

Relationship of 25 Hydroxyvitamin D Levels with C-Telopeptide Levels in Perimenopausal Women

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ABSTRACT

Osteoporosis represents a significant global health challenge, particularly affecting perimenopausal women who experience accelerated bone loss due to declining estrogen levels. The relationship between vitamin D status and bone turnover markers during this critical transition period requires further investigation to optimize preventive strategies. This study [A1] aims to examine the relationship between 25-Hydroxyvitamin D (25(OH)D) and C-Telopeptide (CTx) levels in perimenopausal women in Manado. Vitamin D has an important role in maintaining bone health, and its deficiency can have an impact on a variety of health problems. This cross-sectional study involved 30 participants from Prof. Dr. R.D. Kandou Hospital and network hospitals in Manado. The results showed that 50% of the respondents had sufficient levels of 25(OH)D, while the remaining 50% were in the deficient category. The average level of 25(OH)D was 30.30 ng/mL. For CTx, 60% of respondents were at high risk and the remaining 40% were at low risk, with an average of 0.67 ng/mL. However, a non-parametric correlation test (Spearman's rho) between 25(OH)D and CTx showed statistically insignificant results ($r=0.024$; $p=0.902$). Therefore, this study concluded that there was no statistically significant relationship between 25(OH)D and CTx levels in perimenopausal women in the sample studied.

KEYWORDS

25 Hydroxyvitamin D, Osteoporosis, Perimenopause, CTx.



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INTRODUCTION

25-Hydroxyvitamin D is a stable metabolite of vitamin D and serves as a reliable biomarker for assessing vitamin D status. The role of vitamin D is well established in maintaining calcium and phosphorus homeostasis as well as in bone mineralization (Allaf & Abdul-Hak, 2022; Caroline et al., 2021; Damanik et al., 2019; Grant et al., 2022; Rivera-Paredes et al., 2021; Soininen et al., 2023). Vitamin D deficiency is also associated with several health problems, including increased risk of cancer, dental disorders, diabetes, musculoskeletal disorders, and immunological and cardiovascular complications, demonstrating the critical importance of maintaining adequate vitamin D levels. Thus, menopause and vitamin D deficiency have adverse health impacts that extend beyond osteoporosis to include mood disorders, increased risk of cardiovascular disease, and cancer (Bikle & Schwartz, 2019; Ciebia et al., 2021; Freitas et al., 2021; Merzon et al., 2020; Motlagh et al., 2023; Tsitsou et al., 2023).

The perimenopausal period is a transitional phase between premenopause and menopause, characterized by endocrine, biological, and clinical symptoms. During this transitional period, various complaints related to the menstrual cycle arise, with the main manifestation being irregular menstruation accompanied by increased FSH levels and vasomotor symptoms such as hot flashes. Estrogen levels fluctuate during perimenopause and decrease significantly approximately one to two years before menopause. The average age of

women entering perimenopause is 45.1 years, with a duration of approximately five years. Optimizing mental, physical, and social well-being is the primary goal of preventive intervention efforts in perimenopausal women. Additionally, there is a specific objective to detect as early as possible diseases that can occur during this transition period and the postmenopausal period, such as hypertension, diabetes mellitus, cancer, and bone and muscle health problems, as well as hearing loss and vision and dental issues. Bone and muscle health problems are often associated with decreased estrogen levels in women approaching menopause.

Estrogen plays a crucial role in calcium absorption in the renal tubules and regulation of epithelial calcium channels that facilitate calcium entry into renal tubular epithelium. Calcitriol formation is strongly influenced by estrogen through increased production of vitamin D binding protein, which binds vitamin D. Vitamin D regulates calcium and phosphorus availability in the blood for deposition during bone mineralization processes. Estrogen affects bone resorption through molecular mechanisms in osteoclasts and osteoblasts. A hypoestrogenic environment, such as during perimenopause, impacts vitamin D metabolism; therefore, during perimenopause, a series of bone catabolic activities begin that can lead to osteoporosis.

