The Investigation of the Factors Influencing Bone Mineral Density of Postmenopausal Women

Postmenopozal Dönem Kadınların Kemik Mineral Yoğunluklarını Etkileyen Risk Faktörlerinin Belirlenmesi

(Araştırma)

Hemşirelik Yüksekokulu Dergisi (2007) 12–25

Sena KAPLAN*, Füsun TERZİOĞLU**
*Sağlık Bakanlığı, Sağlık Eğitim Genel Müdürlüğü
**Hacettepe Üniversitesi, Sağlık Bilimleri Fakültesi, Hemşirelik Bölümü

ABSTRACT

Background: Throughout the world, over 200 million people experience bones mineral density loss and approximately 40% of the affected people are women at the postmenopausal period. Because of the bone mineral losses women are at risk of bone fractures and they are subjected to medical treatment for long periods, which negatively affects their quality of life.

Objective: This study was conducted for the purpose of determining some risk factors influencing the bone mineral density of women during the postmenopausal period.

Method: The sample of the descriptive study is composed of 234 women who attended to the Menopause clinic of Ministry of Health Hospital in Ankara and whose femur neck and lumbar2-4 vertebra bone mineral density measurements were made. Data were collected by face to face interview using a data collection form.

Results: In the study, statistically significant differences have been identified between the duration of menopause, prolongation of the lactation period, receive of hormone replacement therapy, current health problems and having a first degree relative diagnosed with osteoporosis and bone mineral density in femur neck and lumbar vertebrae2-4 ($p<0.05$).

Conclusion: This research contributes to the literature relevant to the risk factors of osteoporosis by indicating the adverse affect of prolonged lactation period, early cessation of hormone replacement treatment and having relatives with osteoporosis after menopause on bone mineral density of women during the postmenopausal period.

Key Words: *Bone mineral density, postmenopausal osteoporosis, risk factors, and nursing*

ÖZET

Giriş: Dünyada, 200 milyonun üzerinde insan kemik mineral yoğunluğu kaybı yaşamakta ve etkilenen kişilerin yaklaşık olarak %40'ını postmenopozal dönemdeki kadınlar oluşturmaktadır. Kemik Mineral yoğunluğu kayıplarına bağlı ortaya çıkan kırıklar sonucu, kadınlar uzun süre tıbbi tedavi almakta ve yaşam kaliteleri olumsuz etkilenmektedir.

Amaç: Bu çalışma postmenopozal dönem kadınların kemik mineral yoğunluklarını etkileyen bazı risk faktörlerinin belirlenmesi amacıyla yapılmıştır.

Yöntem: Araştırmanın örneklemini, Sağlık Bakanlığı Ankara Araştırma ve Eğitim Hastanesinin menopoz polikliniğine başvuran femur boynu ve lomber 2-4 vertebra kemik mineral yoğunluğu ölçümleri yapılan 234 kadın oluşturmuştur. Veri toplama formu yüz yüze görüşme yöntemi kullanılarak araştırmacı tarafından toplanmıştır.

Bulgular: Araştırmada, menopoz süresi, uzamış laktasyon, hormon replasman tedavisi alma durumu, genel sağlık sorunu yaşama ve birinci derece akrabalarında osteoporoz bulunma durumu ile femur boyun ve lomber 2-4 vertebra kemik mineral yoğunluğu arasındaki fark istatistiksel olarak önemli bulunmuştur ($p<0,05$).

Sonuç: Bu araştırmada, postmenopozal dönemdeki kadınlarda uzamış laktasyon dönemi ve hormon replasman tedavisinin erken bırakılması gibi faktörler osteoporoz risk faktörü olarak belirlenerek, litaratüre katkıda bulunmaktadır.

Anahtar Kelimeler: *Kemik mineral yoğunluğu, postmenopozal osteoporoz, risk faktörleri ve hemşirelik*

Introduction

Osteoporosis has recently been recognized as a major public health problem by some goverments and health care providers. It is also one of the most important health problem in the postmenopausal stage (1,2). Osteoporosis is the most common clinical skeletal disorder characterized by low bone mass, microarchitectural disruption, and increased skeletal fragility (3,4).

