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## Interrelation among Serum Lithium Levels, Bone Metabolism, and Some Biochemical Parameters in Pre- and Post-Menopausal Women

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**Abstract:** The target of this study is to determine the interrelation among serum Li level on bone metabolism (Ca, P, Parathormone, and Vitamin-D), sex and metabolic hormones (estrogen, FSH, LH and TSH), and some biochemical parameters in premenopausal and postmenopausal women. The study is carried out with 10 women, 5 of which is in the premenopausal period. The serum Li levels, bone metabolism indicators (*i.e.*, ALP, Ca, P, Mg, Cu, and Zn) and some biochemical parameters such as serum triglyceride, alkalene phosphatase, total cholesterol, HDL, LDL, and cholesterol levels were determined. The estrogen blood level of women in menopause period was found to be lower than that of women in pre-menopause period ( $p < 0.01$ ) and the FSH level was found to be higher ( $p < 0.01$ ). In the lipid profile, the triglyceride level in the post-menopause period was found to be low ( $p < 0.05$ ) and HDL ( $p < 0.001$ ), LDL ( $p < 0.001$ ) and the cholesterol levels were found to be high ( $p < 0.001$ ). The alkalene phosphatase ( $p < 0.001$ ) and Vitamin-D levels ( $p < 0.001$ ) were found to decrease. When the mineral levels were investigated, no meaningful difference was observed in the serum magnesium and copper levels while zinc ( $p < 0.01$ ) and phosphorus ( $p < 0.005$ ) levels were observed to increase, the calcium levels ( $p < 0.05$ ) decreased and Li levels considerably decreased ( $p < 0.0001$ ). According to the results obtained it was determined for the first time that Li deficiency can be related with menopause and the related diseases and thus Li therapy can be used in developing new treatment protocols of menopause as an alternative method.

**Keywords:** Bone metabolism, menopause, osteoporosis, serum Li level.

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**INTRODUCTION**

Menopause can be defined as decrease of hormones periodically secreted from the ovaries and full-stop of menstrual bleeding which is a natural consequence of aging. In the period when women try to adapt themselves from a period, when they are physiologically stimulated with estrogen and progesterone, to a period, when they are deprived of these hormones and decrease in estrogen levels, serious complications such as cardiovascular diseases, cancer, bone loss and osteoporosis arise [1].

Osteoporosis is a disease which leads to bone fractures due to decrease in the bone density. In osteoporosis, bones become sensitive due to decrease in bone mass caused by factors related with genetics, hormonal, environmental and diet and bone loss occurs in the endostal region of the skeleton [2]. One of the main reasons of osteoporosis is the deficiency in estrogen. Estrogen is necessary for the normal maintenance of the bone matrix and for incorporation of calcium in the matrix. Moreover, estrogen increases absorption and excretion of calcium and inhibits bone resorption [3].

Today modern menopausal treatment is focused on developing therapy models which would eliminate the symptoms suffered during menopause period with the least side effects. Studies have shown that there is a relation between lithium and sex hormones and it affects these hormones [4]. In another study it was reported that lithium antagonizes the effects of estrogen [5]. Moreover it was shown that lithium affects the wnt path which plays an important role on development and differentiation of bone tissues and hair follicles. In an increased number of studies, it was shown that wnts are key regulators on osteogenic differentiation of mesenchyme stem cells and on bone formation. For example, while a change in the wnt signalization path can cause osteoporosis and osteopenia inactivating mutation of wnt inhibitors lead to hyperostotic skeleton formation and thus an increase in bone mineral density. Lithium blocks the wnt antagonist and decreases fracture risk of the patient [6]. It was shown that lithium can be related with hyperparathyroidism which is a risk factor for osteoporosis. However, the data regarding the relationship between lithium and bone mass is contradictory. Lithium can cause hypercalcemia and parathyroid function disorder [7]. Moreover, the therapeutic effect of lithium can be observed in a very narrow window and the concentrations above this level can cause poisoning or can be lethal. For instance, while its concentration in the plasma and in the serum is above  $1.5 \text{ mmol.L}^{-1}$  poisoning can happen when its concentration in the serum is above  $2-2.5 \text{ mmol.L}^{-1}$  and when its concentration in the serum is above  $3.5 \text{ mmol.L}^{-1}$  in the serum it can be lethal. On the other hand, it is known that lithium therapy is successful only when lithium concentration in the plasma is above  $0.050 \text{ mmol.L}^{-1}$ , and is in the range  $0.5-1.5 \text{ M}$  in the blood and  $0.3-1.3 \text{ mM}$  in the serum [8,

9].

