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BONE MICROARCHITECTURE CHANGES IN PERI- AND POST-MENOPAUSAL WOMEN: CORTICAL POROSITY IS A MARKER FOR ACCELERATED CHANGE DURING MENOPAUSE

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INTRODUCTION

Menopause occurs following ovarian function changes, resulting in the cessation of the menstrual period[1] at an average 51 years of age[2]. Bone density changes during menopause transition have primarily been characterized by dual x-ray absorptiometry (DXA)[3–8], the current clinical standard for assessing BMD[9]. However, DXA is a 2D estimate of density, and cannot quantify bone microarchitecture, which influences bone strength[10].

High resolution peripheral quantitative computed tomography (HR-pQCT) can provide more detailed information on bone changes during menopause. Previous HR-pQCT studies comparing pre- and post-menopause women[11,12] have shown decreasing bone density accompanied by decreasing cortical thickness, trabecular number, and trabecular thickness (Ct.Th, Tb.N, Tb.Th)[11] and increasing cortical porosity (Ct.Po)[12]. However, this data is cross sectional and cannot account for secular differences. Longitudinal HR-pQCT studies avoid these problems by monitoring intra-individual changes.

The purpose of this study is to explore rates of change in bone density and microarchitecture parameters in peri-menopause and post-menopause women.

MATERIALS AND METHODS

Participants

Participants (n=91) were selected from the Calgary cohort (n > 450 at follow-up) participating in the Canadian Multicenter Osteoporosis Study (CaMos) in Calgary, a nation wide prospective population based study[13,14]. Participants were healthy individuals[10] who did not have medical conditions and were not taking medications that affect bone metabolism[15]. Based on menopause information provided at baseline[10], Caucasian women were selected for two groups, peri-menopause (n=26) and post-menopause (n=65). All participants were consented prior to participation in the CaMos study and protocols were approved by the University of Calgary Conjoint Health Research Ethics Board.

Clinical Assessments and Questionnaire

An interview administered questionnaire from the CaMos Study provided information on the subject's sociodemographics and medical information. This includes fracture history, family history, dietary information, and lifestyle habits. Weight and height were recorded to the nearest 0.1kg and 0.1cm following standard protocols[10]. Menopause stage was assessed using a scale of 1 to 5. Women in stage 1 have no signs of starting menopause. Women in stages 2-4, included in the peri-menopause group, are currently undergoing menopause: beginning, in the middle, or near the end of menopause, respectively. Stage 5 women, included in the post-menopause group, have completed the midlife process.

High-resolution peripheral quantitative computed tomography (HR-pQCT)

HR-pQCT (XtremeCT, Scanco Medical, Brüttisellen, Switzerland) scanning was

performed at baseline and follow-up, following our previously published method[10]. A scan at 82 μm nominal isotropic resolution was taken at a standard location below the references line, determined using a scout image. Each scan consists of a 9.02mm region, performed using a standard human in vivo protocol (60 kVp, 1,000μA, 100ms integration time). Patient's left tibia was scanned, except if the participant had a previous fracture, the right was scanned[10].

All scans were performed by trained technicians. Scans were monitored for motion, and those with significant motion were not used in analysis[16]. A standard morphological analysis was executed following the manufacturer's method to determine primary morphological parameters[11]. This includes total and trabecular volumetric bone mineral density (Tt.BMD and Tb.BMD; mg HA/cm^3), trabecular number (Tb.N; mm^{-1}), separation (Tb.Sp; mm) and thickness, (Tb.Th; mm)[11], described in detail elsewhere[10]. Cortical parameters were determined using an automated segmentation method to distinguish the periosteal and endosteal cortex of the cortical shell[12]. This includes total cross sectional area (Tt.Ar; mm^2), cortical volumetric BMD (Ct.BMD; mg HA/cm^3), cortical thickness (Ct.Th; mm)[17,18] , and cortical porosity (Ct.Po; %)[15].

Statistical Analysis

R (version 0.99.489) was used to perform paired and unpaired t-tests to compare changes within groups and between groups, respectively. Results are reported as mean values with a 95% confidence interval. A p-value <0.05 was considered to be significant.

RESULTS

Peri-menopause women were younger (p<0.001) than post-menopause women and less likely to be taking osteoporosis (OP) medications (p=0.03, medication use was captured throughout the study). Calcium intake (diet and supplements), vitamin D, fracture history, and hysterectomy differences were not significant between groups (Table 1). Height, weight, and BMI did not change significantly for either group through the study.

