MELLIFERA RESEARCH ARTICLE

# The Effect of Royal Jelly Supplementation for Three Months on Bone Markers in Postmenopausal Osteoporotic Women

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**A B S T R A C T**

This study aimed to investigate the effect of three months of Royal Jelly (RJ) treatment on bone formation and resorption markers in postmenopausal women diagnosed with osteoporosis. The study included 80 postmenopausal women with osteoporosis (T-score <-2.5) randomly separated into two groups as the RJ group (n: 50) and the control group (n: 30). The RJ group took 1 gram of RJ in 100 ml of liquid every morning for three months. The control group was given a placebo in 100 ml of liquid. Basal bone-formation marker N-terminal propeptide of type 1 procollagen (P1NP) and bone resorption markers, C-terminal telopeptide of type 1 collagen (CTX), sclerostin levels were compared between the groups after three months. No statistically significant difference was determined between the groups regarding age, menopause duration, body mass index (BMI), and lumbar spine bone mineral densitometer (BMD) T-score. There was no statistically significant difference in calcium, 25-hydroxyvitamin D, bone production marker P1NP, bone destruction markers CTX and sclerostin parameters in both groups. This study showed that although RJ has an intense estrogenic effect when given orally to postmenopausal women with osteoporosis for 3 months, it did not affect bone formation and resorption parameters.

Keywords: Royal jelly, osteoporosis, postmenopausal, estrogen

## Introduction

Osteoporosis is a progressive metabolic bone disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [1].

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Osteoporosis affects many people of both sexes and races, and the prevalence will increase as the population ages [1]. Since most patients are women in the postmenopausal period, osteoporosis-related fractures impose a substantial burden of disability, costs, and mortality on postmenopausal women and older men. [2]. The key challenge in assessing the impact of osteoporotic fractures on mortality, disability, and costs is distinguishing the effects of the fractures themselves from the comorbidities and other risk factors that contribute to both the fracture and the outcome [3].

Estrogen plays a pivotal role in bone metabolism, and relative estrogen deficiency during the menopausal period contributes to the development of osteoporosis [4]. Although estrogen treatment effectively prevents and treats osteoporosis, hormone replacement therapy is not generally recommended due to the increased risk of breast cancer and cardiovascular events [*5, 6*]. In addition to estrogen replacement, other pharmacological and non-pharmacological treatment methods for preventing and treating postmenopausal osteoporosis are widely used. However, an effective and generally accepted treatment, completely safe, has not yet been described [7, 8]. This situation leads people to seek alternative treatments.

*Phytoestrogens* are defined as plant substances that cause estrogen effects in the human body, and they are increasingly consumed as a natural alternative to hormone replacement therapies. Numerous studies have examined bone effects in societies that consume the most known phytoestrogen, soybean. Although phytoestrogens are an area mentioned in osteoporosis treatment, more studies are required on this subject [1, 9].

Royal Jelly (RJ) is a glandular white-yellowish secretion produced from the hypopharyngeal and mandibular salivary glands of young nurse bees (aged between 5 and 14 days) [10]. RJ contains a considerable amount of proteins, free amino acids, lipids, sugars, and vitamins of very high biological value, and RJ has been demonstrated to possess numerous functional properties such as antibacterial activity, anti-inflammatory activity, vasodilative and hypotensive activities, disinfectant action, anti-oxidant activity, antihypercholesterolemic activity, anti-tumor activity, and estrogenic activities [11]. It has also been determined that RJ is effective in reducing postmenopausal symptoms in women [12].



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*10-hydroxy-trans-2-paternoicacid* (10H2DA), known as royal jelly acid or queen bee acid, is a unique medium-chain unsaturated fatty acid found only in RJ [13]. 10H2DA constitutes the vast majority of the RJ lipid content (0.75% to 3.39%) and represents one of RJ's main bioactive components [14]. RJ has been shown to have weak estrogenic activity since it competes with 17 beta-estradiol to bind to the estrogen receptor alpha and beta. It has been suggested that this estrogen receptor modulation is probably associated with fatty acids in RJ, such as 10H2DA [15].

In the postmenopausal period, estrogen treatment reduces fracture risk in women at high risk for fracture by increasing bone mineral density (BMD) and preventing bone loss [5]. This study aimed to investigate RJ's effects, which has been determined in previous studies to have estrogenic effects on bone formation/destruction in the postmenopausal period.

## Materials and Methods

This study was conducted on postmenopausal women diagnosed with osteoporosis who presented at the Internal Medicine Endocrinology and Metabolism Outpatient Clinic of Suleyman Demirel University Faculty of Medicine Practice and Research Hospital. The study was approved by the Suleyman Demirel University Scientific Research Ethics Committee (Approval number: 11/02/2015 - 41). The purpose, benefit, and risk of this study were explained to each participant, and a signed informed consent form was obtained from all participants.

The study included a total of 80 female patients, aged 48-74 years, who were in the postmenopausal period and had a lumbar vertebra BMD total T-score of ≤ -2.5. Patients were excluded from the study if they had hypogonadism, hypothyroidism, hyperthyroidism, diabetes mellitus, chronic kidney failure, or any other disease that could lead to secondary osteoporosis.

