

Correlation of Interleukin-1 (IL-1) and Serum Estradiol Levels in Menopausal Women in H. Adam Malik General Hospital

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ABSTRAK

Tujuan : Penelitian ini menggunakan metode penelitian *case series* untuk menilai korelasi antara interleukin-1 (IL-1) dengan kadar estradiol pada wanita menopause.

Metode : Penelitian ini dilakukan di RSUP H. Adam Malik Medan. Penelitian dilakukan pada 1 September 2017 hingga jumlah sampel terpenuhi. Populasi penelitian adalah tenaga paramedis wanita yang sudah tidak mengalami haid selama 12 bulan terakhir di RSUP H. Adam Malik Medan. Dilakukan pengambilan darah dari vena mediana cubiti untuk mengukur kadar estradiol dan IL-1. Data yang didapat dilakukan penilaian dengan uji *Spearman*.

Hasil : Dari 38 sampel pada kelompok wanita yang sudah menopause, ditemukan kadar rerata serum estradiol adalah 42.28 ± 22.86 , dan kadar rerata serum IL-1 adalah 40.84 ± 22.89 . Terdapat korelasi negatif sedang antara estradiol dengan IL-1 jika kadar estradiol menurun, maka akan meningkatkan kadar IL-1

Kesimpulan : Terdapat korelasi negatif sedang antara estradiol dengan IL-1 jika kadar estradiol menurun, maka akan meningkatkan kadar IL-1.

Kata Kunci : Korelasi, *Interleukin-1*, *Estradiol*, Menopausal Women, *Spearman*

ABSTRACT

Objectives : This study uses a *case series* design to assess the correlation between interleukin-1 (IL-1) and estradiol levels in menopausal women.

Methods : This research was conducted at H. Adam Malik General Hospital Medan. The study was conducted on 1 September 2017 until the samples was fulfilled. The study population was female paramedics who had not experienced menstruation during the last 12 months at H. Adam Malik General Hospital Medan. Blood extraction from the mediana cubiti vein was carried out to measure estradiol and IL-1 levels. The obtained data was assessed by the *Spearman* test.

Results: From 38 samples in the group of menopausal women, the average serum estradiol level was 42.28 ± 22.86 , and the average serum IL-1 level was 40.84 ± 22.89 . There is a moderate negative correlation between estradiol and IL-1 if estradiol levels decrease, it will increase IL-1 levels.

Conclusion : There is a moderate negative correlation between estradiol and IL-1 if estradiol levels decrease, it will increase IL-1 levels.

Keywords: Correlation, *Interleukin-1*, *Estradiol*, Menopausal Women, *Spearman*

INTRODUCTION

Humans always experience changes since the process of birth until death. At the beginning of human life, change will lead to the direction of growth and development, while in the end change will lead to retrogression that are covered by death. After the birth process takes place, a woman's life goes through various stages, including: childhood, reproduction and climacteric period. Climacteric period in a woman on average occurs at the age of 45-55 years. The term climacterium is rarely used by women and health professionals. They more often use the term menopause.

Estradiol is part of the estrogen hormone, apart from estron and estriol which are the most important types, and have the strongest estrogenic effect and are the largest part of estrogen. Under normal circumstances, estrogen in circulation reaches osteoblast cells and is active through receptors in the cell cytosol which results in decreased cytokine secretion such as interleukin-1 (IL-1), interleukin-6 (IL-6), and Tumor Necrotizing Factor Alpha (TNF- α), where these cytokines function for bone absorption.

In menopausal women, the ovaries produce very little estrogen. The main source of estrogen during menopause is endogenous adrenal, especially androstenedione which is aromatized by peripheral tissue to estrone, which is then converted to estradiol

MATERIALS AND METHODS

Based on Average levels of the Estradiol Serum of Menopausal Women in H. Adam Malik General Hospital Medan

Table 1. Mean serum estradiol levels in menopausal women in H. Adam Malik General Hospital Medan

Amount	Mean \pm SD
Estradiol (pg / mL)	42.28 \pm 22.89

According to table 1 it is known that the mean estradiol level in menopausal women is 42.28 \pm 22.89 with a minimum value of 13.40 and a maximum value of 97.30. In line with other studies, Malutan *et al.* obtained the average levels of estradiol (17 β -E2) in his study in three major groups: group I (control), group II (premenopause), and group III (postmenopausal) of 22.7 \pm 31.1 pg / mL, 60.8 \pm 133 pg / mL, and 0.115 \pm 0.411 pg / mL, respectively.

