Received: 19 April 2019 | Revised: 1 October 2019 | Accepted: 13 October 2019

DOI: 10.1111/cen.14110

ORIGINAL ARTICLE

WILEY

Fracture rate in women with oestrogen deficiency – Comparison of Turner syndrome and premature ovarian insufficiency

Carol Cardona Attard | Antoinette Cameron-Pimblett | Davina Puri | Jessica Elliot | Jack C. Wilson | Vikram S. Talaulikar | Melanie C. Davies | Gerard S. Conway

Reproductive Medicine Unit, University College London Hospitals, London, UK

Correspondence
Carol Cardona Attard, Reproductive Medicine Unit, Elizabeth Garrett Anderson Wing, Clinic 1, Lower Ground Floor, 235 Euston Road, NW1 2BU London, UK.
Email: carol.cardonaattard@nhs.net

Abstract

Objective: Women with early-onset oestrogen deficiency are at risk of reduced bone mineral density (BMD). We sought to assess fracture history and BMD in women with Turner syndrome (TS) and premature ovarian insufficiency (POI).

Design: A cross-sectional observational study.

Patients: Two hundred and sixty seven women with TS (median age 34.3 years) and 67 women with POI (median age 28.1 years).

Measurements: A questionnaire was used to collect data on fracture history, co-morbidities and drug history including age at first oestrogen exposure. Clinical data included height, weight, serum vitamin D and hip and spine T-scores, which were adjusted for height and age. Fractures were subdivided into major osteoporotic fractures (MOF) and 'other' fracture types.

Results: Overall fracture rate was similar in women with TS and POI (82 [30.5%] vs 22 [32.8%] respectively, $P = .74$). Compared to women with POI, those with TS had more fractures at MOF sites (30.2% vs 52.7%, $P = .012$) and fewer phalangeal fractures (27.9% vs 9.8%, $P = .005$). There was no difference in BMD between women who sustained a fracture compared to those who did not. Women with TS who fractured were more likely to suffer from hearing impairment compared to those with no fracture (62.2% vs 48.1%, $P = .045$).

Conclusions: TS is not associated with an overall excess risk of bone fracture. The higher rate of fractures at MOF sites in women with TS may be secondary to hearing impairment, thin cortical bone and abnormal bone remodelling.

KEYWORDS

bone fractures, bone mineral density, hearing impairment, oestrogen, osteoporotic fractures, premature ovarian insufficiency, Turner syndrome

1 | INTRODUCTION

Adolescence is a time of major increase in bone growth which is reliant on adequate sex steroids.[1] Early-onset oestrogen deficiency presenting with primary amenorrhoea and delayed puberty is associated with reduced bone mineral density (BMD),[2] but the implications of this observation on future risk of bone fracture is unclear. To explore this further, we set out to assess history of bone fracture in women with Turner syndrome (TS) and premature ovarian insufficiency (POI).

Reduced bone density has been widely reported in women with TS.[3-5] BMD in women with TS may, however, be underestimated because of their short stature and smaller bone size, since dual-energy X-ray absorptiometry (DEXA) scanning assesses areal BMD (grams per square centimetre) and not volumetric density (grams per cubic centimetre).[6] BMD adjusted for height is one method of correcting for smaller bone size in women with TS.[2,7] Women with POI have also been shown to have reduced BMD,[8] which is affected by the duration and degree of oestrogen deficiency.[9]

Studies reporting fracture risk in TS have shown varying results with prevalence ranging from 16.7% to 58.0%.[4,6,10-14] An increased risk for fractures in women or girls with TS was noted in several reports [3,4,13-15] but not in others.[11,16] A recent patient survey observed an increased fracture risk in women with TS only above the age of 45.[10] Such discrepancies can be accounted for by different methodologies. Postal questionnaires with response rates of less than 60% [10,13] may lead to over-reporting of fractures. A higher fracture risk may have been reported in girls with TS in the study by Ross et al[15] where control data was obtained from medical records, whilst girls with TS were interviewed. Risk factors for fracture in women with TS included hearing impairment, especially the conductive type,[12] low BMD,[4,12] frail cortical bone,[14] impaired balance[10] and family history.[13]

There are fewer data on fracture risk in women with POI, particularly those with early-onset. In a systematic review, no increased fracture risk was found in women experiencing early natural menopause before the age of 45.[17] With menopause onset before the age of 40, however, women suffered from twice as many Colles fractures compared to women with later menopause.[18] Similarly, in the Women's Health Initiative Observational Study, women who were menopausal before the age of 40 had a higher risk of fracture at any site in comparison to women who were menopausal after the age of 50.[8]

In this study, we sought to assess whether there was a difference in fracture rates and type, age at fracture and BMD between oestrogen deficient women with TS and POI. To our knowledge, this is the first study to compare fracture rates in women suffering from TS with karyotypically normal women suffering from POI. We also wanted to investigate whether there were any risk factors associated with fracture.

