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ORIGINAL ARTICLE

Decreased bone mineral density in women with Sheehan's syndrome and improvement following oestrogen replacement and nutritional supplementation

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Abstract

Sheehan's syndrome (SS) is an important cause of pan-hypopituitarism in women. There is scanty information on bone mineral density (BMD) in this condition. We determined BMD and the changes in BMD after oestrogen (E2) replacement and nutritional supplementation in women with SS. In a cross-sectional study, BMD was measured by DEXA in 83 patients [age (mean ± SD) 42 ± 9.2 years] and compared with an equal number of matched controls. In a sub-set of 19 patients, we conducted an open-label, prospective study to determine changes in BMD after 1 year of replacement of E2, and calcium and vitamin D3 supplementation. All patients had low serum IGF-1 and E2, while 98% had ≥ 3 pituitary hormone deficiencies. Compared with Indian reference standards, 47% had decreased bone mass (*Z*-score ≤ − 2.0). BMD *Z*-scores were decreased at all sites, being most marked in the lumbar spine and femoral neck. At the lumbar spine, BMD was lowest among the age group 21–30 years. Women with SS also had significantly lower BMD *Z*-scores at all three sites on comparison with ethnic controls. On multivariate analysis, BMD *Z*-score was associated with weight, daily calcium intake and age (lumbar spine). In the prospective study, 1 year of therapy improved BMD *Z*-score at lumbar spine (− 1.4 ± 1.2 vs. − 1.1 ± 1.1, $p = 0.02$), but not at hip or femoral neck. In conclusion, patients with SS had significantly lower BMD compared to controls at all three sites. Replacement of E2 and supplementation with calcium/vitamin D3 lead to significant improvement in lumbar spine BMD.

Keywords Sheehan's syndrome · Bone mineral density · Hypopituitarism · Replacement therapy

Sheehan's syndrome (SS) results from an infarction of the pituitary following severe post-partum haemorrhage [1–3]. It frequently results in a permanent deficiency of multiple anterior pituitary hormones and is a common aetiology of hypopituitarism in many low and low-middle income countries [4–6]. In a study conducted in the Kashmir Valley in India, its prevalence was 3% in women > 20 years of age [6]. This high frequency can be attributed to poor obstetric care, home deliveries by untrained personnel and poor availability of health care. Studies have also reported SS from countries with high socio-economic status, though its prevalence is lower [7, 8]. In a nation-wide, population-based, retrospective study conducted in Iceland, a prevalence of 5.1 per 100,000 women has been reported [8].

Various hormones, including oestrogen (E2), growth hormone (GH) and androgens, play an important role in bone mineral physiology [9–11]. Previous studies in women with hypopituitarism of various aetiologies have reported decreased bone mineral density (BMD) at the lumbar spine and femoral neck, and a higher risk of fractures [12–14]. In addition, an improvement in BMD has been reported after treatment of patients with premature ovarian insufficiency (POI) with E2 [15] and GH [16, 17].

There are sparse data on bone mass in women with SS [18–21]. In addition to developing severe hypopituitarism from a young age, these patients often have nutritional deficiencies which may worsen their BMD [6]. SS is more frequently encountered in women of lower socio-economic

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strata; risk factors such as low dietary calcium intake, protein deficiency and low vitamin D are frequent [22, 23]. In a small study of 34 patients of SS from Turkey, 62% of patients were osteoporotic [18]. Other investigators have also reported on low BMD in women with the disorder, but the role of important modifiable risk factors such as calcium intake, vitamin D3 or GH levels was not reported [19, 20]. In a small cohort of patients, GH replacement for a duration of 18 months did not result in improvement in BMD in women with SS [21]. This is in contrast to many studies that have shown beneficial effects of GH therapy in hypopituitarism from other causes [11, 16, 17]. E2 replacement and nutritional supplementation is universally practiced in women with SS, but its effect on BMD has not been reported thus far.

