Changes in serum calcium and vitamin D3 levels after tibolone treatment and their correlations with health-related quality of life

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Objective: To assess the effects of tibolone on serum calcium and vitamin D3 levels, the effects on health-related quality of life (HRQOL), and the relationship between these variables. Methods: An open-label, prospective, parallel-arm study was conducted at S.C. Das Memorial Medical and Research Center, Kolkata, India, between July 2012, and June 2013. Women aged 34–55 years were eligible when they were experiencing surgical menopause and were symptomatic. Group A comprised patients who chose to receive tibolone (2.5 mg daily for 6 months) and group B comprised those who refused treatment. At baseline and 6 months, body mass index (BMI), serum calcium and vitamin D3 levels and HRQOL were assessed. Results: Of 79 participants, 53 were in group A and 26 in group B. After 6 months, BMI had increased significantly in both groups. The vitamin D level had increased significantly from baseline in group A (P = 0.02), and was higher than that in group B (P = 0.01). HRQOL had also improved significantly from baseline in group A (P = 0.001), and was significantly better than that in group B (P < 0.001). In group A, a significant correlation was found between serum vitamin D3 level and improves HRQOL in menopausal women.

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1. Introduction

The onset of menopause is associated with a number of health challenges for women. For example, the risks for osteoporosis and fractures are increased after menopause. Dietary factors, in particular calcium intake, have been implicated as risk factors in the etiology of osteoporosis. Calcium produces beneficial effects through the protection of bone mass and through bone remodeling [1]. Vitamin D has important roles in calcium and phosphorus metabolism and in bone mineralization. Poor intake of calcium and vitamin D can increase the risk of osteoporosis and fractures. Furthermore, a low calcium intake along with vitamin D deficiency in older patients can lead to a negative calcium balance [2], which causes age-associated secondary hyperparathyroidism. Hypovitaminosis D is also associated with cardiovascular disease, metabolic syndrome, diabetes mellitus type 2, various malignancies, increased mortality, depression, impaired cognitive function, personality traits and a deterioration of general health and well-being [3–5]. Therefore, optimum levels of serum calcium and vitamin D should be maintained [6]. However, in India, vitamin D deficiency is highly prevalent in asymptomatic women from different socioeconomic groups [7].

Postmenopausal women need a recommended dietary allowance of 1000 mg of elemental calcium. Calcium supplementation should be provided to bridge the shortfall between dietary intake and the recommended dietary allowance and it should also be given to patients at high risk of fractures [8].

The main source of vitamin D (a fat-soluble steroid hormone precursor) is sunlight exposure of the skin and its major storage form in the human body is the 25-hydroxy form [9]. In elderly patients, dietary vitamin D supplementation can lower the risks of fractures and falling [10], and in selected individuals measurement of serum 25-hydroxyvitamin D can be helpful.

Hormone replacement therapy (HRT) is one of several treatments used to alleviate the symptoms associated with menopause. To date, no single treatment has been proven to be superior. Notably, few studies have reported the effects of different HRT regimens on serum calcium and vitamin D levels and their inter-relationship with health-related quality of life (HRQOL). The assessment of HRQOL to evaluate patient satisfaction with a specific level of function is gaining importance in clinical practice. It helps to assess the effects of an illness and its treatment as perceived by the patients themselves [11].

Tibolone, a synthetic steroid that is structurally related to norethindrone, is used as HRT in menopausal women. After oral administration, it is converted to three active metabolites [12], each of which has tissue-specific effects. Tibolone has been shown to have protective effects against vertebral and nonvertebral fractures even among women at a low risk of fractures [8]. It has also been shown to suppress accelerated bone turnover induced by a combination of oophorectomy and low dietary calcium [13,14].
Tibolone increases the serum level of insulin-like growth factor 1 through increased secretion of growth hormone, leading to increases in the synthesis of muscle protein, the number of myogenic satellite cells, and the synthesis of tendon collagen [15]. This is important because vitamin D deficiency and consequent secondary hyperparathyroidism can lead to reduced muscle mass and lower muscle strength [16], which in turn leads to an increased tendency to fall and sustain fractures.