2 | MATERIALS AND METHODS

2.1 | Subject recruitment

A cross-sectional observational study was carried out as part of the Reproductive Life Course Project at University College London. Permission to perform the study was obtained from the Chelsea Research Ethics Committee, with study reference number LO/ 2174. Inclusion criteria included women with TS or POI with hypergonadotrophic amenorrhoea before the age of 35 years. Two hundred and sixty-seven women suffering from TS and 67 women with early-onset POI were recruited, whilst 35 (11.6%) women with TS and 14 (17.3%) women with POI declined to participate in the study. A karyotype result was available for 251 (94.0%) women with TS, and the distribution of karyotype groups comprised as follows: 45,X (132 women, 49.4%); isochromosome 45,X,i(X) or 45,X/46,X,i(X) (50, 18.7%); mosaic 45,X/46,XX (27, 10.1%); any Y fragment (19, 7.1%); and other karyotypes (23, 8.6%) including ring 45,X/46,X,r(X), 45,X/47,XXX, partial X deletions, three or more cell lines such as 45,X/46,XX/47,XXX and complex variants. For 16 women (6.0%) with no karyotype data, a clear clinical diagnosis was accepted. Women with POI had karyotypically normal idiopathic hypergonadotrophic amenorrhoea except for one (1.5%) with galactosaemia and nine women (13.4%) with primary hypothyroidism. Informed consent was taken from all participants. All data were anonymized, and questionnaires were coded.

2.2 | Questionnaire and data collection

The questionnaire involved a wide-ranging 280-item medical and psychosocial assessment, including bone health. Self-reported fracture history included age and circumstances at the time of fracture. Fracture related variables included age at diagnosis, age at first oestrogen exposure, whether menarche was natural or induced, history of thyroid dysfunction, coeliac disease, use of growth-promoting treatments, steroids and bisphosphonates, previous pregnancy and whether they were currently taking hormone replacement therapy (HRT) and vitamin D supplements. Women with TS also completed a self-assessment of hearing impairment, where they were asked if they ever had any hearing problems and if they have ever been issued with a hearing aid. Height, weight and BMI were recorded. The most recent serum vitamin D level of each subject was recorded in nmol/L, with results available in 87.4% of women.

For the TS group, data on growth-promoting treatments in childhood was available in 90.3%, of which 134 (55.6%) had received growth hormone (GH), and 46 (19.1%) had received oxandrolone. History of thyroid dysfunction and coeliac disease was available for 94.0% of women with TS. Use of vitamin D supplements was available in 91.9% of women, of whom 58.0% were recorded to be taking a supplement.

In order to explore the influence of the age of first exposure to oestrogen, women with primary amenorrhoea were divided in two groups depending on whether oestrogen replacement therapy was started at or before or after the 14th birthday.

2.3 | Bone mineral density

Bone density was measured using dual-energy X-ray absorptiometry (Hologic® Inc, model Discovery A [S/N 83799]). Thirty-four (12.6%) women with TS and 6 (8.7%) women with POI had not yet attended for a BMD scan.

The routine bone density service at this centre provided BMD and T-scores from which we chose to analyse T-scores as the two are in linear relationship. We chose to use height-adjusted T-scores for analysis as a method for correction for bone size based on the

observation that height accounts for the major part of the difference between BMD and bone mineral apparent density (BMAD).[19] Correction for height and age was performed by using unstandardized coefficients determined by multiple regression and according to the equations: Adjusted Spine T-score = Raw Spine T-score + (1.888 * [1.52 - Height]) + (0.021 * [33.03 - age]) and Adjusted Hip T-score = Raw Hip T-score + (1.984 * [1.52 - Height]) + (−0.002 * [33.03 - age]),[2] where 1.52 is the median height, and 33.03 is the median age for all subjects in the study.

2.4 | Fracture categories

Fracture sites were recorded as forearm, proximal humerus, fingers and toes, hip, other upper limb, other lower limb, vertebrae, skull and face fractures and rib and clavicular fractures. 'Other upper limb' fractures included fractures involving the mid-shaft and distal humerus, elbow and hand/metacarpals, whilst 'other lower limb' fractures included fractures of the mid-shaft and distal femur, lower leg (tibia and fibula), ankle and foot/metatarsals. Major osteoporotic fractures (MOF) were defined as low-fragility fractures occurring at major skeletal sites mainly the hip, vertebrae, proximal humerus and forearm.[20,21] The rest of the fractures occurring at non-MOF sites were classified as 'other' fractures.