Osteoporosis is caused by higher osteoclast activity compared to osteoblast cell activity. One test that can detect early bone mass loss involves measuring bone absorption and reformation processes by assessing biochemical compounds that result from osteoclastic and osteoblastic cell activity (Agrawal & Garg, 2023; Bandeira et al., 2022; Ebeling et al., 2022; Pejić, 2022; Schober et al., 2023). Bone remodeling is a lifelong process influenced by vitamin D receptor activity in bone cells. The magnitude of bone remodeling can be measured using specific biochemical markers, particularly for bone turnover examinations such as C-telopeptide and N-terminal propeptide of procollagen type I.

The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry (IFCC) recommend C-Telopeptide (CTx) testing as an analytical reference standard for bone resorption assessment (Vasikaran et al., 2020). CTx is currently the best marker of bone resorption; CTx represents bone decomposition products released into blood and urine, making it useful for assessing bone turnover. CTx is a biomarker considered to affect bone mineral density. Through this examination, bone remodeling activation can be determined, and if results show abnormal findings or imbalance in bone remodeling, awareness of osteoporosis risk or other possible bone diseases is necessary.

Herrmann M, et al. (2008) concluded that C-Telopeptide and N-Telopeptide markers can help evaluate bone metabolic processes, especially bone resorption. This study found that CTx and NTx produced better results compared to other bone resorption markers, such as pyridinoline cross-links or hydroxyproline.

CTx has been utilized in studies related to bone degeneration by Puspitawati et al. (2020), who measured CTx levels in women with osteoporosis, osteopenia, and normal bone density. Results showed that women with osteoporosis had significantly higher CTx levels compared to those with osteopenia and normal bone density. Research by Kawiyana (2020) also used CTx as a parameter for determining average bone degeneration in postmenopausal women. The study found increased CTx in postmenopausal estrogen-deficient women who

experienced osteoporosis compared to those without osteoporosis. The occurrence of osteoporosis depends on the number and activity level of osteoclast cells; therefore, not all postmenopausal women with estrogen deficiency will experience increased bone resorption rates.

A study conducted by Kumari and Kumari (2020) on perimenopausal and postmenopausal women in Jamshedpur found that 39.03% of perimenopausal women experienced 25-hydroxyvitamin D deficiency, while 60.97% of postmenopausal women experienced 25-hydroxyvitamin D deficiency. The Study of Women's Health Across the Nation (SWAN) conducted research on perimenopausal women and found that during the perimenopausal age range, changes in bone density occurred (LeBlanc et al., 2023). The three-year period before menopause represents a phase of rapid bone density loss (Wilson et al., 2022; Lerchbaum, 2021; Miller et al., 2022). Markers of type I collagen degradation increase during this timeframe. Therefore, it is recommended that every woman in the perimenopausal period assess her bone health status so that treatment can be provided when bone health problems are identified (Jackson et al., 2022; Davis et al., 2020). Based on the publication by Cauley et al. (2022), perimenopausal women with high 25-hydroxyvitamin D levels can reduce their risk of non-traumatic osteoporosis by up to 45% compared to those with low 25-hydroxyvitamin D levels. According to the Central Statistics Agency in 2019, the number of women in Indonesia was 132,890,000, with an estimated 36,544,750 people over 45 years old.

The relationship between 25-Hydroxyvitamin D and C-Telopeptide levels in perimenopausal women has never been studied in the Obstetrics and Gynecology Department/SMF of Prof. Dr. R.D. Kandou Manado Hospital/FK UNSRAT Manado; therefore, the authors are interested in conducting this study.

This study aims to analyze the relationship between 25-Hydroxyvitamin D and C-Telopeptide levels in perimenopausal women attending Prof. Dr. R.D. Kandou Manado Hospital and its network hospitals. The practical benefits of this research include providing baseline data for early detection of bone health problems in perimenopausal women in the Manado region while contributing to academic understanding of vitamin D and bone turnover marker relationships in Indonesian populations. This research addresses a knowledge gap, as no previous studies have examined this relationship specifically in the perimenopausal population at Prof. Dr. R.D. Kandou Manado Hospital/FK UNSRAT Manado, making this investigation both timely and necessary for improving women's health outcomes in North Sulawesi.

METHOD

Research Design

The design of this study is correlative with the cross-sectional study approach in perimenopausal women.

Place and Time of Research

The study population was perimenopausal women who met the criteria in Manado and its surroundings. February 2021 until the sample is met.

