**Research Article**

# Length of Menopause has a Positive Correlation with C-Telopeptide Plasma Level in Pascamenopause Women

## *Lama Menopause Memiliki Korelasi Positif dengan Kadar C-Telopeptide Plasma pada Perempuan Pascamenopause*

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Abstract

**Objective**: To determine the correlation between length of menopause with C-telopeptide in pascamenopause women.

**Method**: An analytic cross-sectional study of 29 pascamenopause women in Malalayang hospital Manado. Sampling method with consecutive random sampling. Data were analyzed with Spearman test with significance level of p<0.05.

**Result**: Among of 29 pascamenopause women with a mean of age 58.62 ± 4.694 years. Mean of length of menopause is 8.76 ± 5.520 years with median 7 years (quartil 5.00 until 11.5 years). Mean of C-telopeptide plasma level is 0.524 ± 0.256 μg/l with median 0.472 μg/l (quartil 0.324 until 0.656 μg/l). We found length of menopause and C-telopeptide plasma level were not distributed normal (p<0.05). Correlation analysis by Spearman found significant positive correlation between length of menopause and C-telopeptide plasma level.

**Conclusion**: There is significant positive correlation between C-telopeptide plasma level with length of menopause in pascamenopause women.

[Indones J Obstet Gynecol 2014; 2: 82-86]

**Keywords**: C-telopeptide plasma level, length of menopause, pascamenopause women.

Abstrak

***Tujuan**: Mengetahui korelasi antara lama menopause dengan kadar C-telopetide plasma perempuan pascamenopause.*

***Metode**: Penelitian ini merupakan studi potong lintang analitik yang mengikutsertakan 29 perempuan pascamenopause secara consecutive sampling yang kontrol di poliklinik bagian kebidanan dan kandungan RS Malalayang Manado secara sukarela yang dinyatakan dengan informed consent. Analisis data menggunakan uji Spearman dengan tingkat kemaknaan p<0,05.*

***Hasil**: Dari 29 perempuan pascamenopause dengan rerata usia 58,62 ± 4,694 tahun. Rerata lama menopause adalah 8,76 ± 5,520 tahun dengan median 7 tahun (nilai kuartil 5,00 sampai 11,50 tahun). Rerata kadar C-telopeptide adalah 0,524 ± 0,256 μg/l dengan median 0,472 μg/l (nilai kuartil 0,324 sampai 0,656). Data lama menopause dan C-telopeptide tidak berdistribusi normal (p<0,05) sehingga untuk mengetahui hubungan antara lama menopause dengan kadar C-telopeptide digunakan analisis korelasi Spearman. Hasil analisis korelasi antara lama menopause dengan kadar C-telopeptide didapatkan nilai r = 0,485 dengan nilai p = 0,008. Hal ini menunjukkan bahwa terdapat hubungan positif antara lama menopause dengan kadar C-telopeptide secara bermakna (p<0,05).*

***Kesimpulan**: Terdapat hubungan positif bermakna antara lama menopause dengan kadar C-telopeptide.*

*[Maj Obstet Ginekol Indones 2014; 2: 82-86]*

***Kata kunci**: kadar C-telopeptide plasma, lama menopause, perempuan pascamenopause.*

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## INTRODUCTION

Menopause is defined as a woman who stops menstruating at the age of 51 to 65 years for more than 12 months spontaneously and the level of follicle stimulating hormone (FSH) blood was >40mIU/ml and estradiol level was <30 pg/ml.[1]

Research in Netherland shows the mean age of menopause was 50.2 years. Approximately 1% of women experience premature menopause before the age of 40 years and 1% of women experience menopause at the age of 58 years.[2] Research on Women's Health Across the Nation shows the mean age of menopause was 51.4 years. The mean age of menopause is 45 years old accompanied by increasing of hormone estradiol in perimenopausal period is one year before the on set of menopause. In developing countries the average age of female menopause occurs earlier than the western countries. Research in Indonesia showed the average age of menopause is 48 to 49 years. Research in

Bitung found that climacterium woman was in the age range 40 to 55 years with a mean age of menopause 48 years.[2,3]

Presence of metabolic and hormonal change is a result of menopause, which one of the hormonal changes is osteoporosis. Osteoporosis is a metabolic bone disease characterized by decreased bone mass due to reduced bone mineral matrix and accompanied by destruction of bone tissue micro architecture that result in decreased bone strength resulting in a tendency to bone fracture.[4] In osteoporosis the bone remodeling abnormalities also occur where the process of bone resorption (bone resorption) more than the process of bone formation (bone formation), where the cells responsible for bone formation while osteoclasts are called osteo blasts are responsible for bone resorption.[1,2,4-6]

