The Effect of Gonadotropin-Releasing Hormone Agonists (GnRHa) on Bone Mineral Density (BMD) in Perimenopausal Women Undergoing Hysterectomy

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Abstract: To determine how the presurgical administration of gonadotropin-releasing hormone agonists (GnRHa) affects the patients' bone mineral density (BMD) and quality of life after hysterectomy. Forty-five women aged 46-55 y/o with uterine myoma candidate for hysterectomy, consecutively have been considered to be evaluated in 2 groups in a prospective follow-up study in an university teaching hospital in Tabriz, Iran, from February 2009 to April 2012. Group one were 22 participants who received a GnRHa for 4 courses before surgery (study group) and group 2 were 23 participants (control group) with no treatment. Bone scans to appraise BMD was performed before and 6 months after the surgery. All signs and symptoms of hypo estrogenic state, pain scores and quality of life measures, were assessed. The mean changes between study group and controls in lumbar spine and hip BMD 6 months after surgery were significant [(p=0.03) and (p<0.001), respectively].The mean changes between groups in T-scores at the level of lumbar spine showed significant difference (p=0.01), but at the level of hip, it were not significant (p=0.69). The same changes between groups in Z-scores were statistically significant (p=0.019) and (p=0.008), respectively. Compared to controls in GnRHa group, low back pain increased significantly (p<0.001), and the quality of life measures was decreased. In perimenopausal women the presurgical short-term administration of GnRHa affects post-hysterectomy bone mineral density and quality of life. Hence unnecessary prescription of these drugs in this period of life should not be advocated.
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1. Introduction

Uterine fibroids are major public health problems in women during the reproductive years and are found at least in 20%-40% of women over the age of 35 years (Day Baird et al., 2003; Viswanathan et al., 2007; Selo-Ojeme et al., 2008). In one-third of cases they cause symptoms severe enough to warrant the therapy and surgery is the standard treatment (Flake et al., 2003). GnRH agonists are commonly employed in the medical management of female disorders that are dependent on estrogen production such as women with menorrhagia, endometriosis, adenomyosis, or uterine fibroids to induce a hypo estrogenic state (Lethaby et al., 2001). It is now well known that short term treatment with GnRH agonists offers an advantageous alternative to hysterectomy or gives an opportunity to improve patients' condition for the surgery and maintains patients' functional abilities (Muneyyirci-Delale et al., 2007). While offering an advantageous and helping to reduce abnormal uterine bleeding and suppress the size of uterine myoma, hormonal ablation may make severe side effects in association with estrogen loss and mimic the menopause state including hot flashes and night sweats, as well as inducing bone loss and raises the risk for osteoporosis (ACOG, 2008). Studies on bone densitometry in most women who were treated with GnRH agonists showed that, there was an increase in bone turnover due to estrogen deficiency during treatment with transient decrease in bone density. Cann and colleagues showed that in most patients after stopping the treatment, the bone was regained, but it may take years to fully recover. Therefore, having low bone density at the beginning of treatment may predispose the patients for osteoporotic fracture by losing sufficient bone, especially in women who are going through natural menopause in the near future (Cann, 1998). To minimize bone loss without compromising efficacy, several investigators have suggested to be given bone-sparing agents in patients receiving GnRH agonists (Long et al., 2010; Aisaka, 2009; Akira et al., 2009). However, some side effects may happen due to too much suppression of plasma sex steroid hormone levels. In the study of Matsuo and colleagues, the results showed that even in the short period of GnRH agonist therapy, BMD values had been decreased significantly (Matsuo, 2003).

Although the role of pre-treatment with GnRH analogues prior to major gynecological surgeries for inducing a hypo estrogenic state has been systematically reviewed with promising results (Lethaby et al., 2001), the long term outcomes on the BMD and quality of life were not assessed in these studies and little is known about their effects on the long-term outcomes in perimenopausal women undergoing hysterectomy with saving ovaries. To compare clinical effect of GnRH agonists, we carried out a prospective follow-up study to determine how the antiestergenic effect of GnRH agonists affects the patients' BMD, signs, symptoms, and quality of life after the hysterectomy.

