Effects of hormone replacement therapy on bone mineral density in Korean women with Turner syndrome

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Effects of hormone replacement therapy on bone mineral density in Korean women with Turner syndrome

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I would like to thank my parents and other family members who always raise me up for support with infinite love and trust.

Finally, I give all this glory to God, who has always guided my life.

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ABSTRACT

Effects of hormone replacement therapy on bone mineral density in Korean women with Turner syndrome

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Turner syndrome is a result of chromosomal abnormalities that occurs in approximately 1 in 2000 to 2500 surviving fetuses. This clinical condition arises due to the loss of all or part of one X chromosome and is characterized by short stature and sexual infantilism accompanied by systemic disorders affecting major organs with a higher incidence of osteoporosis and bone fractures.

Hormone replacement therapy is based on the use of estrogen. In Turner syndrome, this therapy is important for the promotion of puberty, and growth, and the prevention of osteoporosis. The patient response to hormone replacement therapy may vary by race and geographical region, although no such a study has ever conducted in Korea. Therefore, it is necessary to analyze the effects of hormone replacement therapy on bone mineral density in Korean women with Turner syndrome.

Herein, we retrospectively analyzed the medical records of Turner syndrome patients treated at Severance Hospital (Seoul, South Korea) from 1997 to 2019. Our study suggests that the effects of hormone replacement therapy on bone mineral density depend on the timing of initiation and duration of therapy. An early and long treatment duration is important for increasing bone mineral density in Koreans with Turner syndrome.

Key words: Turner syndrome, estrogen, hormone replacement therapy, bone mineral density

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I. INTRODUCTION

Turner syndrome (TS) arises due to the loss of all or part of one X chromosome. This chromosomal abnormality occurs in about 1 in 2000 to 2500 surviving fetuses. TS includes not only the typical 45, - X karyotype, but also various mosaic karyotypes with structural abnormalities of the X chromosome, and there are differences in clinical features according to these karyotypes.[1]

TS is diagnosed at around 15 years of age on average, although it can also be diagnosed at the intrauterine stage and in childhood, adolescence, or adulthood. Clinically, TS is characterized by short stature and sexual infantilism and is accompanied by systemic disorders that affect major organs such as the heart and kidneys, and patients with TS have a high incidence of autoimmune diseases, osteoporosis, and bone fractures.[2-5] Unlike normal oocyte decline that continues for decades, in patients with TS, oocyte decline occurs within months or years after birth, and ovaries degenerate during the fetal stage, childhood, or adolescence. As a result, only 10–30% of TS patients reach puberty naturally. Therefore, estrogen deficiency in these patients is due to ovarian insufficiency, and TS patients who do not exhibit spontaneous pubertal development require estrogen supplementation to induce secondary sexual characteristics.[6,7] Puberty plays an important role in sexual development and is associated with various important changes, such as the development of

secondary sexual characteristics, normal growth, and an increase in bone density.

Since a normal peak bone mass at puberty is essential to protect against bone loss during the following 10–20 years, achieving normal bone density during this period is important for a better quality of life in the future.[8,9] TS affects most aspects of the patient's life and is characterized by the presence of various systemic diseases. It has been widely accepted that estrogen-based hormone therapy can improve the quality of life, morbidity, and mortality in patients with TS.

The beneficial effects of hormone therapy in postmenopausal women and young women without ovaries have been shown in previous studies. However, there is no standard protocol for hormone therapy in TS patients.[10,11]

Clinical guidelines for the care of girls and women with TS recommend hormone replacement therapy (HRT) for the induction and maintenance of secondary sexual characteristics; however, the best strategy for achieving a better bone mineral density (BMD) in adulthood has not yet been established.[1] Few studies have highlighted the importance of early estrogen replacement therapy (ERT) initiation in patients with TS.[12-14] Typically, peak bone density in healthy girls is achieved during the period between the beginning of puberty and the age of 18.[15-18]

The patient’s response to hormone therapy may vary by race and geographical location. Since no such studies have ever been conducted in Korea, it is necessary to analyze the effects of HRT on BMD in Korean women with TS.

The general therapeutic goals for TS patients are to increase the patient’s height, promote the development of secondary sexual characteristics, and improve the quality of life, morbidity, and mortality. Girls with TS are often prone to fractures. Increased bone fragility in patients with TS might be due to X chromosome abnormality and/or estrogen deficiency.[17]

Several studies have examined the relationship between ERT and BMD in patients with TS.[13-14] Herein, we analyzed a large dataset of TS patients and treatment outcomes at tertiary hospitals to investigate the effects of HRT on BMD in Korean women with TS.

Our study will help TS patients in actual clinical practice.

The purpose of this study was to (1) investigate BMD in Korean women with TS, (2) evaluate clinical parameters and their relationship with ERT, and (3) investigate longitudinal changes in BMD.

II. MATERIALS AND METHODS

1. Study design and participants

This retrospective case-control study analyzed the medical records of patients with TS treated at Severance Hospital, Yonsei University College of Medicine (Seoul, South Korea) from 1997 to 2019. This study was conducted with approval from the Institutional Review Board (IRB) of Severance Hospital. TS diagnosis was based on peripheral blood chromosome analysis and clinical findings. A total of 188 TS patients who underwent bone density screening at least once were included in the study. All patients received regular and appropriate doses of estrogen during the treatment.

2. Control group

Healthy controls were selected from the Korean National Health and Nutrition Examination Survey (KNHANES), a nationwide, population-based, cross-sectional health examination survey regularly conducted by the Korea Centers for Disease Control and Prevention under the National Health Promotion Act. The survey selects a representative sample of the noninstitutionalized civilian Korean population using a stratified, multilevel, clustered probability sampling method. The survey samples approximately 10,000 individuals each year without overlap with previous samples, collecting information on socioeconomic conditions, health-related behaviors, quality of life, health care, anthropometric measures, and biochemical and clinical profiles for non-communicable diseases. The survey consists

of three components: health interview, nutrition survey, and health examination. Health interviews and medical examinations are conducted at mobile screening centers by trained employees, including doctors, medical technicians, and health interviewers, whereas nutritionists visit the homes of the study participants to conduct nutrition surveys. Participants of the survey provide written informed consent before enrollment. The KNHANES is conducted after ethical approval by the Institutional Review Board of the Korea Centers for Disease Control and Prevention (2010-02CON-21-C, 2011-02CON-06C). We chose females who participated in the KNHANES during 2010–2011 and excluded those who had a history of thyroid disease, end-stage renal disease, or malignancy, or whose information on dual-energy x-ray absorptiometry (DXA) was incomplete. The average BMD values and Z-scores of the selected individuals from the KNHANES (healthy control group) were considered.

3. Clinical data

We obtained clinical information of all TS patients (BMI, age, height, weight, the presence of spontaneous menarche, chromosome karyotype, Age at ERT initiation, duration of ERT, and BMD) from medical records and DXA data from Severance Hospital. The karyotype was categorized into 45XO and mosaic 45XO/46XX. Spontaneous menarche was defined as menarche that occurs without ERT and lasts for at least a year.

4. Measurement of BMD

Bone density was measured at the lumbar spine L1–L4 and femoral neck in TS patients. BMD was calculated as an absolute value (mg/cm2) and Z-score. The Z-score represents mean BMD with reference to the BMD (adjusted for body surface and vertebral volume) of age-matched healthy controls.[18]

5. Statistical analyses

SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) and R version 4.2.0 for Windows (R studio, Boston, MA, USA) were used for all statistical analyses. Summary statistics were expressed as mean ± standard deviation (SD), and frequency counts were expressed as a percentage. An independent t-test or Mann-Whitney U test was used for comparing groups. The independent t-test was used if the variables were normally distributed, and the variances were equal while the Mann-Whitney test was used for non-normally distributed data. Repeated measures analysis of variance (ANOVA) was used to investigate changes in the analyzed parameters over time. To investigate the relationship between continuous variables, the Pearson correlation coefficient (r) was calculated if both variables showed normal distribution. ANOVA was used to analyze differences between groups. Regression analysis was performed to determine the relationship between age at treatment initiation and treatment duration in the cross-sectional analysis. In all analyses, $p < 0.05$ was considered statistically significant.

III. RESULTS

1. Patient characteristics

The baseline characteristics of the TS group are presented in Table 1.

2. Comparison of BMD in women with TS and healthy Korean women

BMD values and Z-scores of each group were analyzed. BMD at the femoral neck was significantly lower in the TS group compared to that in healthy controls in all age groups (Table 2; Figures 1 and 2). Interestingly, lumbar spine BMD was also significantly lower in TS patients except in the 40–44 years age group (Table 3; Figures 3 and 4).

Table1. Clinical features of the study group

N= 188	Value
Age (years)	28.638 ± 6.115
Age at ERT initiation (years)	18.278 ± 5.719
Height (cm)	146.571 ± 9.678
Weight (kg)	48.925 ± 11.151
BMI (kg/m^2)	22.631 ± 4.285
Karyotype	
Monosomy	51 (27.128%)
Mosaic	137 (72.872%)
GH	
Yes	76 (40.426%)
NO	112 (59.574%)

Data are presented as mean ± SD or N (%). *SD* standard deviation.

ERT estrogen replacement therapy, *BMI body* mass index, *GH* growth hormone.

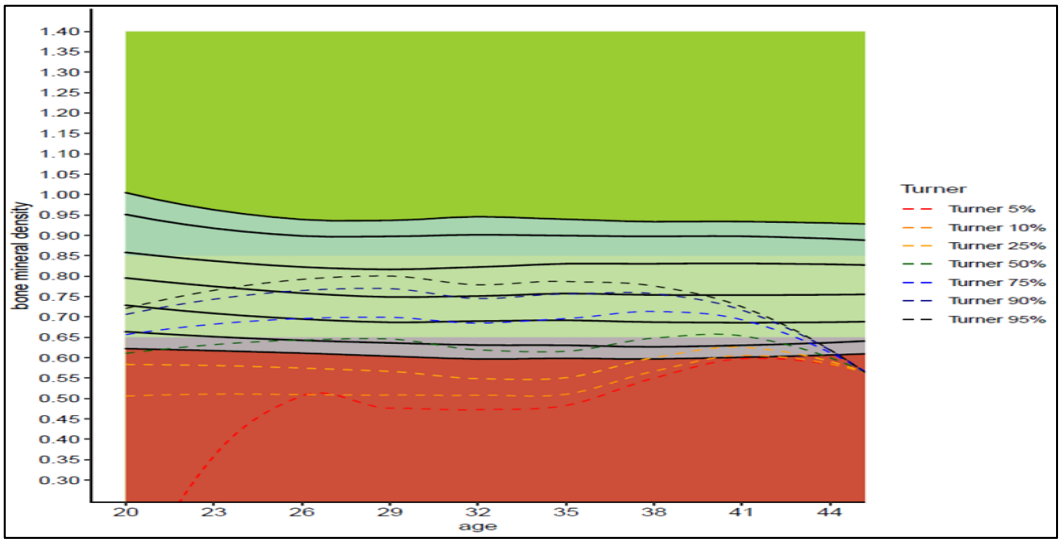


Figure 1. Femoral neck BMD (g/cm2) in Korean women with TS and healthy controls. Solid black lines, data of normal controls from KNHANES; dashed lines, data of TS patients according to the percentile BMD of the femoral neck. BMD was lower in the TS group compared to that in healthy controls.

Table 2. Femoral neck BMD (g/cm2) in Korean women with TS and healthy controls.

Age group	Women with TS	Healthy controls	*p-values*
20–24 years	0.668 ± 0.119 (N = 149)	0.787 ± 0.107 (N = 545)	< 0.001
25–29 years	0.650 ± 0.109 (N = 141)	0.763 ± 0.101 (N = 649)	< 0.001
30–34 years	0.623 ± 0.106 (N = 119)	0.759 ± 0.103 (N = 872)	< 0.001
35–39 years	0.615 ± 0.100 (N = 84)	0.758 ± 0.103(N= 1124)	< 0.001
40–44 years	0.674 ± 0.078 (N = 6)	0.763 ± 0.103 (N = 965)	0.035
45–50 years	0.446 ± 0.008 (N = 2)	0.746 ± 0.106 (N = 1156)	< 0.001

Data are presented as mean ± SD. Unpaired t-test was used for statistical analysis.

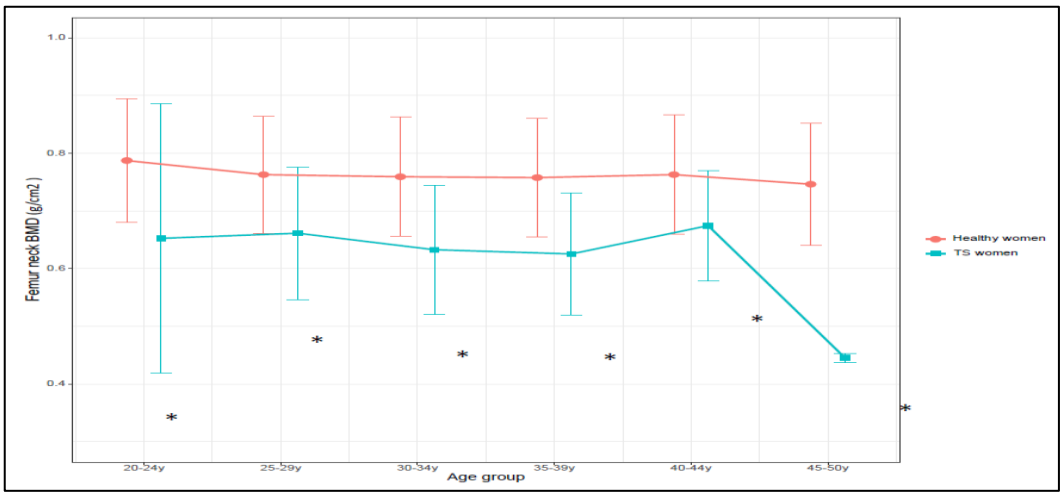


Figure 2. Average femoral neck BMD in Korean women with TS and healthy controls. Femoral neck BMD was lower in Korean women with TS than in healthy controls.
*$p < 0.05$ vs. healthy control of the same age group.

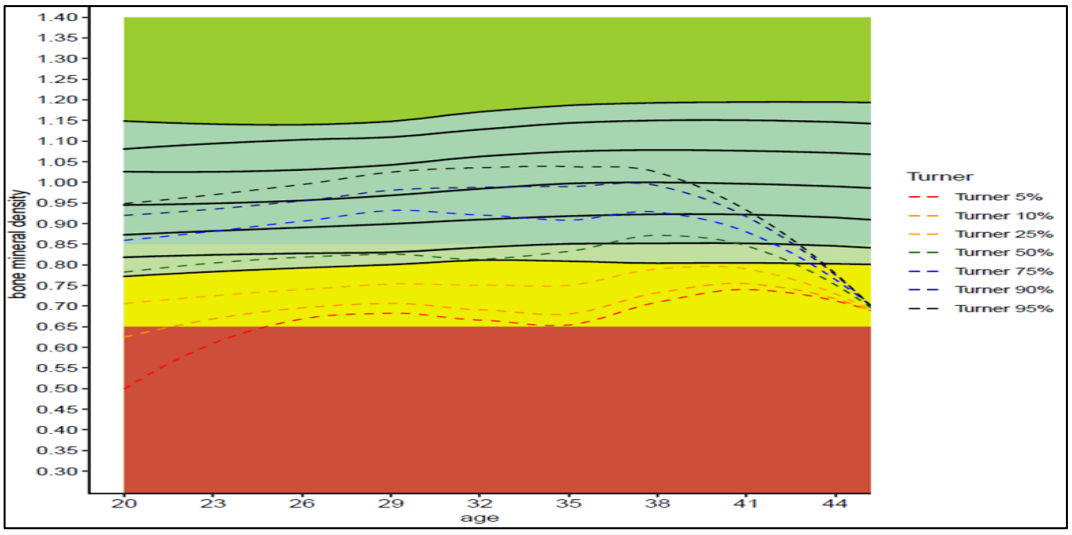


Figure 3. Lumbar spine (L1–L4) BMD (g/cm2) in Korean women with TS and healthy controls. Solid black lines, data of normal controls from KNHANES; dashed lines, data of TS patients according to the percentile BMD of the lumbar spine. BMD was lower in TS patients compared to normal controls.

Table3. Lumbar spine (L1–L4) BMD (g/cm2) in Korean women with TS and healthy controls.

Age group	Women with TS	Healthy controls	*p-values*
20–24 years	0.835 ± 0.126 (N = 154)	0.958 ± 0.111 (N = 545)	< 0.001
25–29 years	0.841 ± 0.121 (N = 142)	0.965 ± 0.107 (N = 649)	< 0.001
30–34 years	0.837 ± 0.124 (N = 119)	0.988 ± 0.114 (N = 872)	< 0.001
35–39 years	0.840 ± 0.124 (N = 85)	0.998 ± 0.116 (N = 1124)	< 0.001
40–44 years	0.847 ± 0.220 (N = 6)	1.000 ± 0.120 (N = 965)	0.150
45–50 years	0.596 ± 0.021 (N = 2)	0.971 ± 0.131 (N = 1156)	< 0.001

Data are presented as mean ± SD. Unpaired t-test was used for statistical analysis.

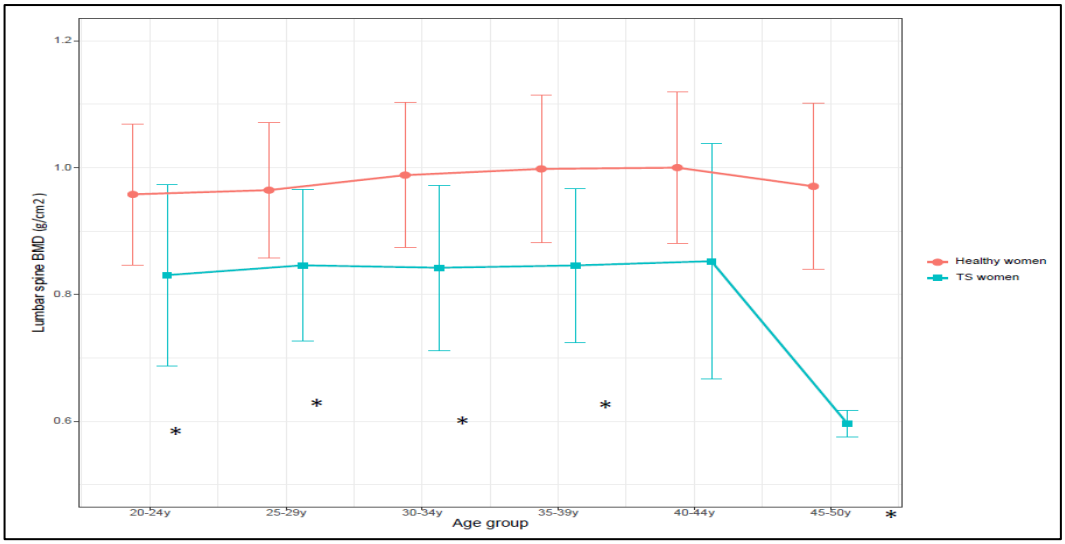
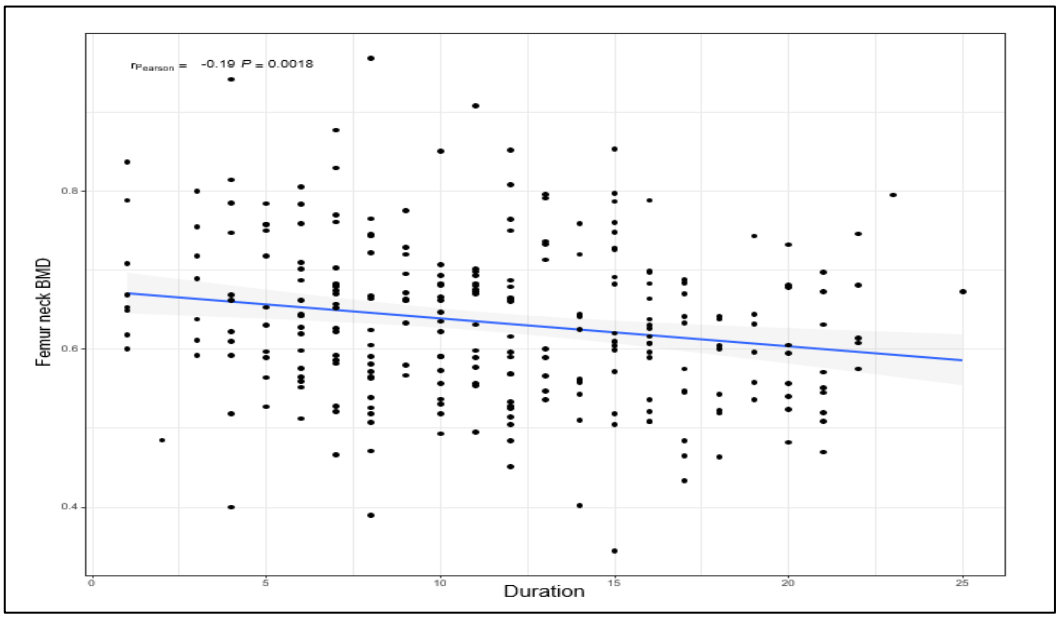


Figure 4. Average lumbar spine (L1–L4) BMD in Korean women with TS and healthy controls. BMD was lower in Korean women with TS than in healthy controls.
*$p < 0.05$ compared to healthy women of the same age group.

