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The Profile of Progesterone Hormone, Vitamin D, and Bone Density in Postmenopausal Women

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Abstract

Decreased levels of progesterone, which plays a role in preventing bone loss, may increase the risk for osteoporosis in postmenopausal women. Vitamin D plays a role in bone formation. This study aimed to analyze the relationship among progesterone, vitamin D, and bone density in postmenopausal women.

This is a cross-sectional study involving 59 postmenopausal women. Levels of progesterone and vitamin D in blood samples were determined using ELISA. Bone density was measured using dental radiography. Subjects were divided into two groups: those aged <60 years and those aged ≥60 years. Categories for levels of progesterone, vitamin D, and bone density were established on the basis of the receiver operating characteristic curve.

Spearman correlation test showed no significant relationship (p>.05) between progesterone or vitamin D levels and bone density in either group. In conclusion, this study showed that neither progesterone nor vitamin D is significantly correlated with bone density in postmenopausal subjects.

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Introduction

Alveolar bone supports the teeth, and its alveolar bone varies among individuals; young people have a solid alveolar bone socket with a smooth wall, while older individuals often have bones affected by osteoporosis. Bone osteoporosis causes reduced bone support to the tooth.[1] Women undergo both menopausal and postmenopausal periods. Menopause is a condition where women no longer experience menstruation permanently, and there is a decrease in estrogen hormone and bone density.[2]

Most experts view estradiol (potential estrogen) as the only bone-active gonadal steroid hormone. However, estradiol and progesterone work together in every tissue in female physiology. A decrease in estradiol levels will increase the release of pro-inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α that play a role in bone damage.[3,4] Increased inflammatory mediators cause postmenopausal decreased bone mineral density, and thus women tend to experience more alveolar bone loss.[5]

At the age >60 years, women often experience senile osteoporosis. This condition occurs due to aging. This occurs due to osteoblast dysfunction in the trabecular and cortical bones, thus increasing the risk of vertebrae and pelvic bone fractures.[6] The onset of menopause is accompanied by decreases in estradiol and progesterone levels. The role of estradiol in human bone health is well known, but not so with progesterone although it also plays a role in human bone health. Lack of estrogen and progesterone is almost indistinguishable, and progesterone deficiency occurs precede low estradiol levels in perimenopause.[3] Estrogen

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usually causes vasodilation and heat dissipation. Both hormones are anabolic and necessary in maintaining skin, bone and muscle metabolism. The anabolic effects play a role in bone and cartilage, thus helping in bone growth through the role of estrogen in stimulating differentiation and activity of osteoblasts.[3,7]

Calcium levels are maintained through bone resorption. In postmenopausal women, physiological hormonal changes lead to decreased calcium levels.[8] Calcium is released from a classified bone matrix to prevent decreased bone density and the risk of osteoporosis.[9,10] Vitamin D maintains calcium levels in the bones by increasing calcium absorption in the intestine and maintaining parathyroid hormone levels to keep calcium levels stable.[11] Limited data analyzing the role of progesterone and vitamin D levels on postmenopausal bone density are available; hence, this study aimed to investigate the association of progesterone and vitamin D levels with postmenopausal bone density.

Materials and methods

This cross-sectional study included postmenopausal subjects aged ≥ 45 years who were living in Central Jakarta in 2017. Prior to this study, all subjects had agreed and were willing to sign informed consent. This research has been approved by the Dental Research Ethics Committee Faculty of Dentistry, Universitas Indonesia. Demographic data was obtained through interview.

In this study, "postmenopausal" was defined as women who had naturally stopped menstruating at least 12 months prior to inclusion in the study.[12] Women who received hormone therapy, who had menopause due to the removal of the uterus or both ovaries, and who were suffering from systemic diseases such as diabetes mellitus were excluded from the study.

Blood was collected from the veins and stored in Eppendorf tubes. Tubes were centrifuged and then refrigerated at −20°C and defrosted at room temperature. Examination of progesterone hormones and vitamin D or (serum 25 (OH) D) was performed using enzyme-linked immunosorbent assay. All assays were performed at TERPADU Laboratory, Faculty of Medicine, Universitas Indonesia.

