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Original Article

Growth and aging of proximal femoral bone - a study with women spanning three generations[†]

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Running title: Developmental patterns of proximal femoral bones among three generations

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Competing interests

The author(s) declare that they have no competing interests.

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Abstract

Osteoporotic hip fracture is a serious clinical event associated with high morbidity and mortality. Understanding femoral growth patterns is important for promoting bone health in the young and preventing fractures in later life. In this study, growth patterns of areal bone mineral density (aBMD) and geometric properties of the proximal femur were measured by dual-energy X-ray absorptiometry (GE Lunar Prodigy, USA). They were studied in 251 girls from premenarche (11.2 ± 0.7 yrs) to late adolescence (18.3 ± 1.1 yrs), and compared to their premenopausal mothers ($n=128$, aged 44.9 ± 4.1 yrs) and postmenopausal grandmothers ($n=128$, aged 70.0 ± 6.3 yrs). Hip axis length (HAL) was the first to reach peak growth velocity (-10.5 months prior to menarche), followed by neck diameter (ND) and neck cross-sectional area (CSA), (-7.1 and -4.1 months prior to menarche, respectively). Both neck-shaft angle (NSA) and aBMD of neck and total hip peaked at menarche. At 18 yrs (7-yr follow-up), girls already had higher femoral neck aBMD but similar HAL and NSA compared with their mothers. Grandmothers had the longest HAL, narrowest NSA, widest ND but lowest aBMD and CSA. Hip Strength Index (HSI), an index of femoral neck strength during a fall, dropped rapidly after menarche in girls but thereafter remained relatively constant. Grandmothers had lower HSI than either mothers or girls. In conclusion, differences in proximal femoral bone mass and structure in adulthood are largely established prior to menarche, indicating that heritable factors are responsible for most of the individual variance. The development of geometric properties precedes aBMD in puberty, resulting in relatively constant hip strength after menarche. This asynchronous growth leads to adaptation of bone strength to the imposed loads, avoiding fractures in a biologically efficient manner. Both deterioration of aBMD and inadequate compensatory change in bone geometry after menopause contribute to the increased fracture risk later in life.

Key words: puberty, women, hip, bone strength, geometry, and density

Introduction

Osteoporosis is the most common metabolic bone disease and is associated with increased risk of fractures (1). The most common fractures are those of the vertebrae (spine), proximal femur (hip) and distal forearm (wrist). Hip fractures account for a 8.4 to 36% of the total fractures, are associated with considerable excess mortality within one year, and approximately 20% of hip fracture patients require long-term nursing home care (2). Annually, 3-4 million osteoporotic fractures occur in Europe resulting in direct costs to the health care services of around 30 billion euros (3). In the US osteoporosis-related fractures resulted in a cost of \$17 billion in 2005, and hip fractures accounted for 14% of incident fractures and 72% of fracture costs (4).

It is widely accepted that optimizing bone strength during growth is important to prevent osteoporosis and related fractures later in life (5). Strength of a bone is determined by both its material and structural properties (e.g., bone geometry) (6). Thus determining geometric measures could be helpful to estimate bone strength. There are a number of reports suggesting that bone geometry plays a key role in hip fracture (6-11). Animal studies show that femoral neck width is a positive predictor for femoral neck strength (12-14). Longer hip axis length is related to higher hip fracture risk, especially the sub-head type (15,16).

During growth, optimal bone strength is better achieved by modifying the distribution of bone mass rather than increasing bone mass alone (17). Hence having more optimal bone geometry is an effective way to reduce the risk of osteoporotic fracture later in life. Cross-sectional studies have demonstrated that the natural age-related decline in cross-sectional area (CSA) and cortical thickness at the proximal femur starts around 20 years of age (18). Another study observed an age-related decline in areal bone mineral density (aBMD) and section modulus (Z) at the proximal femur from 20- to 80-yrs (19). Differences in the BMD of femoral neck in adulthood are largely established before puberty (20), suggesting that the puberty is a critical period for bone growth. However, there are no such longitudinal data from childhood through to old age to confirm whether or not bone traits established in childhood persist to middle age and old age.

