) (Table 3). The MTI for distal tibia cortical thickness was 1.3 years.

## Discussion

The first objective of our study was to define the LSC using short-term precision data in postmenopausal women. These are the first reported LSCs using HR-pQCT measurements for postmenopausal women derived from short-term precision data with adequate degrees of freedom[8]. Generally, bone area and density measures, as well as bone volume fraction, tended to have lower LSCs (i.e., <6.0%) when compared to micro-architectural measures (LSCs >8.0%).

The second objective of our study was to define the MTI required to observe true change in bone properties in postmenopausal women using HR-pQCT. To our knowledge, these are the first MTIs for HR-pQCT derived bone properties. Obtained MTIs suggest that: a) changes in distal radius trabecular bone micro-architecture can be measured within ~2 years, and b) changes in distal tibial cortical area, density and thickness, as well as trabecular area, can be measured within ~1 year. Conversely, measuring change of distal radius cortical bone properties and distal tibia trabecular micro-architectural prop-

| | | Mean of Both Measures ± SD | Median Annual Percent Change (%) | LSC (%)† | MTI (Years) |
|---|---|---|---|---|---|
| **Radius (n=31)** | | | | | |
| **Area** | | | | | |
| Cortical | ($mm^2$) | 38.7 ± 13.3 | -1.1 | 8.1 | 7.4 |
| Trabecular | ($mm^2$) | 239.2 ± 46.0 | 0.3 | 1.1 | 3.7 |
| **Density** | | | | | |
| Total | (mg HA/$cm^3$) | 248.7 ± 55.1 | -1.0 | 3.9 | 3.9 |
| Cortical | (mg HA/$cm^3$) | 771.6 ± 84.2 | -0.5 | 3.1 | 6.2 |
| Trabecular | (mg HA/$cm^3$) | 134.1 ± 44.4 | -0.2 | 3.4 | 17.0 |
| *Meta* | (mg HA/$cm^3$) | 188.8 ± 39.4 | -0.6 | 4.5 | 7.5 |
| *Inn* | (mg HA/$cm^3$) | 96.2 ± 49.8 | -0.2 | 5.9 | 29.5 |
| **Micro-architecture** | | | | | |
| Ct.Th. | (μm) | 533.6 ± 188.1 | -2.0 | 8.7 | 4.4 |
| BV/TV | (%) | 11.2 ± 3.7 | 0.0 | 3.4 | ∞ |
| Tb.N | (1/mm) | 1.8 ± 0.5 | -8.3 | 16.8 | 2.0 |
| Tb.Th | (μm) | 63.6 ± 10.1 | 6.8 | 15.1 | 2.2 |
| Tb.Sp | (μm) | 598.5 ± 397.0 | 9.0 | 17.1 | 1.9 |
| Tb.SpSD | (μm) | 361.9 ± 352.8 | 10.5 | 18.2 | 1.7 |
| **Tibia (n=32)** | | | | | |
| **Area** | | | | | |
| Cortical | ($mm^2$) | 78.3 ± 27.5 | -3.6 | 3.1 | 0.9 |
| Trabecular | ($mm^2$) | 644.7 ± 100.9 | 0.3 | 0.3 | 1.0 |
| **Density** | | | | | |
| Total | (mg HA/$cm^3$) | 236.9 ± 52.7 | -1.4 | 2.5 | 1.8 |
| Cortical | (mg HA/$cm^3$) | 750.7 ± 72.3 | -1.7 | 0.8 | 0.5 |
| Trabecular | (mg HA/$cm^3$) | 158.8 ± 39.0 | -0.1 | 3.6 | 36.0 |
| Meta | (mg HA/$cm^3$) | 265.1 ± 32.5 | -0.4 | 3.1 | 7.8 |
| Inn | (mg HA/$cm^3$) | 110.4 ± 45.0 | 0.1 | 5.3 | 53.0 |
| **Micro-architecture** | | | | | |
| Ct.Th. | (μm) | 733.9 ± 264.5 | -3.1 | 3.9 | 1.3 |
| BV/TV | (%) | 13.3 ± 3.3 | 0.0 | 3.6 | ∞ |
| Tb.N | (1/mm) | 1.8 ± 0.4 | 2.0 | 18.8 | 9.4 |
| Tb.Th | (μm) | 76.8 ± 15.3 | -2.9 | 17.4 | 6.0 |
| Tb.Sp | (μm) | 544.1 ± 251.6 | -2.1 | 19.0 | 9.0 |
| Tb.SpSD | (μm) | 342.7 ± 437.5 | -1.5 | 17.4 | 11.6 |

