Randomized controlled trial of the effect of hysterectomy or LNG-IUS use on bone mineral density: a five-year follow-up

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In the treatment of menorrhagia, levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena®) is compared with hysterectomy in terms of bone mineral density (BMD). In the lumbar spine, BMD decreased among hysterectomized women, but not among LNG-IUS users. **Background:** Osteoporosis is an increasing health problem. Osteoporotic fractures cause excess mortality, morbidity and heavy costs. Hysterectomy and LNG-IUS are the most effective treatment modalities for menorrhagia. However, the effect of these treatment modalities on BMD has not been compared. **Design**: Randomized controlled trial. **Participants**: 107 healthy women, aged 35–49, referred for menorrhagia. **Interventions**: Of the women, 54 were randomized to hysterectomy and 53 to the LNG-IUS group. **Outcome measures**: Bone mineral density measured by dual X-ray absoptiometry from the lumbar spine and the femoral neck at baseline and 5 years after randomization. **Results**: The two groups did not differ in terms of age, parity, body mass index, serum follicle-stimulating hormone, smoking, alcohol use, physical activity or daily calcium intake. There was no statistical significant difference in BMD between the treatment arms. However, lumbar spine BMD decreased significantly in the hysterectomy group but not in the LNG-IUS group. The change in BMD was not explained by factors included in the linear regression model. The BMD change in the femoral neck was similar in both arms. **Conclusions**: Hysterectomy may accelerate age-related loss in BMD, but studies with longer follow-up are needed.

Keywords: bone mineral density, hysterectomy, levonorgestrel-releasing intrauterine system, menorrhagia, randomized controlled trial

Osteoporosis has become a major health problem affecting approximately 30% of postmenopausal women. The estimated lifetime risk for an osteoporotic fracture in a 50-year old woman is approximately 40% [1]. Since osteoporotic fractures are associated with morbidity, mortality and heavy use of healthcare resources [2], prevention of osteoporosis is an important issue.

Almost a third of women suffer of menorrhagia during their lifetime. There are several treatment modalities available, of which hysterectomy and levonorgestrel-releasing intrauterine system (LNG-IUS, Mirena®, Schering Plough) are commonly used and well received by patients and healthcare providers [3,4]. The effect of these treatment modalities on bone mineral density (BMD) has been evaluated to some extent, but comparative studies do not exist.

Studies of hysterectomy and BMD show contradictory results. Some studies have reported increases [5–7], some decreases [8–10], and some no change in BMD after hysterectomy [11–14]. However, these studies have not been randomized trials. LNG-IUS is increasingly used as an alternative to hysterectomy in the treatment of menorrhagia. It releases levonorgestrel giving low serum concentrations (0.34–0.38 ng/ml) and no negative impact on BMD has been reported [15,16]. However, other models of progestins have a different effect on BMD, for example, the subcutaneous levonorgestrel implant which provides serum concentrations of an average of 1.4 ng/ml has a small positive effect on BMD and serum osteocalcin levels [17–19]. However, injectable depomedroxyprogesterone acetate, which gives serum concentrations of an average of 3 ng/ml, was shown to decrease BMD by 6% and increased bone resorption after 2 years of follow-up [20–22].

In this randomized trial we compared the effects of hysterectomy or LNG-IUS on BMD in women treated for menorrhagia.

Methods

A detailed description of the original study design has been reported elsewhere [4]. Of the 107 women referred for menorrhagia between November 1994 and November 1997 to the University Hospital, Helsinki (Helsinki, Finland), 54 were randomly assigned to hysterectomy and 53 to treatment with LNG-IUS. Randomly varying clusters of numbered, opaque, sealed envelopes were used for randomization. Women were

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Table 1. Baseline characteristics of the study population.