Therefore, in order to provide optimum benefit from therapeutic effect of lithium, its accurate, sensitive, selective, and reliable detection in blood, blood plasma, serum, and saliva is of great importance.

Studies have shown that the toxic effect of lithium does not only depend on the amount of lithium administered but also other parameters such as sodium intake affect the mechanism. Therefore, in this study both determination of serum lithium levels in women in pre-menopause and menopause periods and also the relation among lithium levels, bone metabolism (Ca, P, Parathormone, Vitamin-D), sex and metabolic hormones (estrogen, FSH, LH, TSH) and some biochemical parameters were targeted for evaluating efficacy of lithium as a therapeutic agent in treatment of osteoporosis.

## **MATERIAL AND METHODS**

This study is made on volunteering women who had visited Çankırı Karatekin Hospital Outpatient Polyclinics of Gynecology and Obstetrics. The study was carried out with two groups each of which were consisted of 5 female subjects. The first group (Pre-menopause Group) was under the age 45 and had regular periods (menstrual cycle) and who was determined not to be in the menopause period by the doctor and the second group (Post-menopause Group) comprised of women, who were above the age 55 and did not have their periods and they were clinically diagnosed by the doctor to be in the menopausal period. The volunteer subjects were non-smokers and did not have any systemic diseases such as renal failure, diabetes mellitus, heart diseases and who did not use any kind of estrogen preparative before. The subjects, who were included in the control group, were included in this group according to the diagnosis of the doctor and had estrogen value above 30 pg/mL. The subjects with estrogen value below 20 pg/mL were included in the menopausal group. Ethical board permission was obtained from Kirikkale University Faculty of Medicine and each patient was asked to offer their consent via "informed consent form".

10 mL venous blood was taken from the subjects participating in the study into serum tubes and tubes containing anticoagulant for the biochemical analysis. The venous blood samples were centrifuged at 3000 rpm for 10 min.s and the sera were separated from the blood samples. Serum samples were placed in Eppendorf tubes and were kept at -80 °C until they were analyzed.

Water used in the experiments was purified with a MilliQPLUS 185 system (Millipore, St Quentin-en-Yvelines, France). Suprapur nitric acid 65 % and Triton X-100 were obtained from Merck (Darmstadt, Germany). Rhodium standard for ICP TraceCERT®, 1000 mg/L Rh in hydrochloric acid was obtained from Sigma Aldrich.

Serum Ca, P, Zn, Cu, Mg, triglyceride, total cholesterol, HDL, LDL, ALP, FSH, estrogen, and Vitamin D levels were determined via commercial kits in the auto-analyzer. Serum lithium concentrations were determined by ICP-MS Thermo Elemental X7CCT series and PlasmaLab1 software without a dynamic reaction cell. Plasma torch argon purity was higher than 99.9 %.

Blood plasma samples (0.4 mL each) were diluted with purified water, acid, triton X100, and butanol and Rhodium was used as internal standard. The Li measurements showed linearity (from limit of detection to 25 ng/mL or to 250 ng/mL) with a correlation coefficient > 0.99. and also the intra-assay and inter-assay inaccuracy, which was measured as the variation coefficient, was < 5 and 10% respectively.

The data obtained in the study were evaluated via the statistical package program (SPSS 11.5 for Windows Standard Version) and were expressed as mean  $\pm$  standard deviations. Normalization tests of the data obtained were made and in order for to determine the statistical differences among the groups one way variance analysis (ANOVA) and Duncan test were used as post-test.

## **RESULTS AND DISCUSSION**

The serum estrogen and FSH values, according to which the menopause diagnosis is made, are presented in Table 1.

