The Relation of Follicle Stimulating Hormone and Estrogen to Mandibular Alveolar Bone Resorption in Postmenopausal Women

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Abstract

Osteoporosis is one of the degenerative disorders characterized by the bone mass reduction due to an imbalance between bone resorption and formation. Osteoporosis is common in postmenopausal women. Increased FSH (Follicle Stimulating Hormone) hormones and decreased estrogen levels occur post menopause, leading to the increased bone resorption rate. The aim of this study is to analyze the relation of FSH and Estrogen hormone to the mandibular alveolar bone resorption in postmenopausal women. Seventy postmenopausal women aged 48 -87 years in Kenari sub-district, Central Jakarta between February – May 2017 participated in this study. After obtaining the research approval from the ethics commission and informed consent from the subjects, the participants then filled out a validated questionnaire, and a clinical examination was performed. The periapical radiography was taken by referral to the Department of Radiology Universitas Indonesia to assess the radiographic bone resorption rate. Blood samples were taken to assess the FSH and Estradiol levels by ELISA examination technique. The result of this study showed that bone density correlated with age (p=0.01) and estrogen (p=0.02) but there was no correlation with bone resorption and FSH (p>0.05).

The conclusion of this study, there was a significant association between age and estrogen to the bone density of postmenopausal women. However, no association was found between FSH and bone resorption to the bone density of postmenopausal women.

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Introduction

Along with the improvement of the welfare condition, it is predicted that by 2025, the number of elderly in Indonesia will increase, amounting to 36 million people.[1] Based on the 2010 population census, the number of elderly amounted to 18.1 million people or 7.6 percent of the population. In 2014, this number reached more than 18.78 million people.[2] Currently, the number of elderly (senior citizens) in Indonesia is ranked the third largest in the world. The huge number from this category would increase the risk probability in the case of osteoporosis. According to WHO (World Health Organization) data, a greater number of bone fractures occurred in women with osteoporosis due to the group itself represents nearly 50% of the total population at risk.[3]

Postmenopausal phase is a period that occurs after the last menstrual cycle within one year after menopause.[4] This postmenopausal phase is accompanied by a decrease in ovarian estrogen secretion caused by depletion of oocytes and their follicles due to atresia.[5] Postmenopausal conditions are considered as a cause of increased bone resorption in elderly women[6]. This is due to the estrogen hormone deficiency, and increased follicle stimulating hormone (FSH) levels up to 10 - 20 times in the blood circulation and is estimated to increase the risk of osteoporosis up to three times.[7] The

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presence of osteoporosis in postmenopausal women is thought to be able to exacerbate the occurrence of alveolar bone resorption.[8] The results of the study done by Kusdhany suggest that there is a correlation between mandibular bone density with lumbar and femur bone density in postmenopausal women.[9] However, the association of alveolar bone resorption with osteoporosis in postmenopausal women remains unclear.

When the alveolar bone loss occurs, the residual ridge experienced size and shape deformity.[10] The resorption pattern of the remaining bone is affected by various local and systemic factors such as patient age, traumatic damage, pathological condition differences, mineral metabolic abnormalities, osteoporosis, and hormonal imbalances.[11] The presence of alveolar bone resorption characterizes the overall pattern of alveolar bone loss and can be used as a reference in the manufacture of removable denture or implants as rehabilitation treatments to replace extracted teeth that may affect the success of the prosthodontics treatment.

Osteoporosis is characterized by a low bone mineral density and structural changes in bone tissue, causing an increased risk of bone fracture. Osteoporosis is the most prevalent bone disorder worldwide, affecting one in three women and one in eight men over the age of 50 years and is a progressive systemic disease as a result of an imbalance between bone formation and bone resorption.[11-13] The relationship between osteoporosis, oral signs, body mass index, and age are used as parameters of postmenopausal osteoporosis indicator. The mandibular periapical radiographs are used to evaluate the level of alveolar bone resorption.[14]

Hormones are chemical messengers released into the circulatory system that will affect the organs that exist throughout the body. The hypothalamus will control menstruation by secreting the gonadotropin hormone to the pituitary gland.[15] Specifically, during the reproductive period, the pituitary gland will respond by producing two hormones, namely follicle stimulating hormone (FSH) and leutenizing hormone (LH). These hormones will determine the amount of estrogen and progesterone produced by the ovaries.[16]