There are many risk factors for osteoporosis. In the literature, they are reported as racial and genetic traits, sex, low body mass index, nutritional pattern, physical activity status, late menarche, high number of births, prolonged lactation, early menopause, alcohol, tea, smoking and coffee habits, low lifetime calcium intake, vitamin D deficiency, lifestyle lacking weight bearing exercise, use of some drugs and chronic diseases (1,2,5,6,7).

The World Health Organisation (WHO) stresses that throughout the world, over 200 million people experience bone mineral density loss and approximately 40% of the affected people are women at the age of 50 or over. For women over 50, the mortality rate due to femur neck fractures occurring with losses in bone mineral density is four times higher than the mortality rate occurrate due to endometrial cancer and is equal

to that of breast cancer (8). In the United States, one out of four women overs 50 experience bone mineral loss and accordingly bone fractures occur in over 1.5 million women (9,10,11,12). Olso, an estimated $18 billion was spent on fractures and $47 million spent on other factors related to osteoporotic events in 2002 (13).

Fractures occurring related to bone mineral losses, women are subjected to medical treatment for long stages and their independence is restricted with an adverse effect on their quality of life (10,11,12). Furthermore, they run a higher risk of depression, which has a negative effect on the productivity of the women. These fractures put a heavy financial burden on the national economy, as they require long term and expensive treatment (14).

WHO expects nurses to assume important responsibilities and duties in preventive, health services in the framework of a multidisciplinary approach. These duties and responsibilities make it obligatory for nurses to make use of their roles as trainer and consultant. Therefore, nurses are required to determine the groups of postmenopausal women who are at high risk for bone mineral density loss, to offer training and counselling services for early diagnosis and prevention of osteoporosis and to play a part in health training activities throughout the country (7).

Nurses are responsible for promoting community health, preventing disease, disability and premature death and protecting to health of vulnerable populations. First step in the prevention of osteoporosis in women should be to make them aware of the risk factors (15). Therefore nurse need to be aware of the risk factors of osteoporosis and provide early counseling and prevention strategies (16).

The aim of this study was to determine the risk factors influencing bone mineral density of postmenopausal women. There fore it may play a role as a guide in planning and implementation of health services for postmenopausal women.

The study questions addressed in this study were;

1. What is the relationship between level of osteoporosis and the length of time since menapause?
2. What is the relationship between level of osteoporosis and the receiving hormon therapy?
3. What is the relationship between level of osteoporosis and the presence of health problem?
4. What is the relationship between level of osteoporosis and the having first degree relatives diagnosed with osteoporosis?
5. Does level of osteoporosis by lenght of the lactation period, age of menarche
6. Does level of osteoporosis by the education level, body mass index, skin and hair colour
7. Does level of osteoporosis by having a relative with hip fracture

Materials and Methods

For the aim of this study, menaupause department of Ministry of Health Hospital in Ankara/ Turkey was selected as the study site, the sample size consisted of 234 women who attended to the Menopause department and whose femur neck and lumbar$_{2-4}$ vertebra bone mineral density measurements were made between January 18 and May 11, 2002. The sample was restricted to women; attending menopause department in the last year, measured with DXA technique for bone mineral density of FN (femur neck) and LV$_{2-4}$ (lumbar vertebrae), who did not menstruate for over 12 months due to physiological or surgical reasons and who agreed to participate to this study.

The authors of this study collected data through using a semi-structured interview method. Semi structured interviews involved the preparation of a data collection form that served as an interview quide. The interview quide consisted of three parts.

1. Demographic Characteristics; age, marital status, education status and addresses,
2. Osteoporosis Risk Factors; BMI, hair and skin colour, daily tea and coffee comsuption (4>cups), smoking and alcohol consumption, chronic diseases, some medications with known effects on bone metabolism such as corticosteroids, medroxyprogesterone, thyroid hormones, anticonvulsants, aluminum containing antacids, methotrexate sodium, cholestyramine, obstetrical history such as age at menarche and menopause, number of live birth, breastfeeding time in years, historuy of birth control pill use longer than 5 years, menopausal status, use of HRT,
3. DXA results; bone mineral density measurement of femur neck and lumbar vertebrae.

Interviewing and filling in the data collection form took approximately 20 and 30 minutes per women.

