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Abstract

Objective: Peripheral quantitative computed tomography (pQCT) has been increasingly used in stroke research. The correlations between tibial bone measurements by pQCT and hip areal bone mineral density (aBMD) measurements by dual-energy x-ray absorptiometry (DXA) (gold standard for diagnosing osteoporosis) in chronic stroke patients were examined in this study. If the correlations were strong, there may be potential for further pursuit of clinical use of pQCT.

Methods: Seventy-four chronic stroke patients who are household ambulators (22 women, 52 men; ≥6 months after onset) underwent pQCT scanning of the tibial distal epiphysis (4% site) and diaphysis (66% site) and DXA hip scans on both sides. Pearson's correlation coefficients were used to investigate the correlations between the pQCT-derived variables and the DXA-derived total hip and femoral neck aBMD.

Results: All pQCT tibial variables, except the total area, were significantly associated with total hip and femoral neck aBMD. Cortical bone mineral content (66% site) was the only variable that yielded good to excellent correlations with total hip and femoral neck aBMD on both sides (r=0.750-0.833).

Conclusions: Based on the good correlations between tibial pQCT variables and hip aBMD, the clinical use of pQCT in assessing bone health in this population should be further pursued.

Introduction

People with stroke have compromised bone health [1], which contributes to a significantly higher rate of fragility fractures than that in their able-bodied counterparts [2]. A precise tool for evaluating patients' bone health status after a stroke is therefore essential. Dual-energy x-ray absorptiometry (DXA), which measures the areal bone mineral density (aBMD), is considered to be the gold standard for the diagnosis of osteoporosis [3]. The aBMD of the hip region can significantly predict hip fracture in older men and women [4–8]; however, the aBMD measured by DXA is prone to systematic inaccuracies due to its planar nature [9]. In addition, DXA cannot provide information on the cross-sectional geometric properties and cannot perform cortical and trabecular bone analysis separately.

Studying the geometric properties of bone is important because it has been found that cross-sectional geometry and bone mass distribution contribute significantly to bone strength [10]. For example, in a study using proximal femurs excised from 28 human cadavers (aged 54 - 103 years at death), the relationship between bone geometric variables and bone failure load as determined by mechanical tests was investigated. It was found that the bone geometry of the proximal femur alone, as assessed by quantitative computed tomography (QCT), accounts for 43% of the variance in the femoral failure load [11]. Combining both densitometric and geometric variables measured by QCT explained even a higher proportion of the variance (76%) of femoral failure load variance, compared with only 69% when DXA-derived aBMD measurements were used [11]. In another in-vitro study involving 31 human proximal femur specimens (age: 50-89 at death), bone geometric parameters measured by QCT and aBMD combined to account for 90% of variance in maximal compressive strength as determined by a side-impact biomechanical test [12]. In contrast, the prediction model using aBMD alone only accounted for 78% of variance in the maximal compressive strength.

In human clinical studies, the quantitative computed tomography (QCT) technology has been shown to significantly predict fractures in young girls and older adults [13, 14]. For example, in the Hertfordshire Cohort Study, Dennison et al.[13] showed that in a sample of 384 older adults aged 60-75 years, the cortical area (a geometric variable) of the mid-shaft tibia was independently associated with incident fracture over a 6-year follow-up period, after adjusting for the effects of potential confounders (e.g., age, body mass index, physical activity, etc.). There is also evidence that peripheral bone measurements using QCT can confer additional information complementary to that of DXA. Sheu et al.[15] studied the relationship between QCT measurements of the tibia and nonvertebral fracture risk in a sample of 1143 men aged over 69 years. It was found that every standard deviation reduction in 8 out of 11 QCT parameters measured at the tibia was significantly associated with increased risk of nonvertebral fractures, after adjusting for the effects of other factors including femoral neck aBMD measured by DXA, indicating that QCT measurements further improved the ability to identify those at high risk of fractures. In summary, the bone parameters generated by the QCT technology can provide valuable information on the integrity of bone tissue that cannot be assessed by DXA, which might further increase the accuracy of fracture prediction.