During the menopausal and postmenopausal period, an increase in FSH levels above 30 IU/ml and a decrease in estrogen levels less than 40 pg/ml will occur.[17] Estrogen binds to estrogen receptors in osteoblasts that directly modulate the osteoblastic activity and indirectly regulate the osteoclast formation which aims to inhibit the bone reabsorption. Thus, when the estrogen levels decreased then nothing can inhibit the bone resorption process.[17-20]

The estrogen hormone plays an important role in the basic regulation of bone remodeling and therapeutic in women.[21] Decreased estrogen will decrease the osteoitic matrix production, increased trabecular bone formation, and stimulating the bone resorption process and also increasing the bone turnover. However, Manolagas reported that estrogen hormone could decrease the apoptosis process of osteoblast cells to prolong their life, making this as the control mechanism of estrogen in the process of bone formation.[22] Chen et al. also reported that the estrogen hormone affects the apoptosis of osteoblasts and osteoclasts through the mechanism of phosphorylation.[23] Hughes et al. proves that estrogen could also induce apoptosis and osteoclast cells death, confirming that it can directly decrease the resorption activity.[24]

The occurrence of alveolar bone resorption in osteoporosis women remains controversial among some researchers in the context of assessing the association between the severity of alveolar bone resorption with the hormone levels of FSH and estrogen. The aim of this study is to analyze the association of FSH and estrogen hormones to the resorption process of the mandibular alveolar bone in patients with postmenopausal osteoporosis.[25,26]

Materials and methods

This is a cross-sectional study with 70 subjects of postmenopausal women with range of age from 48-87 years. Subjects with a history of bone disease, metabolic or endocrine disorders such as hyperthyroidism and hyperparathyroidism, diabetes mellitus, kidney disease, liver disease, and taking medications known to affect bone metabolism (e.g., corticosteroids, anticonvulsants, and sodium heparin) are excluded.

Subjects were interviewed using a validated questionnaire, containing demographic information including past and present medical history. The standard questionnaires include demographics, body mass index (BMI), the age

of initial menopause, the age of menarche, and also age and history of menopause. Written informed consent is collected from the subject before participation in the study and along with that, this study has also been approved by the ethics committee of the Faculty of Dentistry Universitas Indonesia.

Bone loss seen on the radiograph was measured by drawing a tangent line from the cementoenamel junction (CEJ) of the distal part of 36 tooth and mesial part of 46 teeth to the base of bone loss characterized by intact lamina dura, then the distance was calculated (in mm) relative to the alveolar bone crest using a caliper.

Evaluation of the trabeculation density, quality density on the periapical radiograph includes the radiographic density region of interest (ROI) mandibular cortex, graded with 5x magnification. ROI is a square made of the mesial & distal interdental of 36 and 46 teeth about 1 mm from the alveolar crest and then formed a square of ± 3 mm^2. Measurements are done based on results from Modified Taguchi (1997)[27]; Grade 1: trabeculation is not visible, Grade 2: bone trabeculation looks thin and amount only a few, Grade 3: trabeculation visible as normal bone, Grade 4: thick trabeculation almost enveloping the bone marrow, and Grade 5: solid bone, not visible.

Body mass index is measured as a ration between weight (in kilograms) and height (in squared meters). Levels of Estradiol and FSH were determined by obtaining 5 ml of venous blood samples from every participant. The blood samples were centrifuged at 3000 revolutions per minute (rpm) for 10 min at 18°C, and the serum was frozen at -20°C. The plasmic estradiol level (pg/ml) was measured by enzyme-linked immunosorbent assay (ELISA) (Abbott AXsym System 34-3205/R6). Statistical analyzes used included Kolmogorov-Smirnov test for data normality, and also Spearman's tests for bivariate analysis. Blood samples were collected and immediately transferred to a non-heparin tube for centrifugation. The collected serum is then transferred to a pre-labeled plain tube, stored in an ice box and finally sent to the integrated laboratory of Faculty of Medicine Universitas Indonesia, for an immediate storage at -20°C.

Results

The study included seventy participants, aged 48-87 with average age 59.49 ± 7.74 years. None of the women had a history of taking medication for osteoporosis therapy. All of them also has not undergone any ovariectomy procedure or any experience of wearing a denture. All subjects came from the Kenari district of Central Jakarta The distribution of variables can be seen in table 1.

