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Anogenital index and bone mineral density associations after natural and surgical menopause: a preliminary study

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SUMMARY

OBJECTIVE: The aim of this study was to evaluate postmenopausal women to determine whether an anogenital index (AGI) is associated with bone mineral density (BMD) based on the hypothesis that the effects of menopause are similar for both.

METHODS: A total of 338 generally healthy postmenopausal women who were referred for a routine annual check and 140 women who met the inclusion criteria were enrolled in the study. Based on the menopausal status, the women were classified into natural menopause and surgical menopause. AGI was calculated by dividing anogenital distance by body mass index. The BMD of the femoral neck, body of the femur, and lumbar spine (L1 and L2) was measured using dual-energy x-ray absorptiometry.

RESULTS: There was a statistically significant and same-directional correlation between age and AGI for all cases (r=0.234 and p=0.005). The AGI level decreased as the parity increased (r=-0.582 and p<0.001). The AGI level decreased significantly as the menopause duration was prolonged (r=0.288 and p<0.001). While there was no statistically significant correlation between L2-L4 BMD and AGI (p=0.128), as the femur and femoral neck BMD levels increased, the AGI level increased statistically significantly (r=0.330 and p<0.001, r=0.292 and p<0.001).

CONCLUSION: The AGI levels in healthy postmenopausal women give preliminary information about their BMD status. A decrease in AGI levels may predict lower BMD in postmenopausal women. Further larger and well-controlled studies may be required to determine the relationship between AGI and BMD in the future.

KEYWORDS: AGI. BMD. Postmenopausal osteoporosis.

INTRODUCTION

Menopause is actually the period after a woman's cessation of menstruation is certain. Although it is a term used, the most important fact in this period is the end of woman's reproductive ability her reproductive period[1]. Reproductive aging is influenced by many factors. Along with the gonads, aging of the entire endocrine system and systemic aging are also in question. Although menopause happens at a certain time, various changes begin many years in advance. This period brings with it a series of unique complaints as well as pathological changes that can cause serious diseases in the long term[2]. Regardless of the cause, surgical menopause and loss of estrogens and androgens before the normal age of menopause affect a lot of systemic functions and have long-term health consequences[3,4].

Osteoporosis is a systemic skeletal disease characterized by low bone mass, deterioration in the microarchitecture, quality of bone tissue, and decreased bone strength leading to an increased risk of fracture[5]. Postmenopausal osteoporosis is an important public health disease. Prolongation of life expectancy, development of osteoporosis, and osteoporotic fracture impairment in daily living activities have become more important problems[6]. The most important factors in the development of the disease are age and hormonal changes[7]. Similar to bones, changes occur in skin structure and collagen production in the postmenopausal period. Decreases in estrogen levels, production of collagen changes with an increase in collagen strength, skin elasticity reduction, a severe decline in genital water content, and anatomical changes in female genital organs may also occur. Both the vagina and the external female genitals are affected[8].

The anogenital distance (AGD) is identified as the length (in mm) between the labia posterior commissure and the center of the anus. The anogenital index (AGI) was used to control two variables, namely, height and weight. AGI was calculated by dividing AGD by body mass index (BMI)[9]. Recent studies have found that the AGD of postmenopausal women is significantly shorter than that of premenopausal women[10]. Several studies on adult men, as in women, have provided

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strong evidence of the relationship between AGD length and male reproductive function[11,12].

This study evaluated postmenopausal women to determine whether AGI is associated with BMD based on the hypothesis that the effects of menopause are similar for both.

METHODS

This prospective study was performed between January 2021 and May 2021. Ethical approval was obtained from the Ministry of Health Ankara City Hospital, Ethical Review Board (No. E2/21/79). In all, 338 generally healthy postmenopausal women who were referred for a routine annual check to the Menopause Clinic of the Ministry of Health Ankara City Hospital, and 140 women who met the inclusion criteria were enrolled in the study. According to the analysis of 95% confidence (1-α), 95% test power (1-β), and d=0.5 effect size, the number of samples to be taken in each group was determined as 54, according to the independent samples t-test analysis[13]. This study was conducted following the principles of the Declaration of Helsinki. All patients were extensively informed of the study design and hypothesis. Written informed consent was obtained from all patients enrolled.

Menopausal status was defined as the absence of menstruation for at least 12 months, according to the World Health Organization's definition of menopause. Based on the menopausal status, the women were classified into natural menopause and surgical menopause. All women included in the study were asked to complete the researcher's administered questionnaire regarding age, parity, height, weight, type of birth, menopausal status, time since menopause, surgical history, medical illness history, and drug intake, including hormone therapy (HT). Healthy postmenopausal women who did not have any additional systemic disease and did not receive hormone replacement therapy were included in the study. None of our subjects were using hormone replacement therapy or were receiving medications affecting bone mineralization. The exclusion criteria were as follows: patients with secondary causes of osteoporosis (primary hyperparathyroidism, Cushing's syndrome, rheumatoid arthritis, etc.), liver and chronic kidney diseases, bone diseases, metabolic disorders, or other systemic diseases.