Although central QCT devices have been used to scan central bone sites such as the hip region where post-stroke fractures are more common [2], it has limited applicability due to the high dose of radiation involved (effective radiation dose: 2.5-3.0mSv) [16]. Peripheral QCT (pQCT), which is used for measuring peripheral skeletal sites (e.g., tibia, radius), involves a very low level of radiation (effective radiation dose: <0.01mSv) [16] and is hence more commonly used in the investigation of bone health [17–26]. In clinical research studies,

the most common site used for pQCT scanning in the leg is the tibia [2, 27, 28]. pQCT has also been used in intervention studies to assess the effects of exercise training on the bone health of individuals with stroke, and some favorable changes have been reported in the tibial bone parameters including the trabecular bone mineral content at the distal tibial epiphysis and cortical thickness at the tibial diaphysis [22, 23]. The hip region, rather than the tibia, is the clinical site of interest for fragility fractures, and the clinical relevance of assessment of the tibia with pQCT as a surrogate marker in this population requires further investigation.

Research findings in healthy individuals have indicated that the tibial bone variables measured by pQCT correlate well with the hip bone variables assessed by DXA [29, 30]. For example, the total volumetric bone mineral density measured at the distal tibial epiphysis had moderate to good correlation with the total hip aBMD premenopausal women ($r = 0.70$) [29]. The distal tibial trabecular volumetric bone mineral density was also significantly related to the femoral neck aBMD in adolescent girls ($r = 0.71$) [30]. However, these studies performed pQCT scanning at a distal tibial site where trabecular bone is dominant. The relationship between the pQCT parameters measured at cortical bone sites and the hip bone status is largely unknown. However, cortical bone geometry may be an important contributing factor underlying fragility fracture [31]. The available evidence in adult women also shows that 80% of the bone at the proximal femur is cortical [32]. It can thus be postulated that the integrity of the cortical bone, rather than that of the trabecular bone at the tibia, could be an even better surrogate measure of the hip aBMD.

The objective of this cross-sectional correlation study was to examine and compare the degree of association of pQCT-derived variables at both the cortical and trabecular bone sites of the tibia and the DXA-derived hip aBMD (gold standard for clinical bone health

assessment and diagnosing osteoporosis) in people with chronic stroke. If the correlations were strong, there may be potential for further pursuit of clinical use of pQCT. We hypothesized that the hip aBMD would have good correlations with pQCT geometric and densitomeric parameters at the tibia. In addition, we also hypothesized that hip aBMD would have stronger correlations with the pQCT parameters at the cortical bone site than those at the trabecular bone site of the tibia.

Methods

Subjects

The subjects of our study were recruited on a voluntary basis from stroke self-help groups in the community (i.e., convenience sampling). Potential participants had to fulfill the following inclusion criteria: a diagnosis of stroke with an onset at least 6 months earlier (i.e., chronic stroke) based on patient interviews ; aged 18 years or more; medically stable; and an Abbreviated Mental Test score of 6 or higher to ensure that the individuals had adequate cognitive ability to provide consent to the study and also comprehend the verbal commands during the experimental procedures (e.g., assessment of motor impairment, etc.) [33]. The exclusion criteria were recurrent stroke; neurological disorders in addition to stroke (e.g., spinal cord injury); serious musculoskeletal conditions (e.g., rheumatoid arthritis); a metal implant or recent fracture in the leg (onset within one year); medications prescribed for the treatment of osteoporosis before or after the stroke; and other serious illnesses (e.g., cancer). The study was approved by the Human Research Ethics Review Committee of the University and informed written consent was obtained. The experiment was conducted in accordance with the Declaration of Helsinki.

Assessment

In the first assessment session, which took place at a neurorehabilitation research laboratory in the University, the demographic data, including age, sex, type of stroke, time since the stroke, medical history, and current medications were collected during the patient interviews. The Chedoke-McMaster Stroke Assessment was used to evaluate the motor recovery of the leg and foot regions on the contralesional side [34]. Each body part was rated on a 7-point ordinal scale (range: 1- 7), with higher scores denoting better motor function. The scores for the leg and the foot were summed to yield a composite motor score (range: 2-14). This session was typically 1 hour in duration. The bone imaging took place in the Centre for Osteoporosis Care and Control typically within one week of the first assessment session. The whole bone scanning session normally lasted about 45 minutes.