Variable (n=70)	Mean ± SD	Min-Max
Age (Year)	59.49 ± 7.74	48 -87
Estrogen (pg/ml)	21.88 ±4.26	19.00 -47.30
Follicle Stimulating Hormone (IU/ml)	100.42 ± 38.02	33.30 -200
Bone Density (mmAL/Eq)	70.47 ± 11.20	44.23 – 106.27
Bone Resorption (mm)	4.31 ± 1.50	1.29 – 8.20

Table 1. The Distribution of Variables observed.

The highest level of estrogen hormone is 47,30 pg/ml and the lowest is 19,00 pg/ml. Follicle stimulating hormone level showed that 200 IU/ml is the highest value in this subject. The minimum bone density is 44,23 and the maximum is 106,27.The bone resorption range is 1,29 mm until 8,20 mm. The correlation between bone density, bone resorption and several others factors could be seen in table 2.

Bone Density (n=70)	*p*	Correlation Coefficient
Age	**.01***	**-.41**
Estrogen	**.02***	**-.27**
Follicle Stimulating Hormone	.15	-.17
Bone Resorption	.31	-.12

Spearman's test; *$p < .05$ is significant.

Table 2. Correlation Between Bone Density and Age, Estrogen, FSH and Bone Resorption.

The Spearman's test revealed there is a significant correlation between bone density and age ($p<.05$). The magnitude of the correlation is a moderate negative correlation (-.41). Bone density and estrogen shows the significant correlation ($p<.05$) and the value is a weak negative correlation (-.27). But there is no significant correlation between bone density and follicle stimulating hormone ($p>.05$) and between bone density and bone resorption. ($p>.05$).

Discussion

Osteoporosis occurs in elderly individuals, caused by cessation of ovarian activity. Osteoporosis is an absolute reduction in the quantity of bone or can be simply described as skeletal tissue atrophy. Postmenopausal bone loss is a major determinant of osteoporosis. In the postmenopausal period, the ovaries no longer produce sex hormones, especially estrogen, due to ovarian fatigue, in which decreased estrogen levels lead to increased levels of follicle stimulating hormone produced by the pituitary gland that affects the ovaries in producing estrogen. [28]

In this study, the minimum age of subjects was 48 years old, whereas the maximum age was 87 years old. The numbers obtained in this study are following one research done by Mahmoud. [29] This study shows that there is a significant relationship between bone density and age. This results matched with the opinion of several researchers who stated that age would affect individual bone density. Along with increasing age, the bone mass will also decrease. Increased bone loss occurs with age, especially in elderly.[30] However, Sladina, A. et al. stated that there is no association between age and tooth loss despite age is a risk factor for decreased bone mass in osteoporosis, and is not a causative factor, so it must be distinguished from the physiological aging process.[31,32] However, other researchers also stated that bone mass loss might occur in the postmenopausal period at the rate of 0.5-1% of the total bone weight per year. Along with increasing age of one person, especially in postmenopausal period, the progressive bone mass loss will occur as a result of incomplete bone replacement or remineralization after resorption. [32]

Subjects who have a systemic history such as diabetes mellitus, a malignancy that are currently undergoing radiation therapy, previous hysterectomies, ovariectomies, or tubectomy procedure, and a history of or currently undergoing hormone replacement therapy are excluded in this study. This exclusion were made to avoid factors affecting menopause so that researcher will only examine women who underwent natural menopause.[33] However, it is relatively difficult to find a menopausal subject without a history of systemic disease.

Excessive mandibular alveolar ridge resorption leads to loss of denture support tissue. This is one of the most difficult restorative problems faced by the dentists. Several studies have evaluated age-related mandibular bone changes. However, according to the opinion of Atwood and Coy, there is no correlation between the reduction rate of support of this tissues and age.[34] The contradictive results of these studies led to this study being conducted on the subject of postmenopausal women. This is consistent with Finkelstein JS's study which states women begin to experience bone loss during the end of perimenopause period, which persists even after menopause. In fact, half the bone loss observed in women throughout their lifetime normally occurs during the first ten years of postmenopausal.[21,34,35]

The cause of residual ridge resorption can be multifactorial, that is as a result of a combination of anatomical, metabolic, and mechanical factors. Some researchers have shown that osteoporosis is manifested in the mandible and is one of the major causative factors in the high rate of residual ridge resorption. The diagnosis of osteoporosis can be established by examination of the gold standard radiograph of bone density and from the results of the validated questionnaire. Some researchers suggest that the loss of spongy bone and bone trabeculae suggest an occurrence of osteoporosis. In this study, bone density examination was performed with periapical radiography. This is consistent with Park et al. study which states that bone density assessment can be done with intraoral periapical radiographic techniques.[36,37] However, this decrease is not expected to be interpreted by using conventional radiographs unless it was detected that over 25% to 40% of bone calcium has lost. Many researchers have stated that progressive loss of alveolar bone may indicate the manifestation of osteoporosis.[38]