3. Effects of duration of ERT on BMD in women with TS

The association of ERT duration with femoral neck and lumbar spine BMD and annual change in BMD was evaluated using multiple regression analysis (Figures 5 and 6). ERT duration was significantly negatively associated with femoral neck BMD value ($r = -0.19$, p=0.0018); however, no association between ERT duration and femoral neck BMD Z-scores was observed ($r = -0.037$, p =0.55). Furthermore, the r-value of the femoral neck BMD was low. ERT duration was significantly positively associated with lumbar spine (L1-L4) BMD Z-scores (p = 0.024), but not with absolute BMD values (p = 0.15).

(A)



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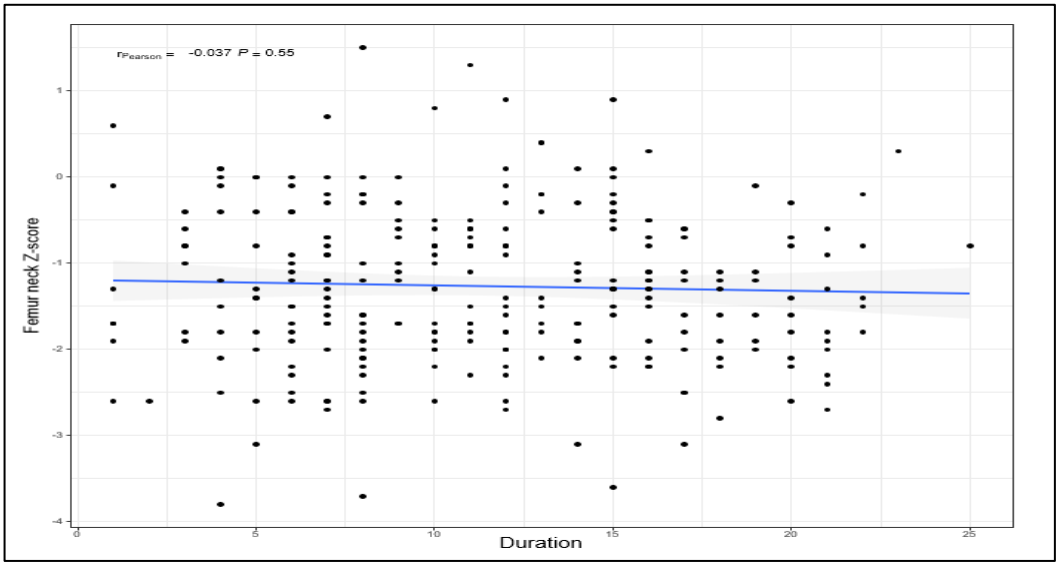
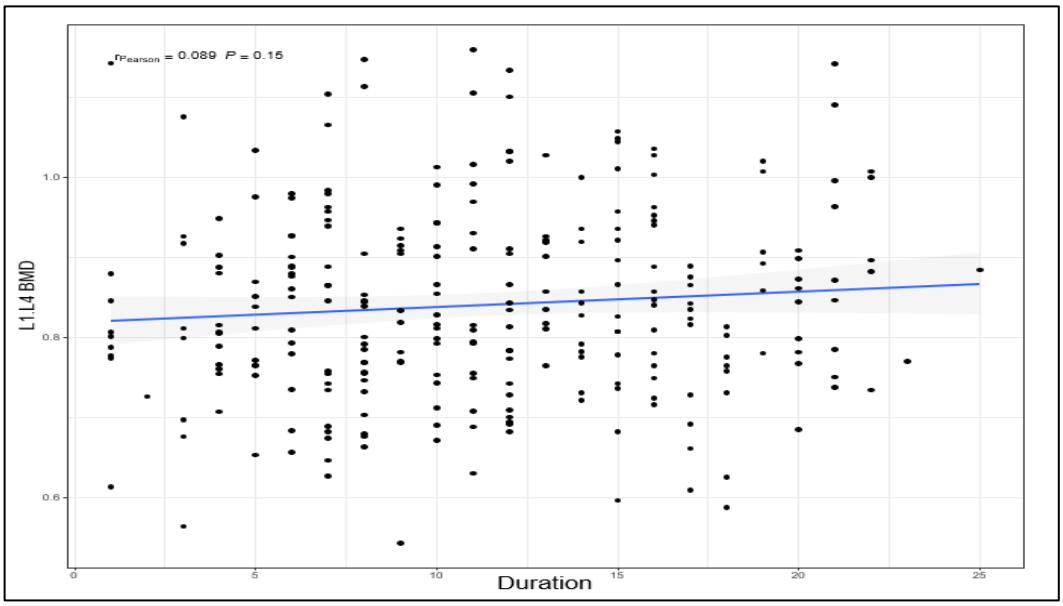


Figure.5. Association between ERT duration and femoral neck BMD. Longer ERT duration tended to be associated with lower femoral neck BMD.

(A)



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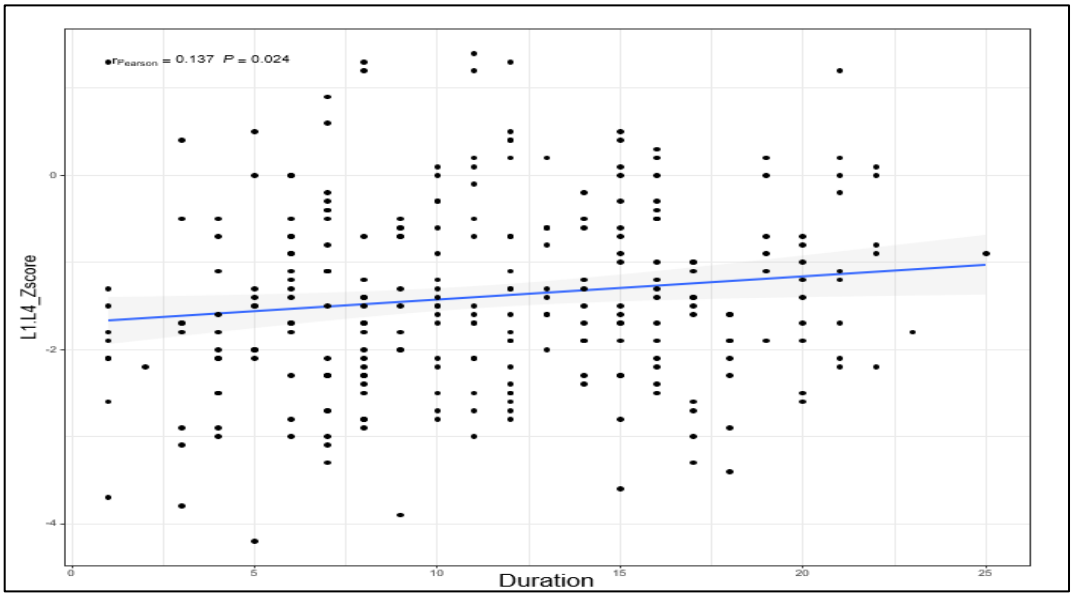
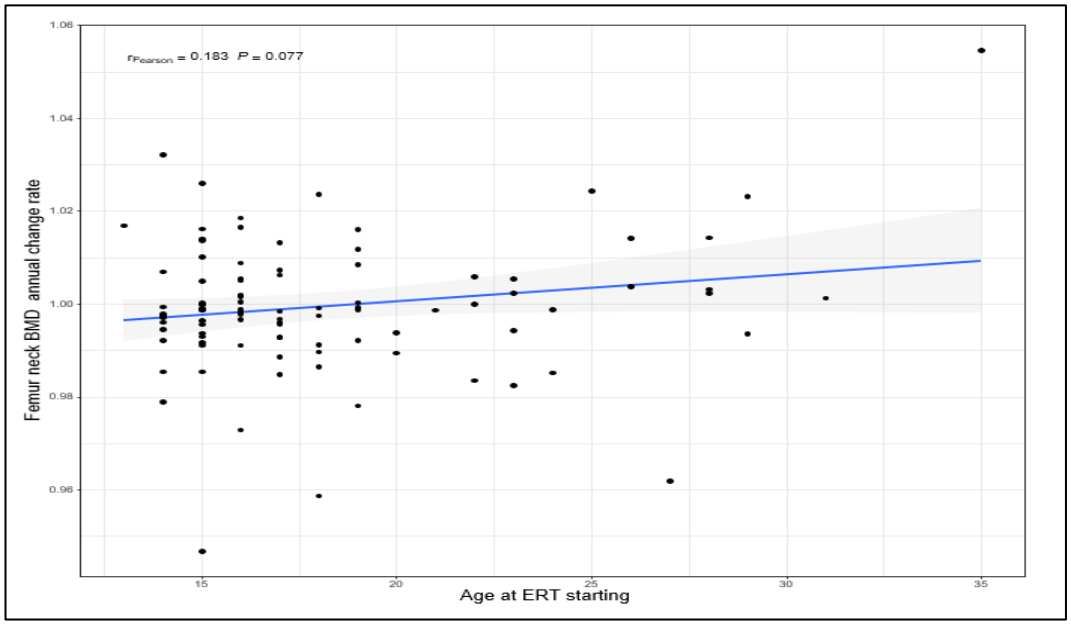


Figure 6. Association between ERT duration and lumbar spine (L1-L4) BMD. Longer ERT duration was associated with higher lumbar spine BMD Z-scores.

4. Association between age at ERT initiation and BMD in women with TS

We examined the association of annual change rate in the femoral neck and lumbar spine (L1-L4) BMD with age at ERT initiation and treatment duration (Figures 7 and 8). Results showed that age at ERT initiation was positively associated with the annual change rate of femoral neck BMD, although the difference was not statistically significant ($r = 0.183$, $p = 0.077$; Figure 7A). Furthermore, the annual change rate in femoral neck BMD was positively associated with age ($r = 0.207$, $p = 0.0088$; Figure 7B). The age at ERT initiation showed no correlation with the annual change rate in femoral neck BMD when analyzed according to the age group, except for the 35-39 years age group (Figure. 7C–F).

(A)



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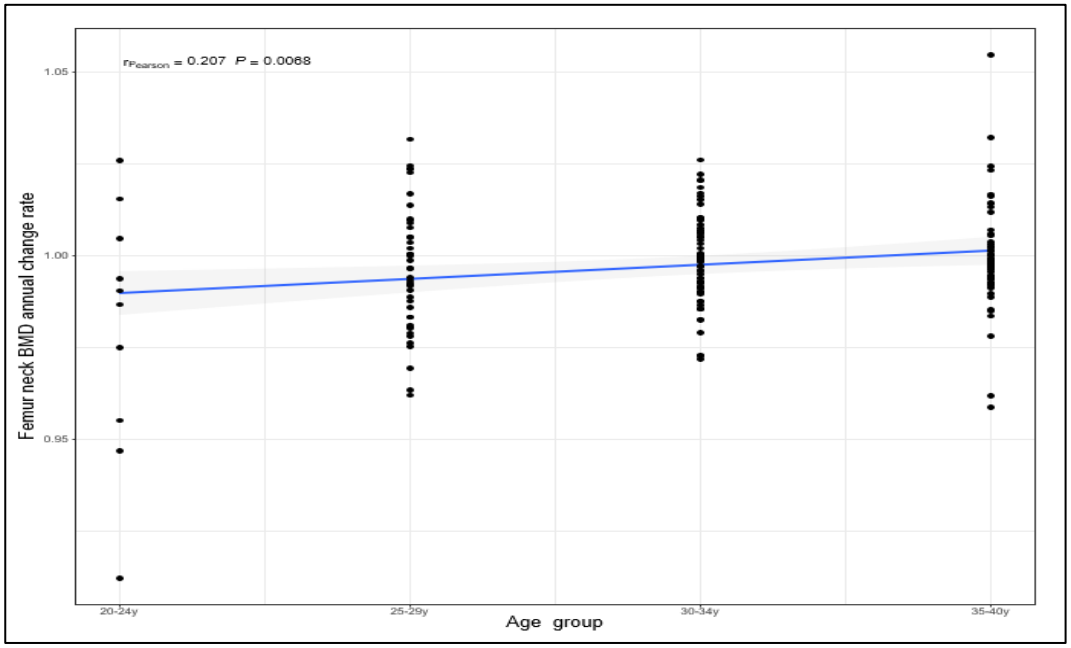
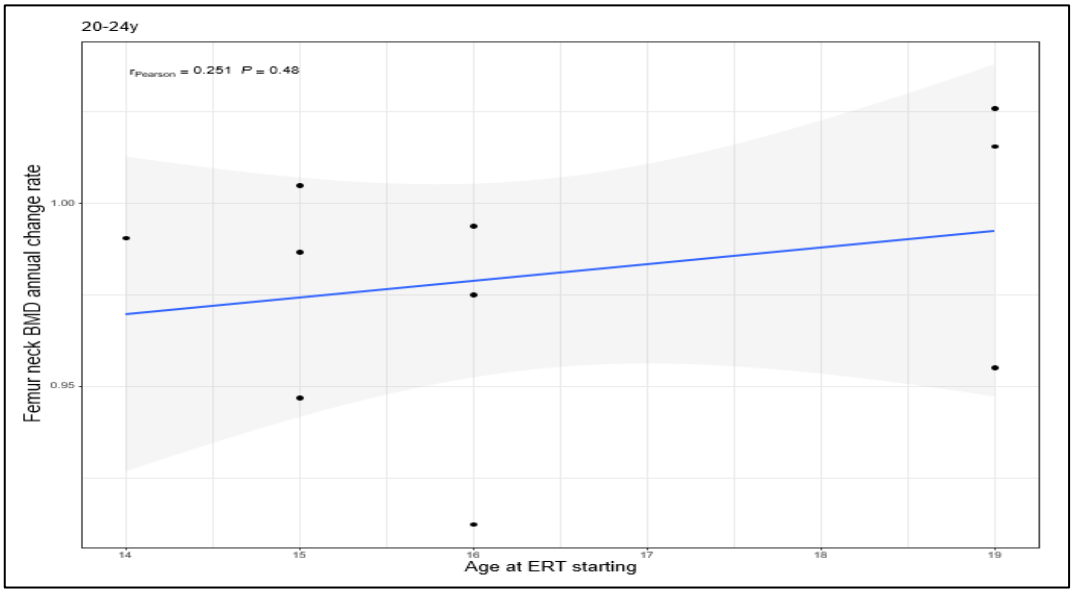


(C)



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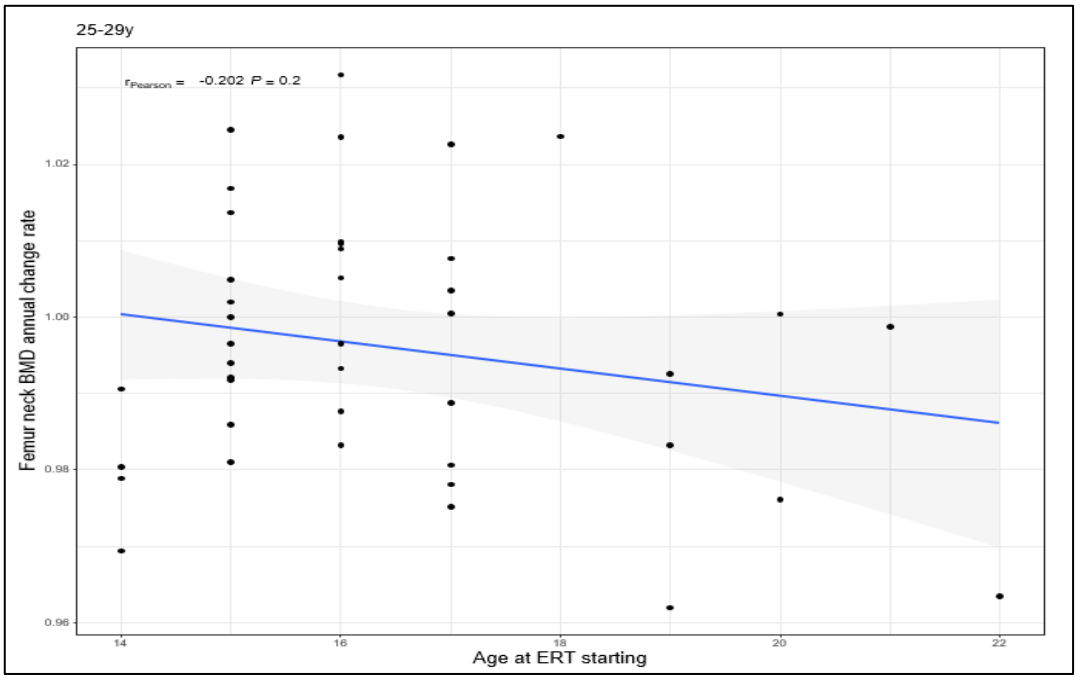

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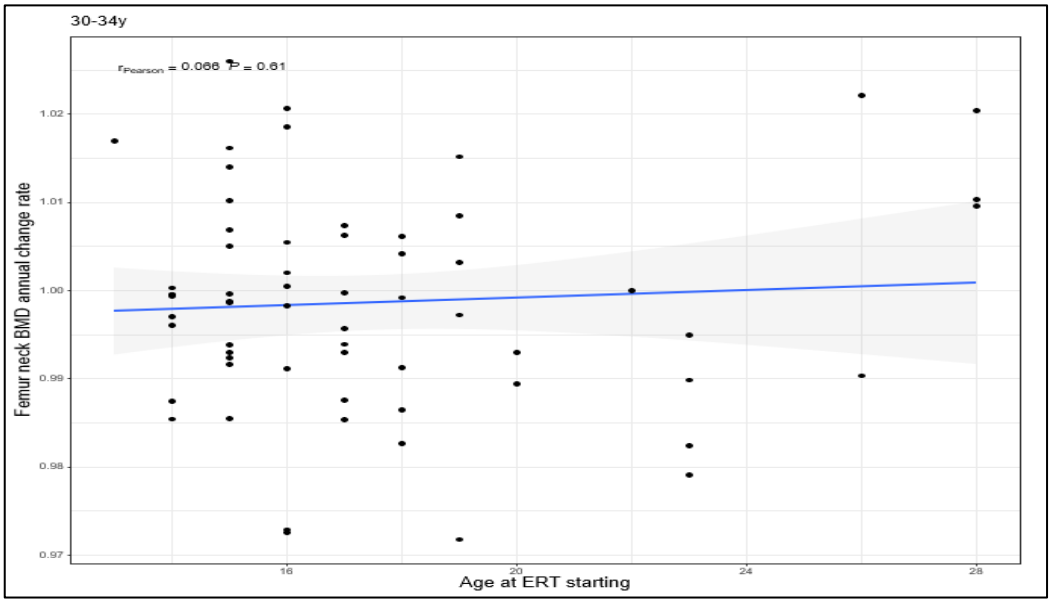