Dual-energy X-ray absorptiometry (DXA) measurements: Hip areal bone mineral density (aBMD)

DXA (Hologic Inc, Bedford, Massachusetts) was used to scan the hip on each side. The total hip aBMD and femoral neck (in g/cm^2), rather than the trochanteric or intertorchanteric regions, were used because only the former measures are used for diagnosis of osteoporosis clinically [35] and more commonly used for prediction of fractures [4–8]. All imaging procedures were performed by the same technician, who had more than 10 years of relevant experience. Regarding the precision of the DXA scanner, the coefficients of variation for the total hip aBMD and the femoral neck aBMD were 1.30% and 1.52%, respectively. These values were determined measuring thirty healthy subjects twice, with repositioning after the first scan. The coefficient of variation values obtained are comparable to those reported in previous studies that examined the precision of the DXA technique (0.67%-1.31%) [36, 37].

Peripheral quantitative computed tomography (pQCT): Bone Size, Geometry and Mechanical Properties

Peripheral quantitative computed tomography (pqCT) (XCT 3000, Stratec Medizintechnik GmbH; Pforzheim, Germany) was used to generate three-dimensional cross-sectional scans of the tibia on both the ipsilesional and contralesional sides. The anatomical reference line was placed at the cortical end plate of the distal medial edge of the tibia after a scout view was obtained. A 2.3-mm-thick scan was obtained at two different sites of the tibia: (i) the tibial distal epiphysis (primarily trabecular bone site; 4% of the total tibia length proximal to the reference line); and (ii) the tibial diaphysis (mainly cortical bone site; 66% of the total tibia length proximal to the reference line). A voxel size of 500 µm and a scan speed of 25 mm/sec were used [19, 20, 22].

All image analyses were performed according to the manufacturer's guidelines using the Stratec software (Version 6.0) that comes with the pQCT device [38]. The images of the 4% site were analyzed using CALCB Contour Mode 2 and Peel Mode 2 (density threshold, 169/400 mg/cm^3). In this analysis method, the outer contour of the bone at this site was detected using a density threshold of 169 mg/cm^3. A density threshold of 400 mg/cm^3 was used to delineate the trabecular from (sub)cortical bone. These thresholds are similar to those used in previous pQCT research studying the distal epiphysis of long bones [22, 39, 40]. The variables generated at the 4% tibial sites are total area (mm^2), total bone mineral content (mg/mm), total bone mineral density (mg/cm^3), and trabecular bone mineral density (mg/cm^3). A compressive bone strength index was also computed based on the formulae: total area × (total volumetric bone mineral density)^2. This bone strength index has been used in other studies as a surrogate of bone strength against compressive forces in the distal end of long bones [41, 42], where compressive forces are more predominant [43]. This index has been

validated in a human cadaver study, which showed that 85% of the variance in failure load measured at the tibia 4% site was accounted for by the compressive bone strength index alone [43].

Analysis of the cortical bone at the diaphyseal site was performed using CORTBD Mode 1 (density threshold, 710 mg/cm^3). With this mode of analysis, densities of 710 mg/cm^3 or greater at the 66% tibial site were considered to be cortical bone. The same threshold was used in other pQCT studies to identify cortical bone [19, 39, 40, 44, 45]. The pQCT variables generated at the 66% site were total area (mm^2), cortical bone area (mm^2), cortical bone mineral content (mg/cm), cortical volumetric bone mineral density (mg/cm^3), and cortical thickness (mm). From these geometric and densitometric variables, a polar stress–strain index (p-SSI, mm^3) was computed by pQCT as an indicator of bone strength against torsional forces in long bone shafts [19, 41, 42] using the following formula [46]:

$$\text{Polar stress strain index} = \sum \frac{[(A_z \times d_z^2)(\text{cortical bone mineral density}/ND)]}{d_{max}}$$

where *A* is the area of each pixel, d_z represents the distance between the pixel and the corresponding torsional (*z*) axis, d_{max} is the maximum distance to the centre of gravity, and ND is the normal physiological bone density (1200mg/cm^3). The polar stress-strain index was used rather than the compressive bone strength index, because the diaphysis is more subjected to torsional forces than compressive forces. In a human cadaver study, biomechanical testing also showed that the stress strain index was highly related to the failure load of the tibia, explaining 76% of the variance [43]. The coefficients of variation for the various pQCT parameters, determined by the same methods as with DXA, ranged from 0.25% to 1.70% . These values were comparable, if not better than those reported in previous studies that examined the precision of pQCT in measuring the tibia (0.9-6%) [47, 48].

