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AU1 Tofupill/Femarelle (DT56a): a new phyto-selective estrogen receptor modulator-like substance for the treatment of postmenopausal bone loss

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Abstract

Objective: To evaluate the efficacy of Tofupill/Femarelle (DT56a), a novel phyto-selective estrogen receptor modulator (SERM), in preserving bone mineral density (BMD) in postmenopausal women.

Design: The study sample consisted of 98 healthy, postmenopausal women who were randomly allocated, on a double-blind basis, to receive either 644 mg/d DT56a (study group) or 344 mg/d DT56a supplemented with calcium (low-dose group) for 12 months. Each participant was assessed with a comprehensive health questionnaire, a detailed physical, and laboratory and pelvic sonogram examinations at entry and every 3 months thereafter. BMD was assessed by dual-energy x-ray absorptiometry (Lunar) of the lumbar spine and femoral neck before the study began and after 12 months of treatment.

Results: After 12 months of treatment, BMD had increased in the study group by 3.6% in the lumbar spine ($P = 0.039$) and by 2.0% in the femoral neck (NS). In the low-dose group, BMD had decreased in the lumbar spine by 0.6% (NS) and by 0.6% in the femoral neck (NS). Comparison of the change in bone density between the groups yielded a significant difference for the lumbar spine ($P = 0.037$). Neither group showed a change in endometrial thickness and sex hormone levels nor reported any side effects of treatment.

Conclusions: Tofupill treatment in postmenopausal women increases BMD without unwanted estrogenic effect. Tofupill appears to be a promising phyto-SERM for the prevention of postmenopausal osteoporosis.

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Key Words: Menopause—Osteoporosis—DT56a—Tofupill—SERM—Bone mineral.

Menopausal osteoporosis and its sequela of osteoporotic fractures present a serious challenge in the modern epidemiology of disease prevention, with incidence rates reaching epidemic levels in the Western world. An estimated 29.6 million women in the United States have osteoporosis, and this number is expected to rise to 35.1 million by 2010 and to 40.9 million by 2020.[1] The lifetime risk of vertebral fracture for white women above the age of 50 is about 1 in 3; for hip fracture, it is 1 in 6.[2]

In the past 30 years, many products aimed at slowing natural age-related bone resorption and enhancing bone formation have been introduced. These include estrogenic compounds, selective estrogen receptor modulators (SERMs), bisphosphonates, calcitonin, and, most recently, parathyroid hormone.[3] Large, well-designed, double-blind, controlled, prospective studies have shown that the use of these products over 2 to 3 years resulted in an average increase of 4% to 6% in bone mineral density (BMD).[2-5] However, all have disadvantages and side effects, and alternatives are still being sought.

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Phytoestrogen, a constituent of soybean, is widely consumed in Asia as part of the normal diet. On the assumption that the low rate of osteoporosis in the Asian population is at least partially attributable to the high dietary content of phytoestrogen,[6,7] industrial groups began to develop a wide range of products containing phytoestrogen, mainly isoflavone (including a synthetic isoflavone), for the prevention of menopausal symptoms. The results so far are inconclusive, with some studies showing a beneficial effect of soy products on BMD[8] and others not.[9]

DT56a (the active substance in Tofupill/Femarelle; Se-cure Pharmaceuticals, Yavne, Israel) is the generic name of a compound isolated from tofu. Tofupill constitutes all the active phytoestrogen ingredients found originally in tofu. A unique enzymatic process of isolation is employed to ensure that the whole isoflavone family, the lignans and the coumestans, remain in their naturally intact form. As such, the product preserves the beneficial effect of the soybean.

Tofupill (DT56a) has been successfully used to treat menopausal symptoms[10] without affecting the sex hormone levels or endometrial thickness.

The aim of the present study was to evaluate the effect of Tofupill on BMD in postmenopausal women.

METHODS

In this randomized, prospective, double-blind study, we examined the effects of two dosages of Tofupill on postmenopausal women seeking hormone replacement therapy at women's healthcare centers in Israel. Inclusion criteria were healthy women with an intact uterus who had no menses within the previous 6 months and who had blood hormone levels indicating menopause: follicle-stimulating hormone (FSH) greater than 30 mIU/mL; estradiol (E_2) less than 150 pmol/L. Exclusion criteria were any preexisting illness known to affect bone metabolism, habitual use of drugs or alcohol, presence of endometrial polyps or hyperplasia, and moderate or severe hypertension.