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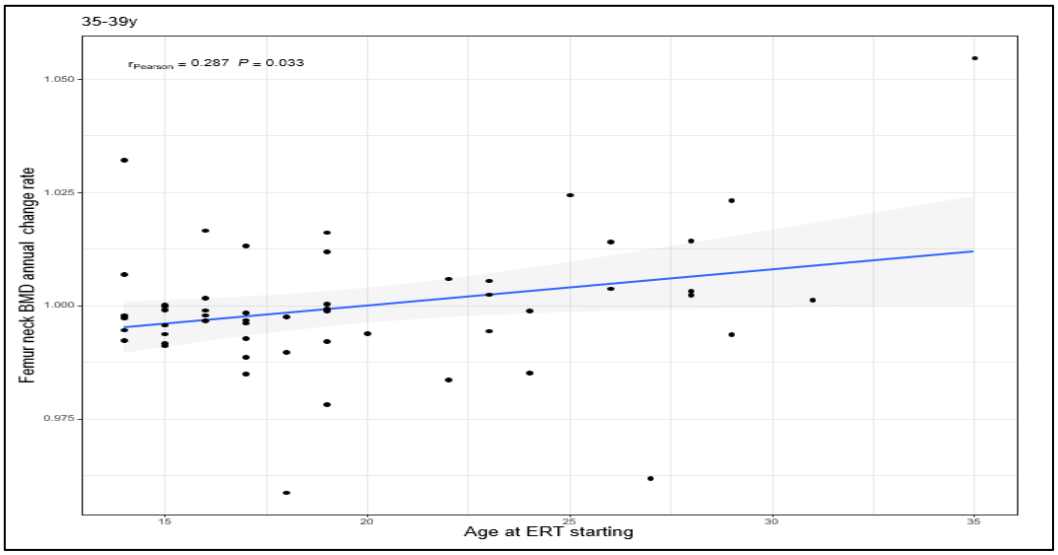
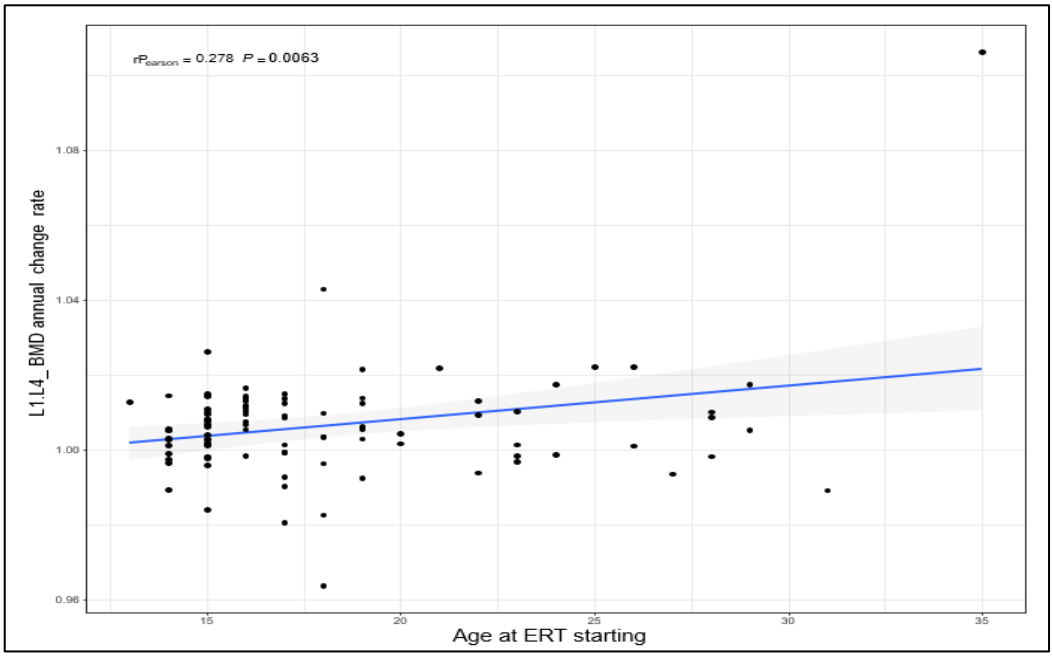


Figure 7. Annual change rate in femoral neck BMD. Age at ERT initiation was positively associated with the annual change rate in femoral neck BMD, although the difference was not statistically significant.

Moreover, the age at ERT initiation was significantly and positively associated with the annual change rate of lumbar spine (L1–L4) BMD (r = 0.278, p = 0.0063; Figure 8A). Conversely, a negative association was observed in the younger age group (r = −0.155, p = 0.042; Figure 8B). The age at ERT initiation showed no correlation with the annual change rate of lumbar spine BMD when analyzed according to the age group, except for the 34–39 years age group (Figure 8C–F).

(A)



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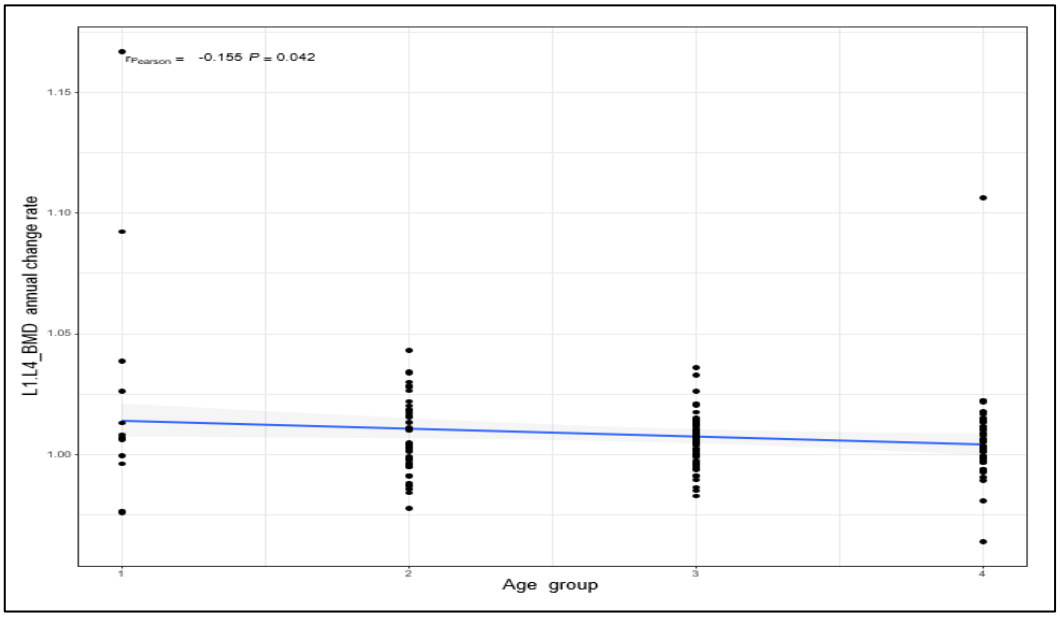

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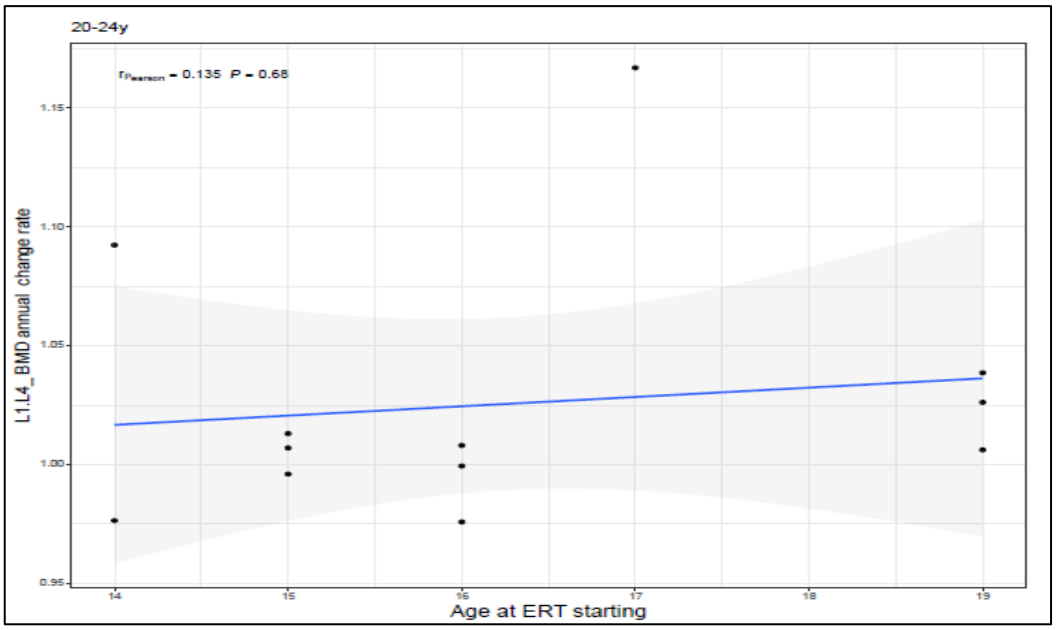

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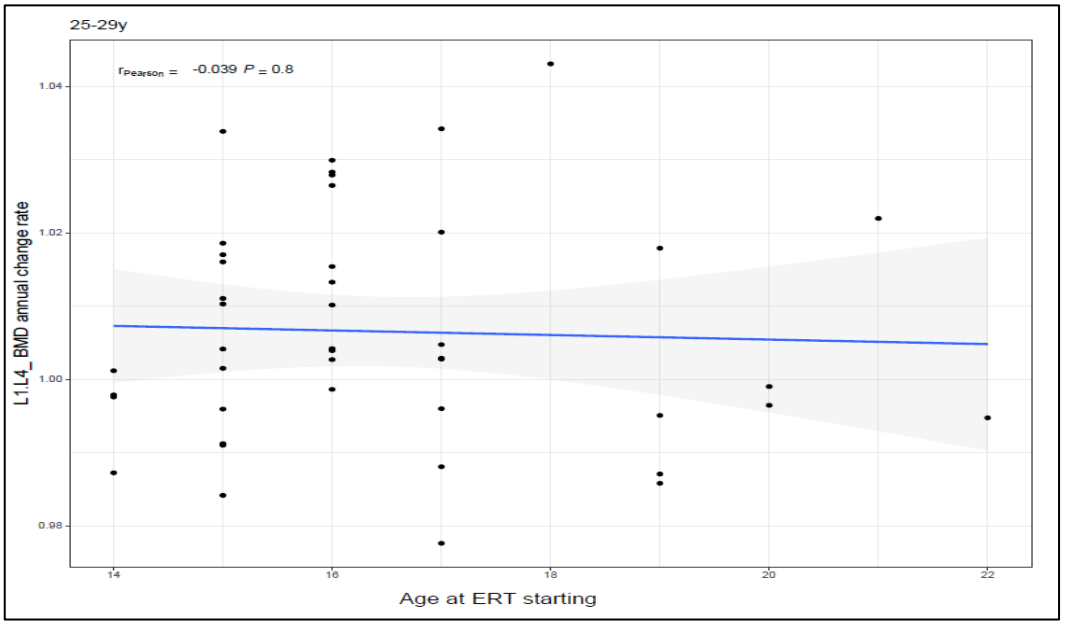

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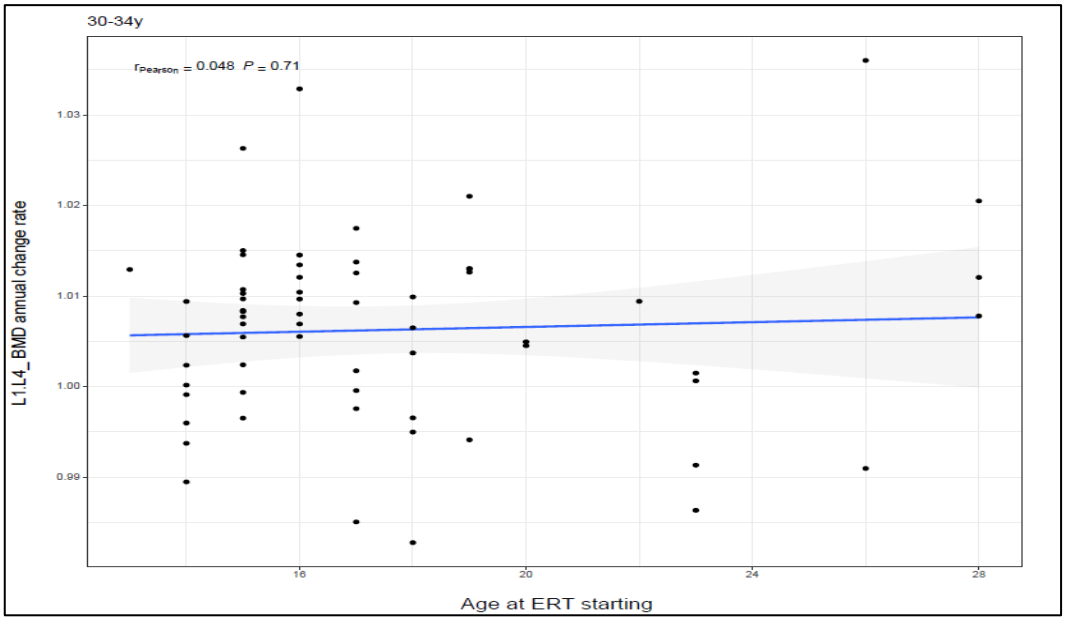

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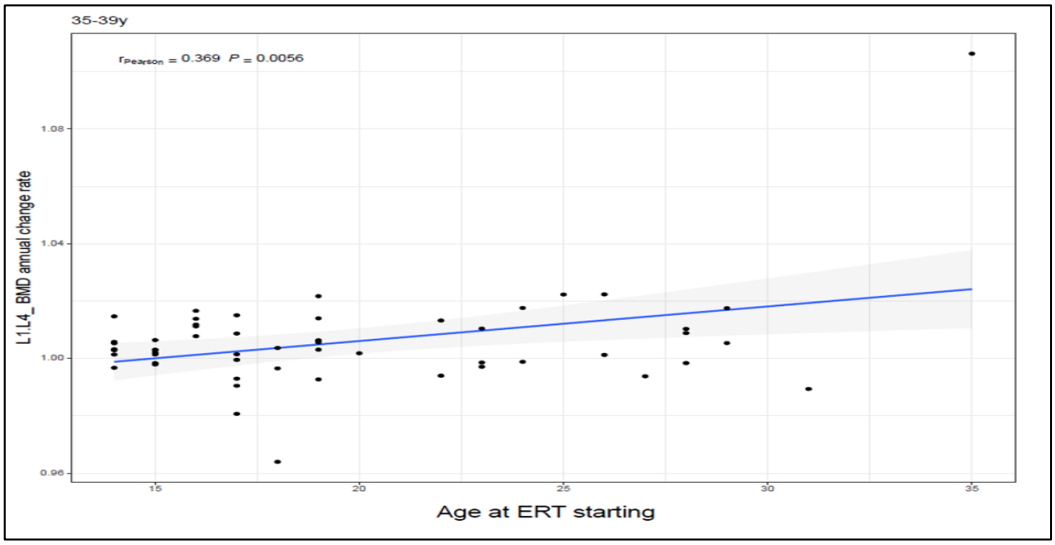

Figure 8. Annual change rate of the lumbar spine (L1–L4) BMD. The age at ERT initiation was significantly and positively associated with the annual change rate of lumbar spine BMD (r = 0.278, p = 0.0063). However, when analyzed according to the age group, no correlation was observed, except for the 35–39 years age group.

5. Comparison of TS patients according to the mosaicism

We investigated the karyotype of women with TS and categorized them into two groups: (1) without mosaicism (45 XO) and (2) with mosaicism. Femoral neck BMD values and Z-scores were significantly higher in women with mosaicism than in those without mosaicism (p = 0.044 and 0.023, respectively; Table 4, Figure 9). However, there was no significant difference in the lumbar spine BMD value or Z-score between TS patients with and without mosaicism (p = 0.124 and 0.365, respectively; Table 5, Figure10).

Table 4. Femoral neck BMD (value and Z-score) by karyotype.

	0 (N=146)	1 (N=355)	*p*
Femoral neck BMD	0.627± 0.109	0.649± 0.112	0.044
Femoral neck Z-score	1.403± 0.963	-1.184± 0.987	0.023

Data are expressed as the mean ± SD. *p* Values were determined using the Student's unpaired t-test.

0) Karyotype 45 XO, 1) Karyotype with mosaicism.

Table 5. Lumbar spine (L1-L4) BMD (value and Z-score) by karyotype.

	0 (N=148)	1 (N=360)	*p*
L1-L4 BMD	0.851± 0.137	0.832± 0.120	0.124
L1-L4 Z-score	-1.3883± 1.222	-1.488± 1.088	0.365

Data are expressed as the mean ± SD. *p* Values were determined using the Student's unpaired t-test.

0) Karyotype 45 XO, 1) Karyotype with mosaicism.

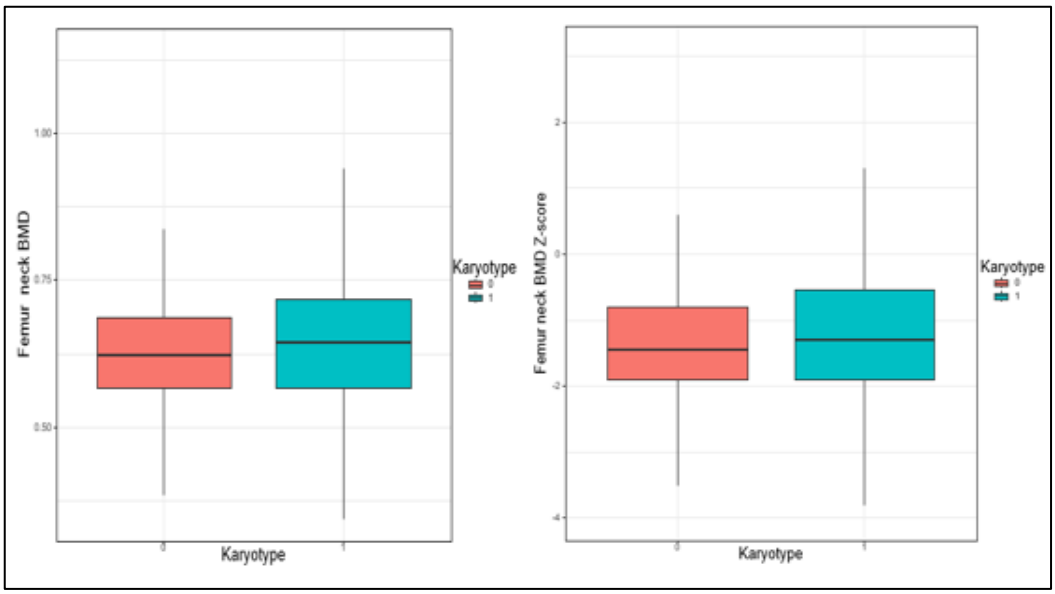

Figure 9. Femoral neck BMD (value and Z-score) by karyotype.