Statistical analysis

Descriptive statistics were used to indicate the central tendency and dispersion of the variables of interest. The DXA and pQCT parameters on the ipsilesional and contralesional sides were compared using paired t-tests. To examine the degrees of association of the hip areal bone mineral density (aBMD) measured by DXA and the pQCT variables measured at the tibia, Pearson's product moment correlation (r) was used. A correlation value of 0.00-0.25 indicates no or little relationship; 0.25 to 0.50 a fair relationship; 0.50-0.75 a moderate to good relationship; and 0.75-1.00 a good to excellent relationship [49]. The correlation coefficients between the tibial bone variables and the total hip aBMD were then compared using a test for comparison of two non-independent correlations with a variable in common [50]. All statistical analyses were performed using Statistical Package for Social Sciences 18.0 (SPSS Inc., Chicago, Illinois). A more stringent level of significance ($p < 0.01$) was set due to the inflated probability of making a type I error associated with multiple comparisons.

Results

Seventy-four people with stroke (22 women and 52 men; mean age: 57.8 years; standard deviation: 10.7 years; range: 30-80 years) participated in this study. None of the enrolled participants dropped out and all subjects completed all required assessments. The average duration since the stroke was 5.1 years (range=0.5-18.8 years). The Chedoke McMaster motor impairment score ranged from 4 to 12 out of 14, indicating that all subjects had some degree of paresis in the contralesional lower limb. Twenty-nine subjects had left paresis, and 45 subjects had right paresis. Fifty-eight subjects were able to ambulate indoors without walking aids (table 1).

Side-to-side differences in hip areal bone mineral density (aBMD) and peripheral quantitative computed tomography (pQCT) measurements of tibia

The pooled data (means and standard deviations) the dual-energy x-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) measurements are reported in table 2. There was a significant side-to-side difference in total hip aBMD between the two sides ($p<0.001$). The side-to-side difference in femoral neck aBMD did not quite reach statistical significance ($p=0.064$). All pQCT parameters demonstrated a significant side-to-side difference at the 4% site and 66% site, except the total area ($p>0.05$).

Insert table 1 and 2 about here

Correlations between hip areal bone mineral density (aBMD) and peripheral quantitative computed tomography (pQCT) measurements of tibia

Insert table 3 about here

At the tibial epiphysis (4% site), moderate to good correlations ($r=0.50$-0.75) were found between the DXA-derived total hip / femoral neck aBMD and most of the pQCT variables measured on both sides (i.e., total bone mineral density, total bone mineral content, trabecular bone mineral density) ($p< 0.001$). The compressive bone strength index showed a good to excellent relationship with total hip aBMD ($r=0.771$-0.776, $p<0.001$), and moderate to good relationship with femoral neck aBMD on both sides ($r=0.681$-0.688, $p<0.001$). In contrast, the degree of association between total area at the tibial 4% site and the total hip /femoral neck aBMD was not significant ($r=0.145$-0.289, $p>0.01$) (table 3). The positive linear relationship between the total hip aBMD and the total bone mineral content at the tibial 4% site is illustrated in figure 1.

Insert figure 1 about here

At the tibial diaphysis (66% site), significant correlations were found between all of the pQCT variables measured and the total hip and femoral neck aBMD ($p<0.05$) (table 3). Specifically, the cortical bone mineral content demonstrated a good to excellent relationship with the total hip and femoral neck aBMD on both sides ($r=0.750$-0.833, $p<0.001$). In addition, the cortical bone area and cortical thickness also showed a good to excellent relationship with the total hip aBMD on both sides. Similar to the 4% site, among all the pQCT parameters, the total area had the weakest correlation with the total hip/femoral neck aBMD ($r=-0.290$-0.369) (i.e., fair relationship). The strong correlation between the total hip aBMD and the cortical bone mineral content of the tibial 66% site is depicted in figure 2.

Insert figure 2 about here

Among all the pQCT variables, the cortical bone mineral content measured at the 66% tibial site yielded the greatest correlation coefficients with total hip and femoral neck aBMD on both sides ($r=0.750$-0.833) (bolded values in Table 3). These correlation coefficients were then compared with other correlation coefficients shown in Table 3 to determine whether the differences were statistically significant. On the ipsilesional side, the total hip aBMD and femoral neck had significantly stronger correlations with the cortical bone mineral content at the 66% site than trabecular bone mineral density and total area at the 4% site, and cortical bone mineral density, total area and polar stress strain index at the 66% site ($p<0.01$).