The patients were randomly separated into the RJ group (n: 50) and the control group (n: 30). The RJ group took 1 gram of RJ in 100 ml of liquid every morning for three months. The control group was given a placebo in 100 ml of liquid every morning for three months.

*Bone specific markers and Bone mineral density*

At the beginning of the study and the end of 3 months, peripheral venous blood samples were taken from the patients between 08.00-10.00 hours, after overnight fasting



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of at least eight hours. Serum was obtained by centrifuging these blood samples at 3500 rpm for 4 minutes. Serums were stored at -80°C until assay of N-terminal propeptide of type 1 procollagen (PINP), C-terminal telopeptide of type 1 collagen (CTX), and sclerostin. The frozen serum samples were thawed back to room temperature, and the P1NP, CTX, and sclerostin levels were determined at 0 and 3 months values using separate commercial kits (Cloud Clone Corp. Enzyme-linked immunosorbent assay (ELISA) kit, Houston, TX, USA, Precoated plate). BMD was measured at the lumbar spine and total hip using dual X-ray absorptiometry (DXA; Hologic Discovery, Hologic, Inc., Bedford, MA, USA).

*Statistics*

The data obtained in the study was analyzed statistically using SPSS 19 for Windows (SPSS, Chicago, IL, USA). The Student's *t*-test and Wilcoxon signed-rank test were used to evaluating the changes in biochemical parameters before and after treatment. Results were stated as mean ± standard deviation (SD) values. A value of $p < 0.05$ was considered statistically significant.



## Results and Discussion

The evaluation was made of 50 patients in the RJ group and 30 in the control group. No statistically significant difference was determined between the two groups regarding baseline anthropometric and laboratory data (Table 1).

**Table 1.** Comparison of baseline clinical. anthropometric. and laboratory characteristics between postmenopausal women receiving Royal Jelly supplementation and placebo.

| | **Groups** | |
|---|---|---|
| **Parameters** | **Royal Jelly** | **Placebo** |
| n | 50 | 30 |

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| | | |
|---|---|---|
| Age (years) | 61.6±7.8 | 62.8±6.8 |
| Duration of Menopause (years) | 12.2±6.6 | 12.9±6.1 |
| Body mass index (kg/m2) | 27.5±3.3 | 28.2±2.6 |
| Lumbar spine BMD (g/cm2) | -2.9±0.38 | -2.8±0.24 |

*Mean (standard deviation) values.

When the calcium levels were compared in the RJ and control groups, there was no significant difference between the baseline and 3-month values (p= 0.314, p= 0.475, respectively).

When the 25-OHD3 levels were compared in the RJ and control groups, there was no significant difference between the baseline and 3-month values (p= 0.906, p= 0.900, respectively).

When the s-CTX levels were compared in the RJ and control groups, there was no significant difference between the baseline and 3-month values (p= 0.06, p= 0.489, respectively).

When the P1NP levels were compared in the RJ and control groups, there were no significant differences between the baseline and 3-month values (p= 0.475, p= 0.639, respectively).

When the sclerostin levels were compared in the RJ and control groups, there was no significant difference between the baseline and 3-month values (p= 0.445, p= 0.546, respectively).



The baseline and 3-month values of calcium, 25-OHD3, s-CTX, P1NP, and sclerostin of both groups are shown in Table 2.

**Table 2.** Comparison of the bone markers between postmenopausal women receiving Royal Jelly supplementation or placebo at baseline and after 3 months of intervention.

| **Bone markers** | **Groups** | **Baseline** | **3 months** | **P values** |
|---|---|---|---|---|
| Calcium (mg/dl) | RJ | 9.4±0.4 | 9.4±0.4 | 0.314 |
| | Control | 9.4±0.35 | 9.3±0.31 | 0.475 |
| 25-OHD3 (ng/mL) | RJ | 16.7±7.8 | 16.8±7.3 | 0.906 |
| | Control | 17.8±8.6 | 17.6±7.7 | 0.900 |
| s-CTX (ng/mL) | RJ | 0.16±0.17 | 0.21±0.09 | 0.06 |

| | | | | |
|---|---|---|---|---|
| | Control | 0.21±0.29 | 0.25±0.14 | 0.489 |
| P1NP (ng/mL) | RJ | 46.1±65.5 | 38.0±45.4 | 0.475 |
| | Control | 36.4±38.8 | 41.6±46.6 | 0.639 |
| Sclerostin (pg/mL) | Basal | 310.8±352 | 215.7± 216 | 0.445 |
| | Control | 251.2±390 | 207±202 | 0.546 |

Mean (standard deviation) values.
S-CTX: serum C-terminal cross-linked telopeptides of type I collagen.
P1NP: amino-terminal propeptide of type 1 procollagen

RJ's effects on bone formation/resorption markers in postmenopausal osteoporotic women were investigated in this study. The results demonstrated that three months of RJ treatment did not affect bone-formation marker, P1NP, bone resorption markers, CTX, and sclerostin.