Circumstances leading to the fracture were subdivided into falls and other trauma, the latter including fractures occurring during sports, play, jumping, punching, motor vehicle accidents, hitting objects and following a seizure.

2.5 | Statistical analyses

Descriptive data were expressed as median and minimum and maximum values for continuous variables, which were not normally distributed; absolute numbers and percentage values were used for categorical variables. For those variables where some data points were missing, percentages were expressed as the proportion out of the total number of women with data available for that variable.

The Mann-Whitney *U* test was used to compare continuous variables between women with TS and POI. Chi-square test was used to compare the different fracture categories and types, circumstances leading to fracture amongst women with TS and POI as well as risk

TABLE 1 Descriptive data (median [and minimum and maximum values] for continuous variables and absolute numbers [and percentage] for categorical variables) for Turner syndrome (TS) vs premature ovarian insufficiency (POI)

Variables	TS N = 267	POI N = 67	*P*
Age (y)	**34.3 (15.0 - 70.9)**	**28.1 (17.4 - 52.7)**	**.002***
Age at diagnosis (y)	**10.0 (0.0 - 35.0)**	**16.0 (0.1 - 32.0)**	**<.001***
Age at start of oestrogen treatment (y)	**14.0 (9.0 - 38.0)**	**16.0 (13.0 - 32.0)**	**<.001***
Age at start of ERT in primary amenorrhoea (y)	**14.0 (9.0 - 35.0)**	**16.0 (13.0 - 23.0)**	**<.001***
Currently on HRT	**234 (87.6%)**	**65 (97.0%)**	**.025***
Primary amenorrhoea	**237 (88.8%)**	**46 (68.7%)**	**<.001***
Secondary amenorrhoea	**29 (10.9%)**	**21 (31.3%)**	**<.001***
Previously pregnant	**24 (9.0%)**	**14 (20.9%)**	**.006***
Adjusted hip T-scores	−0.8 (−2.8 - 2.0)	−1.1 (−2.7 - 0.8)	.092
Adjusted spine T-scores	**−1.0 (−3.4 - 2.7)**	**−1.5 (−4.3 - 1.0)**	**.002***
Height (m)	**1.5 (1.3 - 1.7)**	**1.7 (1.5 - 1.9)**	**<.001***
BMI (kg/m^2)	**25.0 (16.4 - 56.3)**	**22.7 (17.1 - 38.6)**	**<.001***
Hearing impairment	140 (52.4%)	-	-
Use of hearing aid	80 (30.0%)	-	-
Primary hypothyroidism	**99 (39.4%)**	**9 (13.4%)**	**<.001***
Primary hyperthyroidism	3 (1.2%)	0 (0%)	-
Coeliac disease	16 (6.4%)	0 (0%)	-
Vitamin D level (nmol/L)	60.0 (7 - 208)	61.5 (13 - 139)	.460
On Vitamin D supplements	**161 (67.1%)**	**17 (25.4%)**	**<.001***
Use of bisphosphonates	12 (4.5%)	1 (1.5%)	.256
Use of steroids	20 (8.3%)	1 (1.5%)	.050
Suffered a fracture	82 (30.7%)	22 (32.8%)	.737
More than 1 fracture	22 (8.2%)	10 (14.9%)	.096
Earliest fracture age (y)	11.0 (3.0 - 50.0)	10.0 (3.0 - 25.0)	.483

Abbreviations: BMI, body mass index; ERT, oestrogen replacement therapy and HRT, Hormone replacement therapy.
*The ones in bold and with an asterick are statistically significant.