Evaluation of bone mineral density

Results of bone mineral density measurements of femur neck and Lumbar$_{2-4}$ vertebrae are listed and classified into normal, osteopenia and osteoporosis categories. Bone mineral density measurements of women were done by using DXA technique by a specialized expert. Bone mineral density results were compared with the't' score showing the reference values of healthy population between 20-35 and belonging to the same race and sex. Obtained results were evaluated according to diagnostic classification criteria developed by WHO (1998) for osteoporosis. According to the scores of bone mineral density,

- Less than -1 standard deviation is considered as normal
- SD (standard deviation) between -1 to -2 as osteopenia and
- SD over 2.5 as osteoporosis (8).

Table 1. Personal and Obstetric Characteristics of Women

Variable	Frequency (n:234)t	%
Age		
44 year and below	16	6.8
45-50 year	44	18.8
Over 51 years	174	74.4
Educational Level		
İlliterate	53	22.6
Elementary School	142	60.7
High School	33	14.1
University	6	2.6
Body Mass Index (kg/m²)		
Low (<19,9)	2	0.9
Normal (20- 24,9)	42	17.9
High (25- 29,9)	76	32.5
Obesity (>30)	114	48.7
Natural Skin Color		
Light	73	31.2
Brown	113	48.3
Dark	38	20.5
Natural Hair Color		
Blonde	33	14.1
Brown	134	57.2
Black	64	27.4
Red head	3	1.3
Age of menarche		
10 age and below	37	15.8
11-13 ag	140	59.8
Over 13 age	57	24.4
Use of oral contraceptive		
Yes	49	20.9
No	185	79.1
Duration of use oral contraceptive n: 49*		
Less than five years	**39**	**79.5**
Over five years	10	20.5
Number of child n:219**		
None	**5**	**2.3**
1-3	62	28.3
4 and up	152	69.4
Duration of breastfeeding n:214***		
None	**13**	**6.1**
Less than 12 months	97	45.3
Over 12 months		104

* This question is answered by women who were using oral contraceptive. ** This question is answered by women who have childbirth ***This question is answered by women who have had breastfeeding of last child

Data Analysis

In the analysis of the data, SPSS (Statistical Package for Social Science) 10.0 programme was used. In the evaluation of the data, percentages, chi square and Pearson chi square statistical methods were used. Statistical significance was defined as $p<0.05$.

Ethical Considerations

For this study official and ethical approval from the relevant institutions were obtained. The individuals coming to menopause unit were informed about the aim and method of the study; they were told that their participation was voluntary, and that they have the right to withdraw at any point.

Results

Demographic Characteristics:

The study population consisted of Of the 234 respondents to this study, three fourths (74.4%) were over 50 years of age (mean age, 54±5,7). One sixth (16.7%) had a high school education or more. Half (48.7%) were obese. Half (48.3%) had Brown skin and three fifths (57.2%) had Brown hair. Three fifths (59.8%) were between the ages of 11 and 13 when they reached menarche, one fifth (20.9%) use oral contraception and only one fifth of these (10 out of 49) have used oral contraception for more than five years. More than two thirds (69.4%) have 4 or more children, and half (48.6%) breastfed their infants for more than 12 months. Just over half of respondents (55.6%) were married.

Social Characteristics:

Three fourths (75.2%) of respondents entered menopause due to physiological process. Three fifths (59.0%) had been in menopausal for more than 5 years. Half (49.6%) underwent combined HRT. Of these, nine out of ten (91.3%) started treatment within 5 years of menopause. Half (48.3%) drink coffee. A fourth (23.5%) smoke. Of those who smoke, nine tenths (87.2%) had been smoking for more than 5 years. Alcoholism was rare in this sample (0.4%).

Health Characteristics:

