Original Study

Bone mineral density in women with deep infiltrating endometriosis who have undergone early bilateral oophorectomy

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Abstract

Objective: To study bone mineral density (BMD) in women with and without pelvic deep infiltrating endometriosis (DIE) who underwent early bilateral oophorectomy (BO).

Methods: A case-control study was performed in 83 women who underwent early BO before the age of 45 years, 31 for DIE and 52 for another clinical condition. All the women answered a standardized computer-assisted questionnaire to record their clinical and historical data and were medically examined. Lumbar spine and femoral neck BMDs were measured by dual-energy X-ray absorptiometry after early BO. Simultaneously, serum calcium, intact parathyroid, 25-hydroxyvitamin D, and cross-linked C-telopeptide were also measured. Unadjusted and adjusted odds ratios (with 95% confidence intervals [CI]) for endometriosis were calculated using logistic regression.

Results: The mean lumbar spine and femoral neck BMDs were significantly higher in women who underwent early BO for DIE than in those who underwent early BO for another clinical condition. After adjusting for age at BMD measurement, years since menopause, age at menarche and body mass index, odds ratio for endometriosis associated with a 1-SD increase in lumbar spine and femoral neck BMD was 2.59 (95% CI: 1.45-4.62) and 2.16 (95% CI: 1.23-3.81), respectively.

Conclusion: Higher lumbar spine and femoral neck BMDs are associated with an increase in the likelihood of pelvic DIE in women who underwent early BO. This might be expected to the extent that endometriosis is itself associated with enhanced estrogen status, although further studies are needed to confirm such a hypothesis. These findings suggest that BMD measurement could contribute to the hormonal management of surgical menopause in women with DIE.

Key Words: Bone mineral density – Endometriosis – Estrogens – Oophorectomy.

Endometriosis is a chronic recurrent disease, which affects approximately 10% of women of reproductive age. The pathogenesis of endometriosis is complex and involves multiple genetic, environmental, and epidemiologic factors. It is considered to be an estrogen-dependent disease with both an increase in estrogen receptor expression and progesterone resistance in endometrial tissue. Inflammation is also a major hallmark of this disease with an overproduction of prostaglandins, cytokines, and chemokines by ectopic tissue, which in turn increases the dysregulation of steroid actions and enhances endometrial cell proliferation. In the absence of a definitive cure, management of endometriosis symptoms involves several medical and surgical approaches. The goal of medical treatment is to target the estrogen dependence of the disease by creating a hypoestrogenic state to reduce lesion size and inflammation-related symptoms. First-line hormone therapies include gonadotropin-releasing hormone (GnRH) agonists, estrogen/progestin combinations, and progestins with antagonistic properties.

However, the induction of a profound hypoestrogenic state either as a consequence of long-term medical treatments or ultimately, bilateral oophorectomy (BO), results in significant side effects. It is acknowledged that estrogen deficiency is a major contributor to bone loss and osteoporosis-related fractures. Bone is a highly estrogen-dependent tissue and an
increase in the incidence of osteoporosis and fractures has been reported in women with premature menopause regardless of the underlying origin, whether natural or surgical. On the other hand, some data suggest that local estrogen synthesis/metabolism in peripheral tissue could limit the impact of systemic estrogen deficiency after menopause. Several studies have shown an inverse relationship between estradiol (E₂) levels, the level of bone remodeling and the risk of hip and vertebral fracture. Conversely, it has been noted that a high BMD is associated with a greater risk of breast cancer which could be related to a hyper-estrogenic state due to an increase in the intracellular production of estrogens. Considering that endometriosis is also an estrogen-dependent disease, it could be hypothesized that medical or surgical treatments that induce estrogen deficiency might not have the same consequence on bone in women with endometriosis as in women without endometriosis.

Therefore, the goal of this study was to measure BMD in women who underwent early BO for pelvic deep infiltrating endometriosis (DIE) compared to women without DIE with surgically induced premature menopause.