**Table 1.** Serum mineral, lipid, and hormone values of the female subjects.

Parameters	Pre-Menopausal Group	Post-Menopausal Group
Li ( $\mu\text{g/dL}$ )	22,6 $\pm$ 0,40	7,58 $\pm$ 0,21***
Ca (g/dL)	9,84 $\pm$ 0,65	9,59 $\pm$ 1,04*
P (g/mL)	4,16 $\pm$ 0,74	4,46 $\pm$ 0,81*
Zn (g/dL)	100 $\pm$ 24,1	110 $\pm$ 28,4**
Cu	123 $\pm$ 18,8	122 $\pm$ 16,7*
Mg (g/dL)	1,82 $\pm$ 0,138	1,94 $\pm$ 0,18
HDL (mg/dL)	38,5 $\pm$ 7,78	43,7 $\pm$ 8,93***
LDL (mg/dL)	128 $\pm$ 46,1	146 $\pm$ 45,0**
Triglyceride (mg/dL)	156 $\pm$ 104	151 $\pm$ 96,5*
Alkalene phosphatase (U/L)	195 $\pm$ 66,7	231 $\pm$ 86,7**
Cholesterol (mg/dL)	197 $\pm$ 43,2	224 $\pm$ 51,1**
Vitamin D (25-OHD)	12,7 $\pm$ 3,81	5,67 $\pm$ 1,41***
Estradiol (pmol/L)	220,3 $\pm$ 59,7	88.2 $\pm$ 16,2***
FSH (IU/L)	19,7 $\pm$ 10.2	71.5 $\pm$ 15.8**
LH (IU/L)	8.65 $\pm$ 6.21	35.02 $\pm$ 7.13**

\* sign indicates the statistical differences among the groups when  $p < 0.05$ .

\*\* sign indicates the statistical differences among the groups when  $p < 0.01$ .

\*\*\* sign indicates the statistical differences among the groups when  $p < 0.001$ .

In the study, it was determined that the estrogen level of women in the menopausal period is lower than that of the women in the pre-menopausal period ( $p < 0.01$ ) while the FSH level was found to be higher ( $p < 0.01$ ). In the lipid profile, while the triglyceride level was found to be low in the post- menopausal period ( $p < 0.05$ ), the HDL ( $p < 0.001$ ), LDL ( $p < 0.001$ ) and the cholesterol levels ( $p < 0.001$ ) were found to be high. Alkalene phosphatase ( $p < 0.001$ ) and Vitamin D levels ( $p < 0.001$ ) were found to decrease in the post-menopausal period. When the mineral levels were investigated, it was observed that there was no significant change in serum magnesium and copper levels, but zinc ( $p < 0.01$ ) and phosphorus levels ( $p < 0.005$ ) increased, and calcium level ( $p < 0.05$ ) decreased. However, serum lithium level ( $p < 0.0001$ ) considerably decreased.

Considerable physiological changes happen in the bodily functions of women in the period when sex hormones (estrogen and progesterone) are diminished and disappear and as a result of this they become prone to various diseases. Menopause causes important changes to take place in the metabolism and in the lipid profile. Since the protective effects of estrogen diminish in the post-menopausal period the risk to osteoporosis and coronary diseases increase. Today modern menopause treatment works on therapeutic models which would eliminate the symptoms in this period with the least side effect. This study is important with regard to establishing basis for understanding the effect of lithium on treatment of symptoms of menopause (*i.e.*, osteoporosis and coronary diseases).

The target of this study is to determine lithium levels in women in the pre- and post-menopausal periods and to investigate the relation among lithium level, bone metabolism (Ca, P,

Parathormone, Vitamin D), sex and metabolic hormones (estrogen, FSH, LH, TSH) and some biochemical parameters to understand the efficacy of lithium as a therapeutic agent in treatment of osteoporosis.

