

Changes in Bone Mineral Density of Users of the Levonorgestrel-releasing Intrauterine System

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Abstract

Objective: The aim of this study was to evaluate changes in bone mineral density (BMD) in patients using a levonorgestrel-releasing intrauterine system (LNG-IUS) or a TCU380A intrauterine device (IUD) after 2 years.

Patients and Methods: The medical records of all patients who underwent LNG-IUS (n=38) or TCU380A IUD (n=26) insertion from May 2006 through December 2010 were reviewed. The patients were 40 to 45 years old at the time of insertion, had undergone a BMD examination of the femur and lumbar spine before the loop insertion, and had also received a follow-up BMD examination 2 years later. Patients were excluded if risk factors known to affect BMD were noted in their medical records. The 2 groups of patients were compared with regard to age, parity, body-mass index (BMI), and levels of osteocalcin and pyridinoline. Changes in BMI, osteocalcin, and pyridinoline after 2 years were also compared.

Results: The LNG-IUS and TCU380A IUD groups showed no differences in mean age, mean parity, mean BMI, preinsertion or postinsertion BMD values of the femur or lumbar spine, changes after 2 years in the BMD of the femur or lumbar spine, or changes after 2 years in osteocalcin or pyridinoline level ($P>0.05$).

Conclusions: Women using the LNG-IUS for 2 years have changes in BMD and osteocalcin and pyridinoline levels similar to those of TCU380A IUD users. The use of the LNG-IUS for 2 years may have no adverse effect on BMD.

(J Nippon Med Sch 2012; 79: 190–194)

Key words: bone mineral density, levonorgestrel-releasing intrauterine system, TCU380A intrauterine device

Introduction

The levonorgestrel-releasing intrauterine system (LNG-IUS) is a long-acting, reversible progestin-only

contraceptive device. It is highly efficacious and has few side effects¹.

Since its approval by the World Health Organization in 2004, the LNG-IUS has been widely used for inducing amenorrhea; for treating

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menorrhagia, endometriosis, chronic pelvic pain, dysmenorrhea; and for endometrial protection in postmenopausal women during estrogen therapy; its use may prevent the need for hysterectomy in some cases¹. However, although much information is available on the contraceptive efficacy and health benefits of the LNG-IUS, few studies have evaluated bone mineral density (BMD) in users of LNG-IUS¹⁻⁴.

That BMD decreases after long-term use of a progestin-only contraceptive, especially depot medroxyprogesterone acetate, has been known for several years, but a recent study has found that BMD in users of the LNG-IUS is similar to that in users of the TCu380A intrauterine device (IUD) and remains unchanged between the 7th and 10th years of use (1). So far, however, studies have been limited to the BMD of the forearm. Differences in the site of BMD measurement can result in different findings, although several reports have confirmed the relationship between forearm BMD and the bone density of the lumbar spine and femoral neck⁵.

The purpose of the present study was to evaluate the BMD of the femur and lumbar spine among long-term users (2 years) of the LNG-IUS and a control group of users of the TCu380A IUD. We also examined differences between the groups by measuring levels of osteocalcin, a biomarker of bone formation, and pyridinoline, a biomarker of osteoclasts.

Patients and Methods

The medical records were reviewed of all patients who underwent insertion of the LNG-IUS (Mirena[®], Bayer Schering Pharma Oy, Turku, Finland) or the TCu380A IUD (Optima, Injeflex, São Paulo, Brazil) from May 2006 through December 2010. We included patients who were 40 to 45 years old at the time of insertion and had undergone a BMD examination of the femur and lumbar spine before insertion, followed by a follow-up BMD examination 2 years later. We excluded women who met 1 or more of the following criteria: 1) pregnant or lactating during the study period; 2) history of taking drugs known to affect calcium metabolism, such as anticonvulsants, corticosteroids, thyroid