Research Sample

The research sample is a member of the research population that meets the following inclusion and exclusion criteria:

A. The inclusion criteria are:

1. Perimenopausal women aged 45 – 51 years
2. Agree to be the object of research

B. Exclusion criteria include:

1. Have had a spontaneous fracture
2. Thyroid Disease
3. Taking calcium-containing supplements
4. Undergoing hormonal therapy
5. Taking vitamin D supplements
6. Taking calcium supplements
7. Using hormonal contraceptives in the last 6 months
8. Have undergone / had a bilateral salpingo-oophorectomy hysterectomy

Data Collection Methods

1. Data were collected using questionnaire sheets
2. Blood collection and sample examination were carried out at Prodia's Manado branch laboratory

Large Sample Estimate

- The sample size is calculated based on the formula:

$$n_1 = n_2 = \frac{Z_{\alpha} \times s}{d} = 29.14 = 30$$

$$Z_{\alpha} = 1.96$$

s = standard deviation of serum vitamin D levels, according to the literature 4.82 ng/mL

d = desired accuracy = 1.75 ng/mL

$$n = 29.14 = 30$$

Based on the large calculation of the sample above, it takes at least 30 perimenopausal women.

Research Variables

1. Independent variable : Vitamin D (25 Hydroxyvitamin D)
2. Bound variables : C-Telopeptide

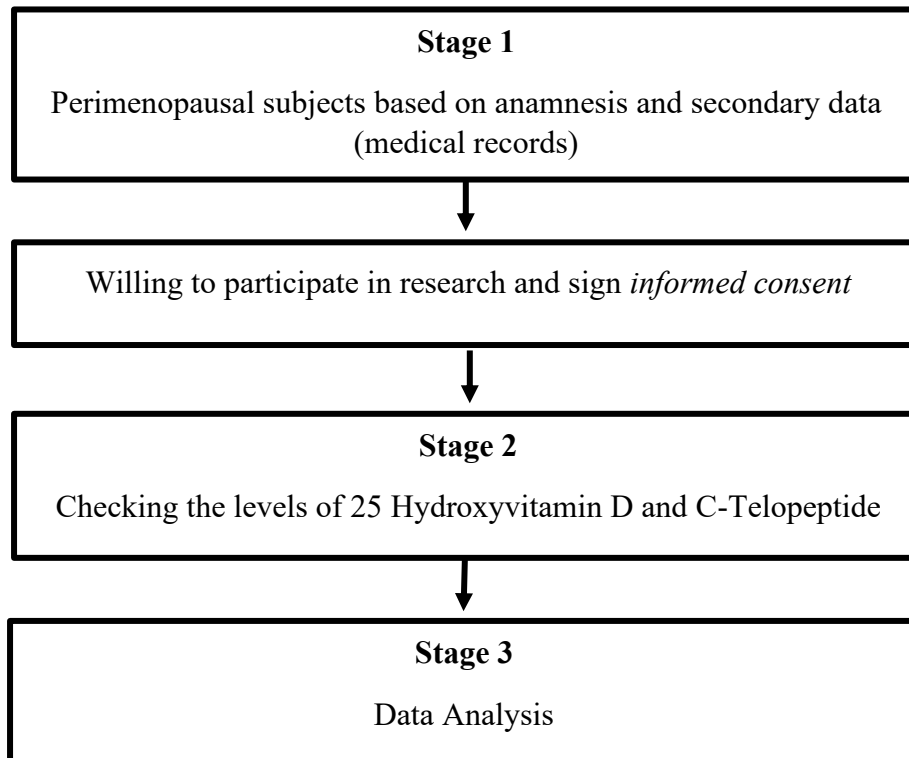
Research Instruments and Materials

- 1) Data were collected using questionnaire sheets
- 2) Blood samples are taken and examined by a private laboratory

How to Take Blood Samples

- 1) In the group of perimenopausal women aged 45 – 51 years who met the inclusion criteria, an explanation was given about the research to be conducted. Research subjects who are willing to participate in the research fill out the consent form that has been provided.
- 2) The subjects were taken 5 cc of blood for 25(OH)D examination and 3 cc for C-Telopeptide (CTx) examination in the cubic vein, then submitted to Prodia's Manado branch laboratory.