Although the lipid profile plays an effective role in menopause, it was shown that triglyceride level causes bone density to decrease in the post-menopausal women. However, it is known that the lipid profile alone cannot be effective on bone density, but estrogen level and the period of menopause would play important roles [10]. Also in our study, the HDL ( $p<0.001$ ), LDL ( $p<0.01$ ), and cholesterol ( $p<0.01$ ) levels of women in menopausal period were found to increase as compared to the values of women in the pre-menopausal period. Considerable decrease was observed in the estrogen level ( $p<0.001$ ) while the FSH ( $p<0.01$ ) and LH levels ( $p<0.01$ ) increased. Since the follicles in the ovaries of women in the menopause period are drained decrease in estrogen and progesterone hormone levels and as a consequence of this increase in the levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) is a part of the natural process. If the blood FSH level is  $> 30$  mIU/mL and the menstrual period had not occurred for one year the subject can be diagnosed with menopause [10].

When the lipid profile was investigated in the post-menopause period the blood triglyceride level ( $p<0.05$ ) was found to be low but the HDL ( $p<0.001$ ), LDL ( $p<0.001$ ) and cholesterol levels ( $p<0.001$ ) were found to be high. It is known that cholesterol level of osteoporosis patients is high [11].

The latest studies have shown that in the menopausal period, total cholesterol and LDL cholesterol ( $p<0.001$ ) levels increase. It was shown that although triglyceride level is high in women in the post-menopausal period, HDL level decreases ( $p<0.001$ ). Thus, it is shown that menopause decreases total and LDL cholesterol levels via decreasing HDL cholesterol and it changes the triglyceride level is high the lipid profile [12]. High LDL values show that the protective effects of HDL decreases. It is shown that hyperlipidemia contributes to osteoporosis and the basis of this process is lipid oxidation. The oxidized lipids are inhibited *in vitro* osteoblastic differentiation [13]. Moreover, the *in vivo* studies showed that diets rich in fat and cholesterol decreases bone mineral density and increases alkaline phosphatase level ( $p<0.001$ ). The increase in the alkaline phosphatase level, which is frequently seen in the menopausal period, shows the increase in the activity in the bone cells and thus the increase in the risk of bone loss [14, 15]. The decrease in level of estrogen hormone, which plays an important role in Vitamin D to be active, during menopausal period can cause serious problems regarding bodily functions in which Vitamin D acts as a mediator [16]. In our study, it was observed that Vitamin D level ( $p<0.001$ ) decreases in the post-menopausal period. However, Vitamin-D and calcium levels and supplementation play critical

role in prevention of osteoporosis and in formation of healthy bone structure [16].

Some minerals (Zn, Cu), hormones (estrogen) and Vitamin D are important factors affecting ligaments and bone matrix [17]. It is known that, in the fight with osteoporosis, calcium and Vitamin-D are the first strategic factors [18]. In the study it was observed that Vitamin D level ( $p < 0.0001$ ) was considerably low in subjects in the menopausal period. Moreover, serum estrogen level ( $p < 0.001$ ) of women in post-menopausal period was found to be lower, but their FSH and LH levels were higher and serum calcium level ( $p < 0.05$ ) was also lower than those in pre-menopausal period. Regarding bone health these values indicate the risk of osteoporosis. Bone minerals are consisted of calcium phosphate. Therefore, regarding bone health, phosphorus is as important as calcium [20]. The typical adult diet contains phosphorus in abundance. It was observed that phosphorus level ( $p < 0.5$ ) in women in the menopausal period, who participated in our study, did not change much. This shows that the women who participated in this study do not take such supplementations. In the study made against the common view, the main cause of osteoporosis is not the deficiency in estrogen and calcium but the deficiency in the micronutrients [20]. Low serum ALP level which indicated weak bone formation is a sign of low serum zinc level [21]. In our study we found that in women in menopausal period serum ALP level ( $p < 0.01$ ) and thus zinc level ( $p < 0.01$ ) were found to be high. High zinc level causes copper level ( $p < 0.5$ ) to be low. Studies made indicate that low copper level can cause osteoporosis, anemia, and neurodegenerative disorders [21]. It was observed that serum copper level ( $p < 0.05$ ) was lower in women in menopausal period than those in pre-menopausal period. This indicates risk of osteoporosis in the patients in the menopause period who participated in our study.

There is a positive correlation between magnesium level and bone mineral density. It is mentioned that serum magnesium level in women, who had osteoporosis, was lower than those who had osteopenia and who did not have osteoporosis or osteopenia [22]. No important difference was observed in serum magnesium levels of women who were in menopausal period and who were not in menopausal period.