Bone density measurements were performed by evaluating trabecular density. These measurements were obtained using periapical dental radiography with mandibular cortex density of the region of interest (ROI). Each region was enlarged five times. The ROI was determined on the mesial and distal sides of the dental interdental 36 and 46 about 1 mm from the top of the alveolar bone box made about three mm.[2] Measurements were performed based on results from Modified Taguchi.[13] Descriptive statistics were obtained and tested for normality using the Shapiro–Wilk test for distribution. The categorical determinations of the progesterone, vitamin D and bone density variables were based on the receiver operating characteristic (ROC) curve. Bivariate analysis was performed using Pearson and Spearman's correlation tests with P<.05 being considered statistically significant.

Results

Fifty-nine postmenopausal subjects ultimately participated in the study. Postmenopausal subjects aged <60 years had a mean age of 53.88 ± 3.04 years, whereas subjects aged ≥60 years had a mean age of 66.08 ± 4.61 years, Subject aged <60 years had progesterone (0.15±0.11) and bone density level (72.79±11.17) higher than progesterone (0.12±0.09) and bone density level (68.16±12.63) in subject aged ≥ 60 years old. The mean vitamin D level (55.80 ± 73.62) was lower in subjects aged <60 years than vitamin D level (72.59 ± 79.06) in subjects aged ≥ 60 years (Table 1).

Postmenopausal (n=59)	<60 years		≥60 years	
	Mean (SD)	Min–Max	Mean (SD)	Min–Max
Age (Years)	53.88 (3.04)	48–59	66.08 (4.61)	61–77
Progesterone (ng/ml)	0.15 (0.11)	0.10–0.65	0.12 (0.09)	0.10–0.57
Vitamin D (ng/ml)	55.80 (73.62)	21.72–294.05	72.59 (79.06)	19.42–309.02
Bone Density	72.79 (11.17)	45.62–93.34	68.16 (12.63)	44.23–106.27

Table 1. Distribution of Variables Observed.

For progesterone, the area under the ROC curve was 0.41 (95% CI: 0.26–0.56). Based on ROC curve analysis, the cutoff value prediction was.11. Progesterone level was therefore categorized to be <.11 ng/ml and ≥.11 ng/ml at age <60 years and ≥60 years,

respectively. In the vitamin D variables, the area under the ROC curve was 0.71 (95% CI: 0.57–0.84). Based on the ROC curve analysis, the cutoff value prediction was at 25.47 ng/ml; hence, vitamin D level was categorized to be <25.47 ng/ml and ≥25.47 ng/ml at age <60 years and ≥60 years, respectively. The bone density variable had an area under the ROC curve of 0.36 (95% CI: 0.21–0.50). Based on the ROC curve analysis, the cutoff value prediction was at 63.94; hence, the bone density was categorized to <63.94 and ≥63.94 at ages < 60 years and ≥60 years, respectively (Table 2).

Variables		Postmenopausal (n=59)	
		< 60 years old	≥ 60 years old
Progesterone (ng/ml)	<0.11*	19 (55.9%)	18 (72.0%)
	≥0.11*	15 (44.1%)	7 (28.0%)
Vitamin D (ng/ml)	<25.47*	15 (44.1%)	1 (4%)
	≥25.47*	19 (55.9%)	24 (96.0%)
Bone Density	<63.94*	8 (23.5%)	8 (32.0%)
	≥63.94*	26 (76.5%)	17 (68.0%)

*Cutoff value determinant based on ROC curve

Table 2. Grading of Study Population based on Progesterone Hormone, Vitamin D, and Bone Density.

The cutoff value of progesterone based on the ROC curve showed that subjects aged <60 years of age (55.9%) and those aged ≥60 years (72.0%) had progesterone levels less than 0.11 ng/ml. The majority of subjects aged <60 years (55.9%) and ≥60 years (96.0%) had vitamin D levels ≥25.47 ng/ml, while subjects with bone density ≥63.94 were aged <60 years (76.5 %) and ≥60 years (68.0%) (Table 2).

Data analysis using Pearson correlation analysis revealed a negative correlation between age and bone density (r=−.09) in subjects aged <60 years but no significant correlation between age and bone density (p>.05). Spearman's correlation test results showed that both progesterone (r=.01) and vitamin D (r=.16) had a positive correlation with bone density but both did not have a significant correlation with bone density in subjects aged <60 years (p>.05) (Table 3).