Several studies have shown that alternative treatment methods are effective in postmenopausal osteoporosis. The effects of tea consumption on osteoporosis were investigated in postmenopausal osteoporotic patients. The positive effects on BMD were determined depending on the type of tea (green tea, oolong tea, black tea, or others] and amount [16]. In recent years, herbal drinks such as Persimmon (Diospyros kaki L.f.) leaves, Noni leaf, Herba Epimedii, Salvia miltiorrhiza, icariin, and tanshinones, and products made from these are very useful in postmenopausal osteoporosis due to anti-oxidant effects and the inhibition of osteoclastic activity [17]. A meta-analysis showed that the isoflavones found in some legumes are selectively modulating estrogen receptors. Isoflavone treatments effectively maintain BMD and reduce accelerated bone resorption in postmenopausal osteoporosis patients [18]. In a rat model study of oophorectomy-induced osteoporosis, the Cissus quadrangularis plant, a phytoestrogen, was determined to significantly increase the bone level formation marker, P1NP, due to the flavonoid content [19]. Previous studies have shown that RJ also has bone-sparing properties in postmenopausal osteoporosis. In a rat model of postmenopausal osteoporosis by oophorectomy, oophorectomized rats supplemented with 50 mg/kg RJ for twelve weeks exhibited higher BMD than those who did not receive RJ [20].

Similarly, in rats undergoing oophorectomy and in tissue culture, RJ is as effective as 17 beta-estradiol in correcting bone mineral



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density [21]. RJ has also been shown to stimulate the proliferation of mouse osteoblast-like cell lines and the production of type-1 collagen. It has been suggested that these effects are made by increasing the osteoblastic activity through interaction with the estrogen receptors of a component or components in the content of RJ [22]. Similarly, Moutsatsou et al. showed that the fatty acids found in RJ lead to mineralization in osteoblasts. These effects were demonstrated to be an estrogen receptor-mediated activity since it was inhibited when an estrogen receptor antagonist was added [23]. We have not evaluated the effects of RJ at the molecular level. If studies were done at the molecular level, probably the difference could be detected.

In the current study, no significant change was determined in circulating bone turnover parameters. In a similar previous study, 150 g / day of RJ was administered for three months to patients in the postmenopausal period but without osteoporosis. No significant change was found in bone-formation marker P1NP and bone-resorption marker CTX, and no bone-protective efficacy of RJ was demonstrated [24]. Although it has been shown that 10 mg/kg of RJ does not have bone-sparing activity in rats with oophorectomy-induced postmenopausal osteoporosis [25], RJ has been shown to improve lipid metabolism, erythropoiesis, glucose intolerance, and mental health in studies performed with 3-g and 6-g daily dose [26,27]. Since these parameters were not included in our study, non-osteoblast effects could not be evaluated.

Unfortunately, there is no definitive standard formula for RJ. The composition of RJ may vary depending on seasonal and regional nutritional conditions [10]. It is necessary to ensure RJ's standards, and further studies are required to determine the most suitable dose for humans and investigate its effectiveness in more extensive clinical studies.

This study's limitations can be considered primarily the low number of patients enrolled in the study and that the most effective dose of RJ for a person is unknown. Furthermore, the follow-up duration was short. Larger series with a long period of follow-up duration is required to show RJ's effectiveness on osteoporosis.



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## Conclusion

Although RJ has been previously shown to have estrogenic activity, the results of this study demonstrated that a daily dose of 1 gr did not affect bone formation/resorption markers in postmenopausal osteoporotic women.

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## Postmenopozal Osteoporozu olan Kadınlarda 3 aylık Arı Sütü (Royal Jelly) Kullanımının Kemik Belirteçleri Üzerine Etkisi

**Öz:** Bu çalışmada postmenopozal dönemdeki osteoporozu olan kadınlarda 3 aylık arı sütü (royal jelly) kullanımının kemik yapım ve yıkım belirteçlerini değerlendirerek kemik üzerindeki etkilerinin değerlendirilmesi amaçlanmıştır. Postmenopozal seksen kadın katılımcı, rastgele olarak arısütü verilenler (n=50) ve verilmeyenler (n=30) olarak ikiye ayrılmıştır. Arısütü alan gruba üç ay boyunca içerisinde 1 gram arısütü olan 100 mL sıvı verilmiştir. Kontrol grubuna ise yine 100 mL sıvı olacak şekilde plasebo verilmiştir. Kemik yapım belirteci olan N-terminal propeptit tip 1 kollajen (P1NP) ve kemik yıkım belirteci olan C-terminal telopeptit tip1 kollajen (CTX), sklerostin seviyeleri 0. ve 3. Ayda olmak üzere her iki grupta incelenmiştir. Sonuç olarak yaş, menopoz süresi, vücut kitle indeksi ve lomber vertebra kemik mineral dansitometri T skoru açısından benzer iki grupta kemik yapım ve yıkım beliteçleri açısından fark saptanmamıştır. Östrojenik etkisi yüksek olan arı sütünün 3 aylık süre boyunca kullanımı ile osteoporoz üzerine etkisi gösterilememiştir.

Anahtar Kelimeler: Arı sütü, osteoporoz, postmenopoz, östrojen



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