In most of the studies made, lithium was found to be related with sex hormones and affected these hormones. It was found that lithium therapy cause induced proliferative and morphogenetic changes induced by estradiol in the uterus. In another study, it was mentioned that lithium antagonizes the effects of estrogen [23]. Therefore, it is expected that women in menopausal period have low lithium levels. In this study, we obtained the data supporting this view and when serum mineral levels of women in menopausal period were compared with those who were not in menopausal period, it was observed that serum lithium level ( $p < 0.0001$ ) of women in pre-menopausal period was much lower than all other mineral levels. Therefore, findings of our study

indicate that finding serum lithium levels to be much lower in subjects in the menopausal period compared to those who are not in menopausal period is an indicator for the possibility of using lithium to antagonize the effects of estrogen encountered in osteoporosis and thus lithium can be used as an effective therapeutic agent.

As a result, in this study, together with hormonal changes in menopause, changes are observed in the mineral levels and lithium level was found to be considerably lower in women in menopausal period. Along with this, Vitamin D level was also found to be lower and all these were risk factors for osteoporosis. However, this also indicated that lipid profile alone would not play a role. Lithium deficiency was found to be related with menopause, and in relation with this, with osteoporosis. These results indicate that lithium therapy can be considered as an effective alternative method for treatment of menopause and of osteoporosis related with menopause which is a very risky period for women as they become prone to various diseases in this period.

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**Türkçe Öz ve Anahtar Kelimeler**

**Menopoz Öncesi ve Sonrası Kadınlarda Serum Lityum Seviyeleri, Kemik Metabolizması ve Bazı Biyokimyasal Parametreler Arasındaki İlişkiler**

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**Öz:** Bu çalışmanın hedefi, premenopozal ve postmenopozal kadınlarda serum Li seviyesinin kemik metabolizması (Ca, P, Parathormon ve D vitamini), cinsiyet ve metabolik hormonlar (estrojen, FSH, LH ve TSH) ve bazı biyokimyasal parametrelerin arasındaki ilişkiyi belirlemektir. Çalışma 10 kadın üzerinde yürütülmüştür, bunlardan 5'i menopoz öncesi periyotta bulunmaktadır. Serum Li seviyeleri, kemik metabolizması göstergeleri (örneğin ALP, Ca, P, Mg, Cu, Zn) ve serum trigliserit, alkalen fosfataz, total kolesterol, HDL, LDL ve kolesterol seviyeleri gibi bazı biyokimyasal parametreler belirlenmiştir. Menopoz periyodunda bulunan kadınların estrojen kan seviyeleri pre-menopozal periyottaki kadınlara göre daha düşük çıkmıştır ( $p < 0,01$ ) ve FSH seviyeleri ise daha yüksek bulunmuştur ( $p < 0,01$ ). Lipid profilinde, menopoz sonrası dönemdeki trigliserit seviyeleri düşük çıkmıştır ( $p < 0,05$ ) ve HDL ( $p < 0,001$ ), LDL ( $p < 0,001$ ) ve kolesterol seviyeleri ise yüksektir ( $p < 0,001$ ). Alkalen fosfataz ( $p < 0,001$ ) ve D vitamini seviyeleri ( $p < 0,001$ ) azalmaktadır. Mineral seviyeleri incelendiğinde, serumdaki magnezyum ve bakır seviyelerinde anlamlı bir değişme gözlenmezken çinko ( $p < 0,01$ ) ve fosfor ( $p < 0,005$ ) seviyelerinin yükseldiği, kalsiyum seviyelerinin ( $p < 0,05$ ) azaldığı ve Li seviyelerinin de ciddi biçimde azaldığı ( $p < 0,0001$ ) görülmüştür. Elde edilen sonuçlara göre, ilk kez Li azlığının menopoz ve bununla ilgili hastalıklarla ilişkili olabileceği ve bu sebeple Li terapisinin alternatif bir yöntem olmak üzere menopoz için yeni tedavi protokollerinin geliştirilmesinde kullanılabileceği bulunmuştur.

**Anahtar kelimeler:** Kemik metabolizması; menopoz; osteoporoz; serum Li düzeyi.

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