In this study, we conducted a 7-yr longitudinal study of the growth patterns of proximal femoral bone traits in a cohort of 251 girls from premenarche (Tanner Stage 1 & 2) to late adolescence. In addition, these bone traits were also measured in the girls' biological mothers and grandmothers. By

comparing the data among these three generations it was possible to infer the patterns of change in proximal femur traits from premenarche to postmenopause. Also we assessed the peak velocity time (PVT, the age at which the growth velocity of the selected variable reached a maximum) of aBMD at the femoral neck and total hip, hip axis length (HAL), neck shaft angle (NSA), cross-sectional area of neck (CSA), cross-sectional moment of inertia (CSMI) of neck, and hip strength index (HSI) from DXA scans. Determining PVT is useful in terms of understanding growth trajectories and temporal relationships between different bone properties, and to specify the time point to start intervention for optimization of bone strength during puberty. A family-based study design like that used here may be the best alternative to unfeasible, ultra-long-term longitudinal studies.

Subjects and Methods

Subjects

The study population of this report is a part of the CALEX family study that has been described elsewhere (21-23). Briefly, 396 Caucasian girls recruited in the city of Jyväskylä and its surroundings in Central Finland participated in the laboratory tests 1-8 times over a maximum period of 8 years (from 2000 to 2008, mean duration of total follow-up was 7.5 years). Of 396 eligible girls, 258 girls had bone assessments at baseline (mean age 11.2 yrs), 200 at 12 months, 221 at 24 months, 87 at 42 months and 235 at 84 months. In addition, 257 biological mothers and 154 grandmothers of these girls were invited to participate in one-time bone measurements. Postmenopausal mothers (n=129), premenopausal grandmothers (n=26), and those who at the time of recruitment had diseases or medication known to affect bone metabolism were excluded. We had to exclude seven 11-yr girls, one 18-yr old girl because of having diseases or taking medicine that affected bone metabolism or unqualified bone image. Finally, 251 11-yr girls (mean age 11.2 ± 0.7 yrs), 189 12-yr girls (mean age 12.2 ± 0.7 yrs), 210 13-yr girls (mean age 13.2 ± 0.7 yrs), 74 14-yr girls (mean age 14.4 ± 0.9 yrs), 224 18-yr girls (mean age 18.3 ± 1.1 yrs), 128 premenopausal mothers (mean age 44.9 ± 4.1 yrs), and 128 postmenopausal grandmothers (mean age 70.0 ± 6.3 yrs), were included.

The study protocol was approved both by the ethical committee of the University of Jyväskylä and the Central Finland Health Care District. All the participants and their legal guardians (for minors)

provided written informed consent (volunteers without monetary compensation) in accordance with the ethical committees of the Central Finland Health Care District.

Measurements

1 Anthropometry

Height and weight were obtained by duplicate measurements with subjects wearing light clothes and on bare feet. Height was determined using a fixed wall-scale measuring device to the nearest 0.1 cm. Weight was determined within 0.1 kg for each subject using an electronic scale and was calibrated before each measurement session. The mean of the two measures was used as the final results. The age of menarche was defined as the first onset of menstrual bleeding and this information was solicited, by questionnaire, retrospective phone call, and/or interview during a clinical visit. We use the term "premenarche" to mean "before menarche".

2 Bone measures

Bone measures of the left hip were assessed using dual-energy X-ray absorptiometry (DXA, GE Lunar Prodigy Advance, Madison, WI, USA; software enCORE version 13). The Advanced Hip Assessment (AHA) included in this software calculates bone geometry and bone tissue distribution within the femoral neck from a planar scan. The femur ROI is placed automatically in the proximal part of the femoral neck. However, we made a manual adjustment if an obvious error in ROI position was observed. One technician performed data acquisition and analysis. Quality Assurance (QA) test was performed following the instructions of enCORE Operator's Manual each morning before measurement. If manual adjustment of the ROI was needed, a repeated scan was performed and the new scan was used as final result. Left femur was scanned unless the left side is not appropriate due to hardware or fracture. The hip axis length (HAL, cm) was evaluated as the linear distance from the pelvic rim to the lateral edge of the femur below the greater trochanter and along the femoral neck axis. Neck diameter (ND, cm) was the average diameter in the ROI. Femoral neck-shaft angle (NSA, degree) was the angle of the intersection of the neck and shaft axes. The software iteratively assessed all cross-sections in the femoral neck region of interest and identified the plane with the minimum cross-sectional moment of inertia (CSMI, cm^4), which is a measure of