Five tibia scans were removed, three for motion, and two for scan abnormalities. On average, time between baseline and follow-up was 5.8 years (SD 0.67) and 5.4 years (SD 0.39) for peri- and post-menopause women.

Table 1: HR-pQCT parameters at baseline

	Peri- N =26 Mean, 95% CI	**Post- N = 65 Mean, 95% CI**	**P Value***
Age (yrs)	55.1 (52.9, 57.3)	62.5 (61.0, 64.0)	<0.001
Height (cm)	161.68 (159.5, 163.8)	160.4 (158.6, 162.1)	0.415
Weight (kg)	68.9 (62.6, 75.2)	74.7 (70.7, 78.7)	0.125
Body Mass Index (kg/m^2)	26.3 (24.0, 28.6)	29.2 (27.3, 31.1)	0.088
Calcium Diet (mg)	728.5 (537.6, 919.4)	729.9 (618.1, 841.8)	0.989
Calcium Supplement (mg)	448.1 (257.7, 638.5)	604.3 (458.2, 750.5)	0.239
Vitamin D (IU)	474.4 (267.6, 681.2)	532.3 (404.4, 660.2)	0.633
Fracture History [a]	6/26	23/65	0.255
Hysterectomy [a]	7/26	22/65	0.924
OP Medication [a]	4/26	26/65	0.031

*T-test comparing groups. [a] Chi squared comparison.

Bone microarchitecture differences between groups were observed at baseline (Table 2), with significantly higher Tt.BMD and Ct.BMD and lower Ct.Po in peri-menopause women.

Table 2: HR-pQCT parameters at baseline

	Peri- N = 24 Mean, 95% CI	**Post- N = 62 Mean, 95% CI**	**P Value***
Tt.BMD	299.7 (278.4, 321.0)	270.3 (257.8, 282.8)	0.016
Ct.BMD	925.5 (897.9, 953.0)	861.9 (848.6, 875.3)	<0.001
Tb.BMD	170.0 (155.9, 184.1)	162.3 (154.0, 170.5)	0.327
Tb.N	1.61 (1.53, 1.68)	1.53 (1.47, 1.59)	0.160
Tb.Th	0.1 (0.1, 0.1)	0.09 (0.09, 0.09)	0.722
Tb.Sp	0.5 (0.5, 0.6)	0.58 (0.56, 0.61)	0.089
Ct.Th	1.3 (1.2, 1.4)	1.17 (1.11, 1.23)	0.116
Ct.Po	5.3 (4.1, 6.5)	7.72 (7.13, 8.31)	<0.001
Tt.Ar	616.1 (565.2, 666.9)	637.5 (613.0, 661.9)	0.392
Ct.Ar	105.0 (99.3, 110.8)	98.6 (94.0, 103.1)	0.112
Tb.Ar	511.1 (459.2, 562.9)	539.5 (513.3, 565.7)	0.280

* = T-test (unpaired) comparing baseline between groups

Within each group there were significant changes between baseline and follow-up scans. Both groups experienced significant decreases in Tt.BMD, Ct.BMD, and Ct.Th while Ct.Po, Tt.Ar, and Tb.Ar increased.

Comparing rates of change between groups (Table 3), there is a significant increase in rate of Ct.Po change in peri-menopause women and increased rate of Tt.Ar change in post-menopause women.

Table 3: Percent change of HR-pQCT and DXA parameters between baseline and follow-up

	Peri- N= 26 Mean Percent Change, 95% CI	**Post- N= 64 Mean Percent Change, 95% CI**	**P Value ****
Tt.BMD	-0.514 (-0.741, -0.288) [a]	-0.534 (-0.727, -0.341) [a]	0.910
Ct.BMD	-0.713 (-0.948, -0.478) [a]	-0.645 (-0.797, -0.494) [a]	0.629
Tb.BMD	0.086 (-0.247, 0.419)	-0.145 (-0.390, 0.100)	0.298
Tb.N	-0.118 (-0.753, 0.517)	0.046 (-0.451, 0.544)	0.712
Tb.Th	0.314 (-0.361, 0.989)	-0.003 (-0.540, 0.534)	0.509
Tb.Sp	0.229 (-0.429, 0.887)	0.174 (-0.322, 0.669)	0.901
Ct.Th	-0.344 (-0.660, -0.029) [b]	-0.335 (-0.662, -0.007) [b]	0.973
Ct.Po	9.023 (5.917, 12.129) [a]	6.324 (5.137, 7.511) [a]	0.046
Tt.Ar	0.062 (0.032, 0.093)[a]	0.126 (0.096, 0.157)[a]	0.017
Ct.Ar	-0.280 (-0.621, 0.060)	-0.247 (-0.614, 0.120)	0.915
Tb.Ar	0.156 (0.102, 0.209) [a]	0.164 (0.097, 0.230) [a]	0.889

