Abnormal Trabecular Bone Score, Lower Bone Mineral Density and Lean Mass in Young Women With Premature Ovarian Insufficiency Are Prevented by Oestrogen Replacement

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Background: Low bone density (BMD) and fractures commonly affect women with premature ovarian insufficiency (POI). However, bone microarchitecture and body composition data are lacking.

Objective: To assess and characterise musculoskeletal phenotype and effects of oestrogen replacement therapy (ERT) in women with POI.

Method: Cross-sectional and longitudinal studies of 60 normal karyotype women with POI, aged 20-40 years, from 2005-2018. Dual x-ray absorptiometry (DXA)-derived spinal (LS) and femoral neck (FN) BMD, trabecular bone score (TBS), appendicular lean mass (ALM), total fat mass (TFM), and fracture prevalence were compared with 60 age-, and BMI-matched population-based controls. Longitudinal changes in bone and body composition variables and ERT effects were analysed using linear mixed models over a median duration of 6 years.

Results: Women with POI were subdivided into spontaneous (s)-POI (n=25) and iatrogenic (i)-POI (n=35). Median(range) age of POI diagnosis was 34 (10-40) years with baseline DXA performed at median 1(0-13) year post-diagnosis. ERT was used by 82% women (similar for both POI groups). FN-BMD were lowest in s-POI (p<0.002). Low TBS was more common in s-POI ([44%], p=0.03), versus other groups. LS-BMD and ALM were lower in both s-POI and i-POI groups than controls (p<0.05). Fracture prevalence
was not significantly different: 20% (s-POI), 17% (i-POI), and 8% (controls) (p=0.26). Longitudinal analysis of 23 POI women showed regular ERT was associated with ALM increment of 127.05 g/year (p<0.001) and protected against bone loss. However, ERT interruption was associated with annual reductions in FN BMD and TBS of 0.020g/cm² and 0.0070 (p<0.05), respectively.

**Conclusion:** Deficits in BMD, trabecular microarchitecture, and lean mass were present in women with POI. However, regular ERT protected against declines in bone variables, with an increase in ALM. Assessment of skeletal and muscle health, and advocating ERT adherence, is essential in POI to optimise musculoskeletal outcomes.

**Keywords:** premature ovarian insufficiency, osteoporosis, bone mineral density, trabecular bone score, body composition, appendicular lean mass

**INTRODUCTION**

Up to 4% of women (1) are affected worldwide by Premature Ovarian Insufficiency (POI), a condition in which cessation of female gonadal function occurs before age forty years. POI is broadly categorised into spontaneous and iatrogenic POI. Spontaneous POI (s-POI) is idiopathic in most cases, but can be associated with chromosomal and genetic defects, environmental factors, autoimmune diseases (most commonly thyroid and adrenal disease) and various infections. In contrast, iatrogenic POI (i-POI) is secondary to medical and surgical causes such as chemotherapy, ionising radiotherapy, or bilateral oophorectomy (2).

POI is associated with increased mortality and morbidity due to the lack of oestrogen’s beneficial effects on various tissues and organs in the body, especially cardiovascular, neurocognitive, and musculoskeletal systems (3). Prompt diagnosis and management of POI and its sequelae can significantly reduce morbidity and mortality in this group.

While there is no unified definition of osteoporosis and osteopenia in adults aged < 50 years, researchers have indicated low bone mass and osteoporosis prevalence to be around 8-15% in women with POI (4, 5); the risk is dependent on the degree and duration of oestrogen deficiency. There is preferential loss of trabecular bone, leading to an almost 26% reduction in lumbar spine (LS) bone mineral density (BMD) compared with age-matched population controls (6). Although the exact prevalence of fractures remains unknown, it is anticipated to be high, with fractures occurring at a younger age (7). Small studies show that oestrogen can maintain and restore bone mineral density (BMD) in POI (8, 9) but the optimal formulation, dose and type of oestrogen replacement therapy (ERT) is unknown. Defining the musculoskeletal phenotype in POI, including BMD, fracture prevalence, body composition and effects of oestrogen on these indices, is important for the optimal management of these women.

Dual-energy X-ray absorptiometry (DXA) is routinely used to assess fracture risk, but it has disadvantages, including two-dimensional projection of areal-BMD (a-BMD), inability to differentiate between trabecular and cortical bone, and underestimation of BMD in women with short stature, such as Turner syndrome (TS). More recently, techniques such as trabecular bone score (TBS), can provide additional information relating to trabecular microarchitecture and are independent predictors of fracture risk.