bone's resistance to bending forces. The method was developed by Yoshikawa and colleagues (24). A strong linear association between the CSMI measured directly and using DXA has been reported in cadaveric bones ($r^2 = 0.96$). The cross-sectional area (CSA, without bone marrow, cm^2) was measured in the plane of where CSMI was obtained. Hip Strength Index (HSI) is an index of the strength of the femoral neck during a fall, taking age, weight, height and neck geometry into account (24). Higher values of HSI indicate a stronger femoral neck and better ability to sustain the loads experienced during a fall (25). HSI was calculated as following:

$$\text{HSI} = \text{strength} / \text{stress}$$

where,

$$\text{strength} = 185 - 0.34(\text{age} - 45); \text{Age} > 45 \text{ years}$$

$$\text{stress} = \text{moment} * y / \text{CSMI} + \text{force} / \text{CSA}$$

$$\text{moment} = d1 * 8.25 * \text{weight} * 9.8 (\text{height} / 170)^{1/2} * \cos(180^\circ - \theta)$$

$$\text{force} = 8.25 * \text{weight} * 9.8 * (\text{height} / 170)^{1/2} * \sin(180^\circ - \theta)$$

$d1$ = Distance along the neck axis from the center of the femoral head to the section of minimum CSMI.

y = Distance from centre of mass to the upper neck margin, along the section of minimum CSMI.

θ = Angle of the intersection of the neck and shaft axes

The coefficients of variation (%CV) for aBMD, HAL, NSA, CSA, CSMI and HSI were 0.9%, 2.3%, 4.1%, 2.6%, 1.8%, and 5.2%, respectively. The %CV was calculated both in children (22) and adults.

Statistical analysis

All data were checked for normality before further analysis. If data were not normally distributed, their natural logarithms were used. The descriptive statistical analysis and comparison of three

generations was done in SPSS 21.0 for WINDOWS (SPSS Inc., Chicago, IL, USA). Analysis of variance (ANOVA) was used to compare differences among different age groups. Given the significant influence of body size on DXA measurements, height was included as the covariate and analysis of covariance (ANCOVA) with the least significant difference (LSD) post-hoc test was used to compare bone parameters. However HSI was not adjusted for height because height is used in the calculation of HSI. The longitudinal analyses of girls' data (from premenarche to late adolescence) were performed using MLwiN 2.02 software (Institute of Education, University of London, London, UK). Hierarchical (multilevel) models with random effects were used to quantify the growth patterns of bone traits. The hierarchical model allows inclusion of the data from every subject regardless of irregularity of temporally spaced follow-up or missing data. Time relative to menarche (TRM), instead of age, was entered as the explanatory variable in the form of polynomial functions to explain the growth of target variables. Up to fifth-order polynomial functions were used in the models. The best model was determined by three criteria: the largest reduction in the deviance ($-2 \times \log$ -likelihood ratio of the reduced model compared to the full model), the lowest within-individual variance, and the necessary parsimony of the model. The PVT was determined from the maximum in the growth velocity curve. Time of plateauing was determined as the time at which the growth velocity decreased to 0. A $P < 0.05$ was considered statistically significant.

Results

The growth patterns of aBMD, HAL, NSA, ND, CSA, CSMI and HSI at the femoral neck and total proximal femur in girls from premenarche to late adolescence are shown in Figure 1. All these parameters increased markedly before or around menarche except for NSA and HSI. The neck-shaft angle shifted decreased then plateaued around 36 months after menarche. Hip strength index decreased until menarche and then maintained a relative constant value throughout puberty. The Hip axis length, total aBMD, neck aBMD and CSA growth accelerated early and reached a plateau around 20, 49, 57 and 62 months after menarche, respectively. Neck diameter and CSMI curve showed a slow but steady increase after rapid growth around menarche.