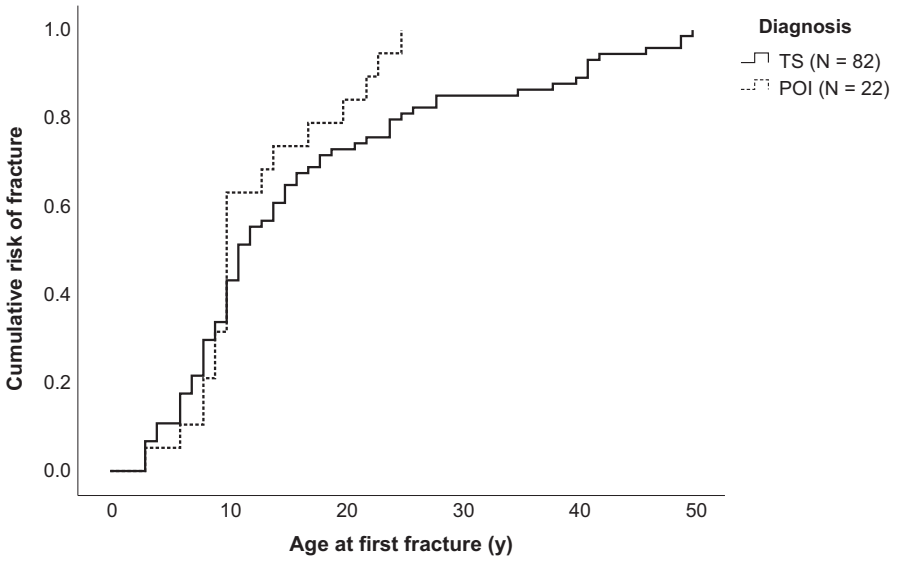

FIGURE 1 Kaplan-Meier estimate for age at first fracture in Turner syndrome (TS) and premature ovarian insufficiency (POI). Median age TS 11.0 (Standard Error [SE] 1.0) vs POI 10.0 (SE 0.4), Log Rank $P = .147$

factors for fracture between fracture and non-fracture subgroups. The median age at fracture for the different fracture categories and types were calculated and compared between groups using the Mann-Whitney *U* test. The Kruskal-Wallis test was used to compare the adjusted T-scores between women who sustained a MOF to women who sustained a non-MOF and women who did not fracture. Earliest fracture age survival curves were derived using Kaplan-Meier estimates. Statistical analyses were performed using IBM Statistical Package for the Social Science programme (SPSS®) version 25. Statistical significance was defined by a two-sided *P*-value < .05.

3 | RESULTS

Descriptive data for women with TS and POI is summarized in Table 1. The TS group differed from those with POI in the following respects: they were older, shorter of stature, had greater BMI, were diagnosed and started on oestrogen replacement therapy at a younger age, were more likely to present with primary amenorrhoea and have hypothyroidism and more likely to be taking vitamin D supplements but less likely to be taking HRT. Prior pregnancy was more common in women with POI. Age- and height-adjusted BMD T-scores were lower for the spine but not hip in women with POI compared to women with TS.

There was no difference in serum Vitamin D levels or use of bisphosphonates between the two groups, though history of steroid use was more common in women with TS with borderline statistical significance. Medical conditions for which steroid therapy was required included asthma, inflammatory bowel disease, inflammatory arthritis including psoriasis and psoriatic arthritis, recurrent acute urticaria, Wegener's granulomatosis and secondary adrenal insufficiency.

3.1 | Fractures

Eighty-two out of 267 women with TS suffered from a total of 112 fractures (mean of 1.4 fractures per person), whilst 22 out of 67 women with POI sustained a total of 43 fractures (mean of 2.0 fractures per person). There was no difference in the proportion of women who suffered from at least one fracture or more than one fracture between women with TS and POI (Table 1). In order to assess the influence of older age for women with TS, we used cumulative survival curves for age at first fracture in TS and POI, which show no difference in median age of fracture event between the two groups (Figure 1).

When the fracture sites were compared between women with TS and POI, finger and toe fractures occurred more commonly in women with POI (Table 2). None of the women with POI suffered from a hip or proximal humerus fracture, whilst these occurred in 3 and 5 women with TS respectively. Thus, women with TS sustained more fractures at MOF sites compared to women with POI (59 fractures [52.7%] vs 13 fractures [30.2%] respectively, $P = .012$). 'Other fractures' included a total of 53 (47.3%) fractures in women with TS and 30 (69.8%) fractures in women with POI ($P = .054$). There was no difference between the two groups in the number of fractures or fracture age for subgroups based on fracture sites such as forearm, other upper limb, other lower limb, vertebral, skull and face and rib and clavicular fractures individually. None of the fractures were classified as atypical fractures. All vertebral fractures occurred at the age of 18 years or above. The majority of forearm fractures (76.5% of forearm fractures in TS and 83.3% of forearm fractures in POI) occurred in childhood and adolescence (≤18 years) with a median age of 13.0 (interquartile range [IQR] 8.0) for TS and 11.5 (IQR 7.3) for POI.