TBS is computed from LS DXA images and constitutes a textural representation that assesses pixel grey-level variations in the LS, providing an indirect analysis of trabecular microarchitecture (10). Despite data from longitudinal studies in older populations showing TBS predicts fractures independently of BMD and FRAX® (11–14), data are limited in women with POI, in premenopausal women, and in younger men. In a small cohort of women with TS, a recognised genetic cause of POI, our group has previously reported an age-related decrease in TBS (15).

With recent insights gained from muscle-bone cross signaling (16), it is now evident that muscle plays an essential role in maintaining and preserving skeletal health. Studies in typical menopausal women suggest an accelerated decline in muscle mass, increase in abdominal adiposity, and reductions in lean body mass (LBM) due to oestrogen deficiency, with preservation in women using ERT (16). However, data in women with POI are scant and there is a growing need to analyse changes in body composition, as well as in bone variables in women with POI.

The aims of this study are to:

1) compare clinical and densitometric data, including skeletal and body composition assessments, between women with normal karyotype POI and age-matched healthy Australian women (controls) from the population-based Geelong Osteoporosis study (GOS), 2) analyse the longitudinal changes in women using ERT (16). However, data in women with POI are scarce and there is a growing need to analyse changes in body composition, as well as in bone variables in women with POI.

The aims of this study are to:

**METHODS**

**Study Participants**

**Women With POI**

This retrospective, observational study included women aged 20 to 40 years who had POI and underwent one or more DXA scans between January 2005 to May 2018 at Monash Health, Clayton, Victoria, Australia. Participants were identified from the Monash Health Early Menopause Clinic, in addition to a comprehensive search of the bone density unit’s database for all women documented as having hypogonadism, and aged 20 to 40 years.
Women with TS, hypogonadotropic hypogonadism, or a history of breast cancer were excluded (Figure 1). The study was approved by the Monash Health Human Research Ethics Committee (Reference number 07062A).

During the study period, all DXA scans for the POI women were performed at Monash Health on a single Lunar Prodigy device (GE Healthcare, 133 Piscataway, NJ) using software version 11 to measure skeletal and body composition.
parameters. Baseline and serial DXA scans conducted during the study period for each woman were included in the analyses.

For skeletal assessments, all women with POI had BMD (g/cm²) measured at the lumbar spine LS (L1-L4) and femoral neck (FN). TBS measurements were obtained from DXA spinal images using TBS Insights Software (version 3.0.2.0; Medimaps, Geneva, Switzerland). The coefficients of variation CV for TBS and BMD using a LS phantom measured daily on the GE Lunar Prodigy were 0.94% and 0.92%, respectively.

On the day of the DXA scan, each participant’s height (m) and weight (kg) were measured with a wall-mounted stadiometer and electronic scale, respectively. Body composition measures including total fat mass (TFM) (g) and appendicular lean mass (ALM) (g) were derived from the whole-body scan and both parameters were also adjusted for height to yield FMI (TFM/ht² in g/m²) and ALMI (ALM/ht² in g/m²), respectively. The CV for percentage body fat of a total body phantom measured weekly was 3.11%.

Data regarding age and cause of POI, comorbidities, and medication use (including ERT) were verified from hospital medical records and the adult menopause clinic database. Moreover, details on ERT use, including age at initiation and ongoing use at the time of DXA scanning, were also retrieved. A history of all documented fractures was established from medical records or by radiologically proven fractures from the hospital’s radiology database.

Controls

The data for control participants were obtained from the Geelong Osteoporosis Study (GOS), an Australian longitudinal, population-based study, which aims to define the epidemiology of osteoporosis and fracture risk in men and women; a comprehensive description of the study has been provided elsewhere (17). A Lunar DPX-L (Lunar; Madison, WI, USA) was used for the women’s skeletal and body composition assessments, including LS BMD, FN BMD, TFM and ALM.

TBS (L1-L4) was retrospectively calculated from the same DXA spinal images using TBS Insights software (version 2.2; Medimaps Group, Geneva, Switzerland). The coefficient of variation (%) for TBS was 1.93%. Body weight (± 0.1 kg) was measured using electronic scales and height (± 0.1 cm) using a wall-mounted stadiometer. Fracture history was determined by self-report and confirmed radiologically where possible. The provision of de-identified data for this study was approved by the Human Research Ethics Committee of Barwon Health.