Among all proximal femur bone material and geometric traits, HAL was the first to reach the peak velocity (10.5 months prior to menarche), followed by ND and CSA, (7.1 and 4.1 months prior to menarche, respectively). Both NSA and aBMD of the neck and total hip peaked at menarche (Figure 2). The peak velocity (per month) of HAL, neck diameter, total aBMD, neck aBMD and CSA were 0.44cm, 0.11mm, 6mg/cm², 0.6mg/cm², and 1.19 mm², respectively.

To evaluate how bone traits at the hip compared across different periods of women's life, we compared these traits among premenarcheal and late adolescence girls to their pre-menopausal mothers and postmenopausal grandmothers. For girls at 11 years of age, all of their proximal femoral bone traits were lower than those of girls at the age 18 yrs except for the NSA, which decreased with age. At the age of 18 yrs (7-yr follow-up), girls already had a higher aBMD at femoral neck than their mothers, whereas aBMD at total hip, HAL, NSA and HSI were similar. However, the ND, CSA and CSMI of the femoral neck were still significantly lower in 18 year-old girls than their premenopausal mothers (all were $p < 0.05$) (Table 1). Compared to 18-yr girls and their mothers, grandmothers had lower aBMD, CSA and HSI, but higher ND (Table 1 and Figure 1). After adjusted for height, the significant differences of aBMD, ND, CSA and CSMI remained. While NSA was smaller in grandmothers and mothers, compared with 18-yr girls. Grandmothers had the longest HAL, narrowest NSA, but lowest aBMD and CSA.

Discussion

In this 7-yr longitudinal follow-up study from premenarche to late adolescence in girls, we found that the growth velocities of geometric parameters of the proximal femur, such as CSA, CSMI of femoral neck, hip axis length and neck diameter, peaked earlier than aBMD. However, the Hip strength index (reflecting the strength of the femoral neck relative to the loads imposed during a fall) remained relatively constant after menarche. These two observations together suggest an asynchronous but well-coordinated growth pattern of the bone adapting to stress during puberty. After puberty, using the data from the three generations to infer lifelong trends, our data indicate that bone density and most of the geometric parameters as well as hip strength index are maintained from late adolescence until menopause but decline thereafter.

Peak velocity time

Our previous study looking at the tibia demonstrated that growth velocities of length and CSA peak earlier than that of aBMD (23). Similarly, other researchers have observed such phenomenon in the forearm (26-29). The rapid growth in bone dimensions without a concomitant increase in bone mineral density may contribute to lower mineralization of bone tissue, which is considered to be one of the reasons underlying the elevated risk of forearm fracture during the pubertal growth spurt (30-32). Evidence for such a “mineralization deficit” (33,34) was also found in this current study at the proximal femur: the PVT of hip axis length and CSA of femoral neck preceded that of aBMD, indicating that the hip bone mass accrual lags behind the increase in bone size. However, there are no reports of increased hip fracture risk during the pubertal growth spurt. This may be explained by the fact that the proximal femur is much stronger, both in absolute terms and relative to the applied loads, compared to the radius and ulna (35). In addition, the hip is surrounded by more soft tissue than the forearm and this may further reduce the risk of fracture in a fall (32).

Development patterns of proximal femoral bones in three generations

The fracture risk is closely related to the decrease of aBMD, which has been the most widely studied among all bone traits. In our study, we found that aBMD at the femoral neck and total hip peaked around 18-yrs of age while grandmothers had the lowest aBMD because of the rapid bone loss after menopause as described in many earlier studies (36,37). The CSA of the femoral neck, excluding the bone marrow cavity, was maintained until mid-age. Grandmothers had much smaller CSA than their daughters and their 18-yr granddaughters, despite the fact that their femoral neck diameter was the widest. This apparent paradox may be explained by the growth difference of periosteal diameter (PD) and endosteal diameter (ED), which were unfortunately not measured in this current study. Gayani Alwis and colleagues scanned 1,760 population-based Caucasians aged 6-90 yrs using DXA and analysed by hip structural analysis (HSA)(38). They found that PD and ED of the femoral neck both increased with age, but that ED increased more than PD. Duan and his colleagues also observed that less age-related periosteal than endocortical widening produced cortical thinning in

femoral neck, increasing the risk for structural failure in both sexes(39). Thus the change of geometry of femoral neck contributed to femoral fragility in old age.

