

# Correlation Between Leptin and Estradiol Serum Level to Hot Flashes on Menopause Woman

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## ABSTRACT

The most common and disturbing symptom of menopause is a hot flash. One of the substances that is thought to play a role in hot flashes is leptin. Leptin functions to maintain energy balance in the body. Estrogen has the effect of increasing the sensitivity of leptin in the brain so that in the menopausal state where estrogen deficiency occurs, it causes leptin sensitivity to decrease which will eventually increase leptin levels.

This study is an analytic study with Case Control design by examining women in H. Adam Malik General Hospital Medan at November - December 2019 to see the correlation between serum levels of leptin and estradiol with the presence of hot flashes and without hot flashes in menopausal women. The sample of this study is 50 people by consecutive sampling. Serum levels of leptin and estradiol are examined by conducting laboratory tests on venous blood using the ELISA (Enzyme Linked Immunosorbent Assay) method. Then data is collected and analyzed using statistical analysis.

There was a significant difference in serum leptin levels in menopausal women with symptoms of hot flash ( $25,87 \pm 1.23$ ) and without hot flash ( $23.86 \pm 0.75$ ) ( $p < 0.001$ ). Mean of estradiol level in hot flashes group ( $25.52 \pm 2.85$ ) and without hot flash group ( $26.12 \pm 1.45$ ) there was no significant differences in serum estradiol levels in menopausal women with or without symptoms of hot flash ( $p = .922$ ). Correlation was obtained between serum leptin and estradiol levels in the event of hot flash  $-0.294$  ( $p = 0.154$ ) which indicates a negative correlation with a weak strength between serum leptin level and estradiol level in menopausal women with symptoms of hot flash. This suggests that the higher the leptin, the lower the estradiol levels.

**Keywords:** Leptin Serum, Estradiol, *Hot Flash*, Menopause.

## Introduction

The most frequent and disturbing symptom of menopause is hot flash or in Bahasa Indonesia known as "semburan panas". This symptom is experienced by about 75% of women who experience menopause. Hot flash refers to a vasomotor symptom due to the reactivity of blood vessels which is characterized by prominent vasodilation and followed by vasoconstriction. The mechanism causing the hot flash is still unknown, but it is thought to be related to the disruption of the temperature regulation mechanism in the hypothalamus which is triggered by a decrease in estrogen levels. Hot flashes can occur at any time and are spontaneous or can be triggered by a variety of ordinary situations, such as embarrassing situations, sudden changes in environmental temperature, stress, alcohol, caffeine, or warm drinks. Although the causes of hot flashes are mostly the same, the experiences experienced by each woman vary. <sup>1,2,3,4</sup>

The impact of hot flashes on a woman's quality of life can be calculated and sometimes underestimated. Hot flash can interfere with work and daily activities, such as sleep, causing fatigue, loss of concentration, causing symptoms of depression so that it can interfere relationship with family including sexual function and marital relations. Hot flash in about 20% of women is a problem and has a negative impact on quality of life. <sup>2,5</sup>

One of the substances that is thought to play a role in hot flashes is leptin. Leptin is a protein that is encoded by the obesity gene (*ob*), secreted by adipocyte cells, and acts on the central nervous system. This protein serves to maintain energy balance in the body which works in reducing food intake, regulating body weight, and increasing energy expenditure.<sup>6,7,8</sup> Leptin pulsation is positive and is strongly related to estrogen levels in women with normal cycles. Estrogen has the effect of increasing the sensitivity of leptin in the brain so that in the menopausal state where estrogen deficiency occurs, it causes leptin sensitivity to decrease which will eventually increase leptin levels. Sower et al found that an increase in leptin levels during the menopause transition.<sup>9,10,11,12</sup>

In menopausal women with hot flashes, leptin levels tend to increase. The role of leptin in the hot flash mechanism may be related to its function in regulating energy expenditure. In rats that were injected with exogenous leptin, an increase in core body temperature was found to be one of the earliest causes of hot flash events in menopausal women. Serum leptin levels are also related to the incidence, frequency, duration, and severity of hot flashes. In other words, leptin levels play an important role in the pathogenesis of hot flashes.<sup>8,13</sup>