3.2 | Risk factors for fracture and reduced BMD

Women with TS who fractured were older compared to those who did not fracture (median age 36.7 [16.0- 70.2] vs 33.0 [15.0- 70.9] respectively, $P = .012$) and were more likely to suffer from self-reported hearing impairment (62.2% vs 48.1%, $P = .045$). Karyotype distribution did not differ between women who suffered a fracture compared to those who did not ($P = .24$), with a similar proportion of

TABLE 2 Total number (and percentage) of patients according to fracture site in Turner syndrome (TS) compared to premature ovarian insufficiency (POI)

Fracture site	TS N = 112	POI N = 43	P[a]
Forearm	47 (42.0%)	12 (27.9%)	.107
Proximal humerus	5 (4.5%)	0 (0%)	-
Vertebrae	4 (3.6%)	1 (2.3%)	.694
Hip	3 (2.7%)	0 (0%)	-
Fingers and toes	**11 (9.8%)**	**12 (27.9%)**	**.005***
Skull and face	5 (4.5%)	1 (2.3%)	.537
Other upper limb	14 (12.5%)	5 (11.6%)	.882
Other lower limb	16 (14.3%)	9 (20.9%)	.314
Clavicle and ribs	7 (6.3%)	3 (7.0%)	.869

[a]Chi-square test.
*The ones in bold and with an asterick are statistically significant.

monosomy 45X in both groups. Previous treatment with GH or oxandrolone did not affect fracture risk, and there was no difference in the current use of HRT or Vitamin D supplements, serum Vitamin D level, BMD, history of steroid use, pregnancy, thyroid dysfunction or coeliac disease in women with TS who fractured compared to those who did not fracture. Bisphosphonate use for osteoporosis, was, however, more common in women with TS who fractured (9.8% vs 2.2%, P = .006), compared to the non-fracture subgroup. No significant correlations between fracture and risk factors were identified in women with POI when analysed separately.

Women suffering from fractures at MOF sites were older compared to women who did not fracture (median age 36.2 [19.1-70.2] vs 31.3 [15-70.9], P = .021), and a greater proportion were taking vitamin D supplements (71.7% vs 56.0%, P = .038), had a history of bisphosphonate use (14.5% vs 1.7%, P = <0.001) and suffered from coeliac disease (11.1% vs 4.2%, P = .047). No other risk factors were associated with MOF or 'other' fracture subgroups when analysed separately.

Analysis of the circumstances leading to fracture showed that fractures at MOF sites were secondary to falls in 51.9% of women with TS and 44.4% of women with POI (P = .68). Other traumatic injury was responsible for the majority of fractures in the 'other' fracture category in women with TS (55.3%) and in women with POI (71.4%).

A possible influence of the timing of induction of puberty in women with TS and POI who had experienced primary amenorrhoea was assessed by comparing outcomes in those who started oestrogen replacement therapy after the age of 14 years with those who started oestrogen at or before the age of 14, as late and early puberty groups respectively. The late puberty group had lower median (range) adjusted spine T-scores (−1.3 [−4.1 - 1.2] vs −1.0 [−4.3 - 2.7], P = .001), but not at the hip. Adjusted spine T-scores were lower in women with POI and primary amenorrhoea compared to women with TS and primary amenorrhoea (−1.6 [−4.3 - 1.0] vs −1.0 [−3.4 - 2.7] respectively, P = .005). This difference in spine T-scores between women with TS and POI was not observed in women with secondary amenorrhoea. Compared to women undergoing early induction of puberty, the late puberty group was not at an excess risk of fracture (P = .89).

Women taking HRT had a higher spine BMD (−1.1 [−4.3 - 2.7] vs −1.4 [−3.4 - 2.2], P = .031), whilst women with a history of bisphosphonate intake had lower hip (−1.4 [−2.8 - 0.2] vs −0.9 [−2.8 - 2.0], P = .045) and spine T-scores (−2.7 [−3.4 - −0.6] vs −1.1[−4.3 - 2.7], P = <.001). BMD was not different in women with a history of coeliac disease, vitamin D supplementation or thyroid dysfunction and similarly, it was not different in women with TS who received GH or oxandrolone therapy.

4 | DISCUSSION

In this cross-sectional observational study, overall fracture rate in women with TS was not different from that of women suffering from early-onset POI, with no difference in the age at first fracture. Women with TS suffered from more fractures at MOF sites, whilst women with POI suffered from more phalyngeal fractures. Height- and age-adjusted BMD was not different in women with TS and POI who suffered from any type of fracture, including a MOF, compared to women who did not. In women with primary amenorrhoea, women with POI had a lower spine BMD and started oestrogen replacement therapy at an older age compared to women with TS.

Approximately one-third of TS and POI women suffered from at least one fracture in this study. It is difficult to assess how this compares to the general population as epidemiological data are derived using different methods. In an epidemiological study of fractures carried out in England, the age-standardized lifetime fracture prevalence in women was 32.0% (95% CI 31.3 to 32.8), with more than 30% of women having experienced a fracture by the age of 34.[22] Similarly, in a longitudinal study of children and adolescents, 39.9% of girls at the age of 18 years had fractured during growth.[23] In another study, the residual lifetime risk of fractures in women aged 60 years or older was 44% (95% CI, 40 to 48).[24] Therefore, fracture prevalence in our cohort of women suffering from TS and POI appears to be similar to that observed in these general population studies.