The aim of the present study was to assess the effects of HRT with tibolone on serum calcium and 25-hydroxyvitamin D, levels in symptomatic women after surgical menopause, to evaluate the effects on HRQOL as measured using the Menopause Rating Scale (MRS), and to assess the relationship between variables.

2. Materials and methods

The present open-label, prospective, parallel-arm study was conducted at S.C. Das Memorial Medical and Research Center in Kolkata, India, between July 1, 2012, and June 30, 2013. Women aged 34–55 years were eligible for inclusion when they had been experiencing surgical menopause for 3–4 months (attributable to benign gynecologic causes) and had menopausal symptoms. The ethics committee of S.C. Das Memorial Medical and Research Center approved the study. Informed written consent was obtained from all participants.

After taking a detailed history and clinical examination for every participant, the body mass index (BMI) was calculated (weight in kilograms divided by the square of height in meters). All women were counseled about the importance of HRT and were offered tibolone. Patients who agreed to undergo treatment with tibolone (group A) were advised to take one tablet of tibolone (2.5 mg; Livial, Organon, Mumbai, India) daily for 6 months. Compliance was verified verbally and pill counts were performed at follow-up visits. Patients who refused treatment with tibolone (group B) were advised to continue with their usual lifestyle pattern and to attend follow-up visits.

All women underwent measurement of their serum calcium and 25-hydroxyvitamin D, levels at baseline and after 6 months. The serum calcium level was measured with the cobas c system (Roche Diagnostics, Mannheim, Germany). The serum vitamin D, level was measured using the Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany).

At baseline and after 6 months, every participant used the MRS to assess their HRQOL. The scale was developed in the early 1990s because there was a lack of standardized scales to assess the severity of menopausal symptoms and their impact on HRQOL. It is easy for any woman to complete the scale herself. A decrease in the MRS score indicates an improvement in HRQOL. The scale includes 11 items, each of which is rated between 0 (no symptoms) and 4 (very severe symptoms).

On the basis of a pilot study and assuming a standard deviation in MRS of 3.5 in each group and a dropout rate of 10%, with two patients in group A for every one patient in group B, the minimum sample size required to detect a difference of five points on the MRS was 29 (20 in group A; nine in group B). The following tests were used as appropriate: unpaired or paired t-test, Mann-Whitney U test, Wilcoxon signed-rank matched-pair test, and Spearman rank correlation test. The variables were tested for normality; all had an acceptable Kolmogorov–Smirnov coefficient and were thus tested with parametric tests, apart from the MRS score, which required a non-parametric analysis. The analyses were performed with InStat version 3.0 (GraphPad Software, La Jolla, CA, USA). P < 0.05 was considered statistically significant.

3. Results

Of 79 participants, 53 agreed to undergo treatment with tibolone (group A) and 26 declined HRT for fear of adverse effects (group B) (Fig. 1). No significant differences in age, BMI, calcium or vitamin D, levels, or MRS score were recorded between the two groups at baseline (Table 1).

After 6 months of follow-up, the serum vitamin D, level was significantly higher in group A than in group B (Table 1). BMI increased significantly between baseline and 6 months in both groups, but no difference between groups at either stage was recorded (Table 1). There was no change in the serum calcium level after 6 months. MRS score decreased significantly between baseline and 6 months in group A, and was significantly lower in group A than in group B at 6 months (Table 1). The MRS score was also significantly correlated with the vitamin D, level in group A (Table 2).

4. Discussion

The present study has shown that tibolone causes a significant rise in the serum vitamin D, level among menopausal women after 6 months of treatment. However, no significant change in calcium level was recorded. Both groups had a significant rise in BMI after
correlated with changes in adrenal function, an effect that is independent of adrenocorticotropic hormone levels. However, BMI, body mass index, while decreasing the fat mass [18,19]. However, BMI increased significantly in patients who did and did not take tibolone. Such an increase in BMI could be explained by the fact that elevated levels of luteinizing hormone in the menopause are correlated with changes in adrenal function, an effect that is independent of adrenocorticotropic hormone levels [19].

In conclusion, the present study has shown that HRT with tibolone causes a significant rise in the vitamin D level without having any significant effect on the serum calcium level. A study with a larger sample size and additional investigation of lipid parameters is necessary to elucidate the overall benefits of tibolone in menopausal women.

Conflict of interest

The authors have no conflicts of interest.