In view of the above-mentioned lacunae in our knowledge, we conducted a large cross-sectional study of 83 patients with SS to determine the prevalence of low bone mass and its associated risk factors. In addition, in a subgroup of patients, we prospectively studied the effect on BMD of replacement of E2, along with supplementation of calcium and vitamin D3.

Materials and methods

Patients and controls

We included 83 patients with SS, presenting to our clinic from 2011 to 2016, in this study. SS was diagnosed by a history of post-partum haemorrhage followed by absent lactation or menstrual disturbances, clinical and laboratory evidence of deficiency of one or more pituitary hormones, and an absence of radiological features of a pituitary mass lesion [2]. Exclusion criteria included other aetiologies of hypopituitarism such as pituitary tumour, surgery, radiotherapy and lymphocytic hypophysitis, and chronic disorders such as liver or renal impairment. Patients on long-term steroids, anti-epileptic drugs and bisphosphonates were also excluded.

The patients had an age of (mean ± SD) 42 ± 9 years and belonged mainly to middle (77%) and lower (12%) socioeconomic strata. Their age at delivery was 27.7 ± 5.5 years (range 18–44 years) and duration of illness was median (range) 14 years (1–43 years) (Table 1). All patients denied a history of smoking and alcohol intake. Thirty-one patients were fresh referrals to our clinic while 52 were in previous follow-up. Thirty-one (37%) patients had received E2 replacement for a varying duration of time (1.8 ± 3.2 years, range 1–16 years).

Eighty-three women, matched for age, BMI, and socioeconomic strata with patients with SS, were recruited as controls (Table 1). None had a history of post-partum haemorrhage or amenorrhea or lactational failure. The control subjects were from the same geographical region as the patients and were selected from volunteers in the local population. All patients and controls gave written informed consent and the study was approved by the institutional ethical committee.

Study protocol

A detailed clinical and hormone assessment was performed in all patients at the time of inclusion in the study. Daily dietary calcium intake was assessed using a food frequency questionnaire, which took into account different foods eaten in summer and winter months. A fasting serum sample was collected for measurement of T4 or FT4, TSH, IGF-1, FSH, prolactin, E2, intact PTH and 25-hydroxyvitamin D3 [25(OH)D]. Early morning and stimulated serum cortisol, taken 1 h after intramuscular injection of 250 µg synthetic aqueous ACTH (Synacthen®, Mallinckrodt, Dublin, Ireland), was measured in all patients. Secondary thyroid hormone deficiency was diagnosed by low FT4 (< 10 pmol/l) and low or normal TSH values, and E2 deficiency through low serum E2 (< 99 pmol/l) and low or normal FSH. ACTH deficiency was defined by peak serum cortisol < 500 nmol/l along with low or normal ACTH. GH deficiency was diagnosed as serum IGF-1 below the age and sex defined lower range for healthy women. Magnetic resonance imaging (MRI) of the sellar and suprasellar region was performed in all women, using the Signa HDxt 3.0T platform (Wipro GE Healthcare, India).

Prospective study

Twenty patients with SS, age ≤ 42 years, who had previously never been treated with E2, were recruited for this open-label, non-randomized study. Patients had an age of 37.2 ± 4.7 years and duration of illness of 10.2 ± 4.9 years. All subjects had hypothyroidism and 14 (70%) had hypocortisolism. Thyroid and ACTH hormone deficiencies were corrected with appropriate doses of levothyroxine (75–100 µg/day) and prednisolone (2.5–5 mg/day in 2 divided doses) prior to start of E2. All patients had GH deficiency (low IGF-1), but this could not be corrected due to financial considerations. No patient had a personal or family history of thrombo-embolic disorder, breast or endometrial cancer. The women were screened by clinical examination, mammogram and vaginal Papanicolaou smear prior to initiation of E2 therapy.