Patients' data (height, weight, body mass index, AGD, and AGI) were collected on the same day during the outpatient examination. An AGD measurement was conducted using a paper ruler in the lithotomy position to define the distance between the posterior commissure of the labia and the anus center. BMI was calculated as female weight (kg) divided by squared height (m^2). AGI was calculated by dividing AGD by BMI.

Bone mineral density measurements

The BMD of the femoral neck, body of the femur, and lumbar spine (L1 and L2) was measured by dual-energy x-ray absorptiometry using a QDR 4500A (Hologic, Bedford, MA, USA) densitometer and was expressed in absolute values as grams of mineral content per square centimeters of bone area (g/cm^2).

Statistical analysis

Statistical analysis was performed using the SPSS software (Statistical Package for the Social Sciences) version 22 (SPSS Inc., Chicago, IL). Data are presented as mean±standard deviation (SD) and 95% confidence interval (CI). The Kolmogorov-Smirnov test was used to investigate whether the normal distribution assumption was met. Descriptive statistics were given as mean±SD or median ($25–75^{th}$) percentiles, where applicable. While the mean differences between types of menopause were compared using Student's t-test, the Mann-Whitney U test was applied for the comparisons of non-normally distributed data. Degrees of association between continuous variables were evaluated by Spearman's rank-order correlation analysis. Multiple linear regression analysis via stepwise procedure was applied for determining the best predictor(s), which affects the AGI levels. Any variable whose univariable test had a p-value of <0.10 was accepted as a candidate for the multivariable model along with all variables of known clinical importance. Coefficient of regression, 95% confidence interval, and t-statistic for each independent variable were also calculated. Data analysis was performed using the IBM SPSS Statistics version 17.0 software (IBM Corporation, Armonk, NY, USA). A p-value of <0.05 was considered statistically significant.

RESULTS

For our study, 338 postmenopausal women were initially examined. After the exclusion criteria, 140 women met the inclusion criteria and formed the study population; 86 patients were in the natural menopause group and 54 patients were in the surgical menopause group.

The demographic characteristics of the participants are listed in Table 1. There was no statistically significant difference in terms of mean age, BMI, duration of menopause, and BMD levels between the surgical menopause group and the natural menopause group (p>0.05). Compared to the natural menopause group, the parity of the surgical menopause group was statistically significantly higher, and the AGD level was statistically significantly lower (p<0.001). The mean AGI level was also statistically significantly lower in the surgical menopause group compared to that in the natural menopause group (p<0.001).

Table 1. Demographic and clinical characteristics for menopause types.

	Total (n=140)	Natural (n=86)	Surgical (n=54)	p-value
Age (years)	57.6±4.9	57.7±4.4	57.4±5.6	0.668*
Body mass index (kg/m²)	29.2 (26.6–31.0)	28.8 (26.4–30.8)	29.7 (26.6–31.7)	0.103†
Parity	2.0 (2.0–3.0)	2.0 (1.0–3.0)	3.0 (2.0–3.0)	**<0.001**†
Duration of menopause (years)	7.5 (5.0–11.0)	7.5 (5.0–11.0)	7.5 (3.7–10.0)	0.512†
AGD	27.0 (21.0–30.0)	29.0 (22.0–31.0)	23.0 (20.0–28.0)	**<0.001**†
AGI	0.89±0.21	0.95±0.20	0.79±0.19	**<0.001***
L2-L4	1.13 (0.99–1.28)	1.10 (0.99–1.27)	1.15 (0.99–1.34)	0.368†
Femur	1.00 (0.92–1.08)	1.01 (0.91–1.09)	1.00 (0.92–1.06)	0.480†
Femur neck	0.97 (0.90–1.03)	0.99 (0.90–1.04)	0.96 (0.90–1.01)	0.689†

Data were shown as mean ± standard deviation or median (25–75th) percentiles. AGD: anogenital distance; AGI: anogenital index. *Student's t-test; †Mann-Whitney U test. Statistically significant p-values are shown as bold characters.

The results of the correlation analysis between AGI levels and other demographic and clinical characteristics were shown in Table 2. There was a statistically significant and same-directional correlation between age and AGI for all cases (r=0.234 and p=0.005). On the contrary, as the parity increased, the AGI level was decreasing (r=-0.582 and p<0.001). The AGI level decreased significantly as the menopause duration was prolonged (r=0.288 and p<0.001). While there was no statistically significant correlation between L2-L4 BMD and AGI (p=0.128), as the femur and femoral neck BMD levels increased, the AGI level increased statistically significantly (r=0.330 and p<0.001; r=0.292 and p<0.001).