On the contralesional side, the total hip aBMD was more strongly associated with the cortical bone mineral content at the 66% site than the total area at 4% site, and cortical bone mineral density total area, total area and polar stress strength index at the 66% site ($p<0.01$). On the other hand, the femoral neck aBMD was more strongly associated with the cortical bone mineral content at the 66% site than the trabecular bone mineral density and total area at the 4% site, and cortical bone mineral density and total area at the 66% site ($p<0.01$).

Discussion

The principal finding was that most of the pQCT variables measured at the tibia correlated well with the total hip aBMD, except the total area. Among all of the tibial variables, the total hip and femoral neck aBMD showed the strongest correlation with the cortical bone mineral content at the 66% site.

Side-to-side differences in bone parameters

The results showed that the total hip aBMD was significantly lower on the contralesional side than that on the ipsilesional side. The side-to-side difference in femoral neck aBMD showed a similar trend, but significance level obtained was marginal ($p=0.064$), probably due to the inadequate statistical power. Nevertheless, the overall data generated by DXA are in accord with previous reports in indicating that the hip bone density was compromised on the contralesional side [51–53].

All pQCT parameters measured at the 4% site and 66% site showed significant side-to-side differences with the exception of the total area. The contralesional side had significantly lower bone mineral content, bone mineral density, and bone strength index than the ipsilesional side. The findings may suggest loss of bone material on the intracortical and endosteal surface sof the tibia in the contralesional leg post-stroke, with relative preservation of the total area (i.e., bone size). This phenomenon was also in line with previous cross-sectional pQCT studies in stroke [20, 54].

Association between hip aBMD and tibial pQCT parameters

Our hypotheses were supported because the tibial pQCT parameters generally yielded moderate to good correlations with DXA-derived total hip /femoral neck aBMD measurements, and the cortical bone mineral content at the 66% site yielded the strongest correlations with total hip /femoral neck aBMD on both sides.

No previous study has examined the relationship between tibial pQCT parameters measured at a cortical bone site and hip aBMD. Previous studies in healthy subjects have revealed a significant correlation between DXA-derived hip aBMD and pQCT parameters measured at the distal tibial epiphysis, which was mainly a trabecular bone site [29, 30]. In comparison, the association established between the total bone mineral density measured at the distal tibial epiphysis and the total hip / femoral neck aBMD in our study (r=0.592-0.750) was similar to that reported in premenopausal women (r = 0.70) [29] and in healthy adolescent girls (r = 0.71) (i.e., moderate to good relationship) [30].

The total hip /femoral neck aBMD yielded good to excellent correlations with the cortical bone parameters at the 66% site, compared with only moderate to good correlations with the total bone and trabeuclar bone parameters at the 4% site (table 3). A study in adult women showed that the majority of the bone tissue in the proximal femur is cortical [32]. This factor may partly explain why the condition of the tibial cortical bone, rather than the trabecular bone, correlates better with the hip aBMD in our sample, although we do not know the proportion of cortical bone tissue in the proximal femur post-stroke.

Among the various pQCT cortical bone variables, the cortical bone mineral content at the 66% site (r=0.750-0.833), when compared with the cortical bone mineral density at the same site (r=0.463-0.567), showed a significantly higher correlation with the total hip /femoral

neck aBMD ($p<0.001$). With ageing, cortical bone loss occurs at both intracortical and endocortical surfaces, which cause cortical porosity and cortical thinning, respectively. About half of the cortical bone loss at peripheral sites in older adults occurs due to remodeling of the cortex adjacent to the marrow, leading to actual and apparent cortical thinning [32]. A recent cross-sectional study of people with stroke and the current study showed that both the cortical volumetric bone mineral density and the cortical area values measured at the 66% site of the tibia were substantially lower on the contralesional side than those on the ipsilesional side [54]. These findings suggested that both cortical thinning (through endosteal resorption) and increasing cortical porosity (through intracortical bone loss) may accelerate on the contralesional side after a stroke. However, only cortical porosity, but not the loss of cortical bone through cortical thinning, is a factor in the computation of the cortical bone mineral density. In contrast, both intracortical and endocortical bone loss are considered in the calculation of both the cortical bone mineral content of the tibia and the aBMD of the hip, which explains the stronger correlations between these two variables. Our results thus showed that among the pQCT variables, the cortical bone mineral content at the tibia would be a reasonable surrogate to indicate the condition of the hip bone, although it can be argued that other pQCT variables, such as cortical area and cortical thickness at the 66% site, may also be useful, since their correlations with the hip aBMD was not significantly different from those between the cortical bone mineral content and total hip/femoral neck aBMD, albeit slightly lower in magnitude.