Patients were placed on cyclical E2 and progesterone [(ethinyl estradiol 30 µg, levonorgestrel 150 µg) (Ovral-L, Wyeth, Mumbai, India)]. All patients were provided oral calcium carbonate (1000 mg/day) and vitamin D3 (cholecalciferol 60,000 units/month). Patients were seen in follow-up

Table 1 Clinical features of women with Sheehan's syndrome and controls

Variable	Patients ($n = 83$)	Controls ($n = 83$)
Age (years)	42 ± 9	42 ± 9[a]
Age at last delivery (years)	28 ± 5.5	
Duration of illness (years)	14 ± 9	
Home delivery	27 (33)	
History of postpartum haemorrhage	78 (94)	0
Secondary amenorrhea	82 (99)	0
Lactation failure	83 (100)	0
Daily calcium intake (mg/day)	428 ± 169	750 ± 308[b]
Body mass index (kg/m^2)	22.6 ± 4.4	23.0 ± 4.0[a]
Haemoglobin (gm/dl)	10.4 ± 1.5	11.2 ± 0.8[b]
Serum albumin (g/dl)	4.1 ± 0.5	4.4 ± 0.2[c]
Corrected serum calcium (mg/dl)	8.9 ± 0.8	
Serum alkaline phosphatase (IU/l)	157 ± 78	
Serum 25(OH)D (nmol/l) ($n = 71$)	62 ± 49	
Parathyroid hormone (pmol/l) ($n = 70$)	6.8 ± 5.0	
Prolactin (mIU/l) ($n = 74$)	88 ± 95	
E2 (pmol/L) ($n = 69$)	101 ± 49	
Serum IGF-1 (nmol/l) ($n = 75$)	3.4 ± 2.8	
Free T4 (pmol/l)	5.8 ± 4.3	
Peak stimulated cortisol (nmol/l)	189 ± 197	
Severe pituitary hormone deficiency (≥ 3)	81 (98)	

Mean ± SD or *n* (%)

25(OH)D: 25-hydroxy vitamin D; IGF-1: insulin-like growth factor-1

Reference ranges: serum alkaline phosphatase: 35–150 IU/l; serum 25 (OH)D: 75–250 nmol/l; PTH 0.53–5.8 pmol/l; FT4 10–26 pmol/l; prolactin 102–496 mIU/l; serum IGF-1: according to age and sex; serum cortisol 1 h after short ACTH stimulation > 500 nmol/l

[a]*p* not significant

[b]$p = 0.000$

[c]$p = 0.02$

every 3 months to check for side effects and compliance with medicines. During follow-up, one patient developed deranged liver function test at 24 weeks and E2 was discontinued. Biochemistry, hormone levels, and BMD were assessed at the start and after one year of treatment.

Analytical methods

Serum biochemistry was performed on an auto-analyser (Imola Randox, Ramsey, MN). Serum 25(OH)D (analytical sensitivity 3.7 nmol/l) was measured by radio-immunoassay (DiaSorin, Stillwater, MN). A level of 25(OH)D between 50 and 75 nmol/l was defined as insufficiency and < 50 nmol/l as deficiency [24]. Intact PTH (analytical sensitivity 0.13 pmol/l) and IGF-1 (analytical sensitivity 0.6 nmol/l) were measured by immunoradiometric assay (Beckman Coulter, Brea, CA). Serum cortisol, FT4, TSH, E2, FSH and prolactin were measured using a chemiluminescence analyser (Immulite1000, Siemens, Germany).