Characterisitcs	Hysterectomy n = 54	LNG-IUS n = 53
Age (years)		
	43.7 (3.3)	43.3 (3.5)
Follicle stimulating hormone (IU/ml)		
	7.9 (5.2)	7.8 (3.5)
Parity		
	1.9 (1.4)	1.9 (1.0)
Body-mass index (kg/m2)		
	25.4 (4.5)	25.6 (4.8)
Daily calcium intake (mg)		
	1107 (495)	982 (512)
Physical activity (h/week x intensity)		
	7.3 (9.0)	8.5 (9.6)
Smoking		
	16 (30%)	19 (33%)
Alcohol consumption (doses/week)		
<2	27 (50%)	29 (55%)
2.1–5.0	15 (28%)	14 (26%)
>5	12 (22%)	9 (17%)
Lactose intolerance		
	11 (20%)	12 (23%)
Use of diuretics		
	7 (13%)	8 (16%)
Use of oral corticosteroids periodically		
	6 (11%)	3 (6%)
History of fracture*		
	6 (11%)	6 (11%)

*Values are mean (SD), unless stated otherwise. *All distal radius.*
LNG-IUS: Levonorgestrel-releasing intrauterine system

between 35–49 years of age, menstruating, had completed their family size and were eligible for hysterectomy at baseline. Women with submucosal fibroids, endometrial polyps, urinary or bowel symptoms due to large fibroids or ovarian pathology were excluded. LNG-IUS was inserted during the randomization visit. Hysterectomy was performed abdominally, vaginally or laparoscopically. The follow-up visit took place 5 years after the randomization.

The study was approved by the Ethics Committees of the Helsinki University Hospital and the National Research and Development Center for Welfare and Health in Finland (STAKES).

Questionnaire

All women completed a questionnaire at baseline and after 5 years of follow-up including information on weight and height, smoking (cigarettes/day), age at menarche, number of deliveries, daily calcium intake (mg) and physical activity (h/week × intensity). Physical activity intensity was scored as follows;

- No sweating or increased breathing
- Some sweating or increased breathing
- Heavy sweating and heavily increased breathing

Alcohol use and daily medication, as well as history of fractures and lactose malabsorption, were recorded.

Bone mineral density

BMD was measured at the lumbar spine (L2–L4) and right femoral neck (FN) using dual-energy X-ray absorptiometry (DXA, Hologic Inc.*)* at baseline and 5 years after randomization. BMD was expressed in g/cm^2. The precision of the method was 0.9% at the lumbar spine and 1.2% at the FN.

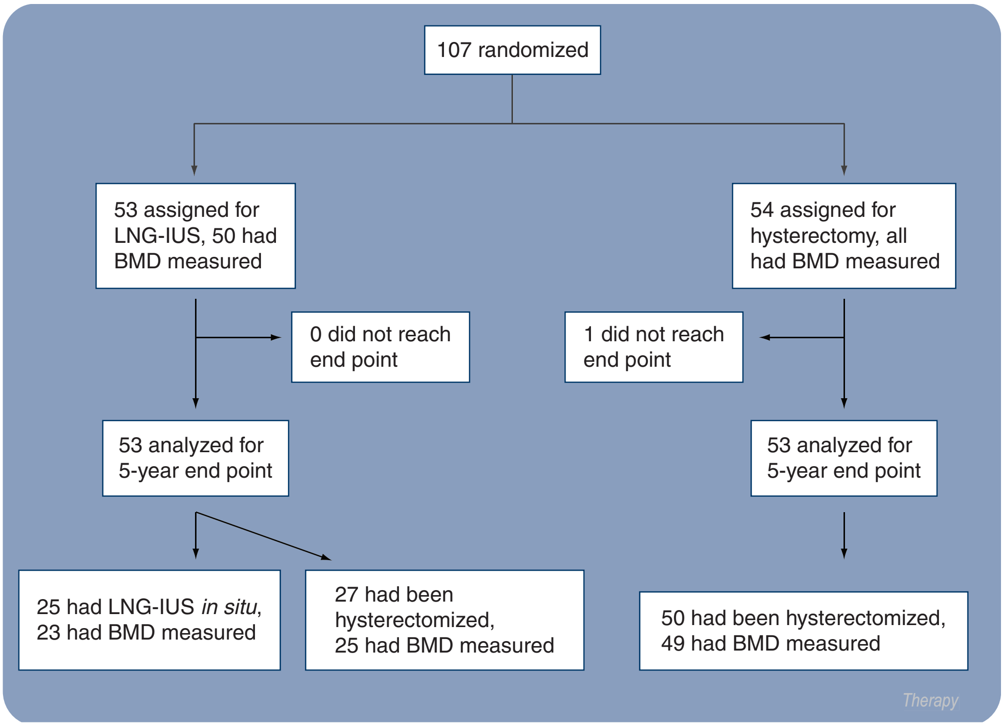
Laboratory investigations

Serum follicle-stimulating hormone (FSH) levels were measured at baseline and after 5 years. Baseline levels were measured at the early follicular phase of the menstrual cycle (days 1–7) using an immunofluorometric method (Wallac, Finland).