2. Materials and Methods

The study was carried out in *Alzahra* Teaching Hospital in Tabriz University of Medical Sciences, Iran, from February 2009 to April 2012. Twenty-two women aged 46-56 y/o with uterine myoma were treated with 4 courses of a GnRHa (decapeptyl) (study group) at a dose of 3.75 mg/28 days before hysterectomy, were matched with 23 controls with no suppressive medication. The study population was selected consecutively. Patients who were recognized to have cancer, diabetes, fall history, thyroid dysfunction, and those who were underweight (body mass index<20), taking medications such as opioids, glucocorticoids, and antidepressants and the smokers were excluded. Patients' consents were obtained after giving adequate information about. The calculation of bone mineral density was determined in the femoral neck and lumbar spine (L2-L4) before, and 6 months after hysterectomy by dual energy X-ray absorptiometry (DEXA) method with Hologic machine (Hologic QDR1000), and results expressed in Hologic standard (driven from USA population) and reported according to WHO criteria (WHO, 1994). According to the WHO diagnostic criteria, T-score below -2.5 and T-score between -2.5 and -1 are defined as osteoporosis and osteopenia, respectively. These figures are calculated separately for two different sites of lumbar spine and femoral neck (Moayyeri et al., 2005). To eliminate the confounding effect of osteoporosis on both groups, Alendronate 70 mg/week (Osteofos) + Calcium 1000 mg/day and vitamin D 800U/d were administrated for both groups. All patients underwent hysterectomy without oophorectomy. Six months after hysterectomy all signs and symptoms of hypo estrogenic state including urinary incontinence, vaginal dryness, hot flushes, night sweats, headaches, decreased libido, and oily skin/ hair were assessed. The pain scores and some quality of life measures, including general health, physical health, mental health, self-care, and ability to work were assessed. Pain scores were assessed using a visual analogue scale at the levels of low back, shoulder, and lower extremities. The study protocol was reviewed and approved by Tabriz Research Affairs Review Board. All data is presented as Means ± SD, N (%). The chi squared ($\chi 2$) test or Fishers Exact tests were performed on data. A repeated measure of ANOVA was used to compare difference between means. Independent samples t-test or U Mann-Whitney tests were used to compare quantitative data of groups and a P-value of less than 0.05 was considered to be significant. The statistical analysis was performed by Statistical Package for Social Sciences program (SPSS version 16.0 for Windows).

3. Results

There was no difference between study group and controls in terms of mean age [49.73±3.32 and 50.87±2.84, (P=0.22)], number of pregnancy [2.45±1.10, 3.18±1.64, (p=0.18)], and parity [2.41±109 and 2.41±109, (p=0.15), respectively], at the study entry. The results of BMD of femur neck and lumbar spine within groups are shown in table 1.

Table 1: Comparison of the BMD of femur neck (FN) and lumbar spine (LS) within groups

Groups	Before (g/cm2)	After (g/cm2)	P-value*
Study group (FN)	0.83±0.08	0.64 ± 0.92	<.001
Controls (FN)	0.82± 0.96	0.80 ± 0.97	<.001
Study group (LS)	1.01± 0.11	0.84 ± 0.23	0.02
controls (LS)	1.01 ± 0.1	0.98 ± 0.19	0.18

*P value< 0.05 was considered significant

Comparison of the mean changes between BMD of lumbar spine and femur neck in both groups showed that the difference was statistically significant (p=0.03 and p<0.001, respectively) (fig 1& 2).The results of T-Scores and Z-Scores of lumbar spine and femur neck in both groups are shown in table 2.