Kim *et al.* research also found that postmenopausal women had significantly lower levels of 17 β -estradiol compared to premenopausal women, proved by an analysis of the study (135.7 \pm 13.7 pg / mL vs 12.1 \pm 0.59 pg / mL). Study report from Puspita *et al.* The mean value of estradiol in 47 menopausal women was 18.62 \pm 16.85 pg / mL. The majority of menopausal women in this study had low estradiol levels (\leq 20 pg / mL). Low levels of serum estradiol in postmenopausal women can be explained from some literature that estradiol (E2 or 17 β -estradiol) which is a steroid hormone derived from cholesterol in some tissues, especially female reproductive organs. In women, estradiol is produced by ovarian follicles. In postmenopausal women, mean serum estradiol levels range from 10-20 pg / mL. Estradiol levels in menopausal women are lower than women of reproductive age according to the phase of the menstrual cycle. ^{52,56}

The process of aromatization that occurs in peripheral tissues is also related to women's body weight. Usually obese women have much higher levels of estradiol compared to other nonobese women because of increased peripheral aromatization. Estradiol levels circulating after menopause range from 10-20 pg / mL, most commonly originating from peripheral estron conversion, the most from peripheral androstenedione conversion. Estron circulating levels in postmenopausal women are higher than estradiol, around 30-70 pg / mL. Women who enter the menopause phase will experience a decrease in ovarian function, which has an impact on decreased production of the hormones estrogen and progesterone.

Based on Mean Levels of Menopausal Women in H. Adam Malik General Hospital Medan.

Table 2. The average table of IL-1 levels in menopausal women in H. Adam Malik General Hospital Medan

Amount	Mean \pm SD
IL-1 serum (pg / ml)	40.84 \pm 41.39

Based on table 2, it is known that the mean IL-1 level is 40.84 ± 41.39 , with a minimum value of 9.52 and a maximum value of 183.32. Moreover, research by Malutan *et al.* comparing IL-1 β levels in several groups. There was a significant difference ($p = 0.001$) of IL-1 β levels in the control and postmenopausal groups ($1,376 \pm 1,537$ vs $5,318 \pm 9,745$). However, when compared with the premenopausal group, no significant differences were found ($p = 0.169$) with a value of $2,579 \pm 2,679$ in the premenopausal group and $5,318 \pm 9,745$ in the postmenopausal group.

Proinflammatory cytokines IL-1 β can also be used as an indicator other than TNF- α in menopausal inflammatory processes such as osteopenia or osteoporosis. IL-1 β levels were significantly different when compared between the osteopenia or osteoporosis group and the control group, which were $6,047 \pm 9,341$ and $2,284 \pm 1,751$ ($p = 0.008$). Through Pearson's correlation, the correlation coefficient (R) of IL-1 β in the postmenopausal group was -0,441 ($p = 0.017$).²⁶

The opposite results was found by Kim *et al.* where serum IL-1 β levels were not significantly different between premenopausal and postmenopausal women (0.81 ± 0.16 pg / mL vs 0.73 ± 0.14 pg / mL). IL-1 β production in response to LPS stimulation (5-10 ng / mL) is indeed higher in older sample ages than younger age, but it is not significant with details of 0.58 ± 0.05 pg / mL (32-41 years), 0.89 ± 0.27 pg / mL (42-51 years), and 0.78 ± 0.20 pg / mL (52-63 years). It is possible that TNF- α and IL-1 β produced locally are not

released into the circulation, although it does induce a systemic response of IL-6. TNF- α ; IL-1 β is known to be able to stimulate IL-6 production, whereas IL-6 influences the TNF- α and IL-1 β synthesis, indicating that the levels of these cytokines are directly related. Monocytes are cellular components of non-specific immune systems that are activated by LPS; upon activation, these monocytes produce various cytokines such as TNF- α and IL-1 β .

The more important thing is LPS that are stimulated by monocytes to produce IL-1 β are reportedly not affected by 17 β -estradiol or progesterone. This is in line with the study of Stock *et al.* which illustrates that there is no significant change in IL-1 β production in postmenopausal women after monocytes from peripheral blood uptake are incubated with 17 β -estradiol. Conversely, several other researchers found the effect of 17 β -estradiol or progesterone on the production of IL-1 β from monocytes.⁵⁷

It is important to understand that IL-1 β is a proinflammatory cytokine from the interleukin-1 superfamily, consisting of 11 members. Together with IL-1 α , these two cytokines are involved in the defense of the immune system against infection. However, its specific role in the immune system is not fully understood. Recent studies mention IL-1 β , IL-1 β / IL-1 α ratio, and IL-1 bioactivity tend to increase in menopausal women, and can return to the range of premenopausal phase values fifteen years after menopause onset. Regarding postmenopausal osteoporosis, IL-1 does inhibit collagen synthesis in osteoblasts, stimulates degradation of extracellular matrix, and promotes osteoclast formation to begin the cycle of bone resorption, characterized by higher IL-1 β levels in postmenopausal women than in reproductive age (control groups). . But no relationship was found between IL-1 α and estradiol.^{26, 48}

