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IMPACT OF PREMATURE OVARIAN INSUFFICIENCY ON BONE HEALTH AND THE ROLE OF EARLY SCREENING

Gynecology

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ABSTRACT

OBJECTIVES Primary objectives were to assess the prevalence of low bone mass (LBM) in women with POI and to suggest when to initiate bone mass screening .

METHODS A cross sectional case control study was done in100 women with POI and 100 age matched controls. Bone mineral density of lumbar spine and femoral neck was estimated using DEXA scan.

RESULTS Low bone mass (Z score < -2.0 in lumbar spine or femoral neck) was found to be significantly high in POI (OR 23.6; 95%CI 5.4-102.5; p=<0.001). Co-relation co-efficient between lumbar spine Z-scores and duration of menopause was 0.1 (95% CI 0.03-0.16, p=0.63) over 20 years of POI, but during the first 8 years it was 0.2 (95%CI 0.07-0.34, p=0.009). 80% (n=24/37) developed LBM within the first 5 years.

CONCLUSIONS The incidence of LBM is significantly high in POI. Rapid bone loss warrants early screening at 5 years of POI.

KEYWORDS

Premature Ovarian Insufficiency, Low Bone Mass, Dexa Scans

INTRODUCTION

Hypergonadotropic hypogonadism before the age of forty affects 1-2% of women. It occurs in 1 in 10,000 women by 20years, 1 in 1000 women by 30 years and reaches 1 in 100 by 40 years [1]. ESHRE (European Society for Human Reproduction and Embryology) 2016 recommends the following diagnostic criteria for premature ovarian insufficiency (POI): (a) oligo/amenorrhoea for at least 4 months, and (b) an elevated follicle stimulating hormone (FSH) >25IU/l on 2 occasions more than 4 weeks apart [2].

The hypoestrogenic state accounts for all the morbidities of POI except for reduced libido which is due to low androgen levels. Minor morbidities include mood swings, vasomotor symptoms, sexual dysfunction, lower urinary tract symptoms and musculoskeletal issues. All cause mortality has also been found to be higher in POI from coronary artery disease (RR-1.09), respiratory disease (RR 1.19) and genitourinary disease (RR -1.39) [1].

Our study was designed to bring out the prevalence of low bone mass in Indian women with POI and to assess how early screening strategies could be advised. There is limited literature available in this regard from India. We have also evaluated hypocalcaemia, hypophosphatemia and hypovitaminosis D which could have confounded the prevalence of low bone mass in POI. No literature was found in this regard from previous studies.

MATERIALS AND METHODS

We conducted a cross sectional case control study in a tertiary referral centre in South India from 1st April 2016 to 30th April 2017.The study was approved by the institutional review board and ethics committee . Informed consent was obtained from each participant. One hundred consecutive cases of POI were recruited from subjects who attended menopause and general gynaecology outpatient clinics. Cases were women <40 years of age with oligo/amenorrhoea for >4 months and FSH >25mIU/ml [2]. Asymptomatic women <40years with normal menstrual cycles were taken as controls after 1- to -1 age matching with the cases. Women taking MHT (menopausal hormone therapy) were excluded. Primary objectives were to assess the prevalence of low bone mass (LBM) in women with POI and to suggest how early screening could be started. Sample size was calculated based on a study done by Uygur et al [3] using nMaster 2.0 software. To compare the proportion of LBM among cases and controls, the number needed was 100 in each group to give a power of 80% with alpha error 5%.

Each participant was subjected to history taking, physical examination, blood investigations and dual energy x-ray absorptiometry (DEXA) scan to estimate bone mineral density (BMD). DEXA was done using Hologic Discovery AQD 4500 series. Age of the patient, age at menopause, duration of menopause, the socioeconomic score utilizing modified Kuppuswamy scale, [4] medical, surgical and family history and degree of physical activity using International Physical Activity Questionnaire (IPAQ) [5] were recorded in the history. A simple physical examination was done to check the height, weight, body mass index and waist circumference. Height and weight were measured using wall mounted stadiometer and electronic weighing scale which were calibrated on a weekly basis. Waist circumference measurement was done using a calibrated tape midway between the lowest rib margin and the iliac crest.