** = T-test comparing percent change between groups. Superscript letters identify significant difference between baseline and follow-up (paired t-test); [a]: $p<0.010$; [b]: $p<0.050$.

DISCUSSION

This longitudinal study provides insight into changes to bone density and microarchitecture during menopause. Significant changes to bone microarchitecture parameters were observed in both peri-menopause and post-menopause women between baseline and follow-up, with loss of BMD, decreasing Ct.Th, and increasing Ct.Po and Tt.Ar as well as significant differences in rates of change of bone microarchitecture parameters. Ct.Po increased at a higher rate in peri-menopause women and Tt.Ar increased at a higher rate in post-menopause women.

Increased rate of change in Ct.Po observed in peri-menopausal women is consistent with data showing increased bone remodeling during menopause[19]. As estrogen deficiency is thought to be involved in cortical bone loss[20] this may be a factor in causing increasing cortical bone loss during menopause.

Rate of bone change during menopause has been investigated with quantitative computed tomography (QCT). This study observed significant changes in trabecular bone[21], whereas we observed greater changes in cortical bone. This different finding could be a result of using a different technology, with HR-pQCT having the ability to measure microarchitecture details not possible by QCT, such as Ct.Po.

Using HR-pQCT our trends in rates of change following menopause are consistent with results from Kawalik et al, however our rates of change are generally lower. This could be due to Kawaliak's study having an older cohort (mean age >75 years)[22], suggesting that older individuals may have higher rates of change. Differences in time to follow-up may also affect results, with a shorter follow-up period being subject to more noise. A shorter follow-up time (one year)[22] may also contribute to larger changes in Kawalik's study.

Cross-sectional area (Tt.Ar) is known to increase with age[10], as observed in both groups, but appears to occur at a faster rate post-menopause compared to peri-menopause. Increasing the periosteal area is thought to account for endocortical resorption, which results in decreased cortical area[23].

Irrespective of group, our data is consistent with previous research showing decreases in bone density over time[4] and detrimental microarchitecture changes[10].

This study has certain limitations. Tt.Ar changes are small and approaching the precision error of HR-pQCT. Hormonal levels are not assessed, which may have an impact on bone changes. While this study spans five years, we do not capture the entire menopause transition and data is only from the tibia.

In conclusion, Ct.Po changed at an increased rate in peri-menopause women while Tt.Ar changed at a decreased rate compared to post-menopause women. These changes may lead to decreased strength and likely increased fracture risk. Understanding how bone microarchitecture changes during and after menopause will have implications for prevention and treatment of low bone density. Future directions include assessing both the radius and tibia to determine if there are differences in skeletal sites.

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REFERENCES

[1] Xu, J. *et al.* Natural history of menopause symptoms in primary care patients: a MetroNet study. *J. Am. Board Fam. Pract.* **18,** 374–382 (2005).

[2] Greendale, G. A., Lee, N. P. & Arriola, E. R. The menopause. *The Lancet* **353,** 571–580 (1999).

[3] Finkelstein, J. S. *et al.* Bone mineral density changes during the menopause transition in a multiethnic cohort of women. *J. Clin. Endocrinol. Metab.* **93,** 861–868 (2008).

[4] Arlot, M. E., Sornay-Rendu, E., Garnero, P., Vey-Marty, B. & Delmas, P. D. Apparent pre-and postmenopausal bone loss evaluated by DXA at different skeletal sites in women: The OFELY Cohort. *J. Bone Miner. Res.* **12,** 683–690 (1997).

[5] Soda, M.-Y. *et al.* Pre- and postmenopausal bone mineral density of the spine and proximal femur in Japanese women assessed by dual-energy X-ray absorptiometry: A cross-sectional study. *J. Bone Miner. Res.* **8,** 183–189 (1993).