Statistical Analysis

The software program IBM SPSS Statistics v23 (IBM Corp, Armonk, NY) was used to conduct all cross-sectional statistical analyses, except when Stata v14.2 statistical software (StataCorp, College Station, TX) was used for mixed model analysis to assess longitudinal densitometric changes. A p value <0.05 was considered statistically significant.

Cross-Sectional Data

For cross-sectional analysis, categorical data for women from both groups were expressed as percentages and continuous data as mean ± SD or median and 25th & 75th percentiles, depending on the data distribution. The distribution of data was explored using the Shapiro-Wilk test. TBS was analysed as both continuous and dichotomous variables using established thresholds for abnormal value, TBS <1.302 (18) where partially degraded and degraded TBS was grouped as low TBS. Differences between groups were determined using the ANOVA for normally distributed continuous variables with Bonferroni’s method for post-hoc analyses; the Kruskal-Wallis test was used for nonparametric variables with the Mann-Whitney U for pairwise comparison. The Chi-square and Fisher’s exact test were used for categorical variables.

Longitudinal Data

Women with POI who had serial DXA scans were included in the longitudinal analysis. Linear mixed model analysis was used to determine the mean change per year (95%CI) in bone (TBS, LS, and FN BMD) and body composition parameters (TFM, FMI, ALM and ALMI) over time, with time defined as the number of years since baseline DXA. To determine the effect of ERT use on longitudinal changes, POI women with continued ERT use (defined as ERT use documented at the time of DXA scans) and interrupted ERT use were analysed separately, and data presented in two-way scatterplots with overlaid linear prediction plots.

RESULTS

Baseline Characteristics

Sixty women with POI and 60 age- and BMI-matched control participants were identified. For cross-sectional analysis, women with POI were subdivided into two groups i) spontaneous POI (s-POI, n=25); ii) iatrogenic POI (i-POI, n = 35). In the i-POI group 27 patients had non-breast cancer malignancy, 27 patients had bilateral oophorectomies and 17 had chemo ± radiotherapy. The baseline characteristics of participants are shown in Table 1.

Across the three groups, BMI and age were well-matched. Compared with the control group, participants in the two POI subgroups were shorter and more ethnically diverse (all p<0.05). The median age of POI onset in s-POI and i-POI group was the same, 32 years. Most women with POI were using ERT (81%); menopausal ERT was used by 67% and 78% of women in s-POI and i-POI groups, respectively, and the combined oral contraceptive pill (COCP) was used by 33% and 12% of women in s-POI and i-POI groups, respectively.

In the i-POI group, four patients were smokers, and four had an additional cause for low bone density, including coeliac disease, hyperthyroidism, another autoimmune disease, and chronic renal failure. Five patients had vitamin D deficiency, one had another autoimmune disease in the s-POI group, and none were smokers. Among the POI women, only one patient in the s-POI group who had an L1 vertebral fracture received antiresorptive therapy with denosumab, which commenced six years after the onset of POI and the baseline DXA scan. The age at menarche was available for 12/25 patients in the s-POI, and
the median age was 14 years. In the i-POI group, this data was available for 13/35 patients, and the median age was 14 years. In the i-POI group, this data was not available in n=6.

Table 1

| Demographics and baseline skeletal & body composition analysis of POI women and controls. |
|---|
| **Age (years)** |
| Control n=60 | 34 (30-38) |
| s-POI n=25 | 35 (29-38) |
| i-POI n=35 | 33 (30-38) |
| **Ethnicity** |
| Caucasian | 59 (98%) |
| Asian | 0 (0%) |
| Black | 0 (0%) |
| Hispanic | 0 (0%) |
| **BMI (kg/m²)** |
| Control (22.48, 30.83) | 21.50, 27.30 |
| s-POI (25.84, 24.80) | 35.20, 31.30 |
| i-POI (25.94, 24.80) | 25.70 |
| **Height (m)** |
| Control (1.66, 1.70) | 1.61 |
| s-POI (1.55, 1.68) | 1.61 |
| i-POI (1.58, 1.66) | 0.25a |
| **Fracture history** |
| Control (5.8%) | 5 (20%) |
| s-POI (0%) | 0 |
| i-POI (0%) | 0 |
| **ERT use** |
| Control NA | 15 (68%) |
| s-POI NA | 29 (91%) |
| i-POI NA | 0.07b |
| **Bone Density** |
| LS BMD (g/cm²) | 1.26 (0.13) |
| FN BMD (g/cm²) | 1.04 ± 0.13 |
| TBS score 1.40 ± 0.11 |
| Low TBS (%) 12 (20%) |
| **Body Composition** |
| ALM (g) | 19627.50 (17718.00, 21360.00) |
| ALMi (g/m²) | 7077.93 (6452.79, 7740.68) |
| TFM (g) | 26856.50 (17984, 40504) |
| TFMi (g/m²) | 9823.08 (6404.68,14134.91) |

*p values reported using: aKruskal-Wallis test; b Fisher’s-exact test; cANOVA; boldface indicates p values that are statistically significant.