METHODS

Study design and population

This case-control study was performed in the Menopause and Metabolic Bone Disease Center at Toulouse University Hospital. All white women less than 50 years of age who were referred to our center between January 2009 and December 2019 for a fracture risk assessment after BO performed before the age of 45 years were identified. Participants were excluded if they had a history of or presented with conditions that affect bone metabolism or when oophorectomy was performed before the age of 30 years. Women who had taken glucocorticoids, anticonvulsants, chemotherapy, and/or any antiosteoporotic drugs for more than 3 months were also excluded. We did not exclude women who had received GnRH agonist treatment before BO or those who received estrogen therapy (ET) after surgery. In addition, women with dual-energy X-ray absorptiometry (DXA) measurements that were nonevaluable due to degenerative spinal changes or artifacts or that were performed more than 10 years after surgery were not selected.

Among the 136 women who were identified, 27 were excluded because of a delay of more than 10 years between BO and the 1st bone mass evaluation, seven because of surgical menopause before the age of 30 years and 19 because of a clinical condition likely to interfere with bone mass (chemotherapy for breast cancer, n = 11, current bisphosphonate/raloxifene treatment, n = 5, bariatric surgery, n = 2 and spontaneous premature menopause before BO, n = 1). Therefore, we included 83 women, 31 of whom had undergone early BO for pelvic DIE and 52 for another clinical condition (ovarian cancer, n = 13; cervical cancer, n = 13, prophylactic BO for a high risk of breast/ovarian cancer with or without BRCA1/2 mutation, n = 8; chronic menorrhagia due to uterine fibroids, n = 6; stage I endometrial cancer, n = 5; bilateral benign ovarian cysts, n = 3; pelvic organ prolapse, n = 1; pelvic varices, n = 2; and delivery complication, n = 1).

Ethical approval was obtained from our hospital’s institutional review board.

Methods

All the women completed a standardized computer-assisted questionnaire, described extensively elsewhere, and this was recorded by the same trained research nurse. The following clinical and historical data were extracted for each woman: age, weight, height, body mass index (kg/m²), reproductive history (age of menarche, prior use of oral contraceptive pills, number of live births, duration of breastfeeding, age at BO, postmenopausal hormone therapy use, and duration of use). The use and duration of use of GnRH agonists before BO were recorded. Smoking status was also determined.

Medical examination

Each woman underwent a medical examination where all recorded data were validated and completed when necessary. Height (cm) and weight (kg) were measured with an automatic scale and body mass index (kg/m²) was calculated.

Laboratory analyses

Fasting blood samples were drawn from all women between 9:00 and 10:00 am. All measurements were performed on fresh serum in the same central laboratory for routine blood parameters including serum electrolytes, kidney and liver function, intact parathyroid, 25-hydroxyvitamin D and cross-linked C-telopeptide (CTX).

Bone mass measurement

Lumbar spine and femoral neck (FN) BMDs (g/cm²) were measured by an IOF-ISCD certified technician in all the women with a single DXA scanner (GE Lunar iDXA, GE Healthcare, Madison, WI). T-scores (standard deviation [SD] from young normal) for each measurement site were calculated using our own normative database for age 25 to 35 years as previously published (n = 110, mean spinal BMD = 1.18 ± 0.12 g/cm²; mean FN BMD = 0.990 ± 0.12 g/cm²).

Statistical analysis

Quantitative variables were expressed as mean values and SD, and qualitative variables in numbers and percentages. T-tests and chi-squared tests were performed to compare baseline characteristics of women who had undergone BO for severe endometriosis and controls (BO performed for another medical condition besides endometriosis). A two-tailed P-value below 0.05 was considered to indicate statistical significance. Spearman’s rank correlation coefficient was used to analyze the correlations between variables. Multivariate logistic regression analyses were performed to analyze the relation of the different clinical variables between the two groups. Unadjusted and adjusted odds ratios according to
potential confounding variables (age at BMD measurement, years since menopause, age at menarche and body mass index) with their corresponding 95% confidence intervals (CI) were computed. For quantitative bone variables, the odds ratios were performed by 1 SD of increase. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

The sociodemographic characteristics of the women are indicated in Table 1. There were no differences in the two groups in terms of age, most of the clinical characteristics or the period between BO and bone mass measurement. There was a significant difference between women whose BO was associated with endometriosis after adjustment for covariates. The average differences in lumbar spine and FN BMD values for another condition. The average differences in lumbar spine and FN T-score values between the two groups were 0.92 and 0.69 SD, respectively. There was no statistically significant difference in lumbar spine and FN BMD between women with DIE who received prior treatment with GnRH agonists and those who did not (data not shown).

