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Correlation of Interleukin-6 with Serum Estradiol Mean Levels in Menopause Women at Rsup H Adam Malik Medan

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Abstract

Aim: To determine the correlation of Interleukin-6 (IL-6) with serum estradiol levels in menopausal women.

Method: This research is a case series research in postmenopausal women to assess the correlation between Interleukin-6 (IL-6) and serum estradiol levels that performed at H Adam Malik General Hospital Medan, starting in August 2017 until 38 samples which met the inclusion and exclusion criteria were fulfill,using non probability sampling technique with consecutive sampling. Serum estradiol and IL-6 levels was examined, then sent to the clinical laboratory. Data tabulated to be analyzed statistically.

Results: The mean serum estradiol level in menopausal women is 29.74 ± 18.69. The mean IL-6 level was 85.03 ± 33.66, in this research showed that in menopausal women there was an increase in IL-6 levels. By using the Spearman Test, the results showed that there was a significant correlation between estradiol and IL-6 with p value <0.004.

Conclusion: There is a significant negative correlation between serum estradiol and IL-6 levels, which means that there is an inverse relationship between serum estradiol and IL-6 levels with weak negative strength, where decreasing estradiol does not always increase IL-6 levels.

Keyword: *Estradiol, Interleukin-6, IL-6, Menopause, Inflammation.*

Introduction

In women with normal menstrual cycles, estradiol is the most estrogen produced by the ovary. Estradiol levels range from 40-80 pg/mL during the reproductive cycle.[1,2] 17ß-estradiol is primary estrogen originating from the ovary. Estradiol (E2 or 17β-estradiol) is a steroid hormone derived from cholesterol metabolism targeting various tissues in the female reproductive organs.The circulating estradiol level after menopause is around 10-20 pg/mL which mostly comes from peripheral conversion of estrone derived from peripheral conversion of androstenedione. The average rate of postmenopausal estrogen production is around 45µg/24 hours. [3-6]

IL-6 levels are increased in postmenopausal women compared to premenopausal women. The decrease in estrogen, especially estradiol, plays a role in increasing IL-6 during menopause. Estradiol plays a role in inhibiting proinflammatory cytokine gene expression,

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NF-κB binding, and the production of proinflammatory cytokines including IL-6.There is also a positive correlation between IL-6 and expression of estrogen (ERα) receptors. [9-12] Interleukin-6 (IL-6) is a cytokine that not only plays a role in the inflammatory process and response to infection but also plays a role in metabolic, regenerative, homeostasis bone, reproduction, and neural processes. IL-6 is a unique cytokine, because besides its activity as a proinflammatory cytokine, IL-6 also plays a role in the anti-inflammatory and regeneration process.[7-8]

There is a hypothesis that estrogen can cause a decrease in serum IL-6 levels because estrogen inhibits osteoblasts as producers of IL-6 and estrogen works as an IL-6 receptor antagonist so that IL-6 work can be inhibited.[13]In the Nasution research which showed that IL-6 production showed a correlation positive with the occurrence of bone resorption in postmenopausal women through the RANKL-independent mechanism.[14] Research conducted by Kim, et al. found that attractively circulating IL-6 is influenced by age and menopause and changes in estrogen after menopause will increase the production of peripheral mononuclear cell cytokines in postmenopausal women which cause an increase in IL-6 which correlates with the occurrence of oxidative stress.[15] Research conducted by Yang, et al, Novella, et al., Rahnama, et al., and Engelmann et al., also showed similar results about the relationship between estrogen levels and IL-6.[16-19]

Material and Method

This research is a case series research to assess the correlation between Interleukin-6 (IL-6) and serum estradiol levels in menopausal women. This research was conducted at H Adam Malik General Hospital Medan and began in August 2017 until the sample size was fulfilled. The research population was female paramedics who had not experienced menstruation during the last 12 months then subjects were determined by using nonprobability sampling technique with consecutive sampling where samples that met the inclusion criteria which is willing to take part in the research, sign informed consent and female paramedics who hadn't menstruation for the past 12 months, and exclusion criteria namely hormone replacement therapy, alcohol consumption, smoking, suffering from diabetes mellitus, having a history of treatment of organic mental disorders, suffering from malignancy. The number of samples obtained is 38 samples.