This study was conducted on the population housewives who routinely perform regular physical activities in the form of domestic work and also regularly consume bean products such as tempe and tofu, known for its phytoestrogens content. Phytoestrogens are phytochemicals that have estrogenic activity. Regular physical activity is useful to prevent weight gain, improve body composition, and improve functional strength as well as physical activity capacity, in which it has the potential to

improve bone mass and reduce the risk of postmenopausal fractures.[39]

Follicle stimulating hormone (FSH) is produced by the pituitary gland that stimulates the maturation of ovarian follicles and produces estradiol during the follicular phase and progesterone during the luteal phase. Increased levels of FSH serve as a hormonal marker to diagnose climacteric syndrome (estrogen deficiency syndrome). Endocrinologically, climacteric is characterized by decreased estrogen levels and increased gonadotropin secretion. This study showed no significant association between FSH and bone density in women with postmenopausal osteoporosis, elevated FSH levels due to reduced estrogen levels resulting in decreased bone density. Hormonal imbalances are common in all aging individuals, and there are other factors in the bone that cause not all aging individuals have osteoporosis.[34] The results of the present study are in line with the results of a study conducted by Drake et al, stating that the suppression of GnRH (gonadotropin releasing hormone) on the secretion of FSH in postmenopausal can improve markers of bone resorption and The FSH does not regulate bone resorption, that could be explained by FSH acting as a better integrated measure of ovarian estradiol production, rather than being due to a direct effect of FSH on bone remodeling.[40]

Follicle stimulating hormone is a glycoprotein hormone secreted by the pituitary gland consisting of two subunits, i.e., α and β non-covalent. The physiological function of FSH in women is to assist the growth of the endometrium, ovulation, and follicular development. Follicle stimulating hormone is known to be found in osteoclasts. The binding of FSH and FSH receptors will inhibit the α subunits action of the G protein to activate protein signaling associated with cell proliferation that will ultimately stimulate osteoclast formation and bone resorption. [28,36]

This study has found that there is a significant relationship between estrogen levels and bone density. Estrogen levels reduced in natural menopause, are well known to reduce bone mass and increase the risk of osteoporosis.[41] Estrogen has a significant effect on cytokine expression and growth factors by osteoblasts and osteoclasts. Bone density is also affected by a variety of factors including the spontaneous elevated levels and activity of pro-inflammatory cytokines (IL-1, IL-6, TNF-α), affecting bone remodeling process and excessive bone resorption, both local and systemic, as well as skeletal loads (bone mechanical load) that gives rise to mechanical stress, strain, or resultant tissue deformation that affect the bone tissue by bone formation on the periosteal surface thus strengthening the bone and decreasing bone turnover which reduces bone resorption.[26,32,33,42] In postmenopausal, bone resorption increases when compared with bone apposition and ER-β (estrogen receptor-β) expression can increase the risk of osteoporosis and fracture in elderly women.[9,42]

The absence of a relationship between FSH and bone density may be due to examination was done are limited to the FSH and estrogen alone, whereas some other pituitary hormones besides FSH may also play a role in bone regulation such as TSH (thyroid stimulating hormone) and prolactin. [43-45]

The results of this study found no significant relationship between bone density and bone resorption in osteoporosis patients. These results are different with the study by Nicopoulou-Karayianni et al. which states that osteoporotic women possess a high risk of tooth loss due to high bone resorption rate compared to healthy women with the same age range.[28,30] The cause of the difference in outcome may be due to the lack of a number of subjects and different methods were used in measuring the alveolar bone resorption. These results also contradict the facts that were based on the results of other researchers who claim that bone mass density is expected to decrease in the third decade of life or several years before menopause. Following the third decade of life, the rate of bone resorption will overcome the bone mass formation rate, thus accelerating the decrease in bone mineral density.[18,43]

Conclusions

This study found a significant association between age and estrogen to the bone density of postmenopausal women. However, no association was found between FSH and bone resorption to the bone density of postmenopausal women.

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Declaration of Interest

The authors declare that there are no conflicts of interest in this study.

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