There was no statistical difference for any of the biochemical parameters between the two groups (Table 2).

Figure 1 shows the distribution of Z-score values at the lumbar spine and FN in women with endometriosis and the controls. The distribution of Z-score values was normal in the controls whereas it was skewed towards the highest values in women with DIE.

Table 3 shows the associations between endometriosis and BMD at the lumbar spine and the FN. Lumbar spine and FN BMD as well as T- and Z-score values remained statistically associated with endometriosis after adjustment for covariates.

TABLE 1. Baseline characteristics and BMD for women in the study with DIE and for the controls

<table>
<thead>
<tr>
<th>Variables</th>
<th>Women with DIE (n = 31) Mean (± SD)</th>
<th>Controls (n = 52) Mean (± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>43.8 (3.8)</td>
<td>42.4 (4.3)</td>
<td>0.131</td>
</tr>
<tr>
<td>Age at BO (yrs)</td>
<td>41.7 (4)</td>
<td>40.3 (4.7)</td>
<td>0.157</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.4 (12.3)</td>
<td>63.3 (11.7)</td>
<td>0.428</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>161.3 (5.1)</td>
<td>164 (5)</td>
<td>0.021</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.9 (3.8)</td>
<td>23.4 (4)</td>
<td>0.107</td>
</tr>
<tr>
<td>Menarche (yrs)</td>
<td>12.7 (1.7)</td>
<td>12.6 (1.2)</td>
<td>0.694</td>
</tr>
<tr>
<td>Ovulation stimulation (%)</td>
<td>9.6</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Pregnancy (n [%])</td>
<td>18 [51]</td>
<td>36 [62.7]</td>
<td>0.19</td>
</tr>
<tr>
<td>Parity (n)</td>
<td>1.9 (1)</td>
<td>1.9 (0.9)</td>
<td>0.352</td>
</tr>
<tr>
<td>Smoking (pack/yr)</td>
<td>6.9 (10)</td>
<td>7.1 (8.3)</td>
<td>0.899</td>
</tr>
<tr>
<td>Duration of ET (mo)</td>
<td>24.9 (26.8)</td>
<td>22.7 (20.1)</td>
<td>0.66</td>
</tr>
<tr>
<td>Duration of GnRH agonist treatment (mo)</td>
<td>9.3 (5.4)</td>
<td>3</td>
<td>0.246</td>
</tr>
<tr>
<td>Duration of ET (mo)</td>
<td>9.3 (5.4)</td>
<td>3</td>
<td>0.246</td>
</tr>
<tr>
<td>Period between surgery and BMD measurement (mo)</td>
<td>11 [35.4]</td>
<td>19 [36.5]</td>
<td>0.92</td>
</tr>
</tbody>
</table>

BMD, bone mineral density; BMI, body mass index; BO, bilateral oophorectomy; DIE, deep infiltrating endometriosis; ET, estrogen therapy; mo, months; SD, Standard deviation; yr, year.

At potential confounding variables (age at BMD measurement, years since menopause, age at menarche and body mass index) with their corresponding 95% confidence intervals (CI) were computed. For quantitative bone variables, the odds ratios were performed by 1 SD of increase. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

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TABLE 2. Biochemical data in the two groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Women with DIE (n = 31) Mean (± SD)</th>
<th>Controls (n = 52) Mean (± SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium (mg/dL)</td>
<td>2.41 ± 0.09</td>
<td>2.39 ± 0.08</td>
<td>0.17</td>
</tr>
<tr>
<td>25-hydroxyvitamin D (ng/mL)</td>
<td>28.4 ± 9.3</td>
<td>26.1 ± 11.9</td>
<td>0.37</td>
</tr>
<tr>
<td>PTH (pg/mL)</td>
<td>36.4 ± 9.8</td>
<td>35.7 ± 14.8</td>
<td>0.81</td>
</tr>
<tr>
<td>CTX (pg/mL)</td>
<td>459 ± 257</td>
<td>485 ± 274</td>
<td>0.55</td>
</tr>
</tbody>
</table>

CTX, C-terminal telopeptide of type 1 collagen; PTH, parathyroid hormone; SD, standard deviation.