Statistical analysis

Power analysis was based on sample standard deviation of 13% and α-level of 0.05 in BMD of both lumbar spine and FN. The study had an 80% power to detect a 10% difference in BMD of FN and lumbar spine. All analyses were performed according to the intention-to-treat principle by using SPSS version 11.0, unless otherwise indicated. Mann–Whitney test was used to test baseline characteristics between the study arms. Changes in BMD were tested by t-test for two independent samples. To compare the BMD at baseline and at 5 years within the groups, the Wilcoxon Signed Rank test was used. A linear regression model was used to test associations between BMD change and explaining factors using a univariate model. The potential explaining factors were added as continuous (body mass index [BMI], age, number of deliveries, intensity of physical activity in h/week × severity, smoking in cigarettes/day) or dichotomized variables (treatment modality, use of estrogen replacement therapy, and use of cortisone and calcium). Probability values of 0.05 or less were considered significant.

Figure 1. Flow chart of patients examined in the study.



BMD: Bone mineral density; LNG-IUS: Levonorgestrel-releasing intrauterine system.

Results

Selected baseline characteristics of the study population are shown in **Table 1**. The groups were comparable.

After 5 years, 50 women in the hysterectomy group had undergone hysterectomy (10 abdominally, 14 vaginally and 26 laparoscopically). Two women cancelled the operation, one decided to have an LNG-IUS, and one was lost to follow-up. **Figure 1** illustrates a flow-chart of the patients. Bilateral oophorectomy was performed in five women. Of the total number of women in the study, 20 (37%) used estrogen therapy (ET). Serum FSH was above 40 IU/ml in seven women and three used ET. Thus, 24 (44%) women had serum FSH greater than 40 IU/ml or used ET. BMD measurements were taken from all women at baseline and from 49 women at 5 years. No fractures were reported by any of the women during the follow-up period.

After 5 years, LNG-IUS was *in situ* in 25 (47%) women in the LNG-IUS group. Of these, 11 used ET. Average use of LNG-IUS was 2 years and 4 months. One patient had undergone thermal ablation of the endometrium and none were lost to follow-up (**Figure 1**). A total of 27 women (51%) had undergone hysterectomy, including four with bilateral oophorectomies. All four women with surgically induced menopause used ET. Thus, of the women randomized to the LNG-IUS group, 15 (28%) used ET. Serum FSH was above 40 IU/ml in eight women and two of them used ET. Thus, 21 (40%) women had serum FSH greater than 40 IU/ml or used ET. BMD was measured from 50 women at baseline and from 48 women at five years. No fractures were reported during the follow-up period.

In the hysterectomy group, BMD decreased from 1.059 g/cm^2 (SD: 0.103) to 1.042 g/cm^2 (SD: 0.106) in the lumbar spine ($p = 0.02$). Thus, the BMD decrease was 0.017 g/cm^2 (SD: 0.037), which corresponds to an annual decrease of 0.24% (SD: 0.740). Corresponding figures for the FN were 0.846 g/cm^2 (SD: 0.097) and 0.816 g/cm^2 (SD: 0.098) ($p = 0.0001$). Thus, the BMD decrease was 0.030 g/cm^2 (0.037), which corresponds to an annual decrease of 0.72% (SD: 0.853).

In the LNG-IUS group, BMD decreased from 1.047 g/cm^2 (SD: 0.109) to 1.039 g/cm^2 (SD: 0.124) in the lumbar spine ($p = 0.930$). The BMD decrease was 0.008 g/cm^2

Table 2. Bone mineral density (g/cm²) over time.