0) Karyotype 45 XO, 1) Karyotype with mosaicism.

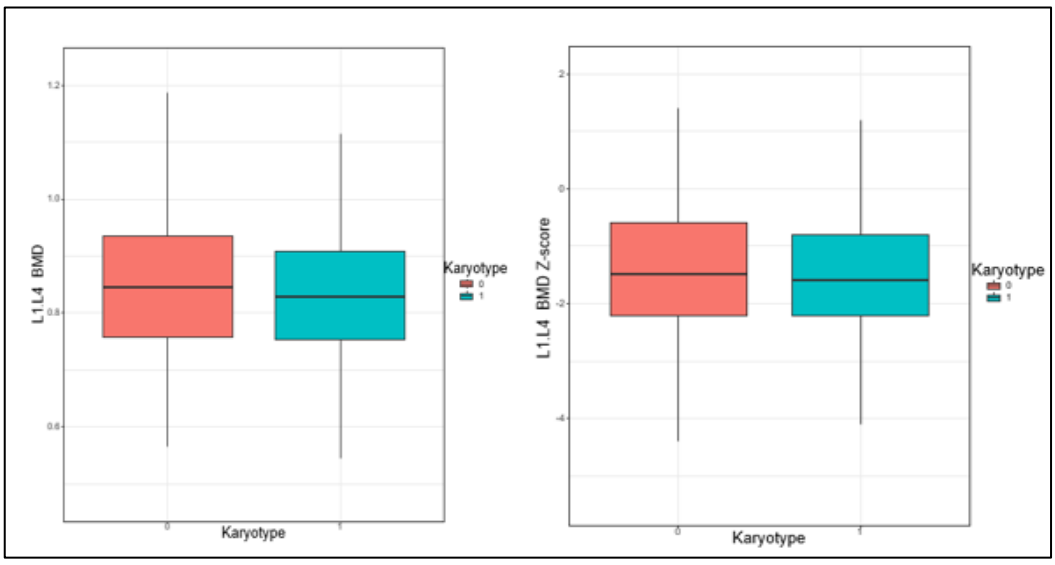

Figure 10. Lumbar spine (L1-L4) BMD (value and Z-score) by karyotype.

0) Karyotype 45 XO, 1) Karyotype with mosaicism.

6.**Analysis of factors responsible for low BMD in TS patients**

We divided TS patients into two groups according to their BMD Z-scores. The group with a BMD score > -2.0 (normal BMD) included 323 patients while that with a BMD score ≤ -2.0 (low BMD) included 94 patients. We analyzed the age at ERT initiation, ERT duration, karyotype, ERT status, and GH use in each group. Results showed that BMI was the only factor that significantly affected femoral neck BMD (Table 6).

Table 6. Factors affecting femoral neck BMD.

BMD Z-score	>-2.0 (N=323)	≤-2.0 (N=94)	*p*
Age at ERT initiation	17.909 ± 4.634	18.615 ± 5.599	0.273
Duration of ERT	10.603 ± 5.815	9.780 ± 6.530	0.248
Karyotype			0.649
0	93 (28.793%)	30 (31.915%)	
1	230 (71.207%)	64 (68.085%)	
Age at BMD evaluation	28.402 ± 5.666	28.606 ± 6.328	0.765
ERT status			0.704
0	6 (1.858%)	3 (3.191%)	
1	317 (98.142%)	91 (96.809%)	
GH			0.273
0	136 (42.105%)	33 (35.106%)	
1	187 (57.895%)	61 (64.894%)	
BMI	23.368 ± 4.520	21.245 ± 3.097	<0.01

Data are mean ± SD or *N* (%). *p* Values were determined using the Student's unpaired *t* test. *Karyotype 0* -45 XO, *Karyotype 1*–mosaic 45XO/46XX. *ERT status 0* – without ERT, *ERT status 1*- with ERT. *GH 0* - without GH, *GH 1* – with GH.

Similarly, we divided TS patients into two groups according to the lumber spine BMD Z-scores. As shown in Table 7, 278 subjects had a normal BMD Z-score (> -2.0) and 144 subjects had a low BMD Z-score (≤ -2.0). The age at ERT initiation, ERT duration, and BMI were significantly associated with the lumbar spine BMD (p = 0.001, < 0.01, and < 0.01, respectively).

Table 7. Factors affecting the BMD in lumbar spine L1-L4.

BMD Z-score	>-2.0 (N=278)	≤-2.0 (N=144)	*p*
Age at ERT initiation	17.368 ± 3.898	19.357 ± 6.106	0.001
Duration of ERT	11.162 ± 5.806	8.821 ± 6.031	<0.01
Karyotype			0.683
0	84 (30.216%)	40 (27.778%)	
1	194 (69.784%)	104 (72.222%)	
Age at BMD evaluation	28.421 ± 5.737	28.333 ± 6.050	0.884
ERT status			0.953
0	6 (2.158%)	4 (2.778%)	
1	272 (97.842%)	140 (97.222%)	
GH			0.066
0	104 (37.410%)	68 (47.222%)	
1	174 (62.590%)	76 (52.778%)	
BMI	23.499 ± 4.298	21.672 ± 4.087	<0.01

Data are mean ± SD or *N* (%). *p* Values were determined using the Student's unpaired *t* test. *Karyotype 0* -45 XO, *Karyotype 1*–mosaic 45XO/46XX. *ERT status 0* – without ERT, *ERT status 1*- with ERT. *GH 0* - without GH, *GH 1* – with GH.

V.DISCUSSION

Herein, we analyzed a large dataset to evaluate BMD in Korean women with TS. Women with TS included in this study were 20–50 years old and had a lower BMD than healthy controls. Similar results have been reported from other countries.[13,28-29]

Our study suggests that estrogen plays a critical role in regulating BMD in women with TS. It has been observed that very few girls with TS exhibit spontaneous puberty, and most of them require ERT to initiate or maintain pubertal development.[19] which, in turn, aids in maintaining secondary sexual characteristics and achieving maximum bone mass.[1]

Previous studies have shown the importance of estrogen for bone health. However, previous studies on the association between BMD in women with TS and the age at ERT initiation are conflicting. Nevertheless, several studies showed that early initiation of ERT is necessary for achieving higher BMD

Many studies indicate that the early induction of ERT is beneficial for achieving higher BMD in adults with TS.[12-13,24] In recent years, ERT has been used to increase or maintain the lumbar BMD.[21-22] The mineral density of cortical bones is lower than that of trabecular bones in girls with TS.[31] Therefore, we investigated the effect of ERT on the femoral and lumbar spine (L1–L4) BMD.

Nishigaki *et al.* reported that the starting age of HRT showed a negative and significant association with BMD, indicating the importance of early introduction of ERT to acquire better bone mineral density.[24]

Although we expected that our results will be similar to those of previous studies,[12,24,28-30] there were significant differences. First, we analyzed the annual change rate of BMD in the lumbar spine and femoral neck according to age at ERT initiation. Results showed that age at ERT initiation is positively associated with the annual change rate of lumbar spine and femoral neck BMD, although statistical significance was not always observed. Second, we analyzed the annual change rate of BMD in the lumbar spine and femoral neck according to ERT duration. We found that ERT duration was positively associated with the increase

in the lumbar spine BMD, whereas femoral neck BMD tended to decrease with long-term ERT. However, it cannot be concluded that our results differ from those of the previous studies[21-22,24,28-30] because we have not analyzed the BMD but its annual change rate. Women with TS who received ERT at an older age had a lower BMD, and changes due to ERT observed in our study were greater than those observed in previous studies.[21-22,24,28-30]

Next, we compared the BMD of women with TS according to the karyotype (Figures 9, 10; Tables 4, 5) and obtained conflicting results. Femoral neck BMD (value and Z-score) was significantly higher (BMD $p = 0.044$, Z-score $p = 0.023$) in TS women with mosaicism. Conversely, lumbar spine BMD (value and Z-score) was higher in women with the 45 XO karyotype, although the difference was not statistically significant (BMD $p = 0.124$, Z-score $p = 0.365$). Since there are several reports of spontaneous menarche in women with mosaic TS, it is generally accepted that BMD is higher in these patients.[29,32]

In our study, femoral neck BMD was higher in patients with the mosaic karyotype compared to those with the 45 XO karyotype, whereas lumbar spine BMD showed the opposite trend. Thus, karyotype might not affect the lumbar spine density in women with TS. This observation can be explained by the fact that ERT initiation is relatively late in mosaic TS patients due to spontaneous puberty or delayed diagnosis, which could be the reason for low lumbar BMD in this subgroup.

As shown in Tables 6 and 7, we analyzed factors affecting BMD of the femoral neck and lumbar spine. Age at ERT initiation, ERT duration, and BMI were significantly associated with the lumbar spine BMD in TS women, and among them, age at ERT initiation was the most important ($p = 0.001$).

Based on the results of this study and those of previous studies,[24,28-30] the relationship between BMD and age at ERT initiation and ERT duration in young adults with TS can be summarized as follows. Age at ERT initiation is significantly associated with BMD, indicating the importance of early ERT initiation in acquiring higher BMD. Furthermore, ERT duration is significantly associated with lumbar spine BMD, confirming its importance in maintaining and improving BMD. Since we also observed annual changes

in BMD even in women with late TS diagnosis and delayed ERT initiation, this therapy may help in increasing the BMD of these patients. Furthermore, age at initiation and the duration of ERT were not significantly associated with femoral neck BMD in women with TS (age at ERT initiation, $p = 0.273$; ERT duration, $p = 0.248$). Only BMI significantly affected the femoral neck BMD ($p = 0.01$). Since the BMD of cortical bones is lower than that of trabecular bones in girls with TS,[31] the BMD of cortical bones, such as the femur, seems to be relatively unaffected by ERT.

Limitations

This study has some limitations. Because of the retrospective nature of the study, the ERT protocol was not unified. Therefore, we were unable to rule out potential biases due to differences in the ERT regimen. Since bone strength is characterized by both BMD and bone quality, evaluation of bone quality is equally important. Recently, trabecular bone score (TBS) has been established for bone quality evaluation[23,26]; however, TBS was not used in our study and only BMD was measured. Another limitation is that we have not evaluated other factors that are known to affect BMD, such as physical fitness and vitamin D deficiency.[23,27]

GH is often administered before initiating ERT in TS patients, which also affects bone density. Thus, the effectiveness of GH in increasing bone density should also be evaluated in these patients. The potential effects of GH on bone density in TS patients have been reported,[33] and combination therapy with estrogen and GH may lead to higher spinal BMD than ET alone.[34] In this study, the effect of GH on BMD was not statistically significant ($p = 0.066$), which might be due to the small number of study subjects.

This study was conducted for exploratory purposes and the sizes of the groups were different. Because cross-sectional analysis lacks the accuracy of cohort studies, we believe that larger cohort studies are needed to confirm the results of this study. To clearly understand the factors affecting BMD in young women with TS, this preliminary analysis will be useful in the future.

V. CONCLUSION

Women with TS have low BMD, which is associated with late ERT initiation and shorter treatment duration. Thus, early initiation and long-term use of estrogens in TS patients can increase BMD. Further studies on a larger cohort are needed to confirm our conclusions.

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APPENDICES

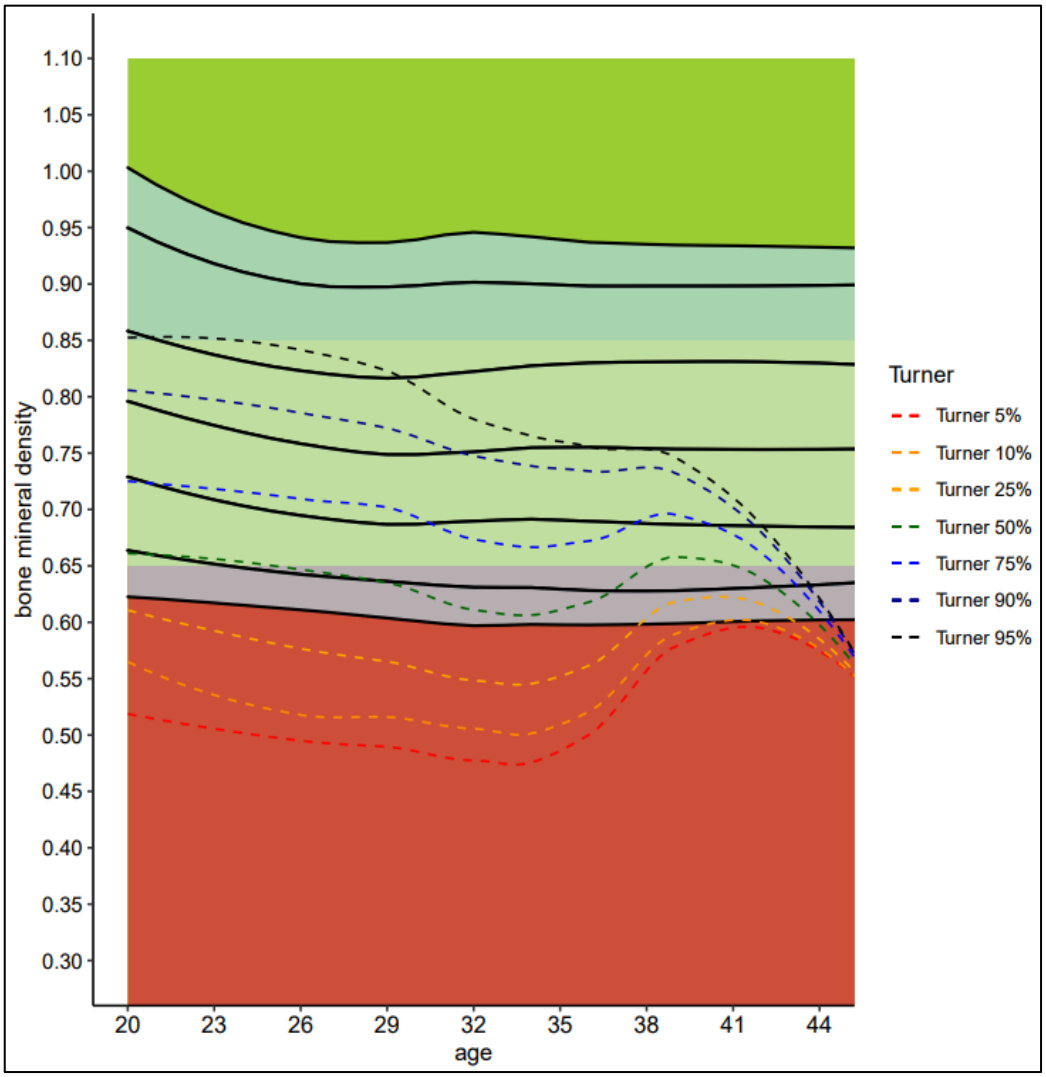


Figure1. Femoral neck BMD (g/cm2) in Korean women with TS and healthy controls. Solid black lines, data of normal controls from KNHANES; dashed lines, data of TS patients according to the percentile BMD of the femoral neck. BMD was lower in the TS group compared to that in healthy controls.

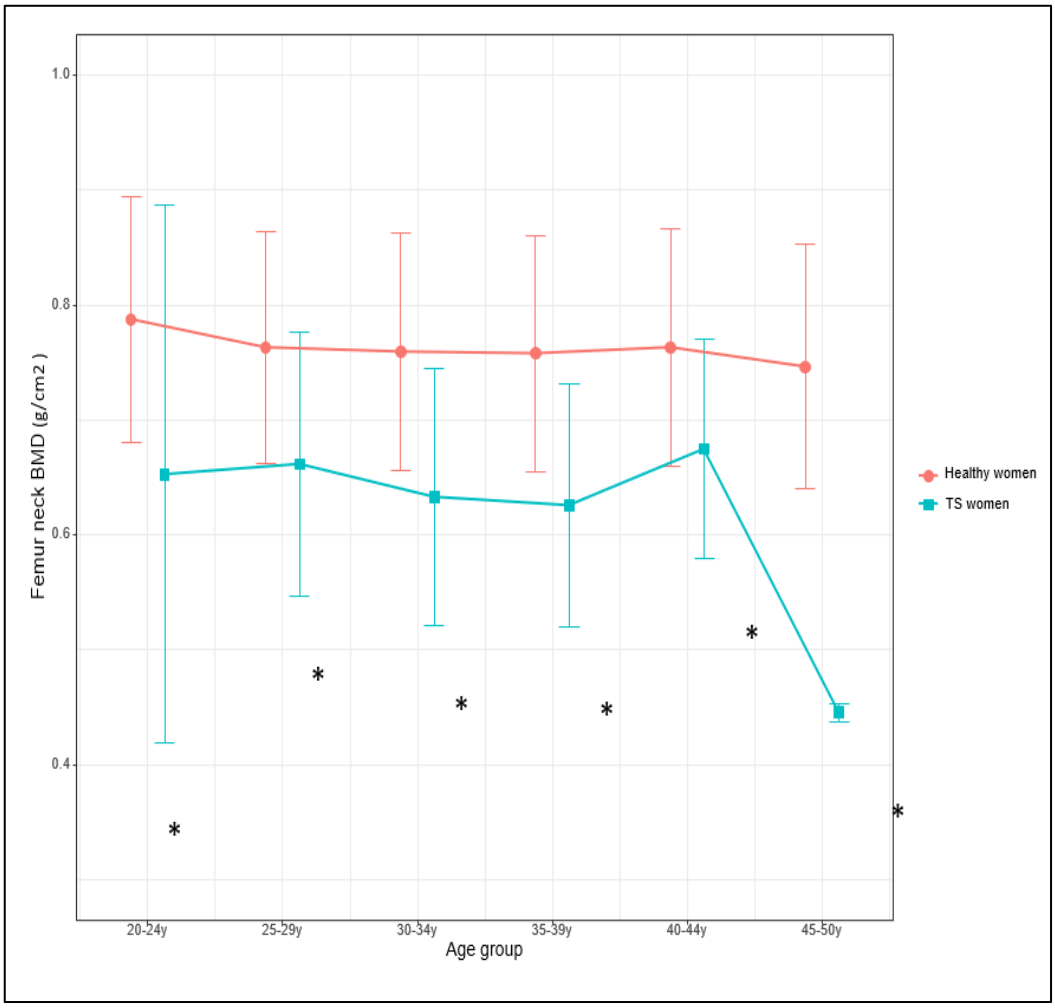


Figure 2. Average femoral neck BMD in Korean women with TS and healthy controls. Femoral neck BMD was lower in Korean women with TS than in healthy controls.

*$p < 0.05$ vs. healthy control of the same age group.