Bone mineral density

BMD of the left total hip, neck of femur and lumbar spine (L1-L4) were measured using dual-energy X-ray absorptiometry (DEXA) (Delphi-010-1549, Hologic, Bedford, MA). The coefficient of variation was 0.25% and least significant change at the lumbar spine and hip was 0.022 and 0.027 g/cm^2, respectively. All subjects were tested on the same instrument. The diagnosis of osteoporosis and osteopenia was defined as *T*-score ≤ − 2.5 and between − 1.0 and − 2.5, respectively, and low bone mass as a *Z*-score ≤ − 2 [25]. The BMD of 237 age-matched Indian women of high socioeconomic status, derived from previously available community data, was used to derive the *Z*-score, using the formula (BMD of subject-mean BMD of reference group of corresponding age category)/standard deviation of reference group) [26]. X-ray of lumbar and thoracic spine was taken in lateral projections to screen for vertebral fractures [27].

Statistical methods

Continuous data were expressed as mean ± SD. The Student's *t* test and Chi square test were used for comparison of continuous and categorical variables, respectively. Variables associated with BMD at the three different sites were studied using Pearson's correlation test. Variables associated with bone mass at each of the sites were further tested using multivariate backward stepwise linear regression. For analysing the prospective data, the paired-*t*-test was used. Analysis of data of follow-up study was done by both per-protocol (19 patients) and intention-to-treat (20 patients) method. A p value < 0.05 was taken as significant. Statistical analyses were performed using statistical program for social sciences (SPSS) version 19.0; IBM, Chicago, IL).

Results

Clinical features

One-third of the women delivered at home (Table 1). A low BMI (< 18.5 kg/m^2) was present in 25% of patients, anaemia (haemoglobin < 12 g %) in 86% and hypoalbuminemia (serum albumin < 3.0 g %) in 7%. All patients had lactation failure, 99% had secondary hypogonadism and 87% had hypothyroidism at presentation. Serum IGF-1 was low in all women while 89% had an inadequate cortisol response after ACTH-stimulation. Deficiency of ≥ 3 hormones was noted in 98% of women. Nineteen (23%) patients had a daily calcium intake of < 300 mg/day. Serum 25(OH)D was deficient in 40% of patients, while 14% had severe deficiency (< 25 nmol/l). Elevated serum alkaline phosphatase and elevated PTH (> 5.8 pmol/l) were detected in 42 and 43% of patients, respectively.

Bone mineral density

A low bone mass (*Z*-score ≤ − 2.0) was noted in 39 (47%) patients. Twenty-two (27%) patients had a low bone mass at the lumbar spine, 28 (35%) at the femoral neck and 12 (15%) at hip (Table 2). Osteoporosis (*T*-score ≤ − 2.5) was present in 26 (48%) women > 40 years. When compared with the reference Indian population, BMD *Z*-scores were decreased at all three sites and were lower in the lumbar spine and femoral neck. *Z*-scores were decreased in all age groups, starting from the age group 20–29 years (Supplement 1). At the lumbar spine, the lowest *Z*-score was detected in the age group 21–30 years, while a low bone mass was present in 50% of patients in this age group (Fig. 1).

On comparison of patients with matched controls, the former had significantly lower areal BMD and BMD Z-scores at each of the three sites (Table 2). The BMD at the lumbar spine and femoral neck was more severely affected as compared with the total hip. No patient had history of hip or spine fractures or radiological evidence of fractures in the lumbar or thoracic spine.

There were no differences in BMD *Z*-score in relation to vitamin D deficiency or E2 supplementation. Body weight and calcium intake had a positive correlation with BMD *Z*-score at all three sites (Supplement 2). Age had a positive correlation with BMD *Z*-score at lumbar spine. However, no correlation was noted with duration of illness and initial level of E2, FT4 or peak cortisol at any site. On multiple linear regression analysis, the BMD *Z*-score was significantly associated with body weight and the daily calcium intake at all sites, and with age at the lumbar spine (Table 3).