Serum estradiol & 1L-6 examination: For estradiol, using the reagent "Vidas Estradiol II". Use one strip "E2II" and one SPR "E2II" for each sample, control or calibrator to be tested. Perform the test as directed at User's Manual. All testing steps are carried out automatically by the instrument. Repeat each vial and return it to a temperature of 2-8° C after pipetting. The test will be completed in about 60 minutes. After the test is complete, remove the SPR and strip from the instrument. For IL-6, Reagent "*Human IL-6 (Interleukin-6) ELISA Kit Elabscience*" is used. And add 100 µL of *Biotinylated Detection Ab working* solution to each tube. Add 100 µL*HRP Conjugated Working Solution* in each tube. Add 90 µL of reagent substrate to each tube. Cover with a new cover. Incubate for 15 minutes at 37° C. Protect the plate from exposure to light. Add 50 Ml*stop solution* to each tube.

Findings: Mean Levels of Estradiol and IL-6 in Menopausal Women for Characteristics of Age, Parity, Body Mass Index (BMI), and Duration of Menopause

Table 1. Mean Levels of Estradiol in Menopausal Women for Characteristics of Age, Parity, BMI, and Duration of Menopause

Characteristics	Total (n)	Mean±SD
Age		
• 40-49 y.o.	17	48.1±23.9
• 50-59 y.o.	21	37.5±21.3
• > 60 y.o.	0	0
Parity		
• Nullipara	0	0
• Primipara	0	0
• Multipara	38	42.4±3.71
• Grandemultipara	0	0
BMI		
• Normoweight	4	44.7±13.9
• Overweight	9	47.9±28
• Obesitas	25	39.8±22.1
Menopause Duration		
• ≤ 2 y.o.	20	53.3±23.5
• 3 y.o.	6	40.6±18.3
• ≥ 4 y.o.	12	24.5±9.2

Table 2. Mean Levels of IL-6 in Menopausal Women for Characteristics of Age, Parity, BMI, and Duration of Menopause

Characteristics	Total (n)	Mean±SD
Age		
• 40-49 y.o.	17	30.3±16.8
• 50-59 y.o.	21	55.5±51.9
• > 60 y.o.	0	0
Parity		
• Nullipara	0	0
• Primipara	0	0
• Multipara	38	44.2±41.7
• Grandemultipara	0	0
BMI		
• Normoweight	4	25.4±16.8
• Overweight	9	19.3±3.9
• Obesitas	25	56.2±46.9
Menopause Duration		
• ≤ 2 y.o.	20	29.7±18.1
• 3 y.o.	6	28.2±10.8
• ≥ 4 y.o.	12	76.6±59.7

Table 1. From the table, it can be seen in the group of 40-49 years having a mean level of estradiol of 48.1 pg/mL, whereas in the age group 50-59 years it has a mean level of estradiol of 37.5 pg/mL, so this indicates that the more increasement of age diminished exposure to estrogen.

Table 2. The table presents data that the longer the duration of menopause, the higher the level of IL-6 that can be seen from IL-6 levels in the group with menopause <2 years, the mean IL-6 level is 29.7 pg/mL, whereas in the age group of menopause> 4 years it was seen that mean IL-6 levels is 76.6 pg/mL.

Means Levels of Estradiol in Menopausal Woman

Table 3. Means Levels of Estradiol in Menopausal Woman

	Mean ± SD
Estradiol (pg/mL)	29.74± 18.69

According to table 3.it is known that the mean estradiol level in menopausal women is 29.74 ± 18.69.

Means Levels of Interleukin-6 (IL-6) in Menopausal Woman

Table 4. Means Levels of IL-6 in Menopausal Woman

	Mean ± SD
IL-6 serum (pg/ml)	85.03 ± 33.66

Based on table 4., it is known that the mean IL-6 level is 85.03 ± 33.66, in this research showed that in menopausal women there was an increase in IL-6 levels.