Table 2: Comparison of the Z-Score (ZS) and T-Score (TS) of femur neck and lumbar spine in GnRHa group (study group) and controls

Groups	Before	After	P value*
Study group (FN)(ZS)	1.29±0.75	0.97±1.13	0.008
Controls (FN)(ZS)	-0.64±0.96	0.62±1.95	0.09
Study group (LS)(ZS)	0.30±1.18	1.15±0.86	0.018
Controls (LS)(ZS)	0.55±1.28	-0.08±1.25	0.34
Study group (FN)(TS)	-1.19±3.90	-1.76±1.05	0.39
Controls (FN)(TS)	-0.11±0.91	-0.36±1.02	0.75
Study group (LS)(TS)	-0.34±1.09	-2.05±0.72	<.001
Controls (LS)(TS)	-0.29±1.23	-6.63±1.13	<.001

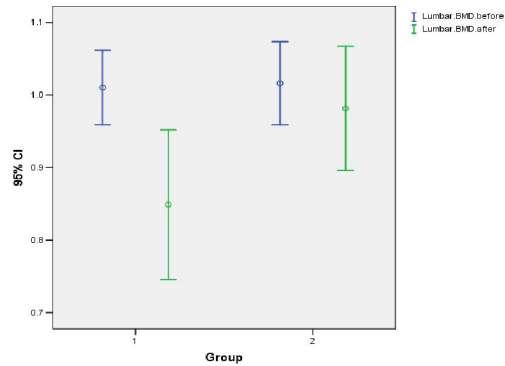*P value< 0.05 was considered significant

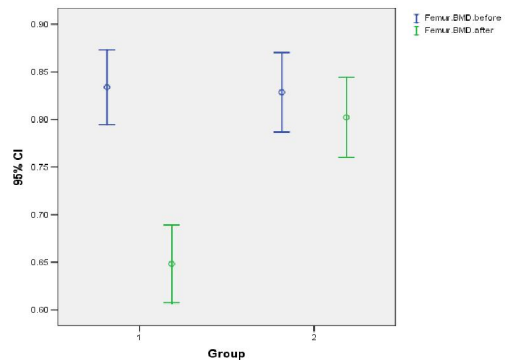**Figure 1:** BMD changes of lumbar spine between studied groups.

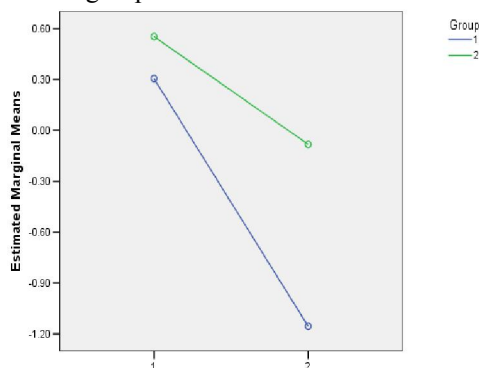**Figure 2:** BMD changes of femur neck between studied groups.

Figure 3: Z-scores changes of lumbar spine between studied groups.

Comparison of the mean changes between Z-Scores of lumbar spine and femur neck in both groups showed that the difference was statistically significant (p=0.019 and p=0.008, respectively) (fig 3). Comparison the mean changes of T-scores between groups at the lumbar spine levels showed a significant difference (p=0.01), but in femur neck it was not significant (p=0.69).

The frequency of femur neck osteopenia after intervention was increased in the study group compared to controls (68.2% vs 8.7%, respectively). At lumbar spine level it was 72.2% vs.17.4%, respectively). Results of the signs and symptoms of hypo estrogenic state before and after surgery showed that the changes in urinary incontinence, vaginal dryness, and hot flushes in the study group compared to controls were significant (p<0.001). Other signs and symptoms were not changed significantly. The frequency of headaches in the study group before and after the surgery was not statistically significant (p=0.5). But in controls there was significant difference in the frequency of headaches before and after the surgery (p=0.013). The headache was relieved in most patients in control group after the surgery if they had any before that. But in the study group it persisted.

The mean of bone pain were assessed by rating scale at the levels of Low back, knee and shoulder. In both groups the severity and the frequency of pain are shown in table 3. Healthy Days Core Module (CDC HRQOL– 4) was used to compare general health in groups. A good vs. Poor general health in groups were as 18 (81.8%) vs. 9 (40.9%). Daily activity reduction was 17(77.2%) vs. 10 (43.4%). Most patients in the study group reported that many days, poor physical health kept them from doing their usual activities such as self-care, and personal work. These changes were reported in 16 (72.7%) of group 1 and 4 (17.3%) of controls.