Prospective study

The duration of E2 deprivation was 8.4 ± 4.2 years (range 1–16 years). After treatment for 1 year, there was significant increase in BMI, haemoglobin, serum calcium, 25(OH)D and IGF-1, as well as a reduction in serum alkaline

Table 2 Comparison of bone density in patients with Sheehan's syndrome and controls

	Lumbar spine		Total hip		Femoral Neck	
	Patients	Controls	Patients	Controls	Patients	Controls
BMD (g/cm^2)	0.81 ± 0.12[a]	0.88 ± 0.11	0.74 ± 0.11[a]	0.80 ± 0.11	0.64 ± 0.09[a]	0.73 ± 0.11
BMD *Z*-score	− 1.12 ± 1.05[a]	− 0.55 ± 0.97	−0.99 ± 0.89[b]	− 0.53 ± 0.98	− 1.53 ± 1.07	− 0.54 ± 1.02
Z-score ≤ − 2.0	22 (26.5)[a]	4 (4.8)	12 (14.5)[c]	4 (4.8)	28 (35.4)[a]	7 (8.4)

Mean ± SD or *n* (%)

Z-score ≤ − 2.0 at any site in 39 (47%) patients

BMD bone mineral density

[a] $p < 0.001$ versus matched controls

[b] $p = 0.002$ versus matched controls

[c] $p = 0.04$ versus matched controls

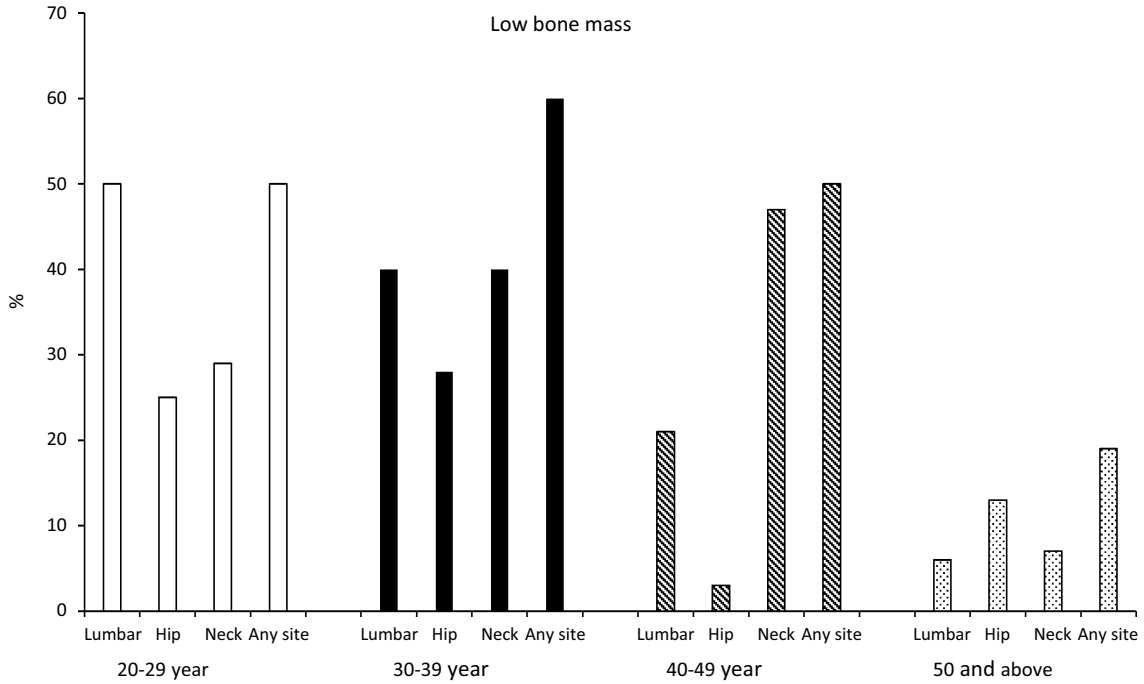

Fig. 1 Age-wise prevalence of low bone mass (*Z*-score ≤ 2.0) at different sites

Table 3 Multivariate linear regression analysis of BMD *Z*-score in patients with Sheehan's syndrome

