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Are patterns of bone loss in anorexic and postmenopausal women similar? Preliminary results using high resolution peripheral computed tomography

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ABSTRACT

This study intended to compare bone density and architecture in three groups of women: young women with anorexia nervosa (AN), an age-matched control group of young women, and healthy late postmenopausal women. Three-dimensional peripheral quantitative high resolution computed-tomography (HR-pQCT) at the ultradistal radius, a technology providing measures of cortical and trabecular bone density and microarchitecture, was performed in the three cohorts. Thirty-six women with AN aged 18–30 years (mean duration of AN: 5.8 years), 83 healthy late postmenopausal women aged 70–81 as well as 30 age-matched healthy young women were assessed. The overall cortical and trabecular bone density (D100), the absolute thickness of the cortical bone (CTh), and the absolute number of trabecules per area (TbN) were significantly lower in AN patients compared with healthy young women. The absolute number of trabecules per area (TbN) in AN and postmenopausal women was similar, but significantly lower than in healthy young women.

The comparison between AN patients and post-menopausal women is of interest because the latter reach bone peak mass around the middle of the fertile age span whereas the former usually lose bone before reaching optimal bone density and structure. This study shows that bone mineral density and bone compacta thickness in AN are lower than those in controls but still higher than those in postmenopause. Bone compacta density in AN is similar as in controls. However, bone inner structure in AN is degraded to a similar extent as in postmenopause. This last finding is particularly troubling.

Introduction

Whereas postmenopausal osteoporosis is a common disease characterized by a systemic deterioration of bone mass and structure, generally starting in the fifth decade of life, bone loss in anorexia nervosa (AN) frequently occurs also in young age. AN usually occurs at a critical time for building up bone mass and, due to early bone loss, is often associated with severely decreased bone mineral density and impairment in bone accrual [1]. Lifetime prevalence of AN in industrialized countries is estimated at 0.5–0.9% in women, and 3–8 times less in men [2,3]. About 50% of adolescent girls suffering from AN have a bone mineral density Z-score <− 1 at one or more sites [4].

According to the Diagnostic Statistical Manual (DSM) of Psychiatric Disorders IV [5], AN is characterized, besides pathological eating behavior and underweight, by fear of gaining weight, distorted body size perception, and amenorrhea in women. Low bone mass and density in AN are due to nutritional deficiencies and alterations in multiple neuroendocrine axes, such as hypogonadism, low insulin-like growth factor-1 and relative hypercortisolemia [1]. In women after menopause, sexual hormone deficiency is assumed to be a precipitating cause of increased bone resorption resulting in osteopenia or osteoporosis. Bone loss in AN, as well as after menopause, often leads to increased bone fragility with a high risk of consequent fractures. Bone microarchitecture and its changes are keys to understand the mechanisms and frequency of fractures. High-resolution peripheral computed tomography (HR-pQCT) is a novel radiologic method that permits high resolution three dimensional measurement of trabecular and cortical bone structure at several locations, mostly at the distal radius and distal tibia [6].

In our previous studies, we could demonstrate – by means of HR-pQCT – that AN affected in young women both trabecular and cortical bone, and despite weight increase, improvement of bone density and microarchitecture showed heterogeneous courses at different locations after two years [7,8]. Postmenopausal women with no history of pathologies affecting bone metabolism indeed undergo bone loss but have

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reached a bone peak mass around the middle of the fertile age span. Young AN patients, however, usually lose bone before reaching optimal bone density and structure [9]. It is therefore of interest to compare how AN and post-menopause affect bone architecture, given the different life phases as well as endocrine shifts. A better insight into bone compartments can not only yield useful data to better understand bone loss etiology but also help in developing better targeted therapeutic strategies, in particular for AN patients. In the present work, we compare bone density and microarchitecture at the ultradistal radius with HR-pQCT technology in three different female cohorts: anorexic, healthy late postmenopausal women, and healthy young women.

Material and methods

Subjects

AN patients were recruited among subjects attending the Psychiatric/Psychotherapeutic Department of the University Hospital of Zurich (USZ). The diagnosis of AN was made according to DSM IV [5] at the Psychiatric Outpatient Department (section of eating disorders) of the USZ. The AN group consisted of 36 women aged between 18 and 30 years. Pregnant women were excluded from the study. All AN patients had a BMI below 17.5 (diagnostic criterion for AN) at recruitment time. However, some weight changes occurred during the time period between the initial recruitment and the physical examinations.

The *postmenopausal control group* was defined as women aged between 70 and 80 years and was recruited consecutively in the Zurich metropolitan area by the Osteoporosis Center of the Department of Rheumatology of the USZ. It consisted of 83 healthy women being able to walk and being independent for daily activities. They took neither medications for osteoporosis treatment nor supplements, such as calcium or Vitamin D. This group had history of neither hip fractures nor bilateral hip replacements nor metabolic conditions influencing bone density and structure.