Research Flow



Variable Operational Definition

1. **Age** is the length of life of the subject from birth to the time the research was conducted.
2. **Perimenopause** is a subject aged 45-51 years who still has irregular periods and has symptoms of climacterium (hot flushes, night sweats, fatigue, muscle and bone pain).
3. **25(OH)D** is vitamin D. 25(OH)D serum examination using *the Chemmiluminescent Immunoassay (CLIA) examination method*. 25(OH)D deficiency if the < level is 10 ng/mL, insufficiency (10-29 ng/mL), sufficiency 30 – 100 ng/mL, Toxicity > 100 ng/mL.
4. **C-Telopeptide** is a specific protein that is a biochemical indicator of the bone resorption process that shows the activity of osteoclasts in bones that gives results in ng/mL. The low risk category of osteoporosis is if the CTx result is < 0.573 ng/mL, while if the CTx value is > 0.573 ng/mL, it is included in the high risk category of osteoporosis.

Data Processing and Analysis

The required data is collected through the form that has been provided and collected in a master table, then processed by computer using the SPSS program (*Statistical Package for Service Solution*). A correlation test will be carried out which will be depicted in the scatter plot correlation graph.

Research Ethics

Each prospective research participant who meets the inclusion criteria will be given an explanation about the research to be conducted. If they agree and are clear about the research to be conducted, the subject will be asked to sign an informed consent or consent to participate in the research.

RESULT AND DISCUSSION

The study was conducted on the perimenopausal female population in hospitals and at the Midwifery Polyclinic of Prof. dr. R. D. Kandou Manado Hospital, Pancaran Kasih Hospital and Bhayangkara Hospital from March 2021 to May 2021 with a total of 30 research subjects. The study subjects consisted of 30 perimenopausal women who all met the inclusion and exclusion criteria and had signed a consent form to participate in the study.

Table 1. Distribution of research subject characteristics

Characteristics	N	%
Age		
45	1	3,3
46	2	6,7
47	9	30,0
48	3	10,0
49	4	13,3
50	5	16,7
51	6	20,0
Final education		
SD	2	6,7
SMP	4	13,3
SMA	8	26,7
D3	1	3,3
S1	13	43,3
S2	2	6,7
Work		
PNS	7	23,3
Private Employees	6	20,0
IRT	13	43,3
Nurse	4	13,3

Based on table 1 of the age of perimenopause, it is known that the lowest age is 45 years old and the highest age is 51 years. The average age of the respondents' perimenopause was 48.53 with a standard deviation of 1.814.

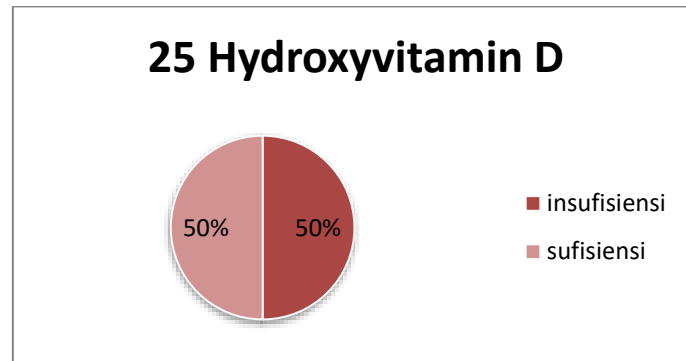
Based on table 1 of respondent education, it is known that most of the respondents have S1 education, namely 13 people (43.3%). While the rest were 2 people (6.7%), 4 people (13.3%), 8 people (26.7%) high school education, 1 diploma education (3.3%) and 2 people (6.7%) S2 education.

Based on table 1 of respondents' jobs, it is known that most of the respondents have jobs as housewives (IRT), namely 13 people (43.3%). While the rest are civil servant jobs as many as 7 people (23.3%), private employee jobs as many as 6 people (20.0%) and nurse jobs as many as 4 people (13.3%).