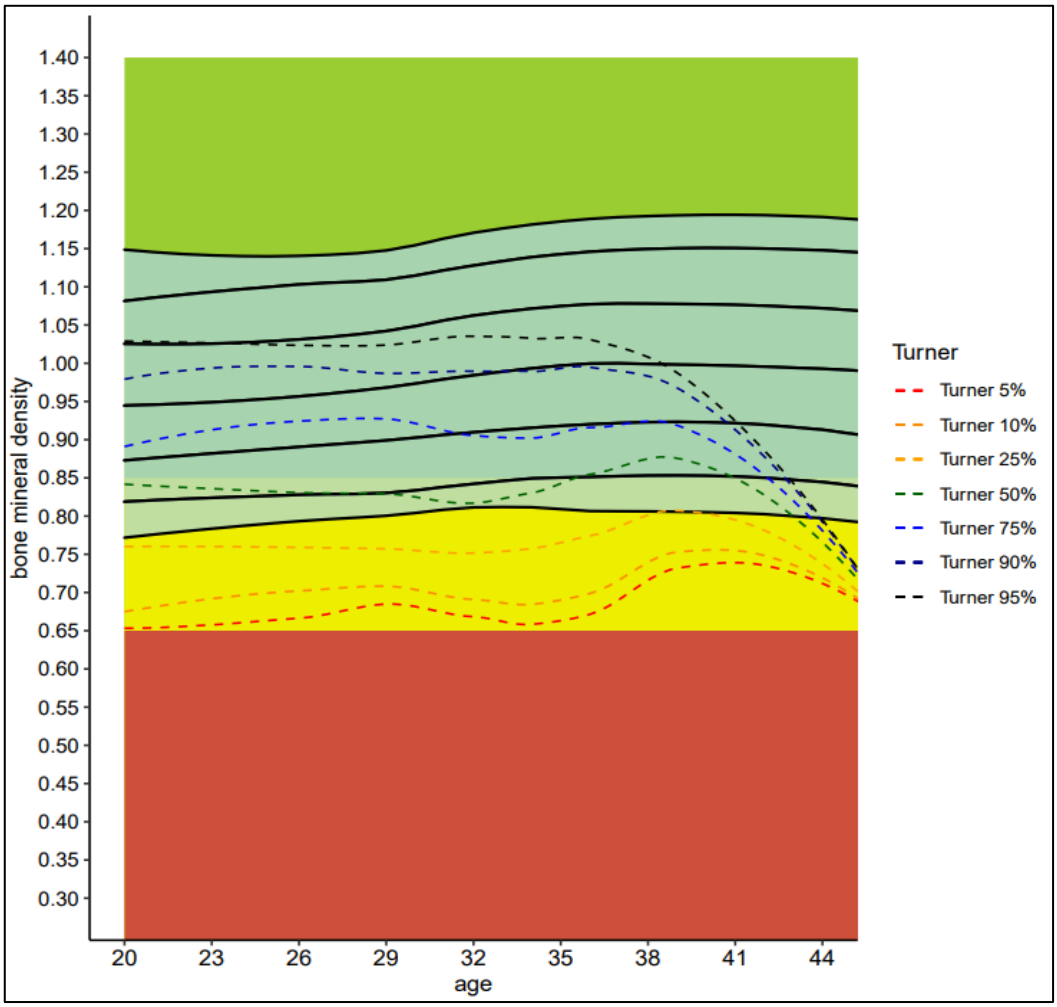


Figure 3. Lumbar spine (L1–L4) BMD (g/cm2) in Korean women with TS and healthy controls. Solid black lines, data of normal controls from KNHANES; dashed lines, data of TS patients according to the percentile BMD of the lumbar spine. BMD was lower in TS patients compared to normal controls.

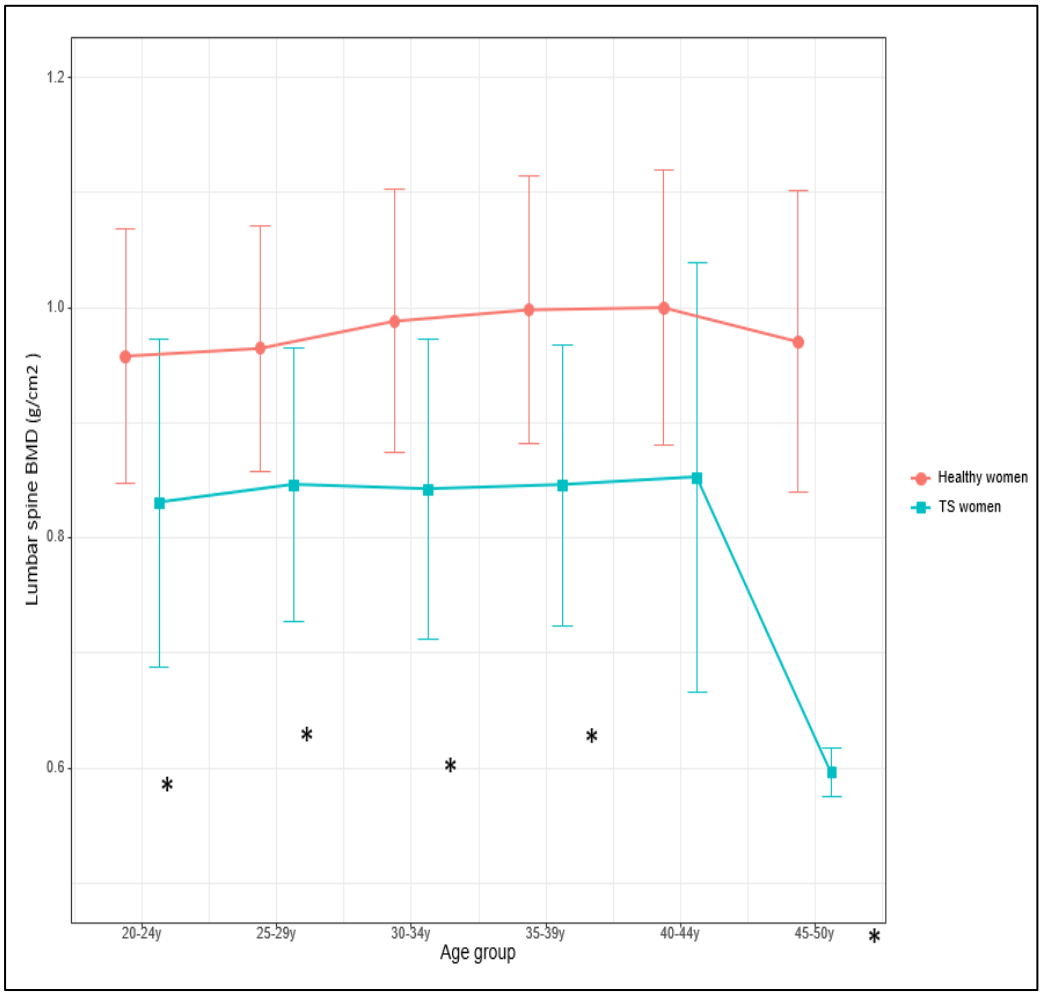


Figure 4. Average lumbar spine(L1–L4) BMD in Korean women with TS and healthy controls was lower in Korean women with TS than in healthy controls.

*$p < 0.05$ compared to healthy women of the same age group.

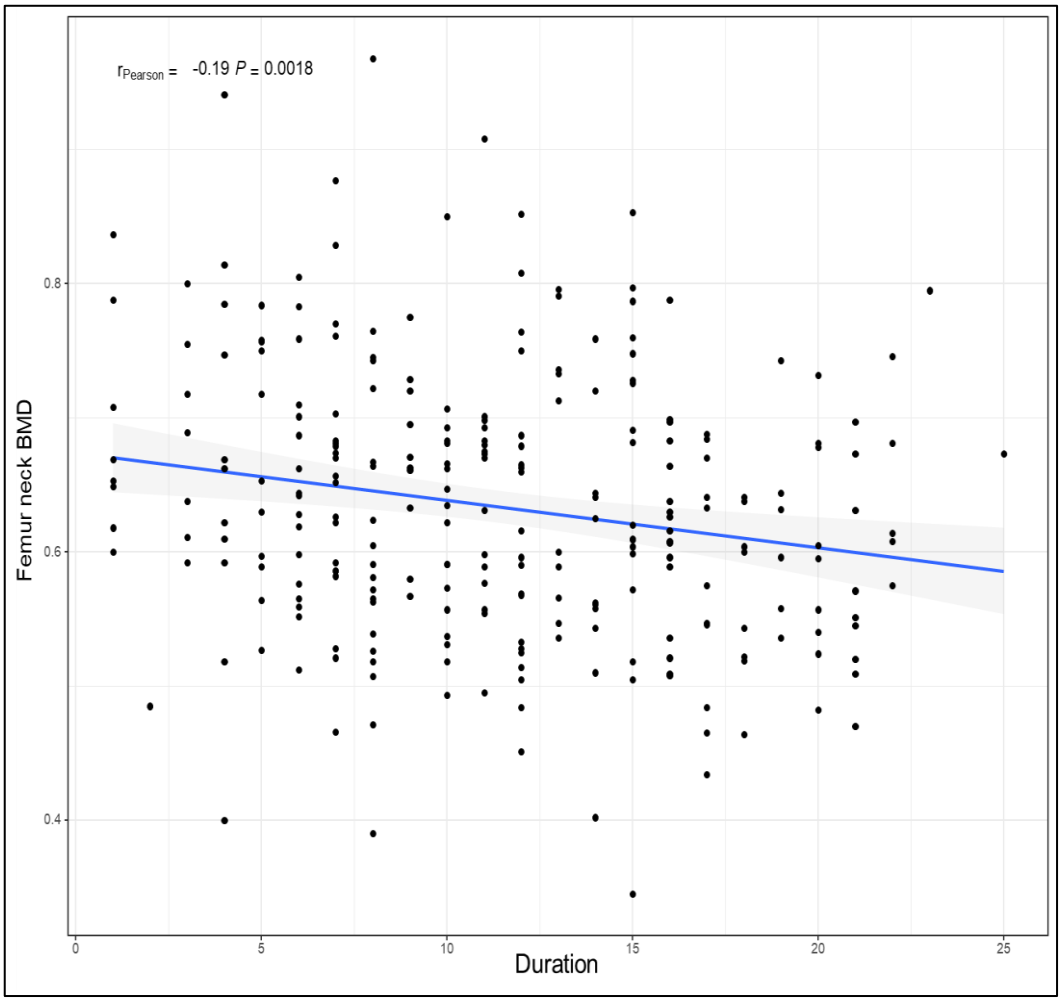


Figure 5A. Association between ERT duration and femoral neck BMD.

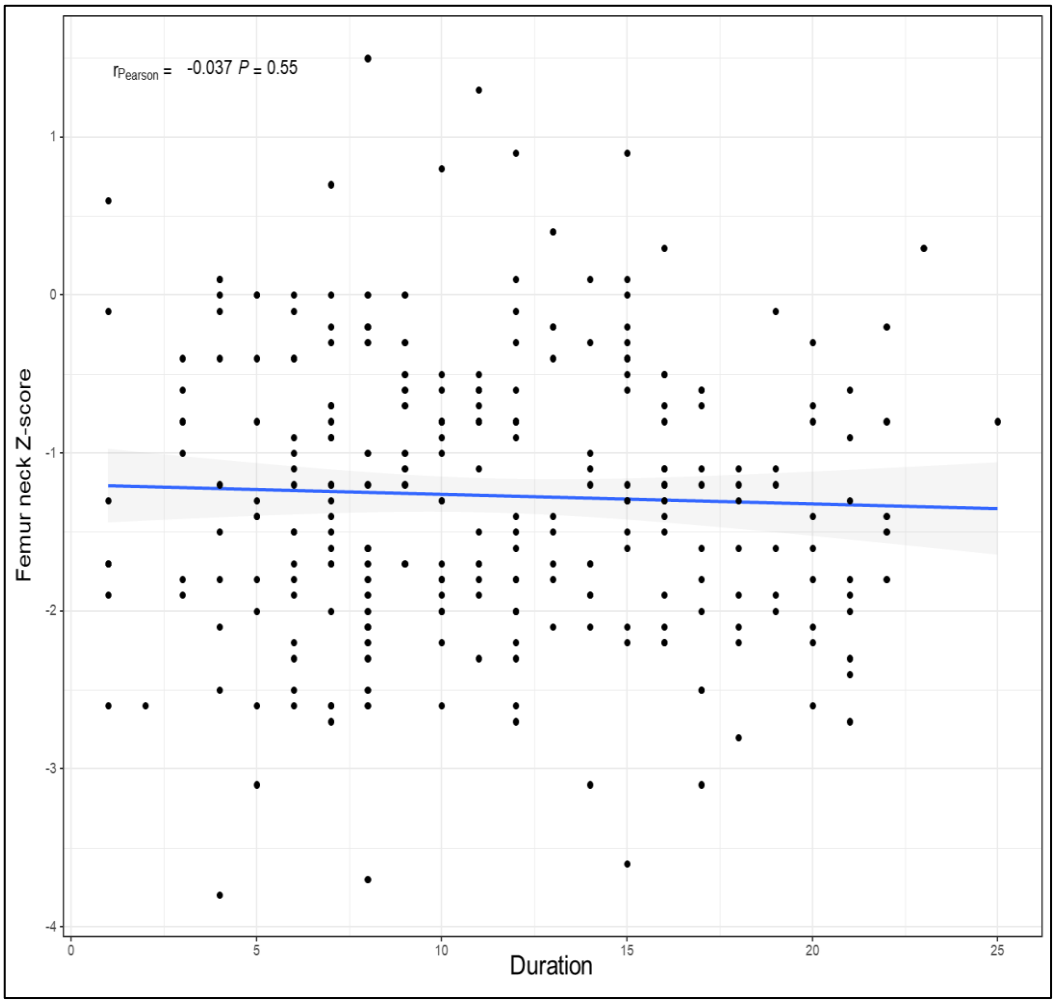


Figure 5B. Association between ERT duration and femoral neck BMD.

Figure.5A-B. Association between ERT duration and femoral neck BMD.

Longer ERT duration tended to be associated with lower femoral neck BMD.

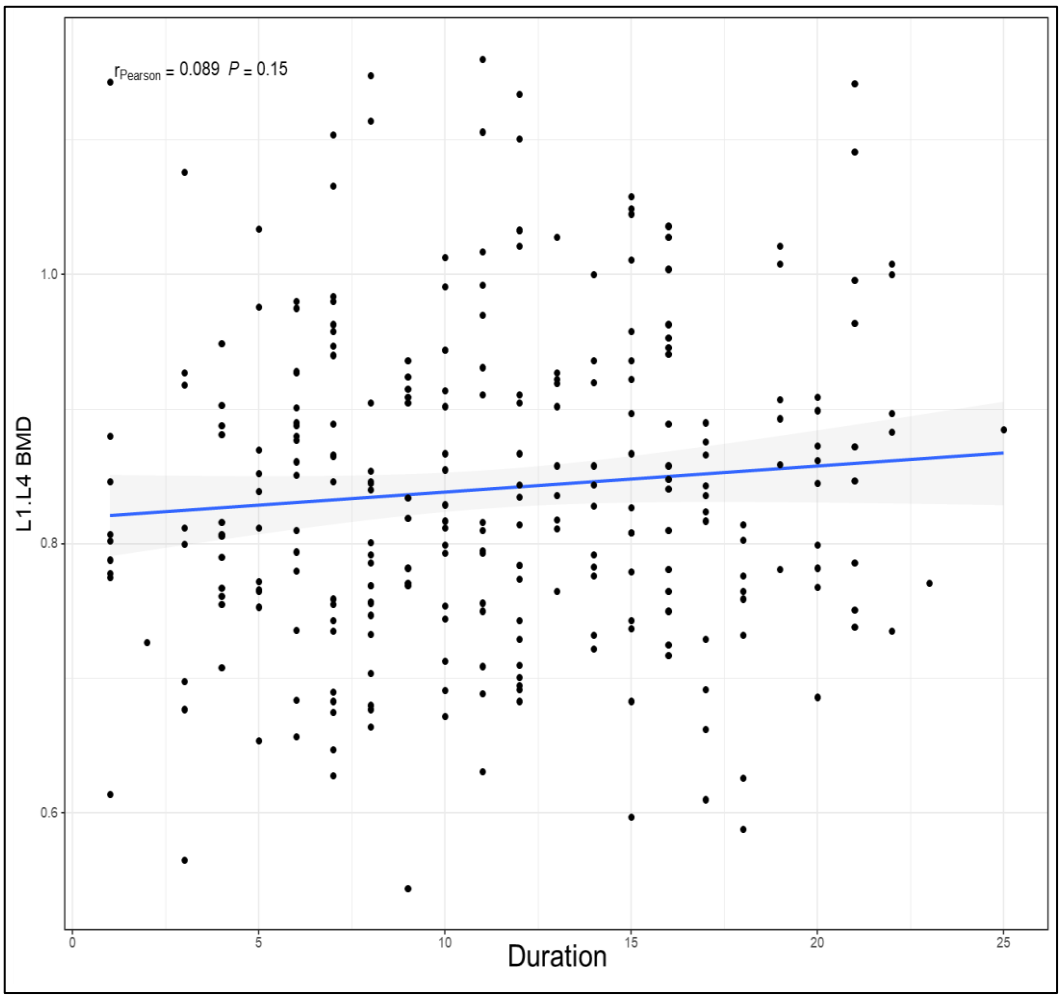


Figure 6A. Association between ERT duration and lumbar spine (L1-L4) BMD.

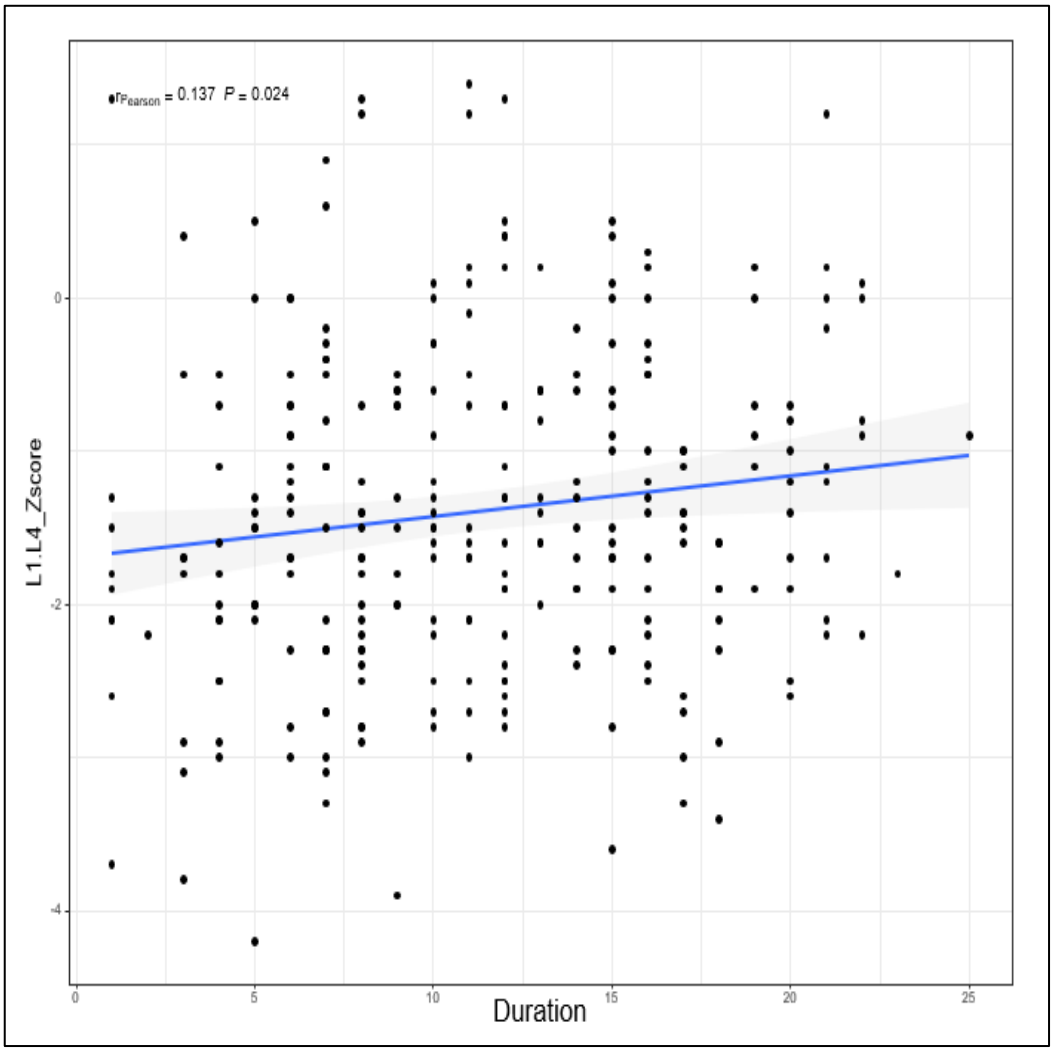


Figure 6B. Association between ERT duration and lumbar spine (L1-L4) BMD.