It is interesting that the total area both at the 4% and 66% site demonstrated the weakest correlations with total hip/femoral neck aBMD in both legs. As shown in this study and previous pQCT reports in chronic stroke [20, 54], the total area was the only variable that showed no significant side-to-side difference, indicating that decline in bone mass and

density in the tibia post-stroke was not accompanied by changes in the total area. In other words, the tibial cross-sectional total area was not a good indicator of post-stroke bone health status. This may explain why the total area had relatively low correlations with total hip/femoral neck aBMD.

While we found good correlation of cortical bone parameters at the tibia and hip areal bone mineral density (aBMD) measurements in people with chronic stroke, the current study could not determine whether these tibial pQCT measurements are useful in predicting hip fracture risk, which will require further study. Previous studies have provided some evidence of the potential usefulness of pQCT measurements of cortical bone at peripheral sites in the prediction of fractures in more central sites in various populations [13, 15, 31, 55]. For example, the thinner cortical bone shell of the tibia was significantly associated with previous prevalent fractures in young adult men [31]. In asthmatic patients who are given oral corticosteroids, a lower cortical volumetric bone mineral density and stress-strain index can significantly predict vertebral fractures [55]. Sheu et al.[15] showed that those in the lowest quartile of polar stress strain index at the 66% tibial site had 10-fold greater risk of developing fracture (majority were hip fractures). However, no studies have incorporated the bone parameters of a peripheral site as potential predictive variables of hip fractures in stroke. This has limited the clinical use of pQCT in stroke but this important field will need further investigations.

In summary, pQCT study is not ready for clinical use yet, as we need to have more studies on the relationship between pQCT and fracture risk. Nevertheless, this study, by examining the correlations between pQCT and DXA measurements, is the first step in validating the pQCT

measurements and exploring of the possibility of future clinical use of pQCT in stroke patients.

Limitations

This study has several limitations. Firstly, there may be sampling bias. While there was a wide range of values for a number of variables (e.g., age, post-stroke duration, motor impairment score, number of co-morbid conditions, etc.), which may increase the generalizability, sampling bias may still exist. All subjects in this study were older than 30 years of age, able to ambulate independently in an indoor environment, and majority of them (91%) engaged in regular exercise (Table 1). All subjects sustained some degree of motor impairment in the lower limb (Chedoke McMaster Stroke Assessment lower limb impairment score <14) but none was considered severe (Chedoke McMaster Stroke Assessment lower limb impairment score <4). In addition, none of the individuals had significant cognitive deficits (Abbreviated Mental score <6), or were taking Vitamin D. The results of this study can only be generalized to other stroke patients who share similar features. Therefore, the results may not apply to those who are younger than 30 years of age, unable to ambulate in the home environment, physically inactive, taking vitamin D, or sustaining cognitive deficits. The result are not also not generalizable to those who had either no paresis or severe paresis in the contralesional lower limb.

Secondly, there are limitations related to the study design. This was a cross-sectional correlational study only. This was not a prospective study with a follow-up period in which pQCT parameters are used to predict and/or confirm hip fracture risk. In addition, while significant differences in hip aBMD and pQCT parameters are identified in this study, they could be contributed by post-stroke changes in the contralesional side or ipsilesional side or

both sides. A prospective study is required to examine the real changes in bone parameters on both sides over time.

Thirdly, there are limitations related to the pQCT technology. Cortical bone cannot be separately assessed at the 4% site of the tibia because of a possible partial-volume effect [46, 56]. The partial volume effect may occur when a single volumetric voxel contains heterogeneous material (e.g., bone material and soft tissue). In regions where the cortical bone shell is thin (< 2mm), the voxels may only be partly filled by bone material and partly filled by soft tissue. This would result in falsely lower density values because a voxel's density value is the mean density of all the tissues within it [46, 56]. A pQCT device with higher resolution is required to more accurately determine the cortical bone variables at the tibial 4% site. The resolution of our pQCT device also could not give us information on bone microstructure such as the number, spacing and thickness of trabecula. The pQCT technology may not be readily available in the average community-based care settings as the device is quite expensive. Proper training is also required so that the quality bone images can be acquired and analyzed consistently.