Fracture occurs only when stresses imposed upon a bone exceed the bone strength. CSMI, a geometrical measure of a bones' resistance to bending forces, can be considered as an index of bone strength. According to our three-generation data, the grandmothers' CSMI was twice that of 11-yr girls. Furthermore, other trends in geometric parameters in the grandmothers, such as wider neck diameters and narrower neck-shaft angles, tend in the direction of enhanced bone strength. Such observations imply that, in terms of bone size and geometry the grandmothers should have a stronger proximal femur, but we know that older women actually have a much higher fracture risk than younger women. This apparent contradiction can be explained partly with reference to the low HSI in grandmothers. In older women, the stresses imposed on bone in a fall exceed the bone strength. The mechanical advantages associated with, for example, wider femoral neck diameter and reduced neck-shaft angle fail to compensate other factors that act to compromise bone strength, such as microstructural deterioration and decreased aBMD. In addition, the grandmothers were much heavier than their 11 year old granddaughters (71kg vs. 39kg) and hence the loads on the proximal femur, during normal activities and in falls, will be correspondingly greater in the older women. Hence discordance between bone strength and imposed stresses results in significant higher fracture risk in older females. In addition, decrease in CSA of femoral neck (without bone marrow) also indicated a thinner cortical thickness in grandmothers, which could result in structural instability caused by a tendency for structural failure by local buckling(39,40). Moreover, studies using computed tomography instead of DXA suggest that the age-related change of cortical thickness is site-specific in the femoral neck, and this may also play a role in the deterioration of bone strength (41,42).

Hip Strength Index decreased before menarche and maintained a relatively constant level until menopause. This suggests that girls have more than sufficient bone strength before puberty, but this situation rapidly alters, for example with the rapid weight gain of early puberty tending to increase bone loading. After menarche the proximal femur growth adapts itself to the imposed loading in order to maintain certain level of HSI by the asynchronous growth speed of geometric and material

parameters. This impressive gene-coded control of growth avoids either wasting of energy or fractures.

This study has some limitations. The bone traits of girl-mother-maternal grandmother trios did not perfectly represent the true longitudinal pattern of bone development and ageing in individuals. The data obtained from close relatives may not be the same as that which would be observed for the same subject followed longitudinally. However, the genetic link and the resemblance in living environment among family members may help minimize possible biases, because the variance in bone properties in the population is largely the result of individual differences in genetic makeup, confounded by lifestyle factors (43,44). Another potential limitation arises from the use of DXA measurements. aBMD, assessed by a 2D imaging technique such as DXA, is an estimate of the average amount of mineral per unit area in a section of bone facing the detector (45-47). Both CSA and CSMI depend of the amount of mineral present in the femoral neck. Thus they consequently are not totally independent of BMD as geometric parameters. Moreover, the hip analysis software could not determine PD and ED, making it difficult to directly explain the change of CSA.

In conclusion, we found that the growth in geometric parameters of proximal femur precedes that of aBMD in puberty. However, the hip strength remained relatively constant after menarche, suggesting an asynchronous but well-coordinated growth pattern of the bone adapting to stress during puberty. This asynchronous growth control leads to a balance of bone strength to stress, avoiding fractures while minimizing wasted energy and resources. Using the data from three generations to indicate life-long change of the bone traits, we infer that both the deterioration of BMD and the inadequate compensatory changes in bone geometric parameters after menopause contribute to the increased fracture risk later in life.