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After adjusting for age at BMD measurement, years since menopause, age at menarche, and body mass index, odds ratio for endometriosis associated with a 1-SD increase in lumbar spine and FN BMD was 2.59 (95% CI: 1.45-4.62) and 2.16 (95% CI: 1.23-3.81), respectively. The association was even stronger when Z-score values were considered. Figure 2 shows the probability distributions of endometriosis according to the level of lumbar spine and FN T-scores, respectively.

**DISCUSSION**

In this case-control study, higher lumbar spine and FN BMD values were found in women who underwent early BO for pelvic DIE than in women who underwent early BO for another medical condition. In addition, BMD was positively and significantly associated with a greater likelihood of DIE in women who had undergone early BO. Each standard deviation of lumbar spine and FN BMD was associated with an increase of more than twice the likelihood of a risk of DIE even after adjustment for covariates.

Bone is a highly estrogen-dependent tissue and it is well established that sex hormones and particularly estrogens affect bone directly or indirectly. Several studies have...
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FIG. 2. Probability of endometriosis according to lumbar spine (A) and femoral neck T-score values (B).

shown that older postmenopausal women with very low or undetectable serum E2 levels have lower BMD, an increase in bone turnover, and an increase in the risk of hip and vertebral fracture compared to women with slightly higher E2 levels. In such women, the administration of an ultra-low dose transdermal E2 resulted in a reduction of bone turnover markers and an improvement in hip BMD.11 Several studies have also reported that on the other hand, high BMD is significantly associated with an increase in the risk of breast cancer,14-18 which was in part related to an increase in estrogen metabolism.

Women suffering from DIE were found to have a higher than normal intracellular production of estrogens.1-3 Blocking E2 production either naturally (menopause) or pharmacologically/surgically (ovarian suppression) causes regression of the disease and its symptoms. However, the recovery of estrogen levels after discontinuation of therapy causes a relapse of the lesions, which suggests that endometriosis grows and regresses in an estrogen-dependent manner. After menopause, endogenous estrogen levels are no longer dependent on ovarian production but rather on a local biosynthesis metabolism in peripheral tissues. Several studies have shown that all enzymes required for the local production of estrogens (aromatase, 17β-hydroxysteroid dehydrogenase, sulfotransferase, etc.) are expressed in bone cells but also in human endometrium and other tissues.19-21 Aromatase (CYP19) is notably a critical enzyme for which an increase in expression has been detected in both the eutopic and ectopic endometrium of women with DIE. The involvement of many other estrogen-metabolizing enzymes and both of the estrogen receptors has also been noted in the increase in local E2 formation/activity. Variations in the genes that code for these estrogen metabolism pathway factors have also been reported to affect individual susceptibility to various sex hormone-dependent health outcomes. Several polymorphisms of the aromatase gene have been found to be associated with the activity or proliferation of estrogen-responsive cells22-24 even though to date none has been reported in association with endometriosis in case-control genetic association studies. It is interesting to note that meta-analyses of genome-wide association studies on endometriosis have identified loci containing genes involved in ovarian steroid hormone pathways, such as growth regulation by estrogen in breast cancer (GREB1), estrogen receptor alpha or follicle stimulating hormone β-subunit.25,26 Whether or not dysregulation of these different steroid target genes in endometriosis also affects bone cell metabolism is unknown although it would be tempting to relate it to the higher BMD found in DIE women in our study.