Figure 6A-B. Association between ERT duration and lumbar spine (L1-L4) BMD. Longer ERT duration was associated with higher lumbar spine BMD Z-scores.

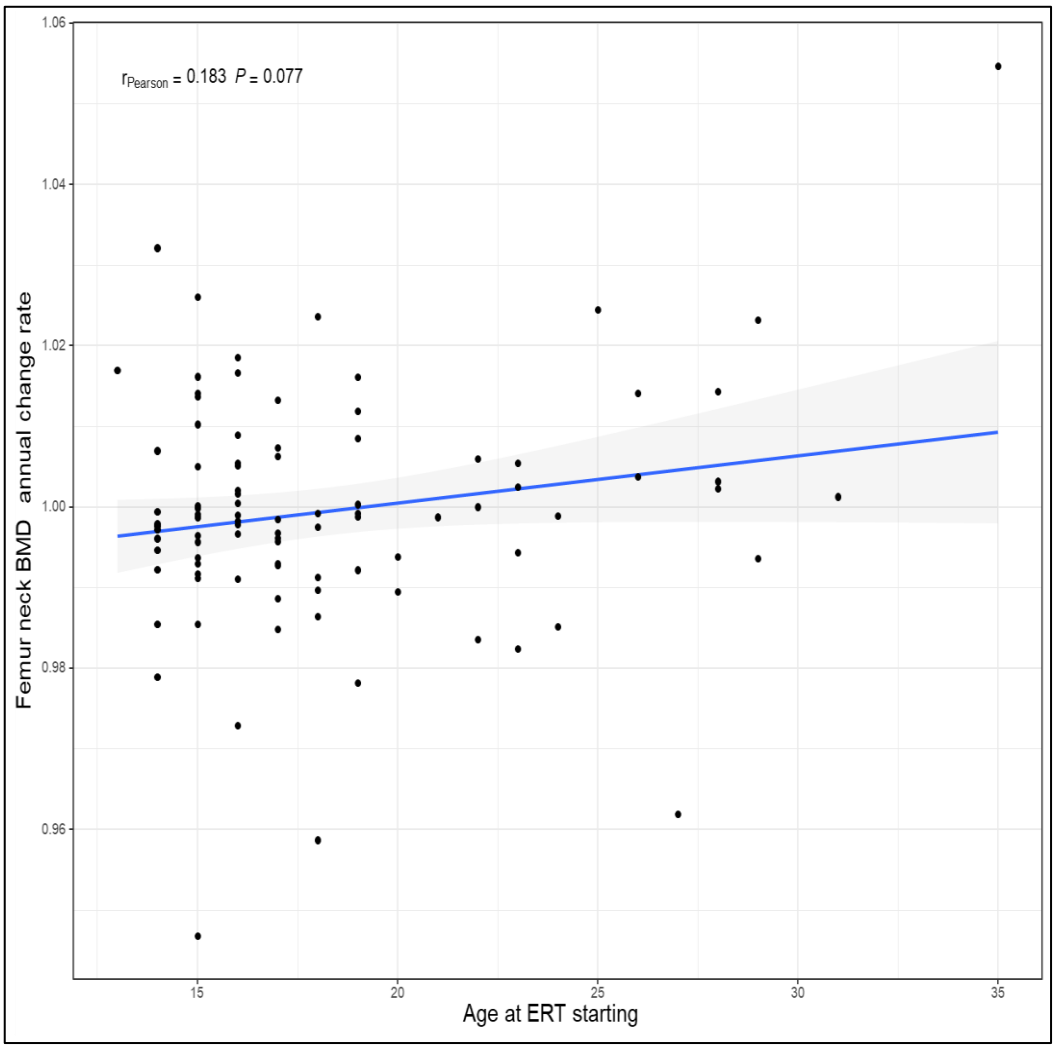


Figure 7A. Annual change rate in femoral neck BMD.

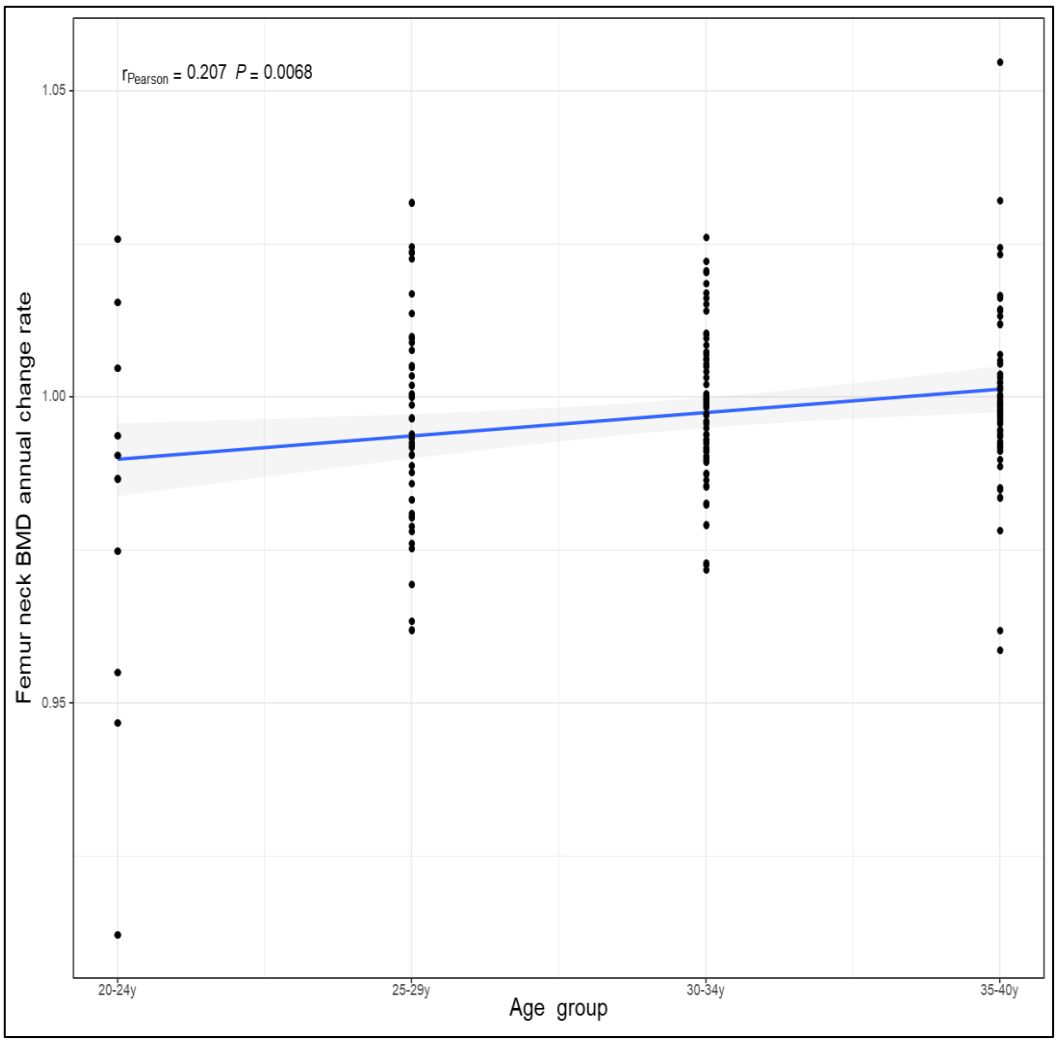


Figure 7B. Annual change rate in femoral neck BMD.

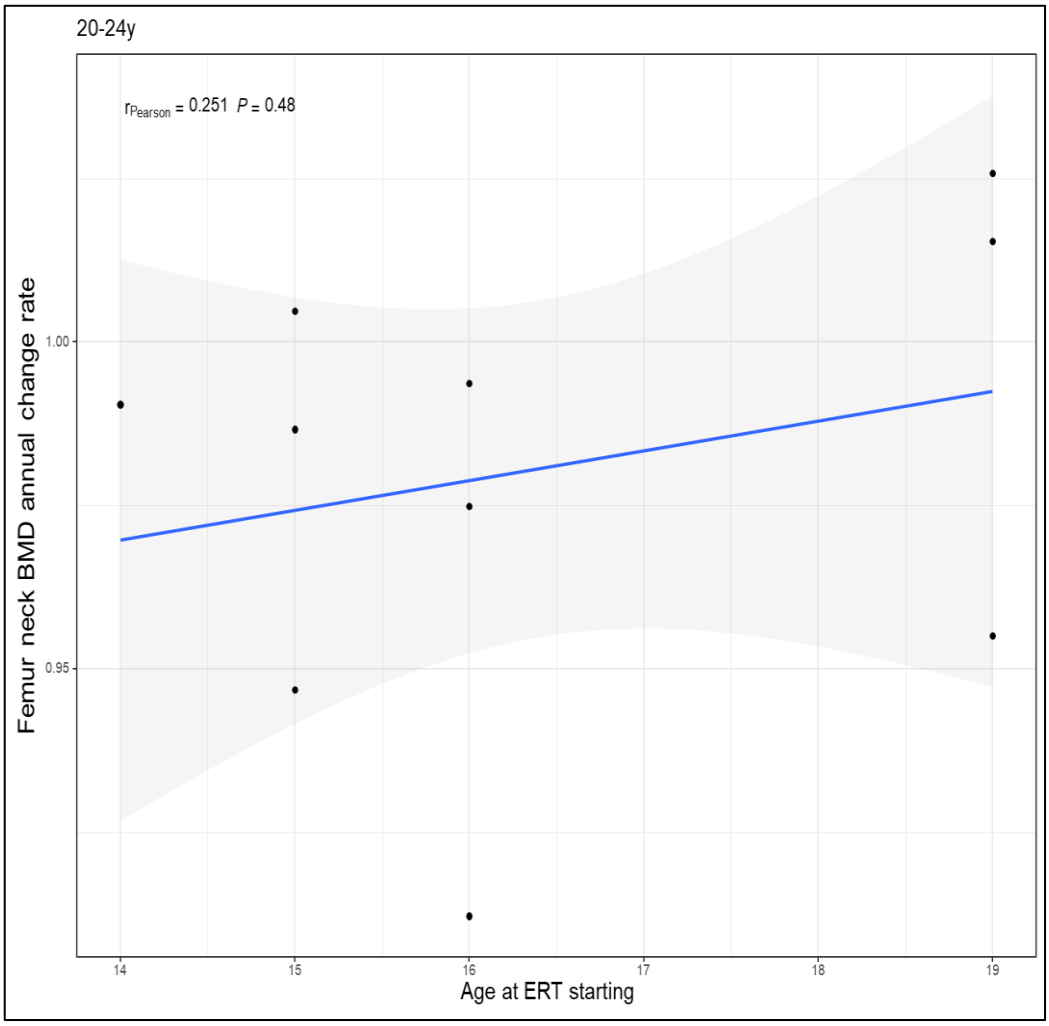


Figure 7C. Annual change rate in femoral neck BMD.

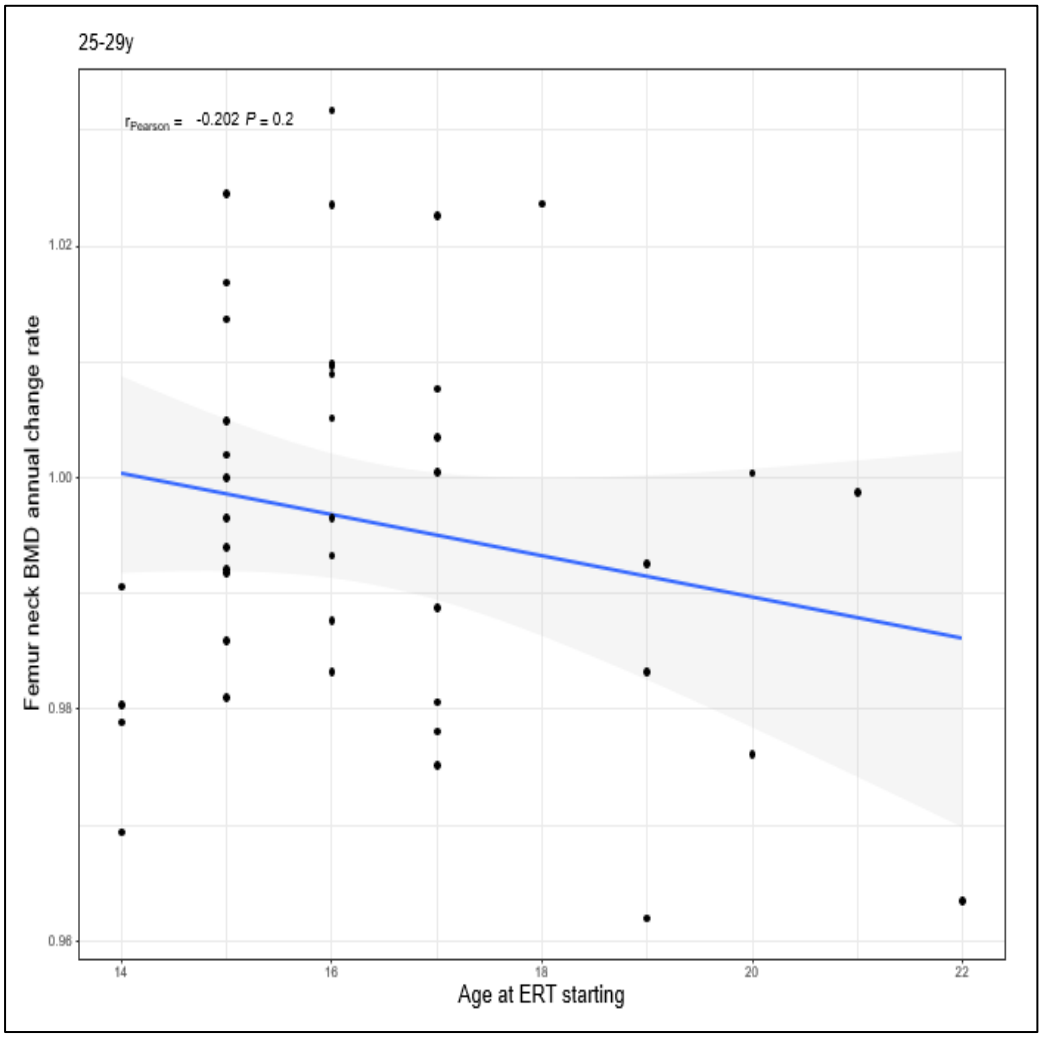


Figure 7D. Annual change rate in femoral neck BMD.

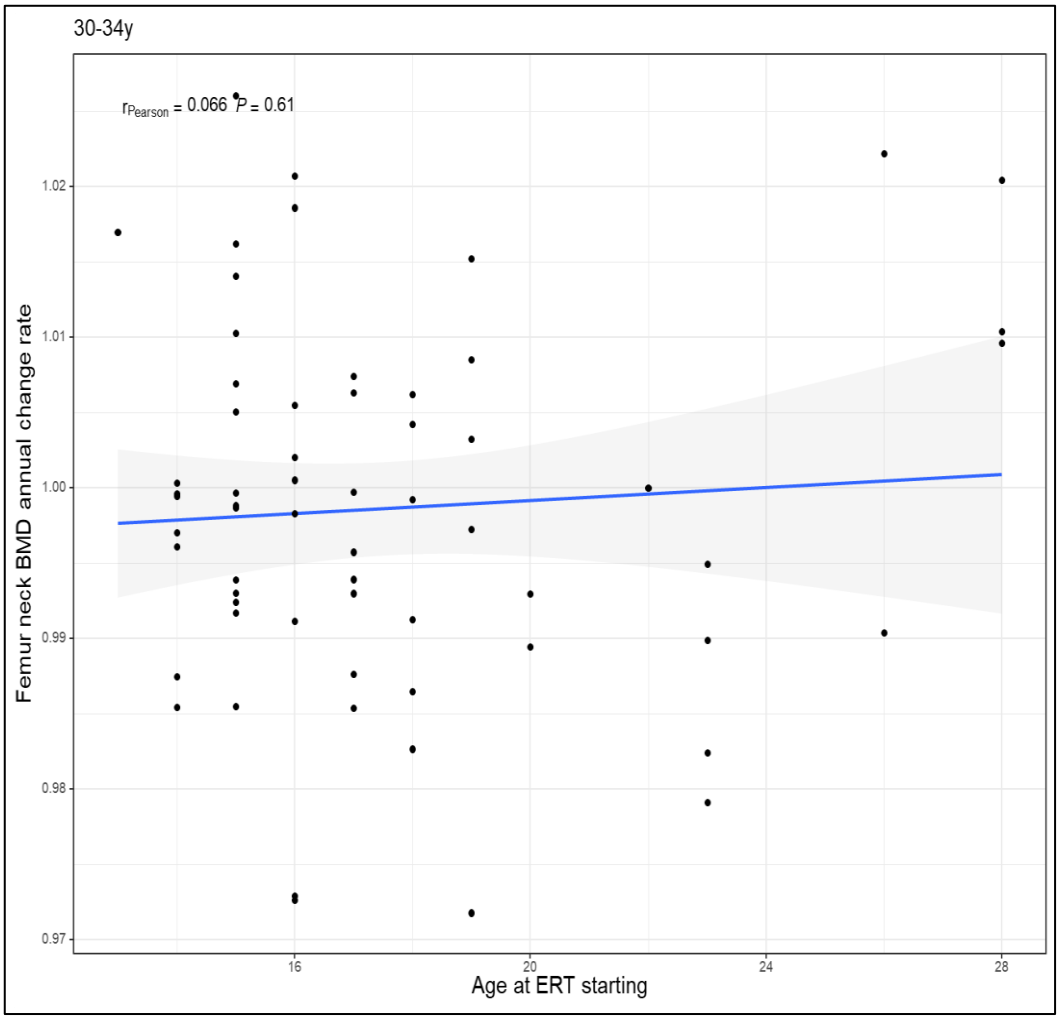


Figure 7E. Annual change rate in femoral neck BMD.