Postmenopausal (<60 years old)	Bone Density (n=34)	
	Correlation coefficient	*p*
Ages (years)	−.09	.60[a]
Progesterone (ng/ml)	.01	.93[b]
Vitamin D (ng/ml)	.16	.34[b]

a. Pearson correlation test (significant p<0.05) b. Spearman's correlation test (significant p<0.05)

Table 3. Correlation between Age, Progesterone Hormone, Vitamin D, and Bone Density in Postmenopausal Women (<60 years old).

Spearman's correlation test results showed a negative correlation between age and bone density (r=−.004) in subjects aged ≥60 years but no significant association between age and bone density (p>.05). Both progesterone (r=.20) and vitamin D (r=.02) were positively correlated with bone density, but neither had a significant correlation with bone density of subjects aged ≥60 years (p>.05) (Table 4).

Postmenopausal (≥60 years old)	Bone Density (n=25)	
	Correlation coefficient	*p*
Ages (years)	−.004	0.98
Progesterone (ng/ml)	0.20	0.32
Vitamin D (ng/ml)	0.02	0.91

Spearman's correlation test (significant p<0.05)

Table 4. Correlation between Age, Progesterone Hormone, Vitamin D, and Bone Density in Postmenopausal Women (≥60 years old).

Discussion

Health management and vulnerability of women to diseases are influenced by hormones and the reproductive stage, that are characteristic of each stage as well as the changes that occur due to aging. In women, the body and mind are substantially influenced by sex hormones derived from the ovaries.[14]

Age has a negative correlation with bone density in a group of subjects aged <60 years, indicating that higher the age, lower the bone density. However, a significant correlation does not exist between age and bone density in this study. Age plays an important role in increasing the risk of fracture and occurrence of osteoporosis.[15] Therefore, early screening is important to determine whether there is a decrease in bone mineral density in postmenopausal women to prevent frequent

bone fractures.[16] The same is true for subjects aged ≥60 years.

Progesterone mainly acts on estrogen primed tissue. Estrogen increases the progesterone receptor in the target tissue, but on the other hand progesterone can reduces the number of estrogen receptors in the target tissue.[7]

The estrogen and progesterone receptors are located in the gingival tissues, periosteal fibroblasts, lamina propria, ligaments, and osteoblasts. Progesterone competes with one of the osteoblast receptors together with glucocorticoids or with the glucocorticoid receptor itself. Both of these lead to inhibition of bone resorption.[7]

In menopausal women, progesterone levels are in the range of 0.06–1.6 ng/ml.[17] This is in line with this study where the cutoff value of the progesterone levels in these women were <.11 and ≥.11. Majority subjects aged <60 years and ≥60 years have progesterone levels <.11 ng/ml (Table 2). Some evidence have revealed that women have a greater risk of suffering from various diseases than men. Progesterone and estradiol are present in high levels in women in their reproductive years that decrease in the postmenopausal period.[18,19]

Majumder et al. showed that alveolar bone changes in postmenopausal women are closely related to bone mineral density.[1] This is in line with previous studies showing a significant association between osteoporosis and bone loss.[20] Osteoporosis is the most common bone disorder in postmenopausal women. Vitamin D and calcium supplements help prevent bone loss due to the reduced bone formation and new bone fractures. Severe vitamin D deficiency will lead to osteomalacia, which is described as an inability to process mineralization in the formation of osteoid.[21] In this study, age, progesterone hormone, vitamin D, and bone density were divided on subjects < 60 and ≥ 60 years old. It aims to see age, progesterone hormone, vitamin D and bone density in subjects who have not entered eldery and who are elderly, because someone is said to be eldery if he was 60 years old or older.[22]