Women with TS incurred more MOFs compared to women with POI, despite the absence of a reduced BMD in women with TS compared to women with POI and the absence of a lower BMD in women with TS who suffered from a MOF compared to those who did not. This may be accounted for by the reduced cortical bone thickness and cortical area in TS, leading to increased bone fragility,[14,25,26] which is also feature of isolated short stature homeobox (SHOX) deficiency, and women with TS are haploinsufficient for SHOX.[27] Moreover, abnormal bone remodelling secondary to increased osteoclastogenesis and bone resorption coupled with blunted or normal bone formation will result in reduced bone strength in women with TS.[28,29] Furthermore, women with TS suffered more often from primary amenorrhoea and thus delayed puberty compared to

women with POI in the present study. Pubertal delay often results in a lower peak bone mass as well as a bone structural deficit.[30]

Females with TS who sustained a fracture were more likely to suffer from hearing impairment, which is a similar finding to that observed in a previous study where sensorineural deafness was associated with a higher fracture risk.[12] A recent population study found a higher risk for fractures involving MOF sites in individuals with severe and profound hearing impairment.[31] Hearing impairment may lead to reduced speech perception and spatial orientation[32] resulting in a higher risk of falls.[33] Moreover, individuals suffering from hearing impairment may also have concomitant vestibular dysfunction,[34] which will lead to more balance issues and in turn a higher risk of falls and fractures as was noted in the study by Wasserman et al[10] Indeed, more than half of fractures at MOF sites in women with TS in our study occurred after falling.

The forearm or upper limb appear to be the most commonly fractured sites in women with TS in this study as in others,[6,12,13] especially those assessing children[10,15] Interestingly, forearm fractures were also common in POI, so this may not be a TS specific observation but studies disagree on this point.[15,16] Forearm fractures are more common than other fractures in normal school-aged children,[35,36] and so we conclude that the forearm fracture frequency observed in the current cohort of women with TS and POI may be similar to that of the general population. The increased bone porosity and the deficit in bone mass compared to longitudinal growth that occurs at peak height velocity during puberty may explain the increased fracture incidence in this age group.[30]

Commencement of oestrogen therapy was not delayed in women who fractured compared to those who did not. However, women with POI and primary amenorrhoea had a greater delay in their start of oestrogen replacement therapy and a lower age- and height-adjusted spine T-score compared to women with TS. This trend for a lower BMD in association with a delay in oestrogen replacement therapy has been observed in other studies.[2,7] Reduced BMD and peak bone mass may result in an increased risk for fracture later on in adult life,[30,37] but our data did not have sufficient power to confirm this.

Fracture risk and BMD were not affected by a history of thyroid dysfunction or serum vitamin D concentrations. This could be because once a diagnosis of TS or POI is made, regular screening for these factors will lead to prompt treatment. Coeliac disease was associated with an increased risk of fractures at MOF sites only, accepting that the number of fractures in this group was small. GH and oxandrolone therapy were not associated with a reduced fracture risk or improved BMD in women with TS, and this lack of effect of GH on BMD and fractures in women with TS was also observed in previous studies.[38,39] We found no association between TS karyotype and fracture similar to other studies.[6,40]

This study has a number of limitations, which include its retrospective nature contributes to recall and reporting bias for data based on a patient-filled questionnaire. However, bone health was a small component of our questionnaire, and this should have limited ascertainment bias. Some of the younger patients who participated in our study had not yet done a DEXA scan so that BMD data for these patients was missing. Adherence to HRT was impossible to measure, and we did not gather information on family history of osteoporosis and fractures. Although we have adjusted BMD for height, areal BMD does not assess the bone micro-architecture. Whilst measurement of BMD by means of peripheral quantitative computed tomography may be more accurate as it allows characterization of volumetric BMD unlike DEXA, we did not have access to this in the routine clinic setting, and our software did not allow for the calculation of BMAD. Our ethical approval did not allow for a control group of healthy young women. Lastly, our cohort of women with TS and especially POI might have been too young to fully assess their risk of osteoporotic fractures.

In conclusion, women with TS do not appear to be at an overall excess risk of fracture compared to women with POI, though did sustain a significantly greater number of fractures at MOF sites. Since BMD was not reduced in women with TS compared to women with POI, other factors such as thin cortical bone, abnormal bone remodelling and hearing impairment may predispose women with TS to more MOFs. Women with TS and POI and primary amenorrhoea, who started oestrogen replacement therapy at an older age had a lower BMD at the spine. This stresses the importance for more timely initiation of oestrogen replacement therapy in such women presenting with hypergonadotrophic primary amenorrhoea.