supplements, thyroid suppressants, vitamin D, calcium supplements, or thiazides; 3) chronic diseases affecting bone metabolism, such as liver disease, diabetes mellitus, hyperthyroidism / hypothyroidism, or hyperparathyroidism / hypoparathyroidism; 4) oophorectomy during the study period; 5) menopause; or 6) a body-mass index (BMI) less than 18.5 kg/m² or greater than 25 kg/m². The groups were compared with regard to age, parity, BMI, and changes in BMD. The changes in BMD were calculated by subtracting the preinsertion value from the postinsertion value. The BMD was measured with a dual-energy X-ray absorptiometer (GE Lunar Expert or GE Lunar Prodigy 9.30, GE Lunar Corp., Madison, WI, USA). The BMD measurements were made with lumbar vertebrae 1 to 4 and total femur values. The osteocalcin and pyridinoline levels were measured before insertion and after 24 months of follow-up in both groups.

The BMD values are reported as mean ± standard deviation (SD). The program IBM SPSS Statistics 18.0 for Windows (IBM Corp., Armonk, NY, USA) was used for statistical analysis. A P value less than 0.05 was considered to indicate statistical significance.

Results

Of the 64 women in the study, 38 women used the LNG-IUS and 26 women used the TCu380A IUD (**Table 1**). The mean ages of the LNG-IUS users and TCu380A IUD users at the time of BMD measurement were 42.92 and 42.26 years, respectively. There was no significant difference between the groups in age, parity, or BMI.

The LNG-IUS and TCu380A IUD groups did not differ in the mean BMD values in the spine (L1-L4) and total femur at baseline or after 2 years of use or in the changes in BMD values at these sites (**Table 2**).

Furthermore, although the pyridinoline level at baseline was higher in LNG-IUS group than in the TCu380A IUD group, the groups did not differ in osteocalcin levels at baseline, osteocalcin or pyridinoline levels after 2 years of use, or in changes

Table 1 Characteristics of study groups

Number	LNG-IUS (n=38)	TCu380A IUD (n=26)	<i>P</i> value
Age (years)	42.92 ± 1.68	42.26 ± 1.45	0.092
Parity	1.84 ± 1.0	1.88 ± 0.90	0.607
Body mass index (kg/m ²)	24.02 ± 2.66	23.19 ± 3.14	0.242

Values are given as mean ± SD

Table 2 Variation in the BMD of the lumbar spine and total femur

	LNG-IUS (n=38)	TCu380A IUD (n=26)	<i>P</i> value
	Mean ± SD (g/cm ²)	Mean ± SD (g/cm ²)	
Lumbar spine (L1-L4) at baseline	1.17 ± 0.16	1.11 ± 0.13	0.318
Total femur at baseline	0.98 ± 0.14	0.97 ± 0.10	0.956
Lumbar spine (L1-L4) after 2 years	1.12 ± 0.15	1.07 ± 0.12	0.374
Total femur after 2 years	0.95 ± 0.09	0.94 ± 0.09	0.753
Difference in the lumbar spine	-0.06 ± 0.04	-0.04 ± 0.04	0.283
Difference in the total femur	-0.03 ± 0.07	-0.03 ± 0.04	0.973

Values are given as mean ± SD

Table 3 Osteocalcin and pyridinoline levels

	LNG-IUS (n=38)	TCu380A IUD (n=26)	<i>P</i> value
	Mean ± SD (g/cm ²)	Mean ± SD (g/cm ²)	
Osteocalcin at baseline	3.09 ± 1.67	3.04 ± 1.32	0.832
Pyridinoline at baseline	5.46 ± 1.69	4.61 ± 1.37	0.044
Osteocalcin after 24 months	5.57 ± 3.28	6.79 ± 6.06	0.743
Pyridinoline after 24 months	16.00 ± 65.16	12.48 ± 30.79	0.126
Difference in osteocalcin	2.47 ± 3.45	3.75 ± 5.46	0.662
Difference in pyridinoline	10.43 ± 65.78	5.68 ± 31.92	0.424

Values are given as mean ± SD

in osteocalcin or pyridinoline levels after 2 years (Table 3).