The study was approved by the Human Investigation Review Board of the Rabin Medical Center, and all participants signed an informed consent form after receiving a comprehensive explanation of the study. At entry to the study, a complete medical and gynecological history was obtained for each woman, and the attending physician completed an assessment questionnaire detailing the woman's menopausal symptoms. In both studied groups, participants who were taking any medications known to affect bone metabolism (SERMS, biphosphonates, calcitonin, 1,25-OH vitamin D) were excluded. All participants underwent a physical examination (blood pressure, height, and weight), a gynecological and breast examination, and transvaginal ultrasonography. Laboratory tests included hormonal and lipid profiles and tests of liver and kidney function. A baseline mammography was done as well, in addition to dual-energy x-ray absorptiometry (DEXA) of the lumbar spine and femoral neck.

For the trial, externally identical study (high-dose) and control (low-dose) capsules were placed in identical white bottles with no identifying marks apart from a serial number. The bottles were placed in front of the participants, and they were asked to choose one at random. The contents were unknown to the research team. Patients were asked to take two capsules a day, for a total of 644 mg/day of DT56a, (Tofupill Se-cure Pharmaceuticals, Yavne, Israel) for the study group and of 344 mg/day DT56a for the low-dose group. The control capsules were supplemented with calcium phosphate (250 mg) and natural vitamin E (8 mg). The duration of the trial was 12 months.

Compliance and side effects were assessed every 3 months, and all tests and assessments done at the time of enrollment were repeated after 3, 6, and 12 months. After 9 months, each participant was interviewed. DEXA of the lumbar spine and femoral neck was repeated after 12 months in the same institute using the same machine.

Data was statistically analyzed by paired sample *t* test and by two-sample *t* test. A *P* value below 0.05 was considered statistically significant.

RESULTS

Of the 98 women who met the inclusion criteria and agreed to participate in the study, data on BMD was gathered on 82 women following 12 months of treatment, 39 of them in the study group and 43 in the low-dose group. Data concerning BMD of 16 participants was not included in the final analysis, 5 in the study group and 11 in the low-dose group. Of these 16 participants, 9 completed the follow-up but BMD tests were not available, and 7 dropped out during the study for personal reasons. Importantly, the baseline characteristics of these 16 participants did not differ from the studied population in any parameter. T1

No side effects or adverse reactions were reported by any of the participants. Baseline characteristics were similar in both study and control groups (Table 1).

The baseline bone density values in the spine were: 1.077 g/cm^2 and 1.062 g/cm^2 in the Tofupill and the low-dose group, respectively; in the femoral neck:

TABLE 1. *Demographic data of both studied groups*

	Study group (n = 39)	Low-dose group (n = 43)	P value
Age (y)	55.51 ± 5.4	55.83 ± 5.1	NS
Time since menopause (y)	5.97 ± 5.8	5.73 ± 4.48	NS
Height (cm)	160.9 ± 6	159.43 ± 6.5	NS
Weight (kg)	66.16 ± 9.2	66.82 ± 11.1	NS
Body mass index (kg/m^2)	25.50 ± 3	26.31 ± 4.3	NS
Smokers, number (%)	3 (8.1)	6 (13.3)	NS

All values except smokers are mean ± SD. NS, Not significant.

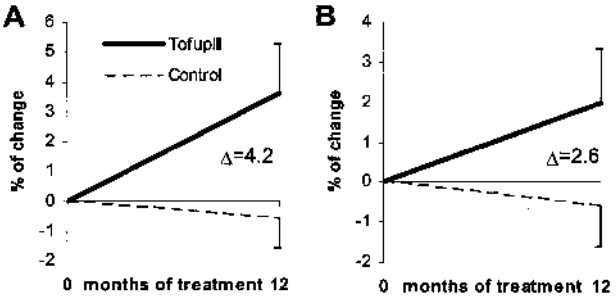

FIG. 1. Effect of Tofupill on BMD after 12 months of treatment. Values expressed as mean changes from baseline ± SEM as measured at the spine (A) and femoral neck (B). In the study group, there was a statistically significant elevation of 3.6% in the spine, compared with a 0.6% reduction in the control group (P = 0.037). The net effect in the femoral neck was 2.6% (NS).