Table 1. General Characteristics and DXA Measurements of Finnish Women in Different Age Groups

	11-yr girls	18-yr girls	Mothers	Grandmothers
N	251	224	128	128
Age (yr)	11.2±0.7	18.3±1.1*	44.9±4.1 ^{†‡}	70.0±6.3 [#]
Height (cm)	145.7±8.1	165.8±5.7*	165.5±5.6 [‡]	159.8±4.9 [#]
Weight (kg)	39.0±8.4	60.0±9.7*	70.0±13.8 ^{†‡}	71.0±11.0 [#]
BMI (kg/m ²)	18.2±2.8	19.8±3.5*	25.5±4.6 ^{†‡}	28.4±8.4 [#]
Neck aBMD(g/cm ²)	0.82±0.09	1.06±0.14*	1.00±0.12 ^{†‡}	0.86±0.14 [#]
Total hip aBMD(g/cm ²)	0.83±0.10	1.08±0.13 *	1.06±0.12 [‡]	0.94±0.14 [#]
HAL(mm)	93.5±6.7	102.8±5.7*	103.9±5.8 [‡]	104.3±5.7 [#]
NSA(°)	130.5±4.0	127.1±3.5*	126.4±3.4	125.3±4.5 [#]
ND (mm)	26.7±2.3	30.6±2.1*	32.2±2.0 ^{†‡}	33.0±2.2 [#]
CSA(mm ²)	101.1±15.8	151.7±22.1*	152.5±20.6 [‡]	131.5±22.6 [#]
CSMI(mm ⁴)	4671±1431	9086±2132*	10204±2157 ^{†‡}	9537±2247 [#]
HSI	1.89±0.45	1.78±0.35*	1.75±0.36 [‡]	1.57±0.42 [#]

Data was shown as mean ± standard deviation. aBMD=areal bone mineral density, HAL=hip axis length, NSA=neck-shaft angle, ND=Neck diameter, CSA=cross-sectional area, CSMI= cross-sectional moment of inertia, HSI=hip strength index. Bone parameters were adjusted for height except HSI.

*: 11-yr girls vs. 18-yr girls p<0.001

[†]: Mothers vs. 18-yr girls p<0.001

[‡]: Mothers vs. Grandmothers p<0.05

[#]: Grandmothers vs. 18-yr girls p<0.05

Figure Legends:

Figure 1. Growth patterns of femoral neck and total hip aBMD, HAL, NSA, ND, CSA, CSMI and HSI. Data for the bone traits are plotted against time relative to menarche (TRM). Gray lines represent longitudinal change of each individual's values and the black lines are the best fitting lines derived from hierarchical models. Mothers' and grandmothers' values are indicated by box with error bars (mean and 95% CI). Label "M" means mothers and "GM" means grandmothers. aBMD=areal bone mineral density, HAL=hip axis length, NSA=neck-shaft angle, CSA=cross-sectional area, CSMI= cross-sectional moment of inertia, HSI=hip strength index.

Figure 2. Peak velocity time of proximal femoral material and structural traits. aBMD=bone mineral density, HAL=hip axis length, NSA=neck-shaft angle, CSA=cross-sectional area.