	Baseline	At 5 years	p*	Decrease in BMD (%)	p‡
Lumbar spine					
Hysterectomy					
Intention to treat (n = 49)	1.059 (0.103)	1.042 (0.106)	0.02	0.24 (0.740)	0.32
Actual treatment (n = 77)	1.059 (0.104)	1.042 (0.108)	0.01	0.22 (0.769)	0.62
LNG-IUS					
Intention to treat (n = 48)	1.047 (0.109)	1.039 (0.124)	0.93	0.07 (0.845)	
Actual treatment (n = 27)	1.037 (0.111)	1.036 (0.133)	0.72	<0.000	
Femoral neck					
Hysterectomy					
Intention to treat (n = 49)	0.846 (0.097)	0.816 (0.098)	0.0001	0.72 (0.853)	0.33
Actual treatment (n = 77)	0.848 (0.096)	0.823 (0.097)	0.0001	0.78 (0.926)	0.13
LNG-IUS					
Intention to treat (n = 48)	0.865 (0.096)	0.845 (0.100)	0.0001	0.54 (0.974)	
Actual treatment (n = 27)	0.872 (0.095)	0.846 (0.104)	0.002	0.42 (0.864)	

Values are mean (SD).
**Data analysed by Wilcoxon signed rank test for change within the group.*
‡Data analysed by Student's t-test for independent samples for change between the groups.
BMD: Bone mineral density; LNG-IUS: Levonorgestrel-releasing intrauterine system.

(SD: 0.044), which corresponds to an annual decrease of 0.07% (SD: 0.845). In the FN, the decrease was from 0.865 g/cm^2 (SD: 0.096) to 0.845 g/cm^2 (SD: 0.100) (p = 0.0001). The BMD decrease was 0.020 g/cm^2 (SD: 0.069), which corresponds to an annual decrease of 0.54% (SD: 0.974) (Table 2). However, after 5 years the BMD changes in the lumbar spine or FN did not differ between the study groups.

Linear regression showed that the BMD decrease in the lumbar spine or the FN was not explained by the treatment modality. Furthermore, univariate regression analysis showed no correlation between any of the potential explaining factors and BMD change in the lumbar spine or FN in the hysterectomy group. However, smoking was associated with a change in BMD in the LNG-IUS group (p = 0.004 for lumbar spine; p = 0.07 for FN). ET use correlated with a change in BMD in FN among LNG-IUS users (p = 0.02).

Since 27 (51%) of the women originally randomized to the LNG-IUS group underwent hysterectomy during follow-up, the results were also analyzed by actual LNG-IUS use (n = 27*)* versus hysterectomy (n = 77). Among hysterectomized women BMD decreased from 1.059 g/cm^2 (SD: 0.104) to 1.042 g/cm^2 (SD: 0.108) in the lumbar spine (p = 0.01). The BMD decrease was 0.017 g/cm^2 (SD: 0.035), which corresponds to an annual decrease of 0.22% (SD: 0.769). In the FN, the decrease was from 0.848 g/cm^2 (SD: 0.096) to 0.823 g/cm^2 (SD: 0.097) (p = 0.0001). The BMD decrease was 0.025 g/cm^2 (SD: 0.033), which corresponds to an annual decrease of 0.78% (SD: 0.926). Among women, who were using LNG-IUS during the whole study the BMD did not decrease in the lumbar spine. BMD was 1.037 g/cm^2 (SD: 0.111). In the FN BMD decreased from 0.872 g/cm^2 (SD: 0.095) to 0.846 g/cm^2 (SD: 0.104) (p = 0.002). The BMD decrease was 0.026 g/cm^2 (SD: 0.052), which corresponds to an annual decrease of 0.42% (SD: 0.864). After 5 years, BMD changes in the lumbar spine or FN did not differ between the study groups.

Discussion

We performed a randomized, controlled trial of the effect of hysterectomy or LNG-IUS on BMD among women treated for menorrhagia. The key finding was that no significant differences were found between the treatment groups. However, in the hysterectomy group, BMD decreased significantly both in the lumbar spine and FN, but not in the LNG-IUS group. This change was not explained by treatment modality, age, parity, BMI, alcohol consumption, physical activity, cigarette smoking, ET, or other drug use. The BMD change in the FN was similar in both arms.