Variables	Lumbar spine		Total hip		Femoral neck	
	Beta-coefficient	*P* value	Beta-coefficient	*P* value	Beta-coefficient	*P* value
Age	0.23	0.026	0.05	0.76	− 0.10	0.43
Duration of illness	0.04	0.81	0.21	0.49	− 0.05	0.79
Years of prednisolone intake	0.05	0.67	− 0.07	0.51	− 0.12	0.36
Daily calcium intake (g)	0.29	0.007	0.29	0.008	0.24	0.034
Weight (kg)	0.23	0.03	0.28	0.01	0.21	0.06

phosphatase (Table 4). A significant increase in BMD *Z*-score was noted at the lumbar spine after 1 year, but not at the hip or femoral neck. The results were similar when analysed by per-protocol and intention-to treat methods. Patients with a duration of illness < 10 years ($n = 8$) had a significant improvement in BMD *Z*-score (-1.62 ± 1.32 vs. -1.34 ± 1.33, $p = 0.001$) at the lumbar spine, in contrast to subjects ($n = 11$) with duration ≥ 10 years (-1.10 ± 1.19 vs. -0.93 ± 0.89, $p = 0.25$).

Discussion

In this large study of women with SS, patients had a delayed diagnosis after post-partum haemorrhage. Many had a poor nutritional status and most had severe hypopituitarism. Patients had low bone mass at all sites, including in younger age groups. Treatment with cyclical E2 and progesterone, along with supplementation with calcium and vitamin D3 for 1 year, resulted in significant improvement of BMD in the lumbar spine.

A low bone mass was present in nearly half of patients in the current study. When compared with the reference Indian population, BMD was significantly decreased at all three sites tested, with greater reduction noted at the lumbar spine and femoral neck. Bone mass was also significantly lower at all sites, when compared with age and BMI-matched healthy Indian women. In previous smaller reports from Turkey and Tunisia, a high frequency of osteoporosis at the lumbar spine and femoral neck has also been reported [18–20]. We also noted low BMD *Z*-scores in all age groups. At the femoral neck, *Z*-score was the lowest in the age group 20–30 years. This may be related to an initial steep decline on bone mass after menopause in patients, at a time when healthy women in this age group are likely to be achieving their peak bone density. Similar

Table 4 Baseline and 1-year post-intervention parameters in 19 patients with Sheehan's syndrome

Variable	Baseline	Follow-up	*P*
Weight	47.6 ± 9.9	54.1 ± 8.4	0.000
BMI (kg/m^2)	20.8 ± 4.4	23.0 ± 4.0	0.000
Calcium intake (mg/day)	459 ± 167	1099 ± 270	0.000
Haemoglobin (g/dl)	10.0 ± 1.6	11.4 ± 1.5	0.013
Albumin (g/dl)	4.1 ± 0.4	4.2 ± 0.3	0.3
Corrected serum calcium (mg/dl)	8.7 ± 0.7	9.4 ± 0.5	0.005
Serum alkaline phosphatase (U/l)	135 ± 47	82 ± 32	0.000
PTH (pmol/l)	5.4 (IQR 3.5–9.5)	7.8 (IQR 6.6–11.6)	0.04
25(OH)D3 (nmol/l)	50.1 ± 31.1	75.7 ± 25.3	0.03
Low T4/FT4	15 (79%)	2 (10%)	0.000
IGF-1 (nmol/l)	2.0 ± 1.9	3.8 ± 2.1	0.04
E2 (pmol/l)	92 ± 37	149 ± 102	0.08
Lumbar spine BMD	0.82 ± 0.13	0.84 ± 0.11	0.02
Lumbar spine *Z*-score	− 1.4 ± 1.2	− 1.1 ± 1.1	0.01
Femur neck BMD	0.63 ± 0.12	0.65 ± 0.12	0.17
Femur neck *Z*-score	− 1.7 ± 1.3	− 1.6 ± 1.4	0.17
Total hip BMD	0.74 ± 0.14	0.75 ± 0.13	0.17
Total hip *Z*-score	− 1.1 ± 1.2	− 1.0 ± 1.2	0.25