The incidence of osteoporosis increases with increasing aging population.[7] Some literature suggests that menopausal women have a significantly higher risk for osteoporosis occurs, in which the ratio of the tendency to suffer from primary osteoporosis in women: men is 5:1. In women aged over 50 years found 30% of osteoporosis, osteopenia 37 to 54% and 54% higher risk of osteoporotic fracture. Research shows that osteoporosis affects 44 million Americans or 55% of the population above 50 years of age. The prevalence of osteoporosis in women aged over 50 years in Indonesia is 34%.[8] Research Ketia et al., 2006 showed the prevalence of osteoporosis in women was 91.7% with a mean age of 66.36 ± 11.74 years. Approximately 35% of postmenopausal women will suffer from osteoporosis, and 50% will have osteopenia.[9]

Bone consists of bone matrix containing 90% collagen (Type-1 Collagen contains N-telopeptides, C-telopeptides and deoxypyridinolines), 10% protein (osteocalcine, osteonectin, osteopontin), bone mineral (calcium and phosphate) and bone cells (osteoclasts, osteo blasts and lining cells). Process off or mation and bone resorption are in balance when individuals aged 30 to 40 years. In normal physiological remodeling process, bone is an organ that always have the turn over, which is a balance process between resorption and formation happen continuously. This balance process of the formation and absorption began to fail and bone resorption process more likely occur when women reach menopause and men reach the age of 60 years. Increased bone resorption process than bone formation in postmenopausal women is caused by a deficiency of the hormone estrogen which would then stimulate the release of mediators that influence the activity of osteoclasts. So that plays a role in the occurrence of osteoporosis directly is the number and activity of osteoclasts is influenced by mediators, which the mediators is greatly influenced by the level of the hormone estrogen.[10]

Correlation between C-telopeptide level with osteoporosis had been reported. Research in Manado showed that there were significant correlation between the level of estrogen, IL 6, and C-telopeptide, which is considered to be mutually influential variables in the occurrence of physiological changes in perimenopausal women. This study also showed increasing rate of bone resorption followed by increasing age, C-telopeptide level and decreasing of estrogen level.[11]

Some the ories shows that differentiation and activity of osteoclasts increased the estrogen de-ficiency. Under normal circumstances estrogen in circulation reached osteo blast cells and move through receptors in the cell cytosol resulted in a decreased secretion of cytokines such as interleukin-I (IL-1), interleukin-6 (IL-6) and Tumor Necroting Factor Alpha (TNF-$\alpha$) in which this cytokine function for bone resorption. Estrogen also increases the secretion of Transforming Growth Factor $\beta$ (TGF-$\beta$) which is the only growth factor (growth factor) which is a mediator to attract osteo blasts to the bone hole that has been absorbed by osteoclasts. Osteo blast cells are the main target cells of estrogen to releases everal growth factors and cytokines. Estrogen effects on osteoclasts have an impact both directly and indirectly. Direct effect of estrogen is to prevent the differentiation of osteoclasts precurs or cells and suppress activation of matur eosteoclasts. While the influence of estrogen will indirectly affect the process of differentiation, activation and apoptosis of osteoclasts. In the differentiation and activation of estrogen suppresses the expression of RANK-Ln, M-CSF on osteo blasts and stromal cells prevent the complex bond between RANK-L and OP Greceptors by producing competing with RANK.[4,5,12]

Examination of bone biochemical markers of bone remodeling activity has been carried out. Several biochemical markers of bone metabolism include bone alkaline phosphatase, osteocalcine, bone Glaprotein (BGP) and C-telopeptide. Several cross-sectional studies showed that bone turn over

increases rapidly after menopause women age where there is an increase in level of osteocalcin and bone alkaline phosphatase by 50% and increased level of C-telopeptide by 50% to 150%. C-telopeptide a specific protein is a biochemical indicator to show the process of bone resorption activity of osteoclasts in bone. Molecular C-telopeptide and bone-specific to a cluster of amino acids to detect the activity of osteoclasts. C-telopeptide examination can be done by ELISA (enzyme-linked immuno-absorbent assays) of serum or urine. Lateef study, 2009 showed elevated level of serum C-telopeptide were significantly increased in postmenopausal women with osteoporosis and without osteoporosis. Increased serum level of C-telopeptide was significant in premenopausal women with level more than 0.573ng/ml would increase the risk off racture is 2-6 times higher bone degradation.[13]

Research Eastell et al., 2007 showed that elevated level of markers of bone formation and bone destruction increases according to age and this process continues until a woman enters a period of 80 years of age or have experienced menopause for 40 years.