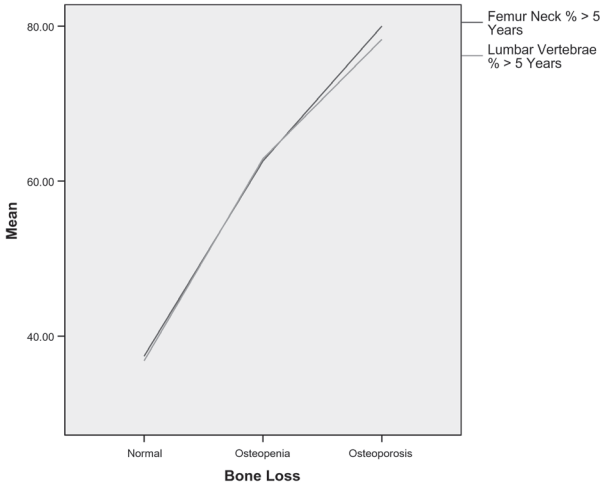
Three fifths (57.3%) of respondents reported one or more health problems. Among women with health problems, two fifths (41.4%) reported rheumatism, a fourth (27.0%) reported thyroid disease, and a fifth (21.7%) reaported diabetes mellitus. Three tenths of respondents (29.9%) use medications regularly. Among women who use medications regularly, almost half (45.7%) use cortisone, two fifths (40.0%) use antacid, a fifth (21.4%) use thyroxin hormone, and a seventh (14.3%) use anticoagulants. Concerning first degree relatives, a fourth (27.4%) had osteoporosis, an eighth (12.0%) had hip fracture, and two fifths (38.9%) had kyphosis and decreases muscle mass.

Osteoporosis

Differences between FN and LV osteoporosis, osteopenia, and normal DXA outcomes were not statistically significant (X^2 = 1.1664; df = 2; n.s.). However, more than a fourth (27.6%) of the DXA outcomes were osteoporotic.

Figure 1 presents the percent more than 5 years lenght of the menopause by level of osteoporosis. An examination of Figure 1 shows that as the severity of the osteoporosis increases, the likelihood that respondents have been menopausal for more than 5 years also increases dramatically. There was little difference in this pattern between the Femur Neck and the Lumbar Vertebrae locations for the DXA.

Figure 1. Percent The Length of Time Since Menopause by Level of Osteoporosis

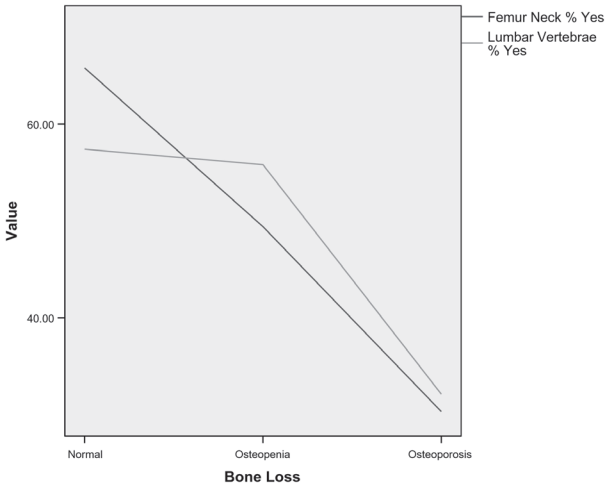


	Femur Neck	Lumbar Vertebrae
Normal	37.40	36.80
Osteopenia	62.60	62.90
Osteoporosis	80.00	78.30
χ^2	26.026	26.568
df	2	2
p	.000	.000

Figure 2 presents the percent receiving hormon therapy by level of osteoporosis. An examination of Figure 2 shows that as the severity of osteopoross increases, the probability that respondents have not receiving hormon therapy also increases clearly. There was little difference in this pattern between the Femur Neck and the Lumbar Vertebrae locations for the DXA.

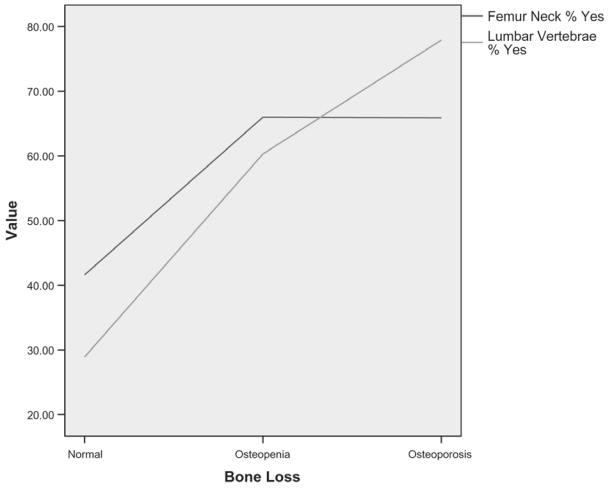
Figure 3 presents the percent presence of health problems by level of osteoporosis. An examination of Figure 3 shows that as the severity of the osteoporosis increases, the likelihood that respondents have been presence of health problem also increases dramatically. There was little difference in this pattern between the Femur Neck and the Lumbar Vertebrae locations for the DXA.