Table3: Reports of bone pain in GnRHa group (study group) and controls

Groups	Study group (n=22) (%)						Controls (n=23)(%)						
	Before			After			Before			After			P value*
Variables	Mid	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe	
Low back	2 (9.09)	2(9.09)	-	2(9.09)	4 (18.1)	16 (72.7)	2 (8.6)	3 (13)	-	2(8.6)	3(13)	2(8.6)	<0.001
Knee	8(36.3)	1(4.5)	-	13(59.09)	7(31.8)	2(9.09)	8(34.7)	4(17.3)	-	6 (26)	7(30.4)	2(8.6)	>0.05
Shoulder	10(45.4)	22(9.09)	-	12(54.5)	4(18.1)	1(4.5)	8(34.7)	3(13)	-	8(34.7)	4(17.3)	-	>0.05

*P value< 0.05 was considered significant

4. Discussion

The results of our study show that 6 months after hysterectomy, despite both groups had been received supportive medication, GnRHa group compared to controls, had significantly reduced BMD of femur neck (p<0.001) and lumbar spine (p=0.03), increased frequency of femur neck (p=0.008) and lumbar spine (p=0.019) osteopenia, severe low back pain (p<0.001), poor general health and reduced daily activity, which compromised their quality of life. GnRH agonist therapy requires special consideration in the management of women going through the menopausal transition due to some possible side effects on the bone mineralization. It is well known that high amounts of plasma sex steroid hormone levels suppression may occur after GnRH treatment (Lethaby et al., 2001). The results of our study were in agreement with Matsuo et al study. They reported a significant decrease in the BMD values even in the short period during GnRH-agonist therapy (Matsuo, 2003). However, Lethaby and colleagues in their study showed no decrease in BMD after treatment (Lethaby et al., 2002). In our study, even the maintaining of the ovaries and supportive treatment in the study group could not lower the side effects. GnRH agonists are increasingly administered for gynecologic disorders. The biologic effect of these agents is stopping the production of estrogen and progesterone and temporary inhibition of hypothalamic function. In transitional years when the ovarian reserve is diminished, the administration of a suppressive agent may progress to irreversible results. A study has been conducted by Palomba and colleagues on the bone metabolism in postmenopausal women who have had drug-induced menopause (with GnRH-a), or menopause as a result of surgery, and in healthy women. These authors showed that only in the women who were previously treated with GnRH-a and tibolone for 12 months, the bone loss was higher after menopause (Palomba et al., 2002). In contrast, there are conflicting data from the administration of GnRH agonists in young patients. Whereas, some studies shown no impairment in BMD in girls with precocious and early puberty during and after GnRHa therapy (Assa et al., 2011; Park et al., 2012). Divasta and colleagues suggested a careful monitoring of BMD in adolescents receiving GnRH agonists. According to these investigators, there was no correlation between duration of therapy with the GnRHa plus add-back and BMD at the hip or spine (Divasta et al., 2007). On the other hand Agarwal and colleagues showed that even though the rate of bone loss from GnRH agonist therapy in young and old patients was equal, administration of GnRH agonist for younger women before reaching to the peak of BMD may put them at the risk of fracture (Agarwal, 2002). Hiroya Matsuo observed those women who were receiving GnRH agonist therapy for endometriosis, and found out that there were both reductions of BMD and an increase in BMD after stopping the treatment. However, even one year after treatment, some of the women had failed to return to their pre-treatment BMD which was compatible with our study. Therefore, it seems that at the transitional age to menopause throughout which there is a natural loss in BMD, the risk of osteoporosis will be increased by these drugs and may be irreversible. It was true, even though the women take calcium supplements during the treatment (Matsuo, 2004), as are shown in our study (table 1). In addition, one study showed that the duration of treatment with these agents has had adverse effect on bone loss and it was significant after a twelve-month treatment compared to the six-month (Bianchi et al., 1995). Zhang et al in their study did not found any adverse effect on bone metabolism at the end of 3-month therapy for the treatment of endometriosis, uterine leiomyoma and adenomyosis (Zhang et al., 1995). In contrast to our study, in their study, the patients were not in menopausal transition and did not undergo hysterectomy. Factors other than changes in markers of bone remodeling and BMD may be involved in some signs and symptoms of these patients. Poiraudeau and co-workers examined the short-term effects (6 months) of estrogen withdrawal on the circulating IGF system and concluded that IGF-I and IGF-II plasma concentrations were both increased following a short period of treatment with a GnRH agonist. The changes in individual IGF peptides were differently correlated with changes in markers of bone remodeling and BMD (Poiraudeau et al., 1997). Administration of supportive agents combine to GnRH agonists has also been demonstrated different results. Ripps and co-workers have shown that prophylactic alendronate as a measure against BMD loss in reproductive-aged women receiving GnRHa therapy for 6 months appears to offer some degree of protection against BMD loss in young women during transient, induced hypoestrogenemia (Ripps et al., 2003). According to Ang et al, actual BMD trends in Asian women who are on bisphosphonate treatment may be different. In contrast to Western populations in their study, the BMD scores in local population showed improvement in the first two years of bisphosphonate treatment but declined subsequently (Ang et al., 2011). By the time of the administration of GnRHa, BMD level may be at critical level and treatment by these agents may induce irreversible changes even for the patients receiving supportive therapy. The increased frequency of bone loss in our study cannot be explained; however, a racial and