Very few studies have evaluated BMD or the risk of fracture in women with endometriosis. Most of the DXA studies published before 1995 reported no significant difference in BMD between women with endometriosis and controls.27-31 In a multicenter trial with 241 menstruating women with laparoscopically proven endometriosis, Ulrich et al32 found no difference in lumbar spine BMD measured by DXA compared to a normal age-matched population from the Hologic reference database. Moreover, there was no relationship between the stage of endometriosis and BMD. However, women with stage IV disease were older and had a BMD comparable to that of women in the other groups, which suggests higher BMD values than their age-matched non-endometriosis counterparts. A large cohort study of 987 women with endometriosis showed that the 20-year cumulative incidence of fracture was not elevated compared to that expected among community women.33 Two hundred fifty-five women had a BO at a median age of 42 years although of the 189 women who had undergone surgery and who were premenopausal at the time of surgery, 68% were given ET within 1 year after oophorectomy. In multivariable analyses, there was no association of fracture risk with endometriosis or the stage of the disease. Of particular note is that the 255 women who had undergone BO were not at an increased risk for fracture (HR: 1.12; 95% CI 0.84-1.49). This would suggest that even premature menopause could have little or no significant impact on the risk of fracture in women with endometriosis. In our study, it is noteworthy that mean lumbar spine and FN Z-score values in women with DIE remained entirely normal despite surgically induced premature menopause. This may indicate that estrogen deficiency did not induce significant bone loss, at least within the first 2 to 3 years after BO. Nevertheless, the possibility of a higher
BMD than normal before oophorectomy, cannot be eliminated.

This study has several strengths and limitations. This is the first study to compare BMD in women who underwent early BO for pelvic DIE with women who also experienced surgically induced premature menopause for another clinical condition. It certainly concerns a relatively small number of women with endometriosis. However, such a surgical procedure is currently relatively uncommon in young women and represents the ultimate management of DIE very often after repeated surgical procedures or multiple medical treatments. All the women were selected from a relatively homogenous population at the same facility through the same selection process. We selected only women with endometriosis for whom BO was performed for chronic DIE. All the women completed a questionnaire survey of considerable length, which allowed us to make adjustments for a wide range of covariates. All BMD measurements were consecutively reanalyzed by the same investigator (CE) blinded for the patient’s medical condition and with the same software (version 14.10). However, a possible bias related to ET cannot be ruled out since approximately one out three women were treated after oophorectomy. For the total population, there was no significant difference in mean lumbar spine and FN BMDs between those who received ET after oophorectomy and those who did not. This could be explained by an identical percentage of treated and untreated women within both the endometriosis and the control group. However, we cannot completely exclude that differences in ET modalities (with regard to dose, time of initiation or duration of therapy) might have interfered with our results and therefore further studies are required. In addition, approximately half of the women with endometriosis had received GnRH agonists before BO. Considering that this has been reported to induce bone loss in the lumbar spine of as much as 4% to 5% in 6 months the mean BMD in women with endometriosis could have been underestimated. For most of these women the length of time between GnRH agonist treatments (usually as one or several 3- to 6-mo treatment courses) and surgery was not known. Therefore, it is possible that BMD returned to baseline levels after cessation of treatment or that in some women add-back therapy may have limited bone loss. Some women in the control group might also have had an estrogen-dependent condition and their BMD might have been consequently affected. However, once again it is more likely that this would have limited the difference in BMD between the two groups. Moreover, the distribution of Z-score values was strictly normal in controls, which suggests an absence of bias in the control selection process. It cannot be determined whether the higher BMD noted in women with DIE was related to a high premenopausal BMD or a lower rate of post-oophorectomy bone loss than in women without DIE. There was no significant difference in the mean CTX levels between women with endometriosis and controls. However, the length of time between BO and the BMD measurements as well as the potential effect of postsurgical ET on bone may have minimized differences in the rate of bone loss between the two groups. Accordingly, women who had received ET after surgery had significant lower CTX values than untreated women (data not shown). Finally our results may not apply to women who underwent BO for less severe endometriosis or women for whom BMD could have been affected by another health problem.

Our results have several potential consequences, the main one being that the long-term risk of fracture might not be of particular concern in women with DIE even in those who experienced premature menopause. Whether this applies to other estrogen deficiency-related health outcomes such as the risk of cardiovascular diseases remains to be determined and further studies are required. It might be possible that the estrogen requirements to prevent the risk of osteoporosis or cardiovascular diseases after premature menopause may be lower in women with DIE than in the general population.

CONCLUSIONS

We found that women who underwent early BO for pelvic DIE had a higher BMD than women who underwent early BO for another reason. This might be expected to the extent that endometriosis is itself associated with enhanced estrogen status, as endogenous estrogen levels have been positively associated with bone mass and negatively with fracture risk. However, long-term studies are needed before definite conclusions can be drawn. In any event, measurements of BMD in women experiencing premature menopause after surgery for DIE might be helpful for monitoring further ET.

REFERENCES