Figure 2. Percent Receiving Hormone Therapy by Level of Osteoporosis



	Femur Neck	Lumbar Vertebrae
Normal	65.80	57.40
Osteopenia	49.40	55.80
Osteoporosis	30.30	32.10
χ^2	12.992	11.106
df	2	2
p	<0.05	<0.05

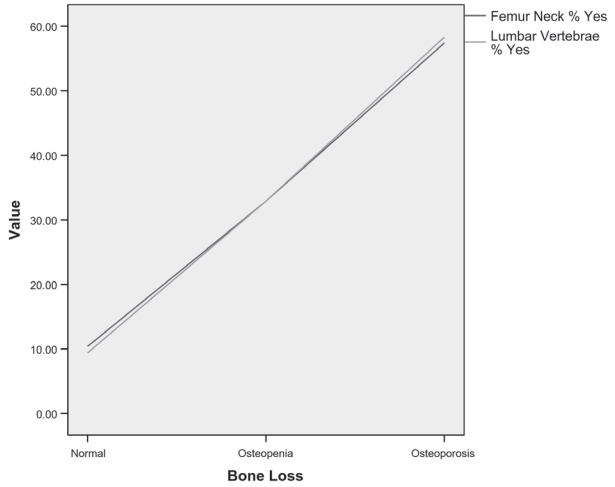
Figure 3. Percent Presence of Health Problems by Level of Osteoporosis



	Femur Neck	Lumbar Vertebrae
Normal	41.60	28.90
Osteopenia	66.00	60.30
Osteoporosis	65.90	77.90
χ^2	11.126	12.872
df	2	2
p	<0.05	<0.05

Figure 4 presents the percent having first degree relatives diagnosis by level of osteoporosis. An examination of Figure 4 shows that as the severity of the osteoporosis increases, the likelihood that respondents have had first degree relatives diagnosis increases dramatically. There was little difference in this pattern between the Femur Neck and the Lumbar Vertebrae locations for the DXA.

Figure 4. Percent having First Degree Relatives Diagnosed with Osteoporosis by Level of Osteoporosis



	Femur Neck	Lumbar Vertebrae
Normal	10.40	09.40
Osteopenia	32.90	32.90
Osteoporosis	57.40	58.30
χ^2	10.109	9.579
df	2	2
p	<0.05	<0.05

There was no significant relationship between education status, place of residence, natural skin and hair colour, body mass index, the habit of smoking, coffee and tea drinking and alcohol use, age at menarche, number of live birth, use of birth control pill, having a relative with hip fracture after menopause and FN and LV2-4 bone mineral densities (P>0.05).

Lenght of lactation was found to be statistically significantly related to LV_{2-4} bone mineral density (p<0.05) while it had no significant effect on FN bone mineral density (p>0.05).

Discussion

In this study, the majority of women whose bone mineral density is in normal ranges were menopausal for five or less years. Women who develop osteoporosis are mostly those who were in menopause for five years or longer (p<0.01). No significant relationship was found between the age at which menopause occurs and FN and LV_{2-4} bone mineral density (p>0.05). In the literature, it has been reported that there is a regular

decrease in bone mineral density every year related to the inadequacy of estrogens hormone (17). In various studies, it has been established that there is a regular loss of bone mineral density in LV bone each year after menopause (6,18,19).

In the postmenopausal stage, reduction in estrogen hormone levels related to loss of ovarian function has an adverse effect on bone mineral density. For years, experts have recommended HT as a first-line therapy to prevent bone loss in postmenopausal women (11,20,21). Current data indicate that mortality from these events, as well as overall mortality, is not increased in HT users (9,11). However recent results of the Women's Health Initiative (WHI), and the Million Women Study (MWS) indicated that the use of HT increase the risk of stroke, thromboembolic events, breast cancer and cholecystitis (9,11).