geographical difference may be a contributing factor. So in patients who were under GnRHa treatment and have been underwent hysterectomy, the impact could be seen sooner than expected as are shown in our study. In addition to raising the risk for osteoporosis, short term treatment with GnRH agonists may cause severe side effects which mimic that of acute menopause and affects quality of life. So improving life style and supplemental therapy may not prevent some of these adverse effects. Therefore, these potential problems may be prevented by avoiding prescribing of these medications to critical stages of life. According to the Friedman and Haas, the utility of pretreatment with GnRH agonists prior to surgery for uterine myoma has been questioned. If the procedure is performed abdominally, there will be no difference in surgical morbidity between patients with a 12- week-sized uterus and those with a 20-week-sized uterus (Friedman and Haas, 1993). Therefore, GnRHa therapy should be considered only for patients who would like to save their uterus and it should be better not administered in unnecessary situations. The mean of bone pain was also assessed by rating scale at the levels of low back, knee and shoulder. Although both groups had been received supportive medication, GnRHa group had more severe low back, knee and shoulder pain than the other group. The general health was poor, and the daily activity, physical health such as self-care, and ability to work were compromised. These all affected the quality of life. The limitation of this study was the small sample size, especially in some areas such as evaluating the antiestergenic effect of GnRH agonists on signs, symptoms, and quality of life, which made statistical analysis impossible. These findings are needed to be confirmed by further larger, well-designed studies. In spite of the efforts performed, much is still needed to explore the long term effects of these agents on perimenopausal women.

5. Conclusion

Based on the results of this study, we conclude that in perimenopausal women, administration of GnRH agonists before hysterectomy affects adversely post hysterectomy bone density and bone loss. Even saving the ovaries and supportive medication in therapeutic group was not effective on the prevention of bone loss. Ten months after starting the GnRH agonist therapy, the intervention group showed a significant decline at the spine BMD sites compared to pre surgical measures. These data suggest that BMD should be carefully monitored in perimenopausal women receiving GnRH agonists. By the time of the administration of GnRHa, caution should be made to the level of BMD, because it may be at critical level, and treatment by these agents may induce irreversible changes even in patients receiving supportive therapy. Therefore, caution should be considered when such medications are prescribed for women during menopausal transition. Pain scores and quality of life measures, including physical activity were significantly worse for women who had been received GnRHa. We recommend routine assessment of BMD before hysterectomy with surveillance thereafter.

Competing Interests
The author(s) declare that they have no conflict of interests.

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