In the next step, the most determinant factors in predicting the change in AGI level were investigated with multivariate stepwise elimination linear regression analysis (Table 3). As a result of univariate statistical analysis, all variables that were found to be p<0.10 were included in the linear regression model as candidate factors. As a result of stepwise elimination, the best predictors that affect the AGI levels are parity, type of menopause, duration of menopause, and femur BMD. In other words, when corrected for other factors, being in surgical menopause continued to decrease the AGI level statistically significantly compared to natural menopause (B=-0.116, 95%CI -0.176 to -0.056; p<0.001).

Table 2. The results of correlation analysis between anogenital index levels and other demographic and clinical characteristics.

	Coefficient of correlation	p-value*
Age	0.234	**0.005**
Parity	-0.582	**<0.001**
Duration of menopause	-0.288	**<0.001**
L2-L4	0.129	0.128
Femur	0.330	**<0.001**
Femur neck	0.292	**<0.001**

*Spearman's rank-order correlation analysis. Statistically significant p-values are shown as bold characters.

Table 3. The best predictors that affect anogenital index levels, the results of multiple linear regression analysis.

	B	95%CI for B		t	p-value
		LL	UL		
Parity	-0.062	-0.086	-0.039	-5.224	**<0.001**
Surgical menopause	-0.116	-0.176	-0.056	-3.827	**<0.001**
Duration of menopause	0.010	0.003	0.017	2.706	**0.008**
Femur neck	0.222	0.057	0.387	2.665	**0.009**

B: coefficient of regression; CI: confidence interval; LL: lower limits of CI; UL: upper limits of CI. Statistically significant p-values are shown as bold characters.

DISCUSSION

This cross-sectional design study investigated the relationship between BMD and AGI in different categories of postmenopausal women: surgical menopause and natural menopause. To the best of our knowledge, this study is the first attempt to investigate AGI and explore the relationship between AGI and BMD in postmenopausal women.

It is known that bone loss due to estrogen deficiency starts after menopause. Multiple clinical studies have established that surgical menopause carries a higher risk of osteoporosis than natural menopause due to long-term low estrogen levels[14,15]. Compared with natural menopause, in surgical menopause due to bilateral oophorectomy, there are no premise hormonal changes because of its instantaneous nature[16]. In addition,

there is a sudden decrease in androgen levels in addition to estrogen in women in surgical menopause, which negatively affects bone density[17]. Dimitrios et al. showed that BMD values were decreased, whether in women with natural or surgical menopause, and found that women with surgical menopause had lower BMD as time progressed than normal menopausal women[18]. In our study, BMD levels were similar in women with natural or surgical menopause, but AGI levels were lower in the surgical menopause group and associated with femur and femoral neck BMD levels.

The decrease in circulating estrogen has similar effects on the skin, muscle, and connective tissue as well as on the bone. Low estrogen levels are associated with accelerated skin aging due to thinning, loss of collagen, and reduced elasticity[19]. There have been a lot of studies on female external genitalia to understand the change after menopause[20,21]. However, the use of AGI in human studies is still rare. Lee et al. have shown that changes in AGD and AGI have the potential to be used as a scale to predict physical changes in the skin after menopause[22]. Similarly, we investigated the change of AGI in surgical and natural menopause groups in our study. It was observed that the decrease in AGI levels was higher in the surgical menopause group compared to the natural menopause group.

We developed our research with the hypothesis that postmenopausal AGI and BMD change might be related, and a statistically significant relationship was found between BMD and AGI levels in our study. The AGI was associated with femur and femoral neck BMD levels. The best predictors that affect the AGI levels are parity, type of menopause, duration of menopause, and femur BMD. We observed significantly negative correlations between AGI and the duration of menopause and parity. But AGI was not associated with L2-L4 BMD levels.

Our study had several strengths. First, it is a prospective study. We have eliminated possible confusion due to exogenous hormonal drugs. This is important because using exogenous HT is associated with higher BMD. In addition, AGI measurements were performed by a gynecologist who was not aware of the patient's condition, thus eliminating the interobserver bias.

Our study has some limitations. The study and the control group consisted of women admitted to the same hospital. Our study is the cross-sectional nature of its design. Longitudinal data from an extended follow-up on a large cohort would be more definitive. Our results cannot be generalized to postmenopausal women using exogenous HT, who were excluded from our analysis.

CONCLUSION

A statistically significant relationship was found between bone mineral density and AGI levels in our study. The AGI levels in healthy postmenopausal women give preliminary information about their BMD status. Decreased AGI level is a potential predictor of bone loss in postmenopausal women. This study is the first attempt to investigate AGI and explore the relationship between AGI and BMD in postmenopausal women. The observational nature and limited sample size of the present study do not allow for generalizations. Therefore, our results should be considered suggestive for larger studies to investigate the relationship between AGI and BMD in the future.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

AUTHORS' CONTRIBUTIONS

GNB: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **EUO, MKK:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – review & editing. **IH:** Conceptualization, Data curation, Methodology, Writing – original draft, Writing – review & editing. **MGO:** Data curation, Formal analysis, Investigation, Writing – original draft, Writing – review & editing.

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