ACKNOWLEDGEMENTS

We would like to sincerely thank all the women participating in the Reproductive Life Course Project and the Turner Syndrome Support Society.

CONFLICTS OF INTEREST

Nothing to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Carol Cardona Attard https://orcid.org/0000-0002-0947-8153

REFERENCES

1. McCormack SE, Cousminer DL, Chesi A, et al. Association Between Linear Growth and Bone Accrual in a Diverse Cohort of Children and Adolescents. *JAMA Pediatr*. 2017;171:e171769.
2. Cameron-Pimblett A, Davies MC, Burt E, et al. Effects of estrogen therapies on outcomes in Turner Syndrome: assessment

of induction of puberty and adult estrogen use. *J Clin Endocrinol Metab*. 2019;104(7):2820-2826
3. Gravholt CH, Juul S, Naeraa RW, Hansen J. Morbidity in Turner syndrome. *J Clin Epidemiol*. 1998;51:147-158.
4. Davies MC, Gulekli B, Jacobs HS. Osteoporosis in Turner's syndrome and other forms of primary amenorrhoea. *Clin Endocrinol (Oxf)*. 1995;43:741-746.
5. Lanes R, Gunczler P, Esaa S, Martinis R, Villaroel O, Weisinger JR. Decreased bone mass despite long-term estrogen replacement therapy in young women with Turner's syndrome and previously normal bone density. *Fertil Steril*. 1999;72:896-899.
6. Nguyen HH, Wong P, Strauss BJ, Ebeling PR, Milat F, Vincent A. A Cross-Sectional and Longitudinal Analysis of Trabecular Bone Score in Adults With Turner Syndrome. *J Clin Endocrinol Metab*. 2018;103:3792-3800.
7. Nguyen HH, Wong P, Strauss BJ, et al. Delay in estrogen commencement is associated with lower bone mineral density in Turner syndrome. *Climacteric*. 2017;20:436-441.
8. Sullivan SD, Lehman A, Thomas F, et al. Effects of self-reported age at nonsurgical menopause on time to first fracture and bone mineral density in the Women's Health Initiative Observational Study. *Menopause*. 2015;22:1035-1044.
9. Popat VB, Calis KA, Vanderhoof VH, et al. Bone mineral density in estrogen-deficient young women. *J Clin Endocrinol Metab*. 2009;94:2277-2283.
10. Wasserman H, Backeljauw PF, Khoury JC, Kalkwarf HJ, Gordon CM. Bone fragility in Turner syndrome: Fracture prevalence and risk factors determined by a national patient survey. *Clin Endocrinol (Oxf)*. 2018;89:46-55.
11. Bakalov VK, Chen ML, Baron J, et al. Bone mineral density and fractures in Turner syndrome. *Am J Med*. 2003;115:259-264.
12. Han TS, Cadge B, Conway GS. Hearing impairment and low bone mineral density increase the risk of bone fractures in women with Turner's syndrome. *Clin Endocrinol (Oxf)*. 2006;65:643-647.
13. Gravholt CH, Vestergaard P, Hermann AP, Mosekilde L, Brixen K, Christiansen JS. Increased fracture rates in Turner's syndrome: a nationwide questionnaire survey. *Clin Endocrinol (Oxf)*. 2003;59:89-96.
14. Zuckerman-Levin N, Yaniv I, Schwartz T, Guttmann H, Hochberg Z. Normal DXA bone mineral density but frail cortical bone in Turner's syndrome. *Clin Endocrinol (Oxf)*. 2007;67:60-64.
15. Ross JL, Long LM, Feuillan P, Cassorla F, Cutler GB Jr. Normal bone density of the wrist and spine and increased wrist fractures in girls with Turner's syndrome. *J Clin Endocrinol Metab*. 1991;73:355-359.
16. Soucek O, Schonau E, Lebl J, Willnecker J, Hlavka Z, Sumnik Z. A 6-Year Follow-Up of Fracture Incidence and Volumetric Bone Mineral Density Development in Girls With Turner Syndrome. *J Clin Endocrinol Metab*. 2018;103:1188-1197.
17. Anagnostis P, Siolos P, Gkekas NK, et al. Association between age at menopause and fracture risk: a systematic review and meta-analysis. *Endocrine*. 2019;63:213-224.
18. Mallmin H, Ljunghall S, Persson I, Bergstrom R. Risk factors for fractures of the distal forearm: a population-based case-control study. *Osteoporos Int*. 1994;4:298-304.
19. Cvijetic S, Korsic M. Apparent bone mineral density estimated from DXA in healthy men and women. *Osteoporos Int*. 2004;15:295-300.
20. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporos Int*. 2014;25:2359-2381.
21. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. *Osteoporos Int*. 2008;19:385-397.
22. Donaldson LJ, Reckless IP, Scholes S, Mindell JS, Shelton NJ. The epidemiology of fractures in England. *J Epidemiol Community Health*. 2008;62:174-180.
23. Jones IE, Williams SM, Dow N, Goulding A. How many children remain fracture-free during growth? a longitudinal study of children and adolescents participating in the Dunedin Multidisciplinary Health and Development Study. *Osteoporos Int*. 2002;13:990-995.
24. Nguyen ND, Ahlborg HG, Center JR, Eisman JA, Nguyen TV. Residual lifetime risk of fractures in women and men. *J Bone Miner Res*. 2007;22:781-788.
25. Bechtold S, Rauch F, Noelle V, et al. Musculoskeletal analyses of the forearm in young women with Turner syndrome: a study using peripheral quantitative computed tomography. *J Clin Endocrinol Metab*. 2001;86:5819-5823.
26. Soucek O, Lebl J, Snajderova M, et al. Bone geometry and volumetric bone mineral density in girls with Turner syndrome of different pubertal stages. *Clin Endocrinol (Oxf)*. 2011;74:445-452.
27. Soucek O, Zapletalova J, Zemkova D, et al. Prepubertal girls with Turner syndrome and children with isolated SHOX deficiency have similar bone geometry at the radius. *J Clin Endocrinol Metab*. 2013;98:E1241-1247.
28. Faienza MF, Brunetti G, Ventura A, et al. Mechanisms of enhanced osteoclastogenesis in girls and young women with Turner's Syndrome. *Bone*. 2015;81:228-236.
29. Gravholt CH, Lauridsen AL, Brixen K, Mosekilde L, Heickendorff L, Christiansen JS. Marked disproportionality in bone size and mineral, and distinct abnormalities in bone markers and calcitropic hormones in adult turner syndrome: a cross-sectional study. *J Clin Endocrinol Metab*. 2002;87:2798-2808.
30. Bonjour JP, Chevalley T. Pubertal timing, bone acquisition, and risk of fracture throughout life. *Endocr Rev*. 2014;35:820-847.
31. Kim SY, Lee JK, Sim S, Choi HG. Hearing impairment increases the risk of distal radius, hip, and spine fractures: A longitudinal follow-up study using a national sample cohort. *PLoS ONE*. 2018;13:e0192820.
32. Keller BK, Morton JL, Thomas VS, Potter JF. The effect of visual and hearing impairments on functional status. *J Am Geriatr Soc*. 1999;47:1319-1325.
33. Jiam NT, Li C, Agrawal Y. Hearing loss and falls: A systematic review and meta-analysis. *Laryngoscope*. 2016;126:2587-2596.
34. Zuniga MG, Dinkes RE, Davalos-Bichara M, et al. Association between hearing loss and saccular dysfunction in older individuals. *Otol Neurotol*. 2012;33:1586-1592.
35. Naranje SM, Erali RA, Warner WC Jr, Sawyer JR, Kelly DM. Epidemiology of Pediatric Fractures Presenting to Emergency Departments in the United States. *J Pediatr Orthop*. 2016;36:e45-48.
36. Joeris A, Lutz N, Wicki B, Slongo T, Audige L. An epidemiological evaluation of pediatric long bone fractures - a retrospective cohort study of 2716 patients from two Swiss tertiary pediatric hospitals. *BMC Pediatr*. 2014;14:314.
37. van Der Voort DJ, van Der Weijer PH, Barentsen R. Early menopause: increased fracture risk at older age. *Osteoporos Int*. 2003;14:525-530.
38. Aycan Z, Cetinkaya E, Darendeliler F, et al. The effect of growth hormone treatment on bone mineral density in prepubertal girls with Turner syndrome: a multicentre prospective clinical trial. *Clin Endocrinol (Oxf)*. 2008;68:769-772.
39. Bakalov VK, Van PL, Baron J, Reynolds JC, Bondy CA. Growth hormone therapy and bone mineral density in Turner syndrome. *J Clin Endocrinol Metab*. 2004;89:4886-4889.
40. Landin-Wilhelmsen K, Bryman I, Windh M, Wilhelmsen L. Osteoporosis and fractures in Turner syndrome-importance of growth promoting and oestrogen therapy. *Clin Endocrinol (Oxf)*. 1999;51:497-502.

How to cite this article: Cardona Attard C, Cameron-Pimblett A, Puri D, et al. Fracture rate in women with oestrogen deficiency – Comparison of Turner syndrome and premature ovarian insufficiency. *Clin Endocrinol (Oxf)*. 2019;91:743–749. https://doi.org/10.1111/cen.14110