All cases were recruited after documenting FSH >25mIU/ml. In addition the following serum parameters were estimated (the normal range according to our lab standardisation is given) - calcium (8.3-10.4mg/dl), phosphate (2.5-4.6mg/dl) and 25 (OH) cholecalciferol level (≥20ng/ml) levels were done for every patient. All the biochemical parameters excluding FSH were done for the controls. Women with Z score≤ -2.0 at either lumbar spine or femoral neck were identified low bone mass as per World Health Organisation criteria. Hypovitaminosis D was defined as serum level <20ng/ml.

The data was analysed using SPSS 16.0 software. Descriptive statistics were calculated to describe the measured variables of cases and controls. Age matching was accounted in the analysis by using conditional logistic regression. Chi-square test was used to test the association between the disease status and outcome variables. The logistic regression analysis was used to do the risk estimate and 95% CI. P value <0.05 was considered as statistically significant.

RESULTS

We evaluated 136 women with premature ovarian insufficiency. Twenty four women were excluded because they were already on MHT. Twelve women were lost for follow up. One hundred eligible women were included in the study. 100 age matched women who had normal menstrual cycles were taken as controls. The demographic factors listed in table 1 showed no significant difference except for hypertension (p=0.04) which was more in cases. Low bone mass (Z score < -2.0 in lumbar spine or femoral neck) was found to be significantly high in cases, p=<0.001 (table 2).

Table 1 Demographic Variables

	Cases (n=100)	Controls (n=100)	P value
Mean Age	36.2 ± 7.5	34.9 ± 5.7	0.3
Mean BMI	24.9 ± 4.8	25.6 ± 4.9	0.5
Diabetes Mellitus	8	5	0.4
Hypertension	15	6	0.04
Serum calcium <8.3mg/dl	5	4	1.0
Serum phosphorus <2.5mg/dl	2	1	1.0

BMI- body mass index

Table 2 Assessment Of Low Bone Mass

	Cases (n=100)	Controls (n=100)	OR	95% CI	P value
Low bone mass (Z score <-2.0 at lumbar spine or femoral neck)	37	3	23.6	5.4-102.5	<0.001

OR-odds ratio; CI – confidence interval

Eight possible confounders of low bone mass were assessed between the groups. BMI <18 (52 vs. 47, p=o.9) and sedentary life style (49 vs. 50, p= o.9), steroid intake (3 vs. 1, p=0.4), biphosphonate intake (3 vs. nil, p=0.1) and family history of osteoporosis (2 vs.3, p=1.0) were found to be similar between the groups. Vitamin D deficiency was significantly more in the controls (51 vs. 73, p = 0.01) compared to subjects probably because the controls were mostly selected from health care workers of our hospital who were doing indoor work. But low bone mass occurred only in 3 of our controls compared to 37 cases (OR 23.6, 95%CI=5.4-102.5, p <0.001), so LBM seems to be a definite consequence of hypoestrogenemia in POI. Low socioeconomic scores (SES) identified using Kuppuswamy scores IV and V (81 vs. 18 p= <0.001) was found to be significantly high in patients. A significantly high proportion of our cases were taking calcium supplements (15 vs. 4, p=0.007). Our data shows significantly high prevalence of low bone mass in POI in spite of calcium supplementation (table 3).

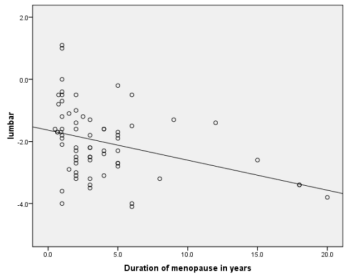
Table 3 Confounders For Low Bone Mass

	Cases (n=100)	Controls (n=100)	p value
BMI<18	52	47	0.9
Sedentary life style (IPAQ –category 1)	49	50	0.9
Low SES score (Kuppuswamy IV & V)	81	18	<0.001
Has family history of osteoporosis	2	3	1.0
Serum Vitamin D <20ng/ml	76	88	0.01
On Steroid therapy	3	1	0.4
Calcium supplements	15	4	0.007
Biphosphonate supplements	3	Nil	0.1

SES-socioeconomic score

Co-relation co-efficient between lumbar spine Z-scores and duration of menopause was found to be 0.1 (95% CI 0.03-0.16, p=0.63) over 20 years after POI (figure 1) but during the first 8 years it was 0.2 (95%CI 0.07-0.34, p=0.009).So there is twice the rate of bone loss occurring during the initial 5 years of POI compared to later years. It is also evident that (figure 1) majority have developed LBM within the first 5 years.