Table 2 Category 25 Hydroxyvitamin D

Category	N	%
Insufficiency	15	50,0
Sufficiency	15	50,0
Total	30	100,0

Based on table 2 of the 25 Hydroxyvitamin D category, it is known that in this study, 15 people (50.0%) were included in the insufficiency category and the rest were included in the sufficiency category as many as 15 people (50.0%). For more details, see the following graph 1:



Graphics 1. Category 25 Hydroxyvitamin D

Table 3. Kadar 25 Hydroxyvitamin D

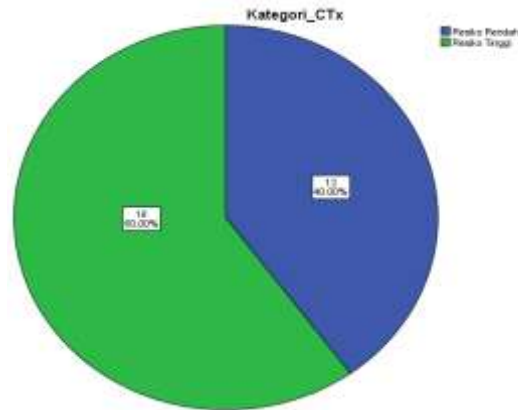
Kadar 25 Hydroxyvitamin D	N	Minimum	Maximum	Mean
25 Hydroxyvitamin D	30	20,7	40,8	30,3033

Based on table 3 Levels of 25 Hydroxyvitamin D, respondents know that the lowest 25 Hydroxyvitamin D is 20.7 and the highest is 40.8. The average of 25 Hydroxyvitamin D respondents was 30.3033 with a standard deviation of 5.34619.

Table 4. Category CTx

Category: CTx	N	Percent
Low Risk	12	40,0
High Risk	18	60,0
Total	30	100,0

Based on table 4 of the CTx category, it is known that most of the respondents have a high-risk CTx category, which is 18 people (60.0%). While the rest have the CTx category with a low risk of 12 people (40.0%). For more details, you can see the following graph 2:



Graph 2. Category: CTx

Tabel 5. CTx Up

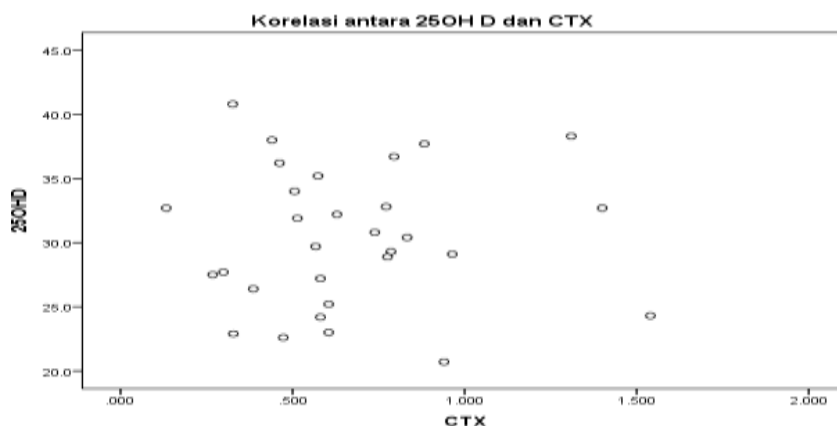
Up to CTx	N	Minimum	Maximum	Mean
CTx	30	0,13	1,54	0,6677

Based on table 5 CTx levels, respondents knew that the lowest CTx was 0.13 and the highest CTx was 1.54. The average CTx of respondents was 0.6677 with a standard deviation of 0.32777.

Table 6 Data Normality Test

	Kolmogorov-Smirnova			Shapiro-Wilk		
	Statistic	df	Itself.	Statistic	df	Itself.
Age	.201	30	.003	.905	30	.011
25(OH) D	.069	30	.200*	.976	30	.723
CTX	.146	30	.100	.924	30	.034

The Shapiro-Wilk test showed that only 25(OH)D was normally distributed ($p > 0.05$), while Age and CTx were abnormally distributed ($p < 0.05$), so a non-parametric correlation test (Spearman's rho) would be performed.



Graph 3. Correlation test between 25 Hydroxyvitamin D and CTx

In the correlation test between 25 Hydroxyvitamin D and CTx which was statistically insignificant ($r = 0.024$; $p = 0.902$).

Sample Characteristics

In this study, as many as 30 research subjects who met the inclusion criteria were taken by examining the levels of 25 Hydroxyvitamin D and C-Telopeptide levels in the blood in perimenopausal women.

Based on table 4.1 of the age of perimenopause, it is known that the lowest age is 45 years and the highest age is 51 years. The average age of perimenopause in this study was 48.53 with a standard deviation of 1.814.