The *healthy young control group* was composed of a total of 30 women recruited among students of Medicine and Psychology at the University of Zurich. Inclusion criteria were: ages 18–30, no current or lifetime eating disorder, not underweight (i.e. current BMI above 18) and no regular intake of medications (except oral contraceptives), neither bone nor other general diseases. Less than 20% of controls reported a history of fractures.

All participants completed questionnaires on socio-demographic data, weight condition and anthropometric data and were examined by a rheumatologist. Furthermore, AN patients and healthy young controls reported on eating disorders, (under)weight history, menstruation, use of medication, hormonal substitution or contraceptives, as well as the intake of vitamins (in particular vitamin D), minerals, or calcium products.

The study was approved by the Ethics Committee of the Psychiatric Department of the University Hospital Zurich. All participants gave written informed consent.

Data acquisition

Bone mineral density and bone micro-architecture were measured at the ultradistal radius of the non-dominant forearm by means of high resolution multislice three-dimensional peripheral quantitative computer-tomography (HR-pQCT) (Scanco Medical AG, Bassersdorf, Switzerland) [10,11]. This is a valid methodology for the study of bone microarchitecture, since it measures true volumetric BMD, distinguishes between cortical and trabecular compartments and has adequate resolution to measure cortical and trabecular structure [12]. The measurement protocol included acquisition of a stack of 60 high-resolution CT slices. Slice thickness was 0.28 mm, pixel matrix of 512×512 and pixel size of 0.17 mm. The recordings were reformatted in order to obtain consecutive cross-sectional slices in 0.17 steps mm in the axial direction thus yielding cubic voxels ($0.17 \times 0.17 \times 0.17$ mm^3). Measurements were performed at the Institute for Biomedical Engineering, University of Zurich and Federal Institute of Technology (ETH).

Quantitative parameters were defined as follows:

D100	mean entire bone (cortical and trabecular) density of the ultradistal part of the radius in grams hydroxyapatite equivalence per cm^3 (grHA/cm^3);
Dcomp	bone density of the cortical part of the bone (grHA/cm^3);
C.Th	absolute thickness of cortical bone (mm);
Dtrab	density of the trabecular area of the bone (grHA/cm^3);
Dmeta	density of the sub cortical area of the trabecular bone (grHA/cm^3);
BV/TV	relative bone volume as part of the total volume (%);
Tb.N	absolute number of trabecules per area (1/mm);
Tb.Th	mean thickness of bone trabecules (mm);
Tb.Sp	mean separation distance between trabecules (mm).

The average short-term precision of the multislice high-resolution 3D-pQCT after repositioning is 1.1% for Dtrab and 1.6% for structural parameters such as TbN [10,11].

Statistical analysis

All parameters were normally distributed according to Kolmogorov–Smirnov and Shapiro–Wilk tests at a significance level of $\alpha = 0.05$. Box-plots were produced for each parameter that was tested for group differences by means of ANOVA (factor "group", i.e. AN, postmenopausal and controls) with post-hoc tests with Bonferroni correction. Differences were considered non-significant for $p > 0.05$, significant for $p < 0.05$, highly significant for $p < 0.01$ and very highly significant for $p < 0.001$. Statistical tests were performed by means of PASW statistical software package V. 18 for Windows (SPSS Inc. Chicago IL, USA).

Results

Table 1 shows the demographic data and other characteristic parameters (age at menarche, age at AN onset, minimum lifetime BMI, duration of AN, duration of amenorrhea) of the three groups (other information on the subjects' history is reported in former work [6]). In the AN group the BMI at the time of examination ranged from 13.1 to 17.9 kg/m^2, there was no primary amenorrhea, and 64% used oral contraceptives for a mean duration of 41.5 months. Less than 20% of AN patients reported a history of fractures. The mean current age and mean age at menarche did not differ between the AN group and controls (see Table 1).

Table 2 lists the parameter values of bone density and microarchitecture. Both tables show the significances (p-values) of the parameters according to the post-hoc tests in the ANOVA. The parameter data and the significance of their differences are represented also in the box-plots of Fig. 1.

The HR-pQCT technology at the ultradistal radius could clearly demonstrate that D100 and CTh are significantly lower in anorexic women compared with in healthy young controls.

Compared to AN patients, in healthy young controls the number of trabecules was very highly significantly higher ($p < 0.001$) and the trabecular separation was highly significantly lower ($p = 0.003$), but not in healthy late postmenopausal women ($p = 1.00$ and $p = 0.112$ respectively) (s. Fig. 1). In addition, healthy late postmenopausal women showed significantly lower values of the following densitometrical and structural parameters at the ultradistal radius compared to both anorexic women and healthy young controls: the integral bone density (D100), the bone density of the cortical compartment (Dcomp), the absolute thickness of the cortical zone (CTh), the density of the trabecular compartment (Dtrab), the density of the sub-cortical area of the

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