Results are as per protocol analysis; BMD results were similar after intention-to-treat analysis

n (%) or mean ± SD or median (IQR)

BMI body mass index (kg/m^2), *BMD* bone mineral density in g/cm^2; *25(OH)D3* 25 dihydroxy vitamin D3, *IGF-1* insulin-like growth factor-1; *E2* estradiol

Fasting E2 was measured in 11 patients before and after therapy

data are not available from previous studies on patients with SS.

Possible reasons for the low BMD noted in this study included the low IGF-1 and E2 noted in all patients, deficiencies of which are known to adversely affect bone mass [11–14]. The occurrence of hormone deficiency from an early age also increased the likelihood of development of decreased bone density. In analysis of 1034 hypopituitary adults enrolled in KIMS (Pfizer International Metabolic) database, women with SS had earlier onset, and more severe hormonal deficiencies, as compared to patients with non-functioning pituitary adenoma [28]. In addition, our patients also had frequent nutritional deficiencies which could, either singly or in combination, adversely affect bone mass. These included a low body weight [29, 30], decreased calcium intake [31] and hypovitaminosis D [24, 32].

Though both IGF-1 and E2 were severely deficient among women in the current study, we did not find any correlation with levels of either hormone with BMD. This may be due to their universal reduction in all the patients. On multivariate analysis, BMD *Z*-scores at all three sites were associated with body weight and daily calcium intake. In a previous study on women with premature ovarian insufficiency (POI), a weight < 55 kg was shown to increase risk of low bone mass by 2.8-fold [33]. In another report, it has found that a calcium intake < 1000 mg/day increased risk of low bone mass by 2.8-fold in patients with POI [34].

In patients whose BMD was prospectively studied, we noted a significant nutritional improvement after 1 year of treatment, with increase in body weight, haemoglobin, serum calcium and 25OHD, and a reduction in SAP. Despite replacement with oral E2, which can result in a decrease of serum IGF-1 [33], an increased IGF-1 was noted after 1 year, possibly due to an improvement in body weight [35]. A significant increase in lumbar spine BMD *Z*-score (> 20%) was noted, though there was no change noted at other sites. However, it was not feasible to determine if the improvement was due to E2 replacement, nutritional supplementation of calcium and vitamin D, or both. In studies of women with anorexia nervosa, who have both nutritional and E2 deficiencies, normalization of nutrition and E2 replacement together provide the greatest improvement in BMD [36]. BMD *Z*-score was improved in women with duration of illness < 10 years, but not those with longer duration, suggesting an earlier diagnosis and treatment was beneficial.

The current study has the advantages of a large patient size, detailed evaluation of bone density and its associated variables and prospective evaluation of BMD after E2 therapy and nutritional replacement. However, the study has certain limitations. Some variables could not be measured in all patients and markers for bone formation and resorption were

not analysed. The prospective study was open-label and did not have a control group. This was mainly due to the difficulties of withholding E2 or calcium/vitamin D replenishment in young women with amenorrhoea. However, the BMD was assessed by a technician without knowledge of the treatment received. Finally, it is feasible that replacement of GH may have further improved in BMD. However, GH replacement therapy is prohibitively expensive in India and is unlikely to be available in most developing countries where the problem of SS is common.

In conclusion, women with SS had a significantly lower bone mass, when compared with matched controls. The adverse effect on bone density at lumbar spine was noted in women as early as 20–30 years of age. Replacement of E2 and nutritional replacement of calcium and vitamin D resulted in significant improvement in bone density at the lumbar spine.

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Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest.

Ethical approval The studies have been approved by the appropriate institutional and/or national research ethics committee and have been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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

Informed consent Informed consent was obtained from all individual participants included in the study.

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