Previous studies focusing on BMD and hysterectomy have produced highly variable results. Some found improved BMD after hysterectomy [5–7], and others no association between BMD and hysterectomy [11–14]. Some studies have reported a decrease in BMD after hysterectomy [8–10]. Studies have mainly been cross-sectional so that no definite conclusions can be drawn. Moreover, it has been difficult to rule out selection bias since none of the studies have been randomized. Even if control groups were included, confounding factors were not considered.

The mechanism by which simple hysterectomy affects BMD may be related to impaired ovarian function [23,24]. Previously we have shown that hysterectomized women have hot flushes more often than women using LNG-IUS. In addition, serum FSH levels were higher among hysterectomized women [23]. The lumbar spine requires higher serum estradiol concentrations than FN to preserve BMD [25]. As BMD in the lumbar spine is more sensitive to changes in hormone levels, hysterectomy may have an effect there but not necessarily in the FN. In addition, the uterus may produce cytokines and growth factors which stimulate bone cell growth *in vitro* [26]. Bone turnover markers, such as osteocalcin and tartare-resistant acid phosphatase 5b, are decreased in hysterectomized women [7].

Low serum concentrations of LNG in LNG-IUS users have only a weak effect on ovarian function. After the first year of use, 85% of all menstrual cycles are ovulatory and systemic adverse effects are rare [27,28]. Therefore it is not surprising that among LNG-IUS users the annual BMD decrease in lumbar spine corresponded to a decrease seen among perimenopausal women in general [29]. Recently Bahamondes and colleagues reported that LNG-IUS was neutral in terms of BMD [16]. The BMD decrease reported among injectable depomedroxyprogesterone acetate users may be due to 20–30-times higher serum concentrations which may have a negative effect on bone turnover. This makes LNG-IUS more meaningful in contraceptive use if risk factors for osteoporosis are present.

In both study groups, BMD decreased in the FN. This is in accordance with Sowers and colleagues, who reported that FN is the most sensitive site to perimenopausal bone loss [30]. FN BMD is linked to the muscle mass, not the fat mass [31]. Since muscle mass is replaced by fat as women get older, this may influence bone loss [32]. Moreover, if muscle strength does not decline, BMD loss at FN decreases [33].

The majority of earlier studies have not considered the effect of confounding factors. Our randomized study design rules out some bias. Furthermore, we included a large number of potential confounding factors in the regression analysis. Smoking was the only factor explaining BMD decrease in the LNG-IUS group. Smoking has several antiestrogenic effects and may decrease BMD [34]. Moreover, tobacco smoke directly impairs ovarian function [35]. The effect of parity may be explained by bone loss during pregnancy and lactation [36]. The positive effect of estrogen on BMD is well demonstrated among ET users [37]. High BMI (kg/cm^2) is also known to be positively associated with BMD [37]. Body weight may affect BMD by greater mechanical strain on bone and peripheral conversion of androstenedione to estrone [38,39].

Study limitations

The study was limited by the relatively small number of patients. According to power calculations, however, it would have been possible to detect a 10% decrease in BMD, if such a decrease existed. In addition, the follow-up period was only 5 years and some women in both groups already used ET. In the LNG-IUS group, almost half of the women ended up having hysterectomy. Therefore we also analyzed the results by treatment in addition to intention-to-treat analysis. It would also have been important to analyze bone turnover markers. For instance, the change in osteocalcin predicts vertebral fracture better than change in the BMD [40]. Finally, we studied only women with menorrhagia and the results may not be generalizable.

Highlights

- Osteoporosis is an emerging public health problem
- This is the first randomized trial of the effect of hysterectomy or LNG-IUS on bone mineral density (BMD)
- No significant differences were found in the lumbar spine or femoral neck BMD between the study arms after 5 years
- Lumbar spine BMD decrease was significant in the hysterectomy arm but not in the LNG-IUS arm
- Hysterectomy may accelerate age-related loss in BMD

Conclusion

The present study is the first randomized trial of the effect of hysterectomy or LNG-IUS on BMD. Our results suggest that hysterectomy may have a negative influence on BMD. However, studies with longer follow-up are needed to confirm this. Since osteoporosis is an increasing public health problem, it may be important to consider BMD when choosing treatment for menorrhagia.

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