[6] Warming, L., Hassager, C. & Christiansen, C. Changes in bone mineral density with age in men and women: a longitudinal study. *Osteoporos. Int.* **13,** 105–112 (2002).

[7] Chapurlat, R. D. *et al.* Longitudinal study of bone loss in pre- and perimenopausal women: evidence for bone loss in perimenopausal women. *Osteoporos. Int.* **11,** 493–498 (2000).

[8] Guthrie, J. R. *et al.* A prospective study of bone loss in menopausal Australian-born women. *Osteoporos. Int.* **8,** 282–290 (1998).

[9] Kanis, J. A. Diagnosis of osteoporosis and assessment of fracture risk. *The Lancet* **359,** 1929–1936 (2002).

[10] Macdonald, H. M., Nishiyama, K. K., Kang, J., Hanley, D. A. & Boyd, S. K. Age-related patterns of trabecular and cortical bone loss differ between sexes and skeletal sites: a population-based HR-pQCT study. *J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res.* **26,** 50–62 (2011).

[11] Boutroy, S., Bouxsein, M. L., Munoz, F. & Delmas, P. D. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. *J. Clin. Endocrinol. Metab.* **90,** 6508–6515 (2005).

[12] Nishiyama, K. K., Macdonald, H. M., Buie, H. R., Hanley, D. A. & Boyd, S. K. Postmenopausal women with osteopenia have higher cortical porosity and thinner cortices at the distal radius and tibia than women with normal aBMD: An in vivo HR-pQCT study. *J. Bone Miner. Res.* **25,** 882–890 (2010).

[13] Kreiger, N. *et al.* The Canadian multicentre osteoporosis study (CaMos): Background, rationale, methods. *Can. J. Aging Rev. Can. Vieil.* **18,** 376–387 (1999).

[14] Tenenhouse, A., Kreiger, N. & Hanley, D. Canadian multicentre osteoporosis study (CaMos). *Drug Dev. Res.* **49,** 201–205 (2000).

[15] Burt, L. A., Macdonald, H. M., Hanley, D. A. & Boyd, S. K. Bone microarchitecture and strength of the radius and tibia in a reference population of young adults: an HR-pQCT study. *Arch. Osteoporos.* **9,** 183 (2014).

[16] Pauchard, Y., Liphardt, A.-M., Macdonald, H. M., Hanley, D. A. & Boyd, S. K. Quality control for bone quality parameters affected by subject motion in high-resolution peripheral quantitative computed tomography. *Bone* **50,** 1304–1310 (2012).

[17] Buie, H. R., Campbell, G. M., Klinck, R. J., MacNeil, J. A. & Boyd, S. K. Automatic segmentation of cortical and trabecular compartments based on a dual threshold technique for in vivo micro-CT bone analysis. *Bone* **41,** 505–515 (2007).

[18] Burghardt, A. J., Kazakia, G. J., Ramachandran, S., Link, T. M. & Majumdar, S. Age- and gender-related differences in the geometric properties and biomechanical significance of intracortical porosity in the distal radius and tibia. *J. Bone Miner. Res. Off. J. Am. Soc. Bone Miner. Res.* **25,** 983–993 (2010).

[19] Akhter, M. P., Lappe, J. M., Davies, K. M. & Recker, R. R. Transmenopausal changes in the trabecular bone structure. *Bone* **41,** 111–116 (2007).

[20] Riggs, B. L. *et al.* A Population-based assessment of rates of bone loss at multiple skeletal sites: evidence for substantial trabecular bone loss in young adult women and men. *J. Bone Miner. Res.* **23,** 205–214 (2008).

[21] Seifert-Klauss, V. *et al.* Bone loss in premenopausal, perimenopausal and postmenopausal women: results of a prospective observational study over 9 years. *Climacteric* **15,** 433–440 (2012).

[22] Kawalilak, C. E., Johnston, J. D., Olszynski, W. P. & Kontulainen, S. A. Characterizing microarchitectural changes at the distal radius and tibia in postmenopausal women using HR-pQCT. *Osteoporos. Int.* **25,** 2057–2066 (2014).

[23] Szulc, P., Seeman, E., Duboeuf, F., Sornay-Rendu, E. & Delmas, P. D. Bone fragility: failure of periosteal apposition to compensate for increased endocortical resorption in postmenopausal women. *J. Bone Miner. Res.* **21,** 1856–1863 (2006).