TABLE 2. *Measures of endometrial thickness, FSH, and E_2, pre- and posttreatment*

	Study group (n = 39)		Low-dose group (n = 43)	
	Pre	Post	Pre	Post
Endometrium (mm)	3.2	2.8	3.7	3.4
Mean FSH (mIU/mL)	73.7	66.9	79.4	73.3
Mean E_2 (μmol/L)	105	92	110	105

Pre, pretreatment; post, posttreatment.

0.881 g/cm^2 and 0.850 g/cm^2 in the Tofupill and the low-dose group, respectively (nonsignificant difference for both).

On DEXA scanning after 12 months, BMD in the lumbar spine increased from baseline in the study group by an average of 3.6% and decreased in the low-dose group by an average of 0.6% (Fig. 1). The improvement in the study group was statistically significant (P = 0.039), and there was a significant difference between the study group and the low-dose group (P = 0.037). BMD in the femoral neck increased by 2.0% in the study group and decreased by 0.6% in the low-dose group (Fig. 1). In the femoral neck, there was no statistical difference in the study group or between the two groups.

Laboratory testing at 12 months yielded no treatment-related changes in serum FSH or E_2 or in endometrial thickness in either the study or low-dose group (Table 2).

DISCUSSION

The finding of a direct relationship between the risk of fracture and BMD[11] has prompted intensive research efforts for an effective treatment or prevention for osteoporosis. Most of the prophylactic hormonal products developed to date lead to persistence of monthly bleeding, which many menopausal women find bothersome. Moreover, there is an accumulation of data on the increased risk of breast cancer and cardiovascular complications in long-term users.[12] Thus, although menopause is a classic state of chronic hormonal deficiency, only 15% to 20% of women continue to use hormone therapy for the long-term.[13] SERMs theoretically represent an ideal solution for osteoporosis because they modulate the estrogen receptors in bone without affecting other potentially hazardous estrogen receptors. Unfortunately, however, up-to-date SERMs do not alleviate the menopausal symptoms that usually bring women to healthcare providers. Moreover, some women who were free of symptoms reported the onset of hot flushes after the use of SERMs.[14] Bisphosphonates have been proven effective against osteoporosis but have not alleviated menopausal symptoms, and their gastrointestinal side effects often lead to nonadherence. The reported average increase in BMD with any of the above agents after 2 to 3 years of treatment was 4% to 6%.[15-21]

The present study found that Tofupill/Femarelle (DT56a) has a beneficial effect on BMD in menopausal women. In a controlled animal study, Somjen and Yoles found that DT56a increased specific creatine kinase activity in bones, a marker of estrogenic stimulation.[22] However, unlike estrogen, there was no increase in creatine kinase levels in the uterus. Both DT56a and estrogen stimulation of creatine kinase were blocked by the SERM raloxifene, indicating that DT56a acts on the same receptor as estrogen and acts like a SERM, stimulating skeletal tissues without affecting the uterus. Another 12-month-long clinical trial by our group showed that Tofupill is also effective against other menopausal symptoms. The data after 3 months of treatment showed a reduction of hot flushes and palpitations in about 75% of participants. without changes in endometrial thickness or in FSH and E_2 levels.[10] These results were stable throughout the 12 months of the study.[23]

The present study supports the use of Tofupill for the treatment of osteoporosis in menopausal women. For

purposes of comparison, our control group necessarily contained women who had recently become menopausal, like the study group. Therefore, their climacteric symptoms, too, were prominent, and we had to offer them some type of treatment to ensure compliance. As a result, we compared the low dose with the high dose of Tofupill. Because BMD decreases rapidly at early menopause, we were able to efficiently evaluate the drug's dose-effect. Moreover, we thought it would be problematical to enroll women in a long-term study on osteoporosis without offering any kind of treatment. This could be not ethical and could result in a high dropout number. Calcium and vitamin E are common supplements for bone health of menopausal women. Thus, as an alternative to a placebo group, we decided that the low-dose group would take a low dose of DT56a with the addition of calcium and a minute amount of vitamin E. This remedy was acceptable from an ethical point of view and resulted in positive response from the participants.

CONCLUSIONS

The results of this study show that Tofupill selectively affects bone formation in postmenopausal women, without affecting the endometrium or sex hormone levels. We suggest that Tofupill, a novel phyto-SERM, is a suitable candidate for the pharmacological treatment of postmenopausal bone loss.

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