The American Medical Association Scientific Council reported that efficient use of HT prevents osteoporosis (22). In the present study, the majority of women who did not receive HT have osteoporotic bone mineral density in FN and LV_{2-4}; this rate is decreasing in women who are on HT. Moreover, the proportion of women whose bone mineral density is in normal ranges is higher among those who receive HT ($p<0.05$). It has been established in many studies that initiation of HT in premenopausal stage prevents bone mineral density losses substantially (23). In the study of Biberoglu et al., bone mineral density showed significant increase at the 12^{th} month of HT treatment in those who receive treatment (24) and this increase was seen at month 24 in the study of Doren and colleagues (25). However, short term use of HT (first year) may increase the risk of thromboembolic events and long term use (for some outcomes, such as cholescystitis and breast cancer, risk increases with duration of HT use. Data support an increased risk of in the first year of use, because may HT users have a longer course, WHI calculated first-year and overall event rates (11).

However, the cessation's of HT causes bone mineral losses to develop rapidly. 49.6% have our samples received HT and 91.3% of these women started treatment within five years of menopause and 85% of them terminated their treatment within 3 years. Ettinger et al. stated that in a random sample of women using postmenopausal HT, most tried to cease therapy in the 6-8 months (26). Another study reported that among women who start to receive HT, half discontinue therapy within 1 year (26). However, the optimal time to start treatment and its duration are still not well defined today, in spite of the benefit risk profile of the WHI study (25).

In the literature, it has been reported that health problems such as hyper/hypothyroidism (dependent on thyroxin treatment), insulin dependent diabetes mellitus, cardiovascular and nervous system disorders have an adverse effect on bone mineral density (2,6,27,28). In the present study, the majority of women with health problems had osteoporotic bone mineral density distribution in FN and LV_{2-4} while this rate fell in women without health problems. In addition, the majority of women whose bone mineral density was in normal ranges were those without health problems. In various studies, it has been established that hypothyroidism related to thyroxin treatment, diabetes mellitus related to insulin treatment, rheumatism, health problems in the cardiovascular and nervous systems are all risk factors for the development of osteoporosis (19). These findings are in keeping with those of our study.

At present, genetic investigations demonstrate the presence of some genes determining the level of bone mineral density. Therefore, women whose first-degree relatives developed osteoporosis are at serious risk for bone mineral density loss (29). In our study, more than half of the women with osteoporotic family history has osteoporosis this rate being lower in women with no family history of osteoporosis. In addition, FN and LV_{2-4} bone mineral density is within normal ranges in women with no family history of osteoporosis ($p<0.05$). Various studies have determined that the majority of postmenopausal women with osteoporosis in the aforementioned bones have first-degree relatives with osteoporosis (23,30,31). However, in the studies of Kavuncu and Ofluoğlu, bone mineral density of women with osteoporotic family history after menopause was not different than that of the control group (2,29).

In the literature, it has been reported that as the estrogens hormone can be synthesised in body fat tissues in the postmenopausal stage, low body mass index is a risk factor for osteoporosis (1,2,5,6). In the present study, this could not be evaluated as the rate of women with low body mass index is 0.9%. Yet, while in more than half of the women whose BMI is at the border of obesity, bone mineral density is osteoporotic, this rate falls in women with normal BMI. In addition, it is striking that the majority of the sample is constituted by women whose BMI is at the margin of obesity and that an important proportion of these women have FN and LV_{2-4} bone mineral density at normal or osteopenic levels ($p>0.05$). In various studies, it has been demonstrated that there is no significant difference between the BMI of postmenopausal women who have osteoporosis and the control group (2,5,6,11,29,32). These results are consistent with our findings.

In the literature, it has been reported that late menarche causes deficiency of estrogens hormone in growth stage, having an adverse effect on the development of the skeletal system (21,33). In the present study, no statistically significant difference in FN and LV_{2-4} bone mineral density was found between women whose menarche was early or late and whose menarche was at normal age ($p>0.05$). In the study of Guithrie et al., no difference was found between postmenopausal women with early (earlier than 11) and late menarche (after 14) in terms of FN and LV_{2-4} bone mineral density (30).

The need for calcium is increased during lactation because of metabolic changes that occur during that time. Especially with prolonged lactation, when calcium need is not met, permanent losses in bone mineral density are seen and cause osteoporosis after menopause (21,33). In addition, increase in serum prolactin and oxytocin values in this stage inhibits the release of estrogens and progestogen hormones, which leads to the decrease in bone mineral density (21). In the present study, it was found that bone mineral density indicated osteoporosis in women whose lactation stage was 12 months or less while in women who breastfed over 12 months the rate of osteoporosis decreased in FN ($p>0.05$) and increased in LV_{2-4} ($p<0.05$). Seeman and Cooper, it has been reported that lactation lasting longer than 12 months has an adverse effect on bone mineral density of FN and LV and causes permanent losses in bone mineral density (21).