Discussion

More than 20 million women worldwide use progestogen-only contraceptives, including injectable progestogens, implants, vaginal rings, intrauterine progestogen-releasing systems, and oral preparations⁶. Concerns have been raised that use of progestogen-only contraceptives can decrease BMD and thus increase the subsequent risk of osteoporotic fracture⁶.

Few studies have examined the effects of

progesterone on bone metabolism⁷. Human osteoblasts express progesterone receptors, and high doses of progesterone stimulate osteoblast proliferation and differentiation⁷. There is no convincing evidence that progesterone deprivation is associated with bone loss⁷. Both testosterone and estrogens inhibit bone resorption and promote bone formation⁷. Inhibition of bone resorption is the predominant effect of estrogens, whereas marked bone formation occurs with androgens⁸.

A main mechanism of action of progestogen-only injectable contraceptives is suppression of ovulation through the feedback inhibition of follicle-stimulating hormone and luteinizing hormone and consequent

suppression of estradiol levels⁶. Because estradiol is important for maintaining bone mass, its suppression by progestogens might reduce BMD⁶.

Progestogen-only contraceptive implants contain etonogestrel (the only compound available in France) or levonorgestrel⁷. They inhibit ovulation via an antigonadotropin effect and alter cervical secretions, which become impenetrable to sperm cells⁷.

So far, the study was to find the correlation between the long-term users of the LNG-IUS and BMD. According to a study by Bahamondes et al., mean BMD did not differ between LNG-IUS users and TCu380A IUD users after 7 years¹². Also women aged 19 to 43 years who had used either the LNG-IUS or the TCu380A IUD for 18 months showed lower BMD at the midshaft of the ulna, but not at the distal radius⁴. Another study in women aged 19 to 43 years who had used either the LNG-IUS or the TCu380A IUD found lower BMD values at the distal radius 36 months after insertion than before insertion; however, no difference was found at the ultradistal radius³.

Studies to date have evaluated BMD at the forearm, but none have evaluated the effect of the LNG-IUS on the BMD of the femur and lumbar spine. When BMD is used to assess the risk of osteoporotic fracture, measurements are usually made of the total hip, femoral neck, and posterior-anterior lumbar spine⁹. Therefore, a study that evaluates the effect of LNG-IUS on the BMD of the femur and lumbar spine is required.

Systemically administered copper can affect bone metabolism. However, the copper TCu380A IUD is a contraceptive device that induces local inflammation in the uterus. The TCu380A IUD has a minimal systemic effect and is considered to be an appropriate control device for evaluating the effect of the LNG-IUS, which induces amenorrhea with long-term use.

We found that BMD levels did not differ between users of the TCu380 IUD and users of the LNG-IUS after 2 years. This finding indicates that long-term use of the LNG-IUS does not decrease BMD.

Osteocalcin is produced by osteoblasts and is often used as a marker of bone formation¹⁰. Higher serum osteocalcin levels correlated strongly with increases

in BMD during treatment with drugs that induce bone formation¹¹. Pyridinoline is released into the blood during bone degradation, and, because of its rapid excretion in the urine, it is used as a marker of bone resorption¹². Our present study found no significant differences between LNG-IUS users and TCu380A IUD users in changes in osteocalcin or pyridinoline levels between preinsertion and after 2 years. Despite the baseline level of pyridinoline was statistically meaningful between the two group ($p=0.044$), we excluded this result because we tried the differences of osteocalcin and pyridinoline level changes after 24 months.

Our study had several limitations. First, the numbers of subjects was small, and the study was retrospective. Therefore, future studies should include a larger number of subjects of different age and should examine many factors that affect BMD, such as genetic factors, physical activity, and hormone status. Despite these limitations, we can conclude that BMD is similar in long-term users of the LNG-IUS and long-term users of the TCu380A IUD. Furthermore, women using the LNG-IUS for 2 years have a mean BMD and levels of osteocalcin and pyridinoline that are similar to those of TCu380A IUD users.

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(Received, October 26, 2011)

(Accepted, December 19, 2011)