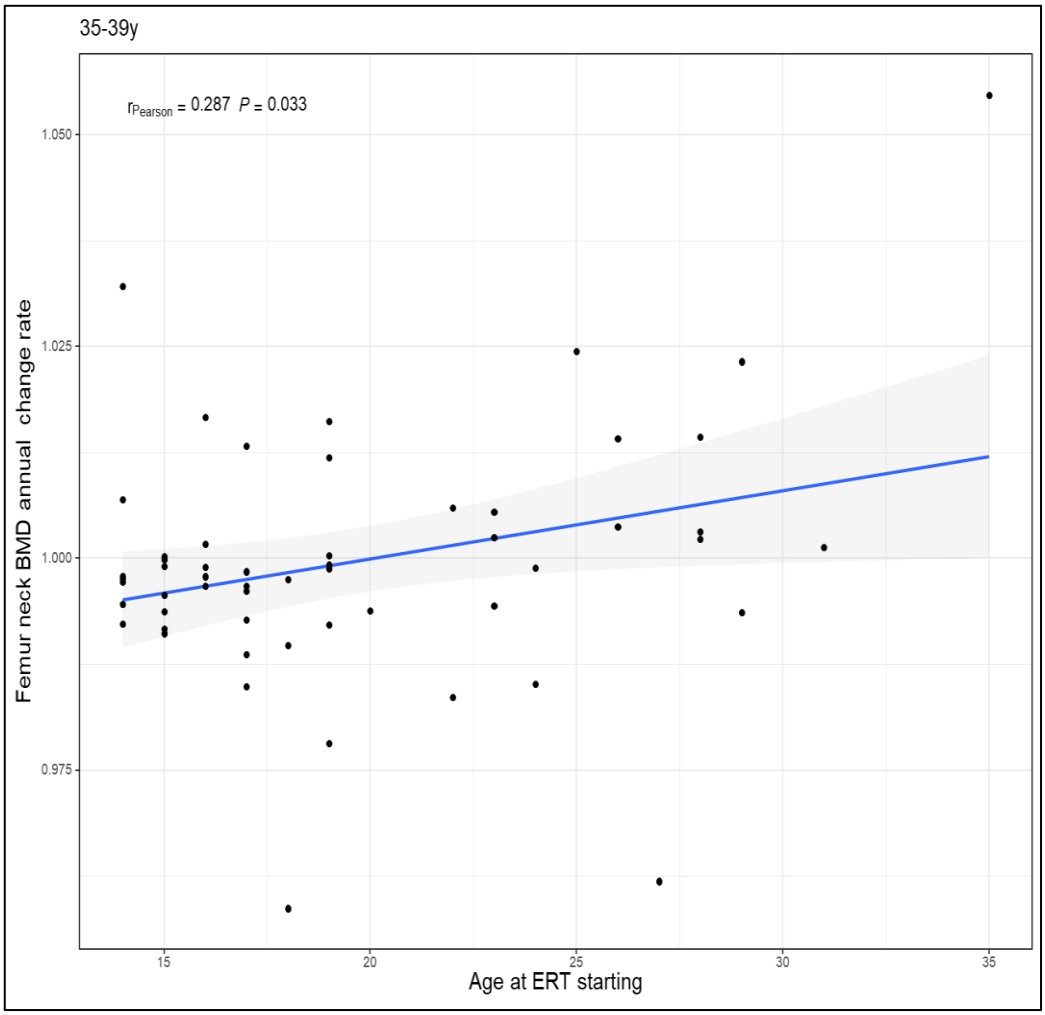


Figure 7F. Annual change rate in femoral neck BMD.

Figure 7A-F. Annual change rate in femoral neck BMD. Age at ERT initiation was positively associated with the annual change rate in femoral neck BMD, although the difference was not statistically significant.

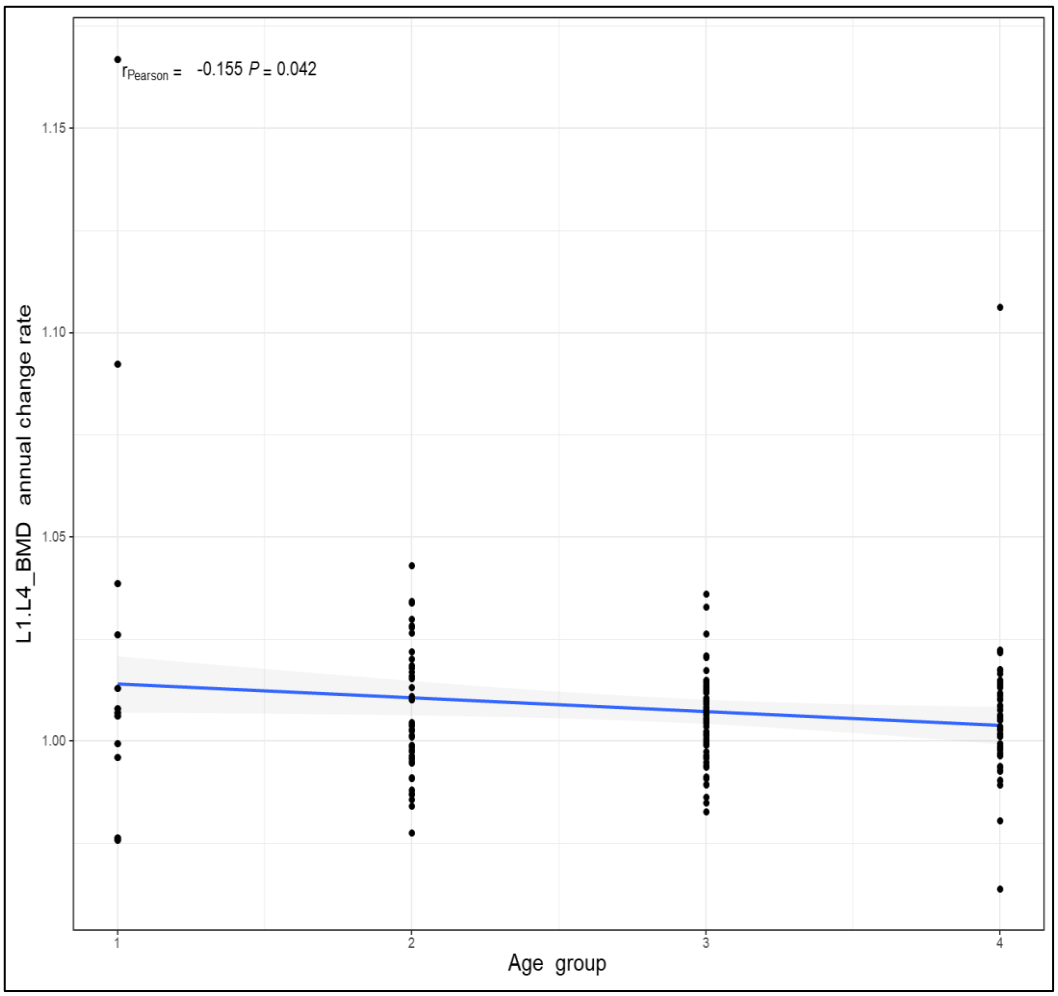


Figure 8A. Annual change rate of the lumbar spine (L1–L4) BMD.

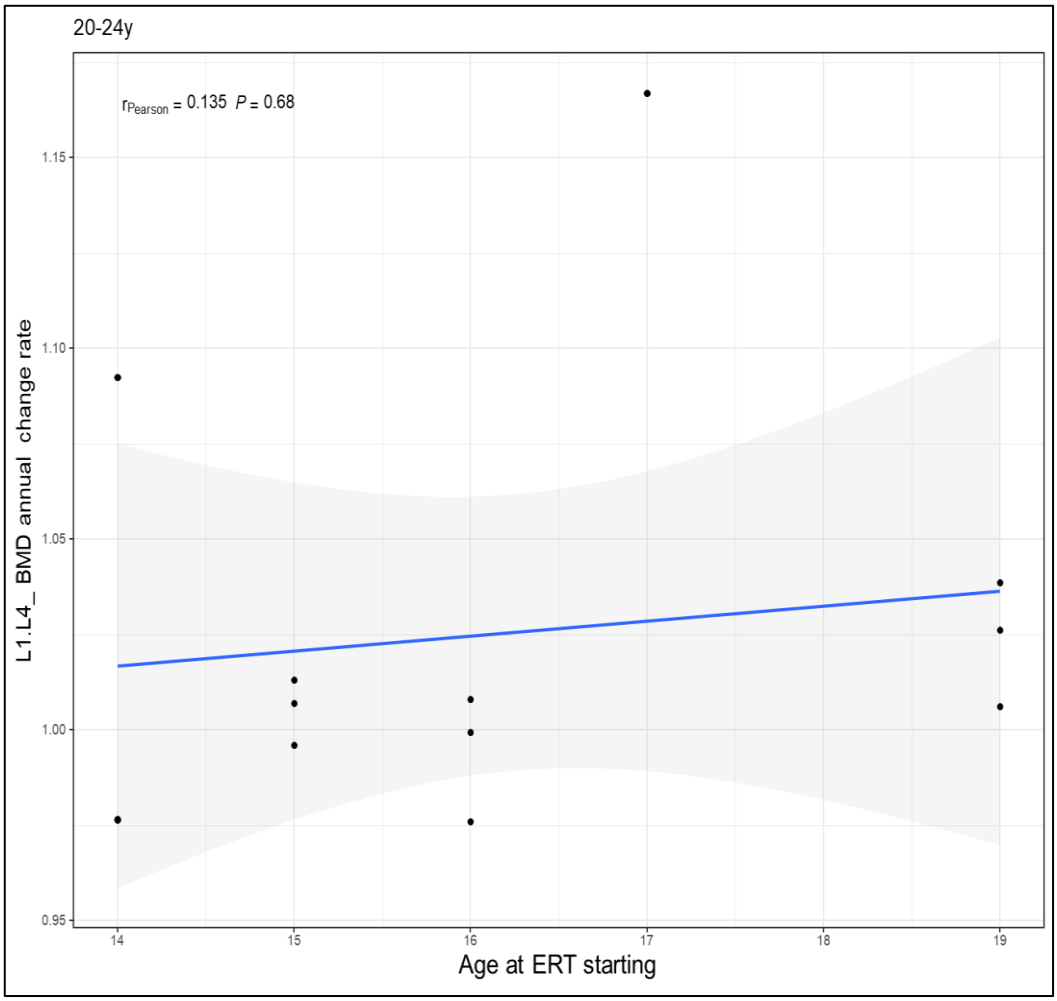


Figure 8B. Annual change rate of the lumbar spine (L1–L4) BMD.

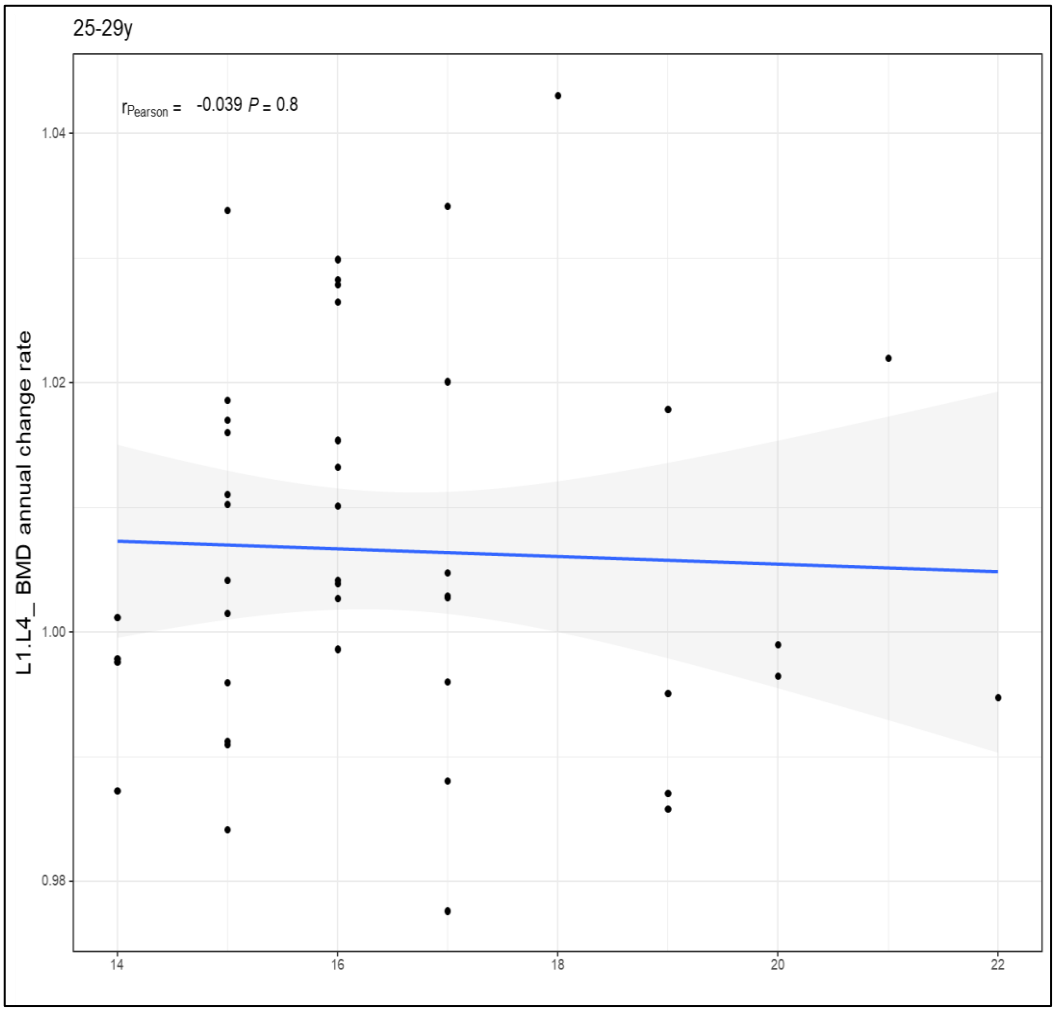


Figure 8C. Annual change rate of the lumbar spine (L1–L4) BMD.

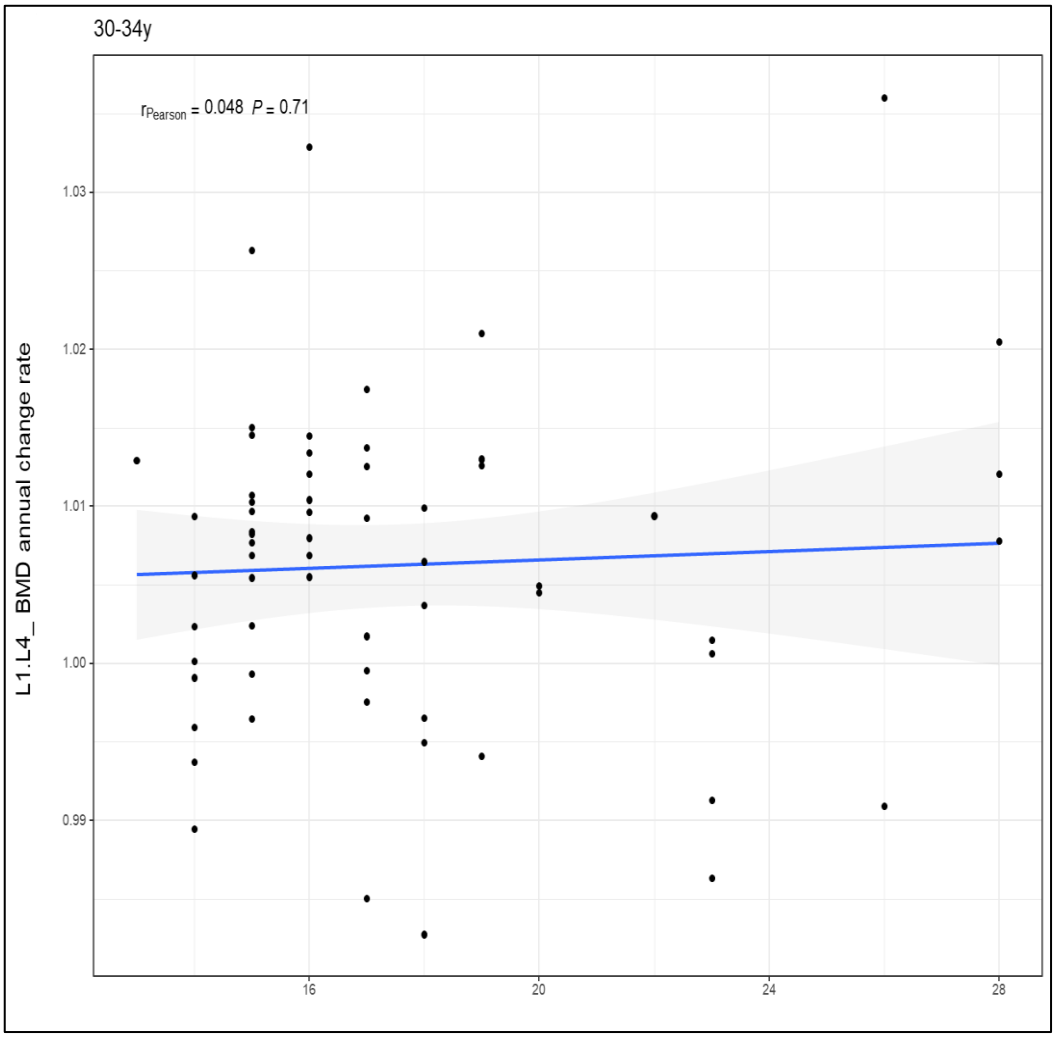


Figure 8D. Annual change rate of the lumbar spine (L1–L4) BMD.

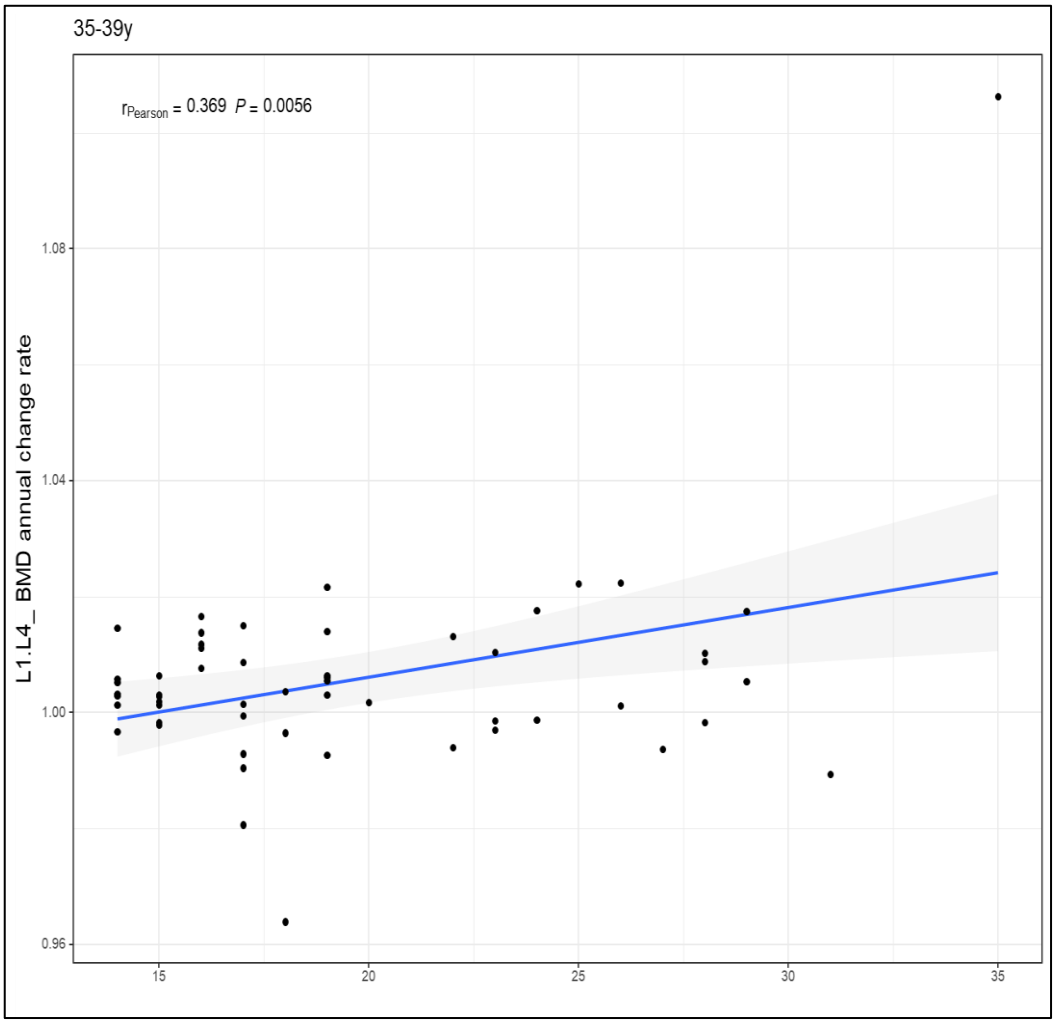


Figure 8E. Annual change rate of the lumbar spine (L1–L4) BMD.