Figure 1.corelation Between Lumbar Spine Z Score And Duration Of Poi



DISCUSSION

Albright et al were the first to demonstrate the relationship between oestrogen deficiency and an increased incidence of fractures in postmenopausal women [6]. Bone loss with natural menopause is reported over a 5-7year period starting 2-3years before menopause, peaking in the first 3 years after menopause at 2.4% annually, and then declining to 1.2% annually [7]. Our study population included Indian women with POI, 66% of whom were in early menopause. This has provided us with valuable data to identify the prevalence of LBM among them and to suggest how early screening could be initiated.

We found significantly higher prevalence of LBM in POI (37 vs. 3, OR 23.6, 95% CI 5.4-102.5, p<0.001) compared to age matched controls. Previous studies support our result [8,9].In these women, hypoestrogenism together with hypoandrogenemia were found to have a deleterious effect on bone mass and BMD status [10]. Lana et al found that serum FSH concentrations, not estradiol, to be positively associated with bone mass loss in skeletal regions (both the spinal column and femoral neck) in patients with spontaneous POI[11]. The lumbar spine was most affected with age at menopause being the most important determinant. Relative risk of fracture was 1.5 times more in women with POI[12]. We could not find any definite co-relation between serum FSH concentration and LBM but the largest proportion of our women (22%) women with LBM were in early menopause with FSH values of 70-80mIU/ml.

The data shows a drop in lumbar spine Z-score by 0.1 unit (95% CI 0.03-0.16, p=0.63) for every one year post menopause (figure 1), but during the first 5 years the co-relation coefficient was twice as high reaching 0.2 (95% CI 0.07-0.34; p=0.009).So bone loss during the first five years of POI appears to be twice as high compared to the years further on. Previous studies on women with surgical premature menopause have found 2 fold higher bone loss with a significant increase in urinary N telopeptide compared to age matched women with intact ovaries.[13] However, by 65-70 years there was no statistical difference in low bone mass between the two groups. HadJidakis et al found that in POI the vertebral and femoral neck BMD at 45-50 years were comparable to that at 65-70 years in women with natural menopause.[14] According to Francucci et al BMD fell in both groups over time, the difference in vertebral BMD did not differ between those with early or natural menopause after the age of 55 years[15]. Our evidence supports these studies which find rapid bone loss during the early years of POI though it is beyond the scope of our study to comment on the long term effects.

The bone mass was significantly lower (37 vs. 3, p<0.001) in POI even though many of them were on calcium supplementation (15 vs. 4, p=0.007). This reveals the need for more interventions in addition to calcium and vitamin D supplementation. MHT, regular exercise, adequate milk intake and sunlight exposure have been proven to be protective against vertebral fractures[16] and could be beneficial to women with POI. Hypocalcaemia (5 vs. 4, p=1.0) and hypophosphatemia (2 vs. 1, p=1.0) were not significantly different between the groups disproving the role of dyselectrolytemia as the cause or effect of bone loss in POI. No previous studies on dyselectrolytemia in POI could be found whose results could be compared.

80% (n=24/37) of our women developed LBM within 5 years of POI. During this period we found twice the rate of bone loss (R=0.2) as compared to the later years (R=0.1). Prior studies on fracture risk have shown an increased vertebral fracture rates in POI[16, 17]. So there is a urgent need to screen these women for LBM. Literature search did not reveal any specific guidelines as to when to start screening these women for LBM. Our study gives first hand evidence supporting initiation BMD screening of lumbar spine at 5 years of POI.

The strengths of our study include the case control design and analysis based on highly objective data including BMD and serum values. Majority of our patients were in the first 5 years of POI (66%) which has helped us to assess how early bone loss begins after POI. Limitations include small sample size and higher prevalence of low SES score among our cases and the lack of long term follow up.

CONCLUSION

The incidence of LBM is significantly high in POI compared to age matched controls (35% vs. 2%, OR 23.6, p=<0.001) .The rate of bone loss during the first 5 years is twice as more compared to the rest of menopause. Our study could not find any association between

hypocalcaemia, hypophosphatemia, hypovitaminosis D and LBM in POI. Women with POI might benefit from MHT as there is significant reduction in bone mass in spite of calcium supplementation. Screening for LBM with lumbar spine Z score as early as 5 years into POI could prevent long term morbidity from osteoporosis.

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