Body composition analysis revealed significantly lower ALM (g) in s-POI [15891.00 (14063.50, 17247.00)] and the i-POI [16952.00 (14613, 19029.50)] subgroups than the control group (both p < 0.001); however, ALMi did not differ between the two POI groups (p=0.160). No significant differences in TFM were observed across the three groups.

Longitudinal Study

Longitudinal densitometric data were available for 24 out of 60 POI women; however, one participant receiving antiresorptive therapy with denosumab in the interrupted ERT group was excluded from the final analysis. The median follow-up duration was six years (range, 1 to 12 years), and 75% of women had follow-up data available for at least five years.

Over the follow-up period, 17 women with POI continued ERT; the majority (14/17) used HRT and 3/17 were on combined oral contraceptive pills (COCP). In the interrupted ERT group (n=6), 3 women who were not receiving therapy at baseline commenced ERT during follow-up; two women never received
ERT; one woman ceased ERT during the study, and the ERT status was unknown for one woman. Longitudinal data were not available for the remaining 36 women because they were either lost to follow-up or did not have a second routine DXA scan at the time of study analysis.

During follow-up, significant longitudinal changes per year were observed in skeletal and body composition variables. Overall, women with POI lost 0.0049 g/cm² per year in FN-BMD (p = 0.038); additionally, a significant increase in ALM and ALMI was noted over time at [(71.61 (95% CI: 8.89, 134.32), p=0.025), (33.62 (95% CI:12.50, 54.74), p=0.002)], respectively (Table 2). No significant changes were seen in TBS, spine BMD, or fat mass (TFM and FMI).

The POI women who continued ERT had an increment of 127.05 g (95% CI: 68.81,185.30, p<0.001) in ALM and no bone loss from the FN. In contrast, a significant decline in FN-BMD (-0.020g/cm² (95% CI: -0.037, 0.0030), p=0.025) and TBS (-0.0070 (95% CI: −0.011, −0.0020), p=0.007) was observed in the ‘interrupted ERT’ group. The findings for the Continued ERT and Interrupted ERT groups remained similar, including the woman from the interrupted ERT group receiving antiresorptive therapy with the vertebral fracture in the longitudinal analysis. The scatterplots for bone and body composition parameters with linear prediction plots are shown in Figure 3.

**Fracture Analysis**

Fracture history was available for all women in POI and the control group. Overall, 5 control (8%), 5 (20%) s-POI and 6 (18%) i-POI women reported fractures with no significant differences observed across the three groups (p=0.275) or between all POI and control women (p=0.15). The mean age in years (range) for sustaining the first fracture was 28.0 (21-37) in the control group, 24.0 (9-34) in the s-POI and 29.5 (16-50) in the i-POI group. For the POI cohort, the time of sustaining fracture since POI onset was unavailable for all the women. In the i-POI group, most women sustained fractures, 67% (4/6) after the POI onset; however, 60% (3/5) women in the s-POI group had fractures before the POI onset.

The fractures in the three groups were mostly non-vertebral with a reported frequency of 4/5 (80%), 4/5 (80%) and 6/6 (100%) in the controls, s-POI group, and i-POI group, respectively. One patient in the controls (vertebral level not specified) and one in the s-POI group had a vertebral fracture (at L1 with 20% reduction in vertebral height). None of the patients in the i-POI group sustained vertebral fractures.

No differences were observed in the skeletal or body composition parameters in the fracture and non-fracture groups in the POI cohort. Moreover, fracture rates were similar between women using ERT at the time of assessment compared with those who were not using ERT.

**DISCUSSION**

This study demonstrated that women with s-POI had the worst skeletal outcomes, including the lowest BMD at both the hip and spine and highest prevalence of abnormal TBS compared with women with i-POI or control women. Moreover, women in both POI subgroups demonstrated significantly lower lean mass (ALM and ALMI) regardless of cause. A 0.62%/year decline in FN-BMD was observed over 12 years, whereas no significant change was observed in LS-BMD, TBS, or FMI. Continued ERT use conferred a protective effect on both bone and body composition indices, with stable FN BMD and an increase in...
appendicular lean mass. Furthermore, a significant reduction in TBS of -0.51% was observed in POI women with interrupted ERT use.