In the study, Willi J (2020) found that the average age of perimenopause in the study of 177 women was 48.60 years. Rui-xia Lia, et al. (2016) conducted a study and obtained the average age of perimenopause for 946 women at 49.24 years.

Based on table 4.1 Respondent education, it is known that most of the respondents have S1 education, namely 13 people (43.3%). It is known that most of the respondents have jobs as housewives (IRT), namely 13 people (43.3%).

In table 4.2 Category 25 Hydroxyvitamin D, it is known that in this study, 15 respondents (50.0%) were included in the insufficiency category and the rest were included in the sufficiency category as many as 15 people (50.0%). In table 4.3 Levels of 25 Hydroxyvitamin D, it is known that the lowest 25 Hydroxyvitamin D is 20.7 and the highest is 40.8. The average of 25 Hydroxyvitamin D respondents was 30.303 with a standard deviation of 5.3462.

In a study conducted by Shurkar S, et al (2013) on vitamin D levels in perimenopausal and postmenopausal women conducted at Dow University Hospital Pakistan. The results were found that about 63% of perimenopausal women and 37% of postmenopausal women involved in the study experienced impaired vitamin D levels.

The range of levels of 25 Hydroxyvitamin D which is good for bone and ectraskeletal health is still widely discussed and the results vary. The International of Medicine (IOM) suggests a level of 25 Hydroxyvitamin D that is good for bone health is 20 ng/mL. Meanwhile, according to *the American Endocrine Society*, the recommended range of 25 Hydroxyvitamin D levels is 40 – 60 ng/mL to get wider benefits.

The research conducted by Priemel, et al. (2010) regarding the level of 25 Hydroxyvitamin D which is good for bone health, namely, in the bone biopsy carried out they did not find any bone pathological abnormalities in the study participants who had levels of 25 Hydroxyvitamin D above 30 ng/mL. From the study, they concluded that the lower threshold of 25 Hydroxyvitamin D levels to maintain bone health was 30 ng/mL.

In a study conducted in Manado, the average level of 25 Hydroxivitamin D in perimenopausal women was 30,303. When viewed from the reference level of 25 Hydroxyvitamin D based on the laboratory, the value of 30.303 is still within the normal limit. However, it is better to increase the level because when entering menopause and postmenopause, it is feared that the effect of decreasing estrogen hormone levels will decrease the level of 25 Hydroxyvitamin D as well. When the group of postmenopausal women with 25 levels of 25 Hydroxyvitamin D at 20ng/mL was increased to 32 ng/mL, they increased their ability to absorb calcium in the intestines by 45-65%.

In this study, the level of 25 Hydroxyvitamin D of the respondents was still within normal limits based on the range of laboratory values. This can be caused because respondents

are likely to get enough sun exposure and intake of foods that contain vitamin D, for example such as fish that are widely found in the Manado area.

Based on table 4.4 CTx category, it is known that most of the respondents have a high-risk CTx category, which is 18 people (60.0%). While the rest have the CTx category with a low risk of 12 people (40.0%). In table 4.5, the respondents' CTx levels were found to have the lowest CTx of 0.13 and the highest CTx of 1.54. The average CTx of respondents was 0.66717 with a standard deviation of 0.32777.

In the remodeling process, bones continuously undergo resorption and reform. This means that bone formation is not limited to the growth phase, and in fact lasts the patient's lifetime. The cells responsible for bone formation are called osteoblasts, while osteoclasts are responsible for bone dissolution. Bone formation mainly occurs during the growth period. Bone formation and dissolution are in balance in individuals aged 30 to 50 years. This balance begins to be disturbed and heavier towards bone resorption when women reach menopause.

Bone resorption marker *examination* to assess bone damage has been used since a few years ago. In addition to assessing bone damage, *bone resorption marker examination* is also used to monitor the development of osteoporosis therapy. In a study conducted by SWAN involving 2375 pre- and perimenopausal women, the results found an increase in *bone resorption marker* values in perimenopausal women.

A study conducted in Saudi Arabia by Salleh M, et al. (2010) reported an increase in bone biomarker levels in postmenopausal women's age group when compared to the premenopausal women's age group. Lateef M, et al. (2009) conducted a study on the correlation of bone mineral density with osteocalcin and CTx bone biomarkers. It was found that low bone mineral density in menopausal and postmenopausal women group, this result indicates a loss of bone structure in line with age and menopause.