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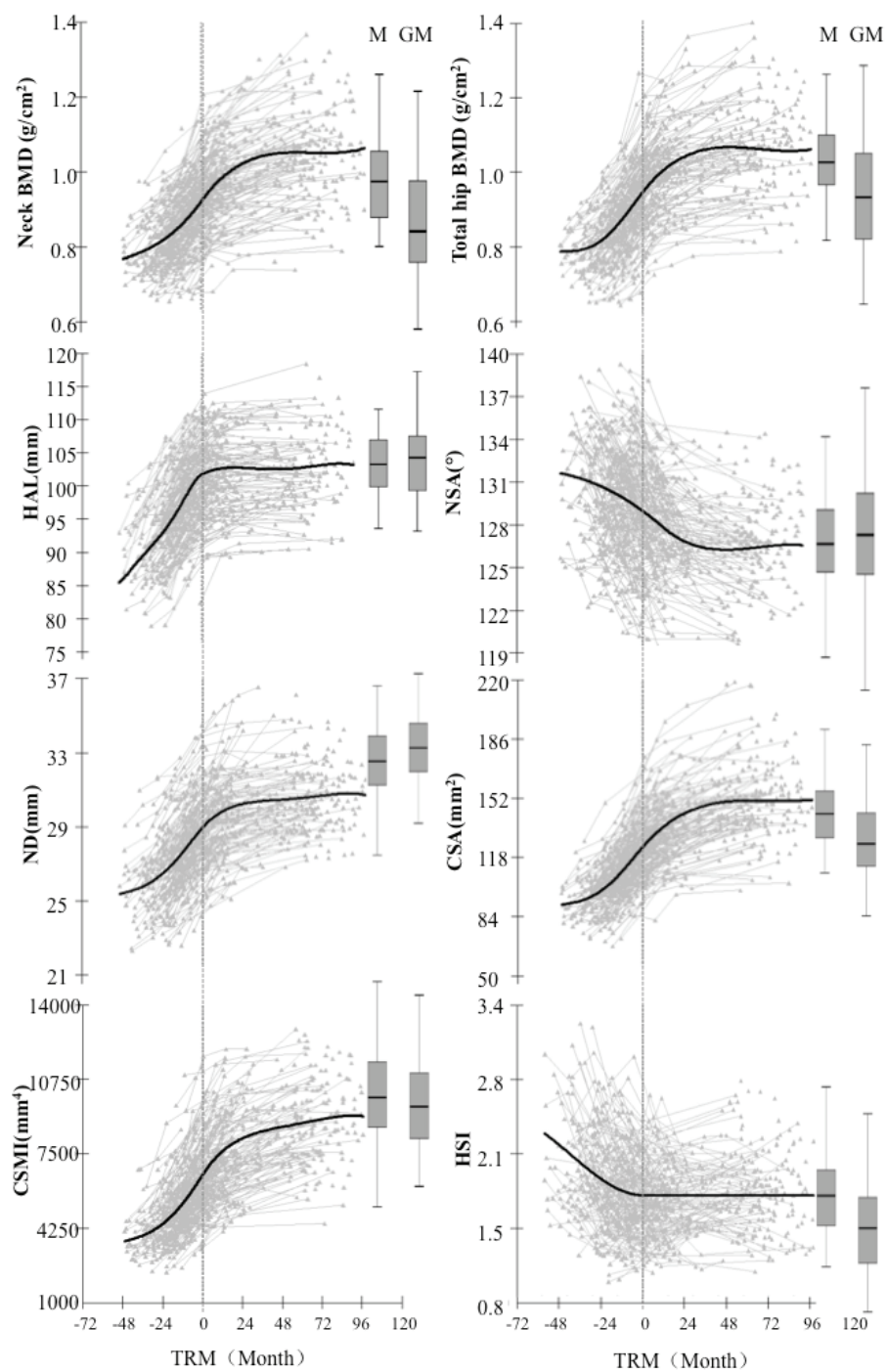


Figure 1

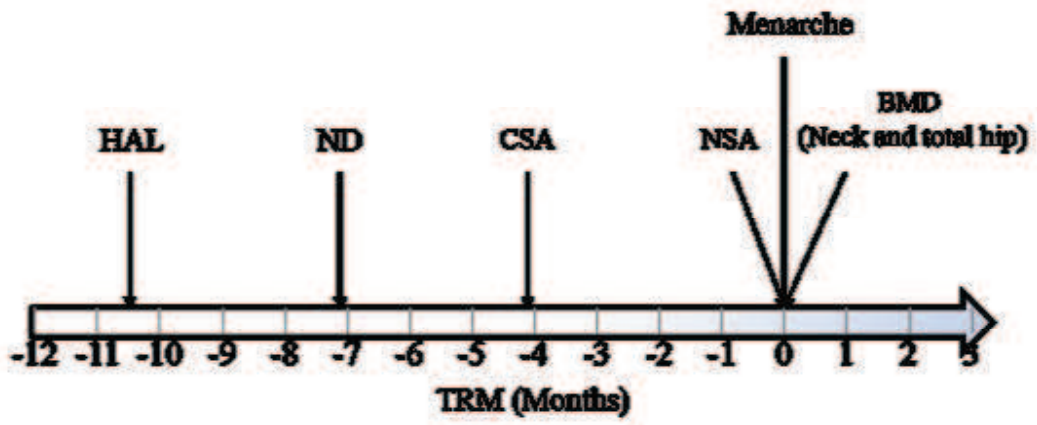


Figure 2