An association of hypoestrogenism with impaired bone health has long been established, where researchers have focused on the impact on BMD. Congruent with previous studies of women with various causes of POI (5, 21, 22), our results also demonstrate lower LS and FN BMD in women with POI compared with control women. The reported prevalence of osteoporosis and low bone mass is consistent with the 8-15% prevalence in previous studies (4, 5).

Our novel finding of increased prevalence of abnormal TBS in s-POI women with normal karyotype is similar to data previously described by our group in a study of 60 women with Turner syndrome (TS), a genetic cause of POI, which showed that a third of these women had abnormal TBS (15).

TBS provides an additional tool to predict fracture risk in older adults, including postmenopausal women. However, studies investigating TBS characteristics and its utility in predicting fracture risk in younger populations are limited. The natural trajectory of TBS can be delineated by a few small studies in healthy premenopausal women aged between 20-50 years (37-40). A 2009 meta-analysis of 23 studies concluded that ERT had small beneficial effect on muscle strength in postmenopausal women (41). In addition, a recent clinical trial in postmenopausal women demonstrated increased muscle mass and function parameters with ERT plus resistance training versus resistance training alone (42). However, data are

### TABLE 2 | Longitudinal changes in bone & body composition outcomes.

| Parameter                          | △/Year (95%CI)          | p-value |
|------------------------------------|-------------------------|---------|
| **All POI cases (n=23)**           |                         |         |
| LS BMD, g/cm²                      | 0.0012 (0.0025, 0.0049) | 0.51    |
| FN BMD, g/cm²                      | -0.0049 (-0.0096, 0.00027) | 0.038   |
| TBS                                | 0.00086 (-0.0032, 0.0049) | 0.677   |
| ALM (g)                            | 71.61 (68.69, 134.32)   | 0.025   |
| ALMI (g/m²)                        | 33.62 (12.50, 54.74)    | 0.002   |
| TFM (g)                            | 51.80 (-324.95, 428.55) | 0.79    |
| TFM (g/m²)                         | 23.19 (-112.27, 158.64) | 0.74    |
| **POI cases with continued ERT (n=17)** |                     |         |
| LS BMD, g/cm²                      | 0.0019 (-0.0019, 0.0058) | 0.32    |
| FN BMD, g/cm²                      | -0.0016 (-0.0038, 0.00059) | 0.15    |
| TBS                                | 0.0002 (-0.0019, 0.0083) | 0.23    |
| ALM (g)                            | 127.05 (68.81, 185.30)  | <0.001  |
| ALMI (g/m²)                        | 47.29 (25.35, 69.23)    | <0.001  |
| TFM (g)                            | 96.60 (-250.01, 443.21) | 0.59    |
| TFM (g/m²)                         | 37.05 (-96.59, 170.69)  | 0.59    |
| **POI cases with interrupted ERT (n=5)** |                     |         |
| LS BMD, g/cm²                      | -0.0035 (-0.0014, 0.0067) | 0.50    |
| FN BMD, g/cm²                      | -0.020 (-0.037, -0.0024) | 0.025   |
| TBS                                | -0.0070 (-0.011, -0.0020) | 0.007   |
| ALM (g)                            | 7.60 (-139.04, 154.25)  | 0.92    |
| ALMI (g/m²)                        | 5.31 (-52.06, 62.68)    | 0.86    |
| TFM (g)                            | -590.48 (-1754.61, 573.64) | 0.32    |
| TFM (g/m²)                         | -154.22 (-537.42, 228.99) | 0.43    |