Correlation between Estradiol and IL-6 levels in menopausal woman

Table 5. Correlation between Estradiol and IL-6 levels in menopausal woman

Correlation	r value	p-value
Estradiol and IL-6	-0.458	0.004

Using the spearman test showed a significant correlation between estradiol and IL-6 levels with p value <0.004. The correlation coefficient is -0.458, which means that there is an inverse relationship between estradiol and IL-6 levels with weak negative forces, where decreasing estradiol does not always increase IL-6 levels.

Estradiol Mean Levels in menopausal woman for Characteristics of Age, Parity, Body Mass Index, and Duration of Menopause: The research conducted by Puspita, E.M in 2017 concluded that the aromatic aromatization process was related to women's body weight.[21] In line with research conducted by Mafucci and Gore in Morisson in 2006, which concluded that almost all mammals and vertebrates have decreased reproductive capacity during the aging process. However, menopause is unique to species with a woman's menstrual cycle. In the end, the limited collection of female ovarian follicles causes a decrease in the circulation rate of steroid hormone estradiol.[23,24]

IL-6 Mean Levels in menopausal woman for Characteristics of Age, Parity, Body Mass Index, and Duration of Menopause: The research conducted by Kim, OY obtained the results that the more age increases the higher the level of IL-6 and in this research concluded that this data is related to advanced age phenomena together with menopause, age-related increase in IL-6 in circulation in line with the findings of previous researches.[25]Many studies have also reported an increase in proinflammatory serum markers, especially IL-6

after menopause, indicating that in addition to age, in postmenopausal women, changes in the immune system have been associated with estrogen deficiency.[20]

Means Levels of Estradiol in Menopausal Woman: According to the 2012 Stanzyckresearch, it was found that estrogen levels were at a low concentration (<30 pg/mL) in prepubertal and postmenopausal women, [26] From Kaur's research in 2017, the mean estradiol value was 27.41 ± 5.05 pg/mL.[27]While the Mawiresearch in 2010 found that the mean serum estradiol was 7.54 ± 4.65 pg/mL in postmenopausal women.[28] Research Lkhagvasuren et al. the mean estradiol was 18.3 ± 13.1 pg/mL.[29]

Consistent with the theory, estradiol levels in postmenopausal women are lower than women of reproductive age in each phase of the menstrual cycle.[30]In menopausal women there is a decrease in ovarian follicular activity, the follicles will experience atresia until there are no more follicles to produce estrogen hormones.

Means Levels of Interleukin-6 (IL-6) in Menopausal Woman: The same result is seen in Jabber et al .'s 2015 research of obtaining data on mean IL-6 values in postmenopausal women of 23.9 ± 5.52.[30] In Rachon'sresearch, et al., the mean serum estradiol was 4.44 ± 2.10 pg/mL.[32] Aging theory is associated with a slight and chronic increase in several serum inflammatory mediators such as TNF-α, IL-6, and IL-1ß. TNF-α and IL-1ß with IL-6 can stimulate their production with each other.[25,33-41]According to Kim's research, 2012, it was found that there was an increase in IL-6 in postmenopausal women, a decrease in the immune system associated with a decrease in estrogen.[25]

Correlation between Estradiol and IL-6 levels in menopausal woman: The decline in estrogen, especially estradiol plays a role in increasing IL-6 during menopause. Estradiol plays a role in inhibiting proinflammatory cytokine gene expression, NF-κB binding, and the production of proinflammatory cytokines including IL-6.[18,25,33-35] Estrogen deficiency in postmenopausal women will stimulate bone loss and increase cytokine production such as IL-1, IL-6, and TNF-α.[14]

Conclusion

The results of this research show that there is a significant weak negative correlation between estradiol and IL-6, which means that there is an inverse relationship between Estradiol and IL-6 with weak negative strength, where decreasing estradiol does not always increase IL-6 levels.

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Ethical Clearance: For research permission, research approval was obtained from the research subject and the Ethics Committee of the Faculty of Medicine, University of North Sumatra who would conduct an assessment of the feasibility of the research proposal.

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