Progesterone was examined in this study because it plays an important role in bone formation in women. Progesterone was first recognized as a hormone that plays a role in bone formation in 1990. Deficiency of osteoblasts depends on progesterone, and differentiation is physiologically increased to 2.7 times in the luteal phase and its concentration is independent of estradiol.[23] Ovarian hormones such as estrogen and progesterone play a role in regulating the protein metabolism and growth function. These hormones have a potential effect in determining the development and integrity of the bone and oral cavity.[7] Bone-forming cells are physiologically influenced by progesterone. Luo and Liao showed that progesterone plays a role in regulating the function of metalloproteinase especially matrix metalloproteinase (MMP) within the osteoblast cells involved in remodeling and bone resorption. MMP initiates bone resorption through bone matrix degradation.[24] This requires MMP-2 activation through a complex process such as membrane-type matrix metalloproteinase-1 (MT1-MMP) and a tissue inhibitor of metalloproteinase (TIMP-2) on the cell surface where progesterone also showed elevated levels of MT1-MMP and osteoblast mRNA.[24,25]

Vitamin D has two important roles in the body: (1) plays a role in the endocrine mechanism and (2) plays a role in the autocrine/intracrine mechanism. The endocrine pathway involves a "classic" mechanism associated with increase calcium absorption in the intestine and osteoclast activity. "Non-classic" mechanism utilize the autocrine or intracrine pathways are associated with signaling and gene expression, protein synthesis, hormones synthesis, regulation of immune response and cell turnover.[26,27] Chronic vitamin D deficiency causes decreased calcium in the blood and increases parathyroid hormone, activating 1,25 (OH) D and osteoclasts.[9] Vitamin D deficiency also causes bone loss and increased bone turnover. Therefore, vitamin D status can be measured and examined in populations at risk, especially in postmenopausal women.[28]

Vitamin D is important in assisting bone growth and preserving homeostasis from bone minerals. Vitamin D deficiency leads to decreased absorption of calcium in the small intestine and kidney by 10%–15% causing decreased calcium levels in the blood.[9,10] Bone mass is formed through the process of formation, resorption, and reform of bone tissue. In the elderly, bone resorption occurs more frequently than formation especially due to hormone deficiency.[9,29] The majority of bone density of the

two subject groups in this study were ≥63.94 (Table 2). This is in line with Sianipar et al.'s study that showed that the mean value of bone density in postmenopausal women is 71.81.[30]

Increased age leads to decreased alveolar bone levels and this event is a physiological phenomenon but postmenopausal changes occur in hormones thereby causing decreased alveolar bone density.[8] In this study, there was no significant correlation between vitamin D levels and bone density in subjects aged <60 years (p=.34) than those aged ≥60 years (p=.91) (Table 3 and 4). This is consistent with the Kamineni et al.'s research that indicating there is no relationship between serum [25 (OH) D] and bone mineral density in the neck, femur, and lumbar bones.[21] In line with this, Alkhenizan et al. also showed the spine or total femoral bone mineral density was not associated with serum (25 (OH) D).[31] Several factors are thought to affect blood levels of vitamin D such as physical exercise, calcium intake, hormone therapy and systemic disease.[9]

Serum 25-hydroxyvitamin D (25 (OH) D) is an accurate description of vitamin D status. Osteoporosis Foundation also recommend that to maintain adequate vitamin D levels, a serum 25 (OH) D may be performed. Vitamin D deficiency criteria widely used by experts is when serum 25 (OH) D <50 nmol/L (<20 ng/ml), when serum vitamin D> 75 nmol/L (>30 ng/ml) is normal and if the level vitamin D 50-–75 nmol/L (20–30 ng/ml) is then defined as vitamin D insufficiency.[10,21,32] In this study, subjects aged <60 years (44.1%) and ≥60 years (4%) had vitamin D levels <25.47 ng/ml (Table 2).

This study shows that there is no significant correlation between levels of progesterone and bone density in subjects aged <60 years (p=.93) or in subjects aged ≥60 years (p=.32). (Table 3 and 4) This differs from the study by Al-Khakani et al. who compared the levels of progesterone in postmenopausal women with osteoporosis with non- osteoporosis. The results showed a significant difference in the levels of the hormone progesterone between postmenopausal osteoporosis and non-osteoporosis (p=.001). There are many mechanisms of progesterone in helping bone growth, one of which can increase levels of insulin like growth factor-1. Various factors can affect the function and work of progesterone in the female reproductive system.[33]

Conclusions

This study showed that neither progesterone nor vitamin D is significantly correlated with bone density in postmenopausal subjects.

Declaration of Interest

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