Although osteoporosis is not a new problem but the problems currently faced by women experiencing menopausal osteoporosis is not only a decline in the quality and function of living in creases morbidity and mortality, but treatment is complicated by osteoporosis who fracturea difficult thing that takes a long time and considerable cost. In osteoporosis accompanied by complications will cause serious morbidity and mortality.[14]

Due to there was not data about correlation between length of menopause with C-telopeptide in pascamenopause women in Manado encourage researchers to conduct this research.

## METHODS

This study is a cross-sectional analytic study performed on 29 patients in Malalayang hospital Manado on April 2013 with consecutive random sampling method.

C-telopeptide examination conducted at the Laboratory Prodia Manado. Blood sampling performed after the study participants under went fasting for 12 hours. Blood was drawn at 0.5cc (0.3 cc) and inserted into the test tubes containing the anti coagulant agent (heparin/EDTA) when inserted into the plasma serum sodium heparin; stabilized at a temperature of 2-25°C for 24 hours, or -20°C for 3 months, or at -70°C for 3 months. If EDTA plasma serum plasma included in the stabilization of the serum is at a temperature of 20-25°C for 24 hours; 4-8°C for 8 days.

Inclusion criteria in this study were postmenopausal patients aged between 51 to 65 years and willing to participate in this study voluntarily stated to informed consent. While the exclusion criteria were a history of previous fractures, participant same norrhoe as in ceremoval of the uterus or ovaries, a history of breast cancer, endometrial cancer and ovarian cancer, women who have previously been diagnosed with osteoporosis, treatment for osteoporosis therapy (bisphosphonates, vitamin D, calcitonin, fluoride, hormone replacement therapy, calcium supplements).

## RESULTS

### Characteristics of Subjects

Distribution of subject characteristics based on age, weight, duration of menopause, and level of C-telopeptide was shown in Table 1.

**Table 1.** Characteristics of Subjects.

| | N | Min | Max | Mean | Std. Deviation |
|---|---|---|---|---|---|
| Age | 29 | 52 | 65 | 58.62 | 4.694 |
| Weight | 29 | 40 | 75 | 56.52 | 10.555 |
| Long menopause | 29 | 2 | 24 | 8.76 | 5.520 |
| C-Telopeptide | 29 | .186 | 1.190 | .52448 | .255876 |

Of the 29 subjects were postmenopausal women with mean age was 58.62 ± 4.694 years. The minimum age of 52 years and maximum age 65 years. The mean body weight was 56.52 ± 10 555 kg with a minimum weight of 40 kg and a maximum weight of 70 kg. For the mean time of menopause was 8.76 ± 5.520 in the shortest menopause is 2 years old and the longest is 24 years old menopause. The mean level of C-telopeptide was 0.524 ± 0.256 mg/l.

Further more, normality test was performed on the length of menopause and C-telopeptide level to determine the distribution of the data. Based on the results of normality test, it is shown that both variables were not distributed normally.

**Table 2.** Normality Tests.

| | Tests of Normality | | | | | |
|---|---|---|---|---|---|---|
| | Kolmogorov-Smirnova | | | Shapiro-Wilk | | |
| | Statistic | Df | Sig. | Statistic | Df | Sig. |
| Long menopause | .210 | 29 | .002 | .863 | 29 | .001 |
| C-telopeptide | .148 | 29 | .102 | .907 | 29 | .015 |

**Table 3.** Spearman Correlation Tests.

| | | Correlations | Long Menopause | C-Telopeptide |
|---|---|---|---|---|
| **Spearman's rho** | Long Menopause | Correlation Coefficient | | .485** |
| | | Sig. (2-tailed) | | .008 |
| | | N | | 29 |
| | C-Telopeptide | Correlation Coefficient | .485** | |
| | | Sig. (2-tailed) | .008 | |
| | | N | 29 | |

*** Correlation is significant at the 0.01 level (2-tailed)*
** Correlation is significant at the 0.05 level (2-tailed)*

Spearman correlation test was performed to determine the correlation between the length of menopause with C-telopeptide level (shown in Table 3), showed that the value of r=0.485 with p=0.008 (p<0.005). This shows that there is a positive relationship between length of menopause with C-telopeptide level were significantly which means that the longer duration of menopause, the greater of C-telopeptide level (p<0.05).