A study conducted in North Sumatra in 2010 regarding the correlation between osteocalcin and CTx levels as a bone biomarker showed that the postmenopausal group of women had higher bone destruction activity compared to women of reproductive age.

It can be concluded that examination of bone biomarkers C-Telopeptide appears to significantly determine bone structure loss and can be used for the assessment of osteoporosis in menopausal patients.

In this study, the average CTx level in perimenopausal women in Manado was obtained at 0.66717 and this value is included in the category of high risk of osteoporosis. So it is recommended that perimenopausal women improve their lifestyle such as diligently exercising, sunbathing, consuming foods that contain vitamin D and calcium. If not treated properly, it is feared that when entering the postmenopausal period, CTx values will be higher and can have a bad impact on bone health. In addition to lifestyle changes, it must be accompanied by a good bone health checkup so that bone health conditions can be monitored.

Correlation Test between 25 Hydroxyvitamin D with CTx

In this study, it was found that the correlation test between 25Hydroxyvitamin D and C-Telopeptide in perimenopausal women was statistically meaningless ($r = 0.024$; $p = 0.902$).

A study conducted by Schwetz V, et al. (2017) regarding the correlation of vitamin D and bone biomarkers in Austria, found that there was no meaningful correlation between the

two variables. In a study conducted in Palestine by Kharroubi et al. (2017) on the relationship between 25 Hydroxyvitamin D levels and bone turnover markers in postmenopausal women, the results obtained were statistically no meaningful relationship.

Garnero et al. (2007) and Labronici et al. (2013) showed no association between 25 Hydroxyvitamin levels and bone mineral density. Researchers conducted a study on 669 postmenopausal women to determine the association between serum 25 Hydroxyvitamin D, markers of blood turnover, and bone mineral density, and fracture incidence in postmenopausal women. The results showed that serum levels of 25 Hydroxyvitamin D below 75 nmol/ml were found in 73% of women, below 50 nmol/l in 35% of women, and below 30 nmol/l in 11% of women. Levels of 25 Hydroxyvitamin D were shown to be associated with parathyroid hormone ($r=0.023$; $p<0.0001$), but were not associated with pelvic bone mineral density and radius or fracture risk. Although age has been adjusted, no association has been found between 25 Hydroxyvitamin D levels and the risk of fracture and loss of bone mineral density.

In this study, the results showed that a decrease in 25 Hydroxyvitamin D levels was not always followed by an increase in CTx levels, and vice versa. This can be affected because in theory, bone health in perimenopausal women is also affected by the hormone estrogen.

Under normal circumstances, estrogen in circulation reaches osteoblast cells, and acts through receptors in the cytosol of these cells, resulting in decreased secretion of cytokines such as: Interleukin-1 (IL-1), Interleukin-6 (IL-6) and Tumor Necrosis Factor-Alpha (TNF- α), which are cytokines that function in bone absorption. On the other hand, estrogen increases the secretion of Transforming Growth Factor b (TGF- β), which is the only growth factor that mediates to attract osteoblast cells to the bone hole where the osteoclast cells have been absorbed. Osteoblast cells are the main target cells of estrogen, to release several growth factors and cytokines as mentioned above, although indirectly or directly they also affect osteoclast cells.

Research conducted in Manado in 2010 showed that there was a significant correlation between estrogen, IL6 and CTx levels where these variables were considered to be mutually influential in the occurrence of changes in bone health in perimenopausal women.

CONCLUSION

This study successfully achieved its primary objective of analyzing the relationship between 25-Hydroxyvitamin D and C-Telopeptide levels in perimenopausal women. The findings contribute to the understanding of bone turnover markers in Indonesian populations and provide baseline data for clinical practice in North Sulawesi. Future research should explore longitudinal changes in these biomarkers throughout the perimenopausal transition and investigate the role of additional factors such as physical activity, dietary patterns, and genetic polymorphisms that may influence bone health in this population. From the results of this study, it can be concluded that the correlation test between 25-Hydroxyvitamin D and C-Telopeptide in perimenopausal women did not obtain statistically significant results.

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