Conclusions and Recommendations

In conclusion, as it has been established that

- Lenght of lactation stage has an adverse effect on bone mineral density
- Menopause stage of over five years, the presence of general health problems, having relatives in whom osteoporosis develops after menopause are risk factors for osteoporosis
- Hormone treatment after menopause prevents decrease in bone mineral density to a large extent, yet early cessation of treatment has an adverse effect on bone mineral density

The following recommendations have been made

In the framework of preventive health services, nurses should offer training and counselling services to the women with risk factors on early diagnosis of osteoporosis and ways of prevention and the risks and benefits of Hormone therapy for women in the premenopausal stage.

It is also our recommendation that risk factors that were not found to be associated with bone mineral density such as education status, place of residence, natural colour of skin and hair, body mass index, the age of menarche, the use of oral contraceptive pills, the number of live births, the age and cause of menopause, the status of cigarette smoking, alcohol use and coffee consumption, having a relative with hip fracture after menopause should be investigated with a larger study, even in the framework of a nation wide project.

Limitations

Nutritional habits and exercise status are risk factors influencing bone mineral density. These risk factors were not considered in this study, as they required detailed evaluated after experts were consulted and the literature on the subject was examined.

Acknowledgements:

We would like to thank to Visiting Professor Rich Zeller in the Kent State University for his excellent comments and helpful suggestion of our manuscript. We are also grateful to the subjects of this study for agreeing to participate in this study. We did not receive any financial support for this study.

References

1. Gökçe Y, Atalay A, Arslan Ş, Başaran A, Cantürk F, Cindaş A, Eryavuz M, İrdesel J, Karadavut K, Kirazlı Y, Sindel D, Şenel K, Güler F & Yıldırım K. Awareness of osteoporotic patients, Osteoporos Int, 2005; 16: 128-133.
2. Ofluoğlu D, Gunduz O, Bekiroğlu N, Panza E, Akyuz G. A methot for determining the grade of osteoporosis based on risk factors in postmenopausal women, Clin Rheumatol 2004; 24: 606-611.
3. Brown JP & Josse RG (2002) Brown JP, Josse RG. (2002). 2002 Clinical practise guidelines for the diagnosis and management of osteoporosis in Canada. CMAJ 167,1-34.
4. Dormire S & Becker H. Menopause health decision support for women with physical disabilities. JOGNN 2007; 36(1); 97- 104.
5. Gur A, Nas K, Kayhan Ö, Birol M, Akyuz, Sindal R, Öncel S et al. The relation between tooth loss and bone mass in postmenopausal osteoporotic women in Turkey: a multicenter study, J Bone Miner Metab 2003; 21: 43-47.
6. Dursun N, Akın S, Dursun E, Sade I, Korkusuz F. Influence of duration of total breast-feeding on bone mineral density in a Turkish population: does the priority of risk factors differs from society to society, Osteoporos Int. 2006; 17: 651-655.
7. Olson A. Osteoporosis, The Nurse Practitioner, 2007; 32(6) pp. 20-27.
8. World Health Organisation (1998). Report of WHO Study Group. Guidelines for preclinical evaluation and clinical trials in osteoporosis. pp. 5-7.
9. Nelson HD. Assessing benefits and harms of hormone therapy: Clinical applications. JAMA 2002; 288: 882-84.
10. Hays J, Ockene JK, Brunner RL, Kotchen JM, Manson JE, Patterson RE, Aragaki AK, Shumaker SA, Brzyski RG, La Croix AZ, Granek IA & Valanis BG. Effects of estrogen plus progestion on health related quality of life. N. Engl. J Med 2003; 348: 1839-54
11. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, La Croix AZ, LeBoff M, Lewis CE, Mc Gowan J, Neuner J, Pettinger M, Stefan ML, Wactawski-Wende J & Watts NB. Women's health initiative investigators. effects of estrogen plus progestin on risk of fracture and bone mineral density : the womens health initiative randomized trial. JAMA 2003; 3290: 1729-38.
12. Aschenbrenner DS. HT Reconsidered. AJN 2004; 104: 51-3.
13. Rohr Cl, Sarkar A, Barbar KR, Clements JN. Prevelance of prevention and treatment modilities used in populations are risk of osteoporosis, JOAO, 2004; 104(7) pp. 281-287.
14. Johnell O. The socio-economic burden of fractures today and in the 21 st century. The American Journal of Medicine 1997; 103: 20-26.
15. Ungan M. & Tümer M. Turkish women's knowledge of osteoporosis. Family Practice, 2001; 18: 199-203.
16. Chen J, Shu Y, Wang T.F, Cheng S & Huang L. Konwledge about osteoporosis and its related factors among public health nurses in Taiwan. Osteoporosis Int 2005; 16: 2142- 2148.
17. Chapurlat RD, Gamero P, Sornay Rendu E, Arlot ME et al. Longitudinal study of bone loss in pre-and perimenopausal women; evidence for bone loss in perimenopausal women, Osteoporosis Int. 2000; 11(6): 493-498.
18. Demster DW & Lindsay R. Pathogenesis of osteoporosis. Lancet 1993; 341: 797-801.
19. Thompson J., Modin G, Arnaud CD & Lane NE. Not all-postmenopausal women an chronic steroid and estrogen treatment are osteoporotic: predictors of bone mineral density. Calcified Tissue International 1997; 61: 377-381.