Based on Correlation between Estradiol and IL -1 at H. Adam Malik General Hospital Medan

Table 3. Correlation of Estradiol and IL-1 levels in Menopausal Women in H. Adam Malik General Hospital Medan

Correlation	Value of r	p-value
Estradiol and IL- 1	-0,593	0.00 0

Using the Spearman test showed that there was a significant negative correlation between estradiol and IL-1 with a value of $p = 0,000$ ($p < 0.05$). The correlation coefficient of -0.593 means that there is an inverse relationship between estradiol and IL-1 with moderate negative strength, where a decrease in estradiol will increase IL-1 levels.

Malutan *et al.* reported that IL-1 β levels were significantly higher in natural menopausal women and / or previous surgery than in the control group (women of reproductive age). Even further, a negative correlation was found between cytokines IL-1 β and TNF- α associated with bone mass density in premenopausal and postmenopausal women, considering that osteoporosis is one of the most frequent incidents in menopausal women.

Pacifici in his report failed to prove that menopausal conditions in women increase circulating IL-1 cytokine levels. This is because only a small portion of the cytokines produced in the bone marrow are released into the peripheral circulation, coupled with the theory that cytokines released into the circulation require cells to be attached.

This inverse relationship between estrogen levels and IL-1 has also been successfully explained through estrogen administration in menopausal women which has been shown to reduce the activity of several proinflammatory cytokines. Synthetic estrogen therapy is able to inhibit the expression of IL-1 β and TNF- α and / or the release of monocytes / macrophages and other hematopoietic cell-line cultures; Estrogen therapy increases the expression of IL-1 type II receptor and reduces the stability of IL-1 type I signal receptors.

It was explained that the production of cytokines in healthy and elderly individuals generally comes from a decrease in the level of existing sex hormones. Sex and sex-related hormones do indeed affect the immune system, such as estrogen as an amplifier of humoral immunity and androgen-progesterone as a natural immunosuppressor. Estradiol works for the inhibition of proinflammatory cytokine gene expression, NF- κ B binding, and proinflammatory cytokine production.

DISCUSSION

Based on Average levels of the Estradiol Serum of Menopausal Women in H. Adam Malik General Hospital Medan that the mean estradiol level in menopausal women is 42.28 ± 22.89 with a minimum value of 13.40 and a maximum value of 97.30. In line with other studies, Malutan *et al.* obtained the average levels of estradiol (17 β -E2) in his study in three major groups: group I (control), group II (premenopause), and group III (postmenopausal) of 22.7 ± 31.1 pg / mL, 60.8 ± 133 pg / mL, and 0.115 ± 0.411 pg / mL.

Based on Mean Levels of Menopausal Women in H. Adam Malik General Hospital Medan that the mean IL-1 level is 40.84 ± 41.39 , with a minimum value of 9.52 and a maximum value of 183.32. Moreover, research by Malutan *et al.* comparing IL-1 β levels in several groups. There was a significant difference ($p = 0.001$) of IL-1 β levels in the control and postmenopausal groups ($1,376 \pm 1,537$ vs $5,318 \pm$

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Based on Correlation between Estradiol and IL -1 at H. Adam Malik General Hospital Medan using the Spearman test showed that there was a significant negative correlation between estradiol and IL-1 with a value of $p = 0,000$ ($p < 0.05$). The correlation coefficient of -0.593 means that there is an inverse relationship between estradiol and IL-1 with moderate negative strength, where a decrease in estradiol will increase IL-1 levels.

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CONCLUSION

The frequency distribution of research subjects based on age in most menopausal women is 50-59 years (55.3%) and parity in menopausal women is dominated by multiparous groups (100%), the highest body mass index in menopausal women is obesity (65, 8%), Most menopause duration ≤ 2 years (52.6%).

Mean serum estradiol levels in postmenopausal women by the age of most of the group 50-59 years was 56.7 ± 19.8 , parity group multipara was 42.2 ± 22.9 , BMI of the obese group was 47.0 ± 25.2 , and long menopause 4 -10 years was 70.0 ± 16.0 .

The mean serum IL-1 level in menopausal women based on age from the 40-49 years group was 65.8 ± 51.9 , the parity of the multipara group was 40.8 ± 41.3 , the BMI of the obese group was 47.0 ± 25.2 , and the duration of menopause ≤ 2 years was 58.7 ± 50.7 . The mean serum estradiol level in menopausal women was 42.28 ± 22.89 . The mean serum IL-1 level in menopausal women was 40.84 ± 41.39 . There is a moderate negative correlation between estradiol and IL-1 if estradiol levels decrease, it will increase IL-1 levels.

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