† *Precision errors ($CV\%_{RMS}$) are published in Kawalilak et al (2014)[8].*

**Table 3.** Mean±SD of combined baseline and follow-up measures, median annual percent change, Least Significant Change (LSC; *2.77*$CV\%_{RMS}$*), and the Monitoring Time Interval (MTI; *LSC/median change*) for the bone outcomes at the distal radius and distal tibia.

erties require longer monitoring times in postmenopausal women (>6 years).

Bone properties with short MTIs had either low precision errors (consequently low LSC) and/or large median annual changes; the opposite seemed to explain long MTIs. For instance, our precision error (expressed as $CV\%_{RMS}$) for trabecular area at the radius was a low 0.4%[8], and though the median change was also low at 0.3% per year, the resulting MTI was 3.7 years. Alternatively, the MTIs for micro-architectural measures at the distal radius exhibited smaller MTIs of ~2 years for trabecular number (Tb.N), thickness (Tb.Th), separation (Tb.Sp) and heterogeneity (Tb.SpSD). These short MTIs may be explained by the observed median annual changes ranging from -8 to 11%, despite of 4-7% precision error in the same outcomes[8]. Longer MTIs (especially for trabecular density and bone volume fraction) appeared to reflect a low (<1%) annual percent change observed in this cohort of older postmenopausal women. For example, bone volume fraction, which had an infinite MTI, was due to near zero median annual percent change. The longer MTIs may also be due to the image processing algorithms used with HR-pQCT to register (match) repeated scans, as well as scan quality. HR-pQCT uses area measures to matches image slices acquired at different time points. With this approach, images that have larger common region between measurement times will have more accurate representation of the true change because of the reduced influence of error (e.g., unequal slice comparison). Similarly, images that are graded as better quality will also have a more accurate representation of true change due to the reduced influence of movement artefacts and associated errors. Impor-

tantly, when compared to the distal radius, the distal tibia scans tended to be more easily landmarked resulting in more shared common region between baseline and follow-up images (radius common region mean: 91±7%; tibia common region mean: 96±2%) and had higher scan quality (radius scan quality grades: 1-3; tibia scan quality grades: 1-2) — likely explaining shorter MTIs for distal tibia outcomes.

This study has strengths and limitations that warrant some consideration. Study strengths pertain to participants pool from a population-based cohort of community-dwelling postmenopausal women[20]. Given the proportionally similar osteopenia and osteoporosis bone health status within our sample relative to postmenopausal women in North America, Europe, Australia, and Japan[29], we anticipate that the observed bone changes and MTIs can be generalized to postmenopausal women of similar ages in these regions. Further, both LSC and median annual percent changes were derived from the same sample by the same operator using the same scanner, thereby minimizing measurement variability and resulting in accurate time interval predictions. With regards to study limitations, our findings were restricted to the monitoring of bone changes in a small sample of postmenopausal women over 1 year. Multiple measurement years in a larger sample may provide a more representative estimates of the annual rates of skeletal changes and associated MTIs[17]. Further, skeletal changes may vary according to the cohort's age, ethnicity, disease status, and sex; therefore, monitoring disease progression and skeletal changes associated with intervention will likely require population-specific MTIs[17].

The results of this HR-pQCT study suggest that, for the distal radius, MTIs of ~2 years duration are required in order to have skeletal changes exceeding the LSC for micro-architectural parameters (trabecular number, thickness, separation and heterogeneity). At the distal tibia, MTIs of ~1 year duration are required in order to have skeletal changes exceeding the LSC for cortical area, density and thickness, as well as trabecular area. HR-pQCT derived MTIs warrant consideration when designing and interpreting prospective studies and interventions in postmenopausal women.

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