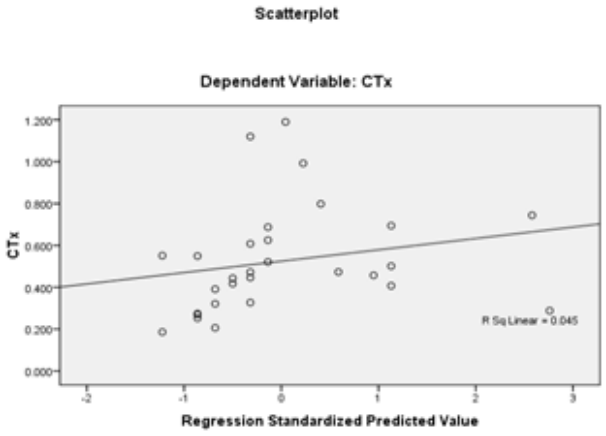


**Figure 1.** Graphic of correlation between the Duration of Menopause with C-Telopeptide Level in Postmenopausal Women.

Figure 1 shows that a significant positive correlation between duration of menopause with level of C-telopeptide. The longer duration of, the greater of C-telopeptide level.

## DISCUSSION

Subjects were postmenopausal women who are willing to participate and fulfill the inclusion criteria of research conducted in the department of Malalayang Manado. Characteristic subject are shown in Table 1 with theme an age of postmenopausal women was 58.62 ± 4.6 94 years old. The mean of menopause duration was 8.76 ± 5.5 20 years, with the shortest period was 2 years and the longest was 24 years old. Research by Kawana et al. Showed that the mean age of postmenopausal women was 55.3 ± 3.7 years.[14] Research by Piedra et al. Showed that the mean age of post menopausal women was 56 ± 7 years.[15] Research Takahashi et al. showed a mean age of postmenopausal women was 54.9 ± 3.6 years.[16]

The mean level of C-telopeptide in postmenopausal women was 0.524 ± 0.256 mg/l. Research by Kawana et al. showed the mean level of C-telopeptide in postmenopausal women (2527 ±

1507 pm ol/l) was found higher than premenopausal women (1345 ± 764 pm ol/l) with (p <0.05).[14] This suggests that elevated level of C-telopeptide as an indicator of bone resorption associated with menopause. Research Piedra et al. showed higher level of C-telopeptide in postmenopausal women obtained 119 ± 66 mg/m mol.[15] Research Takahashi et al. Show α C-telopeptide level (382 ± 208 mg/mmol) was higher than premenopausal 99 ± 186 mg/mmol (p<0.05).[16]

Spearman's test showed that the correlation coe eficient (r) between the duration of menopause and the level of C-telopeptide was 0.485 with p=0.008 (p<0.05). This suggests that there is a positive correlation between duration of menopause with C-telopeptide level. Research conducted in Pakistan found a positive correlation between C-telopeptide with age.[16] Based on research conducted in Manado in 2010 showed the increasing age and decreasing level of estrogen menopausal women with increasing level of C-telopeptide.[11] Research Garnero et al. shows with increasing time post-menopause cause changes in bone mineral density in postmenopausal bone so that examination plays an important marker for assessing the risk of osteoporosis in postmenopausal women.[17] In contrast research Takahashi et al. as many as 102 subjects who tuck postmenopausal women with an age range between 46-90 years found no significant correlation between level of C-telopeptide with α long menopause (r=0.11 with p=0.3973). In the post-menopause women α C-telopeptide level higher than premenopausal obtained. Upon entering the postmenopausal state α C-telopeptide level obtained continued to increase until 43 years after menopause but elevated level of C-telopeptide α urine samples more than the minimum level of C-telopeptide of serum samples. C-telopeptide can be used for indicators of bone resorption time of growth, and the state of postmenopausal osteoporosis in postmenopausal women.[16,17]

## CONCLUSIONS

From these results it can be concluded that there is a significant relationship between the duration of menopause with increasing value of C-telopeptide. C-telopeptide as a biomarker to determine bone loss as the risk of osteoporosis and assess the success of treatment of osteoporosis in postmenopausal women.

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