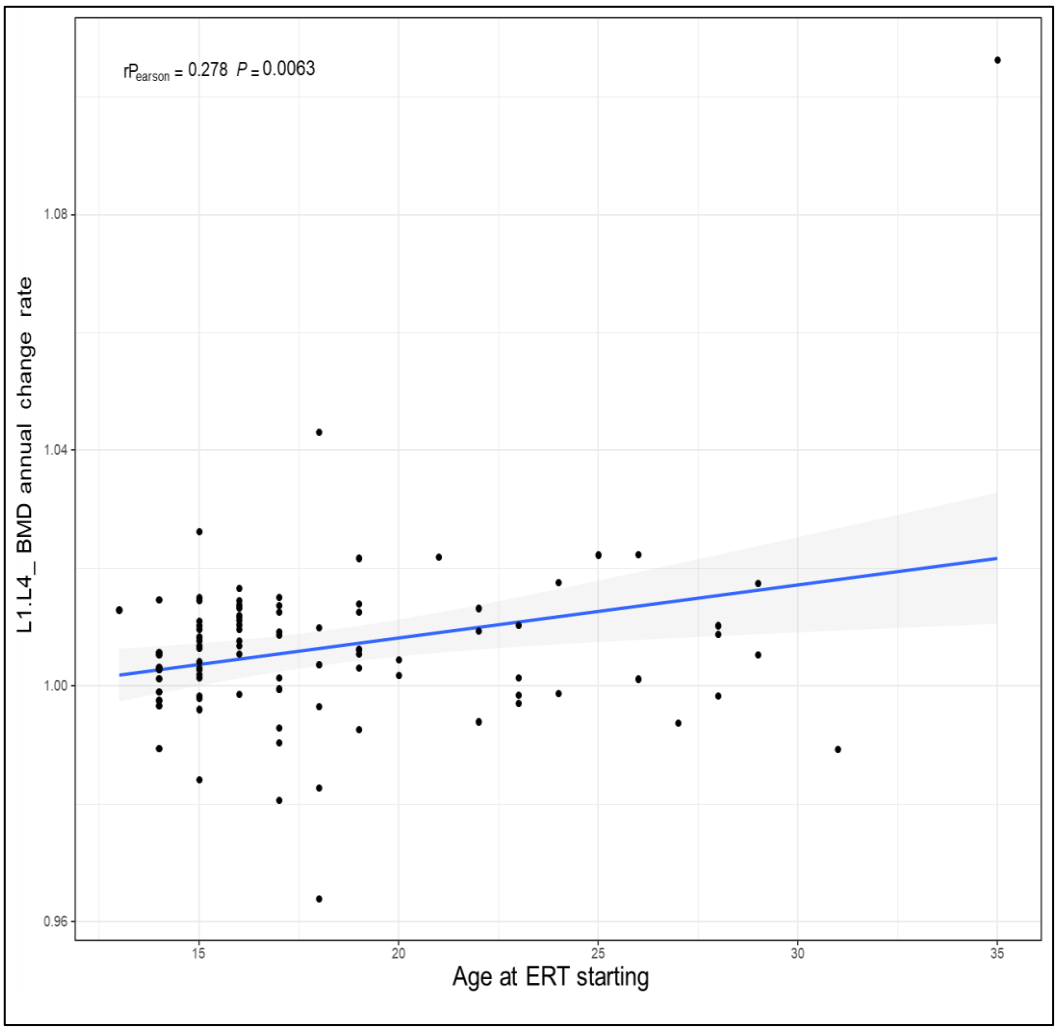
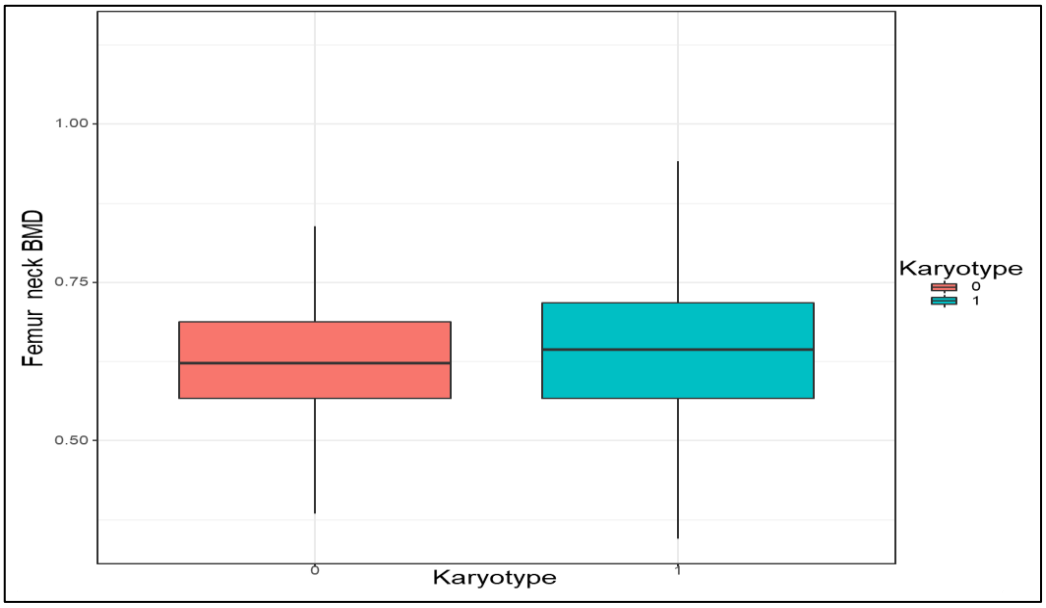


Figure 8F. Annual change rate of the lumbar spine (L1–L4) BMD.

Figure 8A-F. Annual change rate of the lumbar spine (L1–L4) BMD. The age at ERT initiation was significantly and positively associated with the annual change rate of lumbar spine BMD (r = 0.278, p = 0.0063). However, when analyzed according to the age group, no correlation was observed, except for the 35–39 years age group.



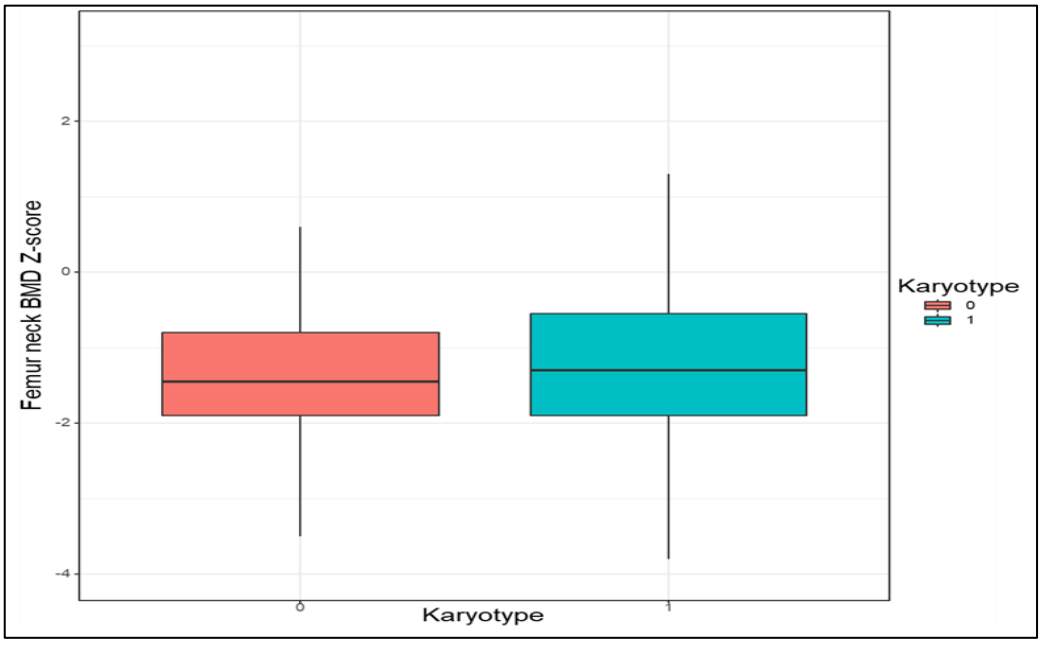
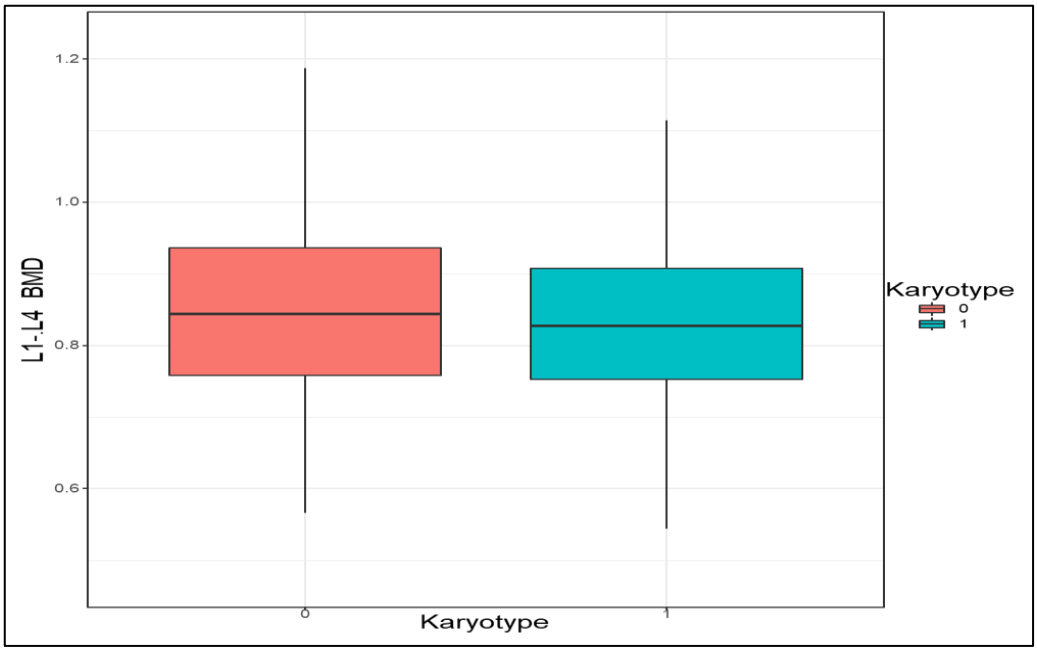


Figure 9. Femoral neck BMD (value and Z-score) by karyotype.

0) Karyotype 45 XO, 1) Karyotype with mosaicism.



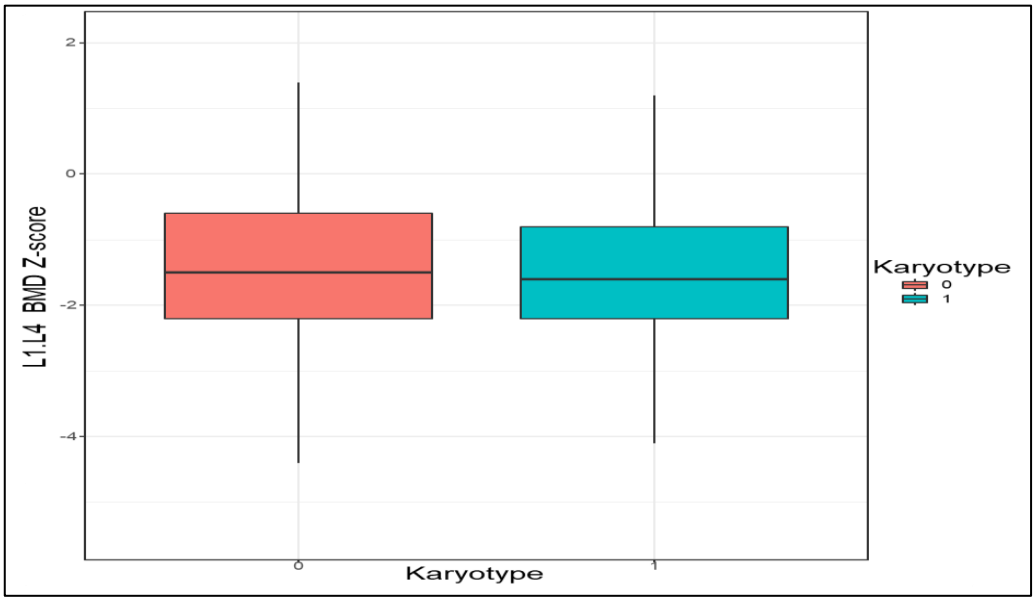


Figure 10. Lumbar spine (L1-L4) BMD (value and Z-score) by karyotype.
0) Karyotype 45 XO, 1) Karyotype with mosaicism.

Table1. Clinical features of the study group

N= 188		Value
Age (years)		28.638 ± 6.115
Age at ERT initiation (years)		18.278 ± 5.719
Height (cm)		146.571 ± 9.678
Weight (kg)		48.925 ± 11.151
BMI (kg/m^2)		22.631 ± 4.285
Karyotype		
	Monosomy	51 (27.128%)
	Mosaic	137 (72.872%)
GH		
	Yes	76 (40.426%)
	NO	112 (59.574%)

Data are presented as mean ± SD or N (%). *SD* standard deviation.

ERT estrogen replacement therapy, *BMI body* mass index, *GH* growth hormone.

Table 2. Femoral neck BMD (g/cm2) in Korean women with TS and healthy controls.

Age group	Women with TS	Healthy controls	*p-values*
20–24 years	0.668 ± 0.119 (N = 149)	0.787 ± 0.107 (N = 545)	< 0.001
25–29 years	0.650 ± 0.109 (N = 141)	0.763 ± 0.101 (N = 649)	< 0.001
30–34 years	0.623 ± 0.106 (N = 119)	0.759 ± 0.103 (N = 872)	< 0.001
35–39 years	0.615 ± 0.100 (N = 84)	0.758 ± 0.103(N= 1124	< 0.001
40–44 years	0.674 ± 0.078 (N = 6)	0.763 ± 0.103 (N = 965)	0.035
45–50 years	0.446 ± 0.008 (N = 2)	0.746 ± 0.106 (N = 1156)	< 0.001

Data are presented as mean ± SD. Unpaired t-test was used for statistical analysis.

Table3. Lumbar spine (L1–L4) BMD (g/cm2) in Korean women with TS and healthy controls.

Age group	Women with TS	Healthy controls	*p-values*
20–24 years	0.835 ± 0.126 (N = 154)	0.958 ± 0.111 (N = 545)	< 0.001
25–29 years	0.841 ± 0.121 (N = 142)	0.965 ± 0.107 (N = 649)	< 0.001
30–34 years	0.837 ± 0.124 (N = 119)	0.988 ± 0.114 (N = 872)	< 0.001
35–39 years	0.840 ± 0.124 (N = 85)	0.998 ± 0.116 (N = 1124)	< 0.001
40–44 years	0.847 ± 0.220 (N = 6)	1.000 ± 0.120 (N = 965)	0.150
45–50 years	0.596 ± 0.021 (N = 2)	0.971 ± 0.131 (N = 1156)	< 0.001

Data are presented as mean ± SD. Unpaired t-test was used for statistical analysis.

Table 4. Femoral neck BMD (value and Z-score) by karyotype.

	0 (N=146)	1 (N=355)	*p*
Femoral neck BMD	0.627± 0.109	0.649± 0.112	0.044
Femoral neck Z-score	1.403± 0.963	-1.184± 0.987	0.023

Data are expressed as the mean ± SD. *p* Values were determined using the Student's unpaired t-test.

0) Karyotype 45 XO, 1) Karyotype with mosaicism.

Table 5. Lumbar spine (L1-L4) BMD (value and Z-score) by karyotype.

	0 (N=148)	1 (N=360)	*p*
L1-L4 BMD	0.851± 0.137	0.832± 0.120	0.124
L1-L4 Z-score	-1.3883± 1.222	-1.488± 1.088	0.365

Data are expressed as the mean ± SD. *P* Values were determined using the Student's unpaired t-test.

0) Karyotype 45 XO, 1) Karyotype with mosaicism.

Table 6. Factors affecting femoral neck BMD.

BMD Z-score	>-2.0 (N=323)	≤-2.0 (N=94)	*p*
Age at ERT initiation	17.909 ± 4.634	18.615 ± 5.599	0.273
Duration of ERT	10.603 ± 5.815	9.780 ± 6.530	0.248
Karyotype			0.649
0	93 (28.793%)	30 (31.915%)	
1	230 (71.207%)	64 (68.085%)	
Age at BMD evaluation	28.402 ± 5.666	28.606 ± 6.328	0.765
ERT status			0.704
0	6 (1.858%)	3 (3.191%)	
1	317 (98.142%)	91 (96.809%)	
GH			0.273
0	136 (42.105%)	33 (35.106%)	
1	187 (57.895%)	61 (64.894%)	
BMI	23.368 ± 4.520	21.245 ± 3.097	<0.01

Data are mean ± SD or *N* (%). *p* Values were determined using the Student's unpaired *t* test.

Karyotype 0 -45 XO, *Karyotype 1*–mosaic 45XO/46XX.

ERT status 0 – without ERT, *ERT status 1*- with ERT.

GH 0 - without GH, *GH 1* – with GH.

Table 7. Factors affecting the BMD in lumbar spine L1-L4

BMD Z-score	>-2.0 (N=278)	≤-2.0 (N=144)	*p*
Age at ERT initiation	17.368 ± 3.898	19.357 ± 6.106	0.001
Duration of ERT	11.162 ± 5.806	8.821 ± 6.031	<0.01
Karyotype			0.683
0	84 (30.216%)	40 (27.778%)	
1	194 (69.784%)	104 (72.222%)	
Age at BMD evaluation	28.421 ± 5.737	28.333 ± 6.050	0.884
ERT status			0.953
0	6 (2.158%)	4 (2.778%)	
1	272 (97.842%)	140 (97.222%)	
GH			0.066
0	104 (37.410%)	68 (47.222%)	
1	174 (62.590%)	76 (52.778%)	
BMI	23.499 ± 4.298	21.672 ± 4.087	<0.01

Data are mean ± SD or *N* (%). *p* Values were determined using the Student's unpaired *t* test.

Karyotype 0 -45 XO, *Karyotype 1*–mosaic 45XO/46XX.

ERT status 0 – without ERT, *ERT status 1*- with ERT.

GH 0 - without GH, *GH 1* – with GH.

ABSTRACT (IN KOREAN)

한국 터너증후군 여성에서 골밀도에 대한 호르몬 치료의 영향

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김선영

터너증후군은 X 염색체 하나의 전체 혹은 일부 소실이 원인이 되어 생존 여아 2,000~2500명 중 1명 정도에서 발생하는 흔한 염색체 이상 질환이다. 임상적으로는 저신장, 성적유치증이 주 증상이며 골다공증이나 골절의 발생 빈도 또한 높다. 터너증후군에서 에스트로겐의 사용을 기반으로 한 호르몬 대체 치료는 사춘기 및 발달의 측면에서 중요하며, 터너증후군 환자에서 호르몬 대체 치료에 대한 반응은 인종과 지역에 따라 차이가 있을 수 있다. 국내에서는 이러한 연구가 진행된 적이 없기 때문에 터너증후군 환자에서 호르몬 대체 치료가 골밀도에 미치는 영향에 대해 알아볼 필요가 있다. 이에 본 연구에서는 1997년부터 2019년까지 세브란스 병원에서 치료받은 터너증후군 환자를 대상으로 의무기록을 후향적으로 분석, 호르몬 대체 치료의 시기나 기간에 따른 골밀도 변화를 확인하였으며, 터너증후군 환자에서 골밀도 증가를 위해 에스트로겐에 기반을 둔 조기 및 장기간에 걸친 호르몬 대체 치료가 중요함을 결론 내릴 수 있었다.

핵심되는 말: 터너증후군, 에스트로겐, 호르몬 대체 치료, 골밀도