20. Maxim P, Ettinger B & Spitainy G. Fracture protection provided by long term estrogen treatment. Osteoporosis International 1995; 5: 23-9.

21. Seeman E & Cooper ME (1998). Effect of early menopause on bone mass in normal women and patients with osteoporosis. The American Journal of Medicine 1998; 85: 213-216.

22. Ballard PA, Purdie DW, Langton CM, Steel SA & Mussurakis S. Prevalence of osteoporosis and related risk factors in UK women in the seventh decade: osteoporosis case finding by clinical referral criteria or predictive model? Osteoporosis International 1998; 8: 535-9.

23. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, Cauley J, Black D & Vogt TM. Risk factors for hip fracture in white women. The New England Journal of Medicine 1995; 332: 767-773.

24. Biberoglu KO, Yıldız A & Kandemir O. Bone mineral density in Turkish postmenopausal women. International Federation of Gynaecology and Obstetrics 1993; 41: 153-157.

25. Doren M, Nilsson JA & Johnell O. Effects of specific post-menopausal hormone therapies on bone mineral density in post menopausal women:a meta analysis. Human Reproduction 2003; 18: 1737-46.

26. Ettinger B, Grady D, Tosteson ANA, Pressman A & Macer JL. Effects of the Women's Health Initiative on women's decisions to discontinue postmenopausal hormone therapy. Obstetrics & Gynecology 2003; 102: 1225-32.

27. Farag NH, Helesen RA, Parry BL, Loredo JS, Dimsdale JE & Mills PJ. Autonomic and cardiovascular function in postmenopausal women: the effects of estrogin versus combination therapy. American Journal of Obstetrics Gynecology 2002; 186: 954-62

28. Grimes DA & Lobo R (2002). Perspectives on the women's health initiative trial of hormone replacement therapy. Obstetrics & Gynecology 2002; 100: 1344-53.

29. Kavuncu H (2000). Osteoporozda Genetik Yatkınlık ve Cinsiyet Faktörlerinin İncelenmesi, (Determination of Heredity and Gender Factors in Osteoporosis), Master of Science Thesis, Fırat University, Elazıg, Turkey.

30. Guthrie J, Ebelling P & Dennerstein L. Risk factors for osteoporosis. Medscape Women's Health 2000; 5: 25-29.

31. Frost M, Blake M & Fogelman I. Quantitative ultrasoundand bone mineral density are equally strongly associated with risk factors for osteoporosis. The Journal of Bone and Mineral Research 2001; 16: 406-416.

32. Checa MA, Rio DL, Rosales J, Nogues X, Vila J & Carreras R. Timing of follow up densitometry in hormone therapy users for optimal osteoporosis prevention. Osteoporosis International, Available at: http://www.springerlink.com/media/2GURM83QUR1YXGBJTE27/Contributions/8/8...Accessed: 18 January 2005

33. Pernoll ML (1991). Current Obstetric & Gynaecologic Diagnosis & Treatment. 70th edition, Prentice Hall International Limited, London.