*Boldface indicates p values that are statistically significant.*

BMI, body mass index; ERT, estrogen replacement therapy; BMD, bone mineral density; LS, lumbar spine; FN, femoral neck; TBS, trabecular bone score; ALM, appendicular lean mass; ALMI, appendicular lean mass index; TFM, total fat mass; TFMI, total fat mass index.
FIGURE 3 | Longitudinal changes in bone and body composition parameters in women (including participant with L1 fracture receiving antiresorptive therapy; n=24) with premature ovarian insufficiency stratified by estrogen replacement therapy (ERT) use. Scatterplots (A–E) shows Δ/Year (95%CI) with p values for skeletal and body composition changes for women who had continuous ERT (solid circles) and interrupted ERT (hollow circles) with solid and dashed regression lines indicate the mean annual change in parameter for continued ERT and interrupted ERT, respectively. The respective changes were (A) LS BMD Δ/Year (95%CI) 0.0019 (-0.0019, 0.0058) p = 0.32, and -0.0035 (-.0014, 0.00059), p = 0.50 (B) FN BMD Δ/Year (95%CI) 0.0016 (-0.0038,0.00059), p = 0.15 and -0.020 (-0.037, -0.0024), p = 0.025 (C) TBS Δ/Year (95%CI) 0.0032 (-0.0019, 0.0083), p = 0.23, and -0.0070 (-0.011, -0.0020), p=0.007 (D) ALMI Δ/Year (95%CI) 47.29 (25.35, 69.23) p=<0.001 and -590.48 (-1754.61, 573.64), p=0.32 (E) TFMI Δ/Year (95%CI) 37.05 (-96.59, 170.69) p=0.59 and -154.22 (-537.42, 228.99) p=0.43 ERT, estrogen replacement therapy; LS, lumbar spine; BMD, bone mineral density; FN, femoral neck; TBS, trabecular bone score; ALMI, appendicular lean mass index; TFMI, total fat mass index.
lacking regarding women with POI (16). Our study’s finding of lower muscle mass including ALM and ALMI in women with s-POI or i-POI is consistent with results from Luo et al., which reported a lower muscle distributing coefficient of the lower limbs (MD) in 240 women with POI compared with peri- or postmenopausal women, not on ERT (43). This contrasts with the case-control study of 140 participants by Freitas et al., which did not observe any difference in the TFM or TLM in women with POI (44); however, the use of ERT for 18 months by these participants may have prevented muscle loss. Similarly, in the longitudinal analysis of our POI cohort, an increase in lean mass (ALM, ALMI) was observed in those with continued ERT use over the follow-up period. Multiple pathophysiological oestrogenic influenced mechanisms potentially contribute to reduced muscle mass including: reduced muscle turnover, defective contractility, increased free radical-mediated apoptosis and impaired bone-muscle cross signaling due to compromised skeletal health in POI (16). Overall, these findings highlight the deleterious effects of oestrogen deficiency on muscle health and potential prevention with ERT.

Limited data are available regarding fracture risk and prevalence in women with POI (7). A case-control study showed an increased prevalence of Colles’ fracture in women with early menopause (45) and findings of increased fracture risk with earlier menopause were also seen Women’s Health Initiative observational study (46). However, prevalent fractures in our study were similar in all three groups, likely explained by our small study size. As fracture risk is time-dependent, increased fracture prevalence in POI women may become significant later in life. We were unable to determine the type of fracture (fragility or traumatic); however, recent data in postmenopausal women indicates increased fracture risk with both fracture types (47).

The strengths of this study include: (i) the use of a novel tool, TBS, for fracture risk assessment, (ii) the presence of an age- and BMI-matched control group for cross-sectional analysis, and (iii) the availability of longitudinal skeletal and body composition data for POI participants. Despite providing important new insights into musculoskeletal health in women with POI, our study also has some limitations. These include: (i) retrospective data collection, (ii) inclusion of BMD and TBS data from one s-POI patient with an L1 fracture could have affected the BMD analysis. However, whether TBS is affected by mild to moderate compression fractures is still debated (48) (iii) small sample size of the longitudinal POI cohort that may have underestimated the effects of ERT on the longitudinal skeletal and body composition parameters; and (iv) lack of a longitudinal control group. The small sample sizes and the use of different ERT preparations by the same woman also precluded the analysis of bone and body composition parameters according to type of ERT and we therefore restricted our analysis to ‘interrupted’ or ‘continued’ ERT use. These considerations highlight the need for adequately powered prospective studies, as currently occurring in the United Kingdom, or randomised clinical trials to answer the important question as to the optimal ERT for bone and muscle health in women with POI. Given the limitation of a small cohort, we could not identify an association between TBS and fractures in women with POI.

CONCLUSION

In this combined study of skeletal and body composition parameters, we demonstrate that lower BMD and spinal trabecular microarchitectural bone deficits, as assessed by TBS, are more common in POI women than healthy pre-menopausal women. Furthermore, these women are also at risk of losing muscle mass; ERT attenuates these changes. This study highlights the need to view bone and muscle health in unison, especially when bone microarchitectural and muscle assessments can be performed simultaneously with routine BMD assessment using commonly available DXA-based techniques.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

NS, HN, FM, AV, and PE contributed to conception and design of the study. NS and HN organised the database. NS and HN performed the statistical analysis. NS prepared the manuscript. All authors contributed to manuscript revision, read, and approved the submitted version.

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