Fourthly, only 74 people with stroke were studied, which cannot be considered a large sample size. The lack of significant side-to-side difference in femoral neck aBMD may be related to the reduced statistical power associated with the inadequate sample size. For example, based on our results on femoral neck aBMD presented in Table 2 (standardized effect size =0.083), post-hoc power analysis indicated that a sample of 74 subjects only yielded a statistical power of 0.11. Besides, a much larger sample size is also required for determining the relationship between pQCT parameters and osteoporosis or fracture risk.

Finally, this was not an intervention study and could not address the effects of treatment on hip aBMD and tibial pQCT variables. A non-randomized controlled study showed that 6 months of treadmill walking exercise induced a significant gain in cortical thickness at the tibial 66% site, but not the total hip aBMD on the contralesional side among individuals with chronic stroke [23]. In contrast, Pang et al.[22] showed in a randomized controlled trial in chronic stroke patients that 5 months of exercise training led to favorable outcome in femoral neck aBMD, accompanied by positive effects on tibial trabecular bone mineral content (4% site), and cortical thickness at the tibial diaphysis (50% site) on the contralesional side [22, 57]. Unfortunately, the pQCT parameters and skeletal site measured in Pang et al.[22] were not exactly the same as in this study, and so a direct comparison cannot be made. Although our study showed that the total hip / femoral neck aBMD yielded moderate to good correlations with many pQCT variables, the available intervention studies, however, indicated that the hip aBMD and pQCT parameters may not always show similar responses to the same intervention.

Future research directions

The results of this study as well as the limitations discussed above provide the basis for future investigations in this area. Firstly, it is important to study the association between the pQCT parameters and the fracture risk. This will necessitate a prospective study with a large sample size to examine whether the bone variables derived from pQCT have any added value in predicting fractures in people after stroke. Secondly, observational research on tibial pQCT parameters in people with stroke has so far been cross-sectional [19, 20, 51]. No study has examined the changes in tibial pQCT parameters over time after stroke. A prospective study with repeated pQCT measurements will provide insights into the how bone densitometric and geometric properties alter on the contralesional and ipsilesional sides post-stroke. Thirdly, to

minimize the partial volume effect and to more accurately measure the cortical bone parameters and bone microstructure at the distal end of long bones, high resolution pQCT can be used in future studies [58]. Thirdly, to improve the representativeness of the sample and generalizability of the results, future studies should involve a large sample size, so that subjects with different characteristics are included. In addition, apart from the hip, the wrist is the second most common site of fracture in people after stroke [2]. It would be interesting to examine the relationship between the DXA-derived aBMD of the forearm and pQCT parameters of the epiphysis and diaphysis of the radius. Finally, intervention studies should be conducted to determine how the hip aBMD and the correlated pQCT variables respond to the same treatment in people with stroke.

Conclusion

In people with chronic stroke, the tibial bone variables measured by pQCT, except for the total area, correlated well with the hip aBMD measured by DXA. In particular, the cortical bone mineral content at the 66% site seemed to be the best option because its correlations with the total hip/femoral neck aBMD were the strongest. Further study with larger sample sizes will be needed to further establish the validity of the use of pQCT measurements of the tibia in the diagnosis of osteoporosis and prediction of hip fracture risk.

Declaration of interest

F.M.H. Lam was granted a full-time research studentship by the Hong Kong Polytechnic University.

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Figure Captions

Fig. 1 Correlations between total bone mineral content (BMC) measured at the tibial 4% site and total hip aBMD

The correlations between total BMC measured at the tibial 4% site and total hip aBMD on the ipsilesional side (r=0.746) (a) and contralesional side (r=0.731) (b) are shown. Each dot represents the data for a single subject.

Fig. 2 Correlations between cortical bone mineral content (BMC) measured at the tibial 66% site and total hip aBMD

The correlations between cortical BMC measured at tibial 66% site and total hip aBMD on the ipsilesional side (r=0.833) (a) and contralesional side (r=0.797) (b) are illustrated.