## Material and Methods

This study is an analytical study with a Case Control design by examining women in H. Adam Malik General Hospital Medan to see the relationship between serum levels of leptin and estradiol with hot flashes and no hot flashes in menopausal women in the period November - December 2019. Target population This research is menopausal women in RSUP Adam Malik Medan. The research subjects were part of the population of the case group were menopausal women who experienced symptoms of hot flash, while the subjects of the control group were menopausal women who did not experience hot flash symptoms who came to H Adam Malik General Hospital Medan. Through the research formula, a total sample of 50 people was obtained for both groups with consecutive sampling technique as a way of taking samples. In each study subject anamnesis, physical examination, and additional examination (MENQOL questionnaire) were conducted on women to determine whether women had hot flashes, then laboratory tests were performed on women to determine serum levels of leptin and estradiol in women as much as 3 mL for each examination at the same time. Serum levels of leptin and estradiol were then measured using the ELISA method. Then the data is analyzed statistically.

## Results

There are 50 subjects in this study. Subject characteristics are illustrated in table 1. below. It appears that the characteristics of menopausal women with hot flash by the number of parity, 22 women (88%) multiparous (2-4x giving birth) and the remaining 3 women (12%) grandemultiparous ( $\geq 5x$  giving birth). In addition, based on the severity of hot flash it appears that the majority of women are 16 people (64%) with mild degrees (1-6) and the remaining 9 people (36%) with moderate degrees (7-12). Based on the duration of menopause, in women who experience hot flashes, as many as 11 people (44%) have been menopausal for  $\leq 2$

years. In women without symptoms of hot flash, based on the number of parity, 20 people (80%) multiparous (2-4 times giving birth) and the remaining 5 people (20%) grandemiparous women ( $\geq 5$  times giving birth). As for the degree of hot flash, in this group all patients did not experience complaints (100%). Based on the duration of menopause, in women who do not experience hot flashes, as many as 10 people (40%) have been menopausal for 3 years.

**Table 1. Characteristic of Menopausal Woman With and Without Hot Flash**

Characteristic	Wanita Menopause		
	<i>Hot Flash</i>	Tanpa <i>Hot Flash</i>	
	N (%)	N (%)	
Parity	Nulliparous	0 (0%)	0 (0%)
	Primiparous	0 (0%)	0 (0%)
	Multiparous	22 (88%)	20 (80%)
	Grandemultiparous	3 (12%)	5 (20%)
Hot flash	None (0)	0 (0%)	25 (100%)
	Mild (1-6)	16 (64%)	0 (0%)
	Moderate (7- 12)	9 (36%)	0 (0%)
	Severe (13-18)	0 (0%)	0 (0%)
Duration of Menopause	$\leq 2$ years	11 (44%)	7 (28%)
	$>2 - <4$ years	8 (32%)	10 (40%)
	$\geq 4$ years	6 (24%)	8 (32%)

**Table 2. Means of Leptin and Estradiol Serum Levels in Menopausal Women With and Without Hot Flash**

Serum	<i>With Hot Flash</i>		<i>Without Hot Flash</i>	
	Mean $\pm$ SD	Min – Max	Mean $\pm$ SD	Min-Max
Leptin	25.87 $\pm$ 1.23	24.2 - 28.3	23.86 $\pm$ 0.75	22.6 - 25.5
Estradiol	25.52 $\pm$ 2.85	18 - 29	26.12 $\pm$ 1.45	24-29

From table 2. the mean leptin serum level in menopausal women with symptoms of hot flash is 25.87  $\pm$  1.23 (95% Confident Interval: 25.36, Min-Max: 24.2 - 28.3). Then, the mean estradiol serum level was 25.52  $\pm$  2.85 (95% Confident Interval: 24.34, Min-Max: 18-29). While the mean value of leptin serum in subjects with symptoms of hot flash was 23.86  $\pm$  0.75 (95% Confident Interval: 23.55, Min-Max: 22.6 - 25.5), and the mean value of estradiol levels in samples without symptoms of hot flash was 26.12  $\pm$  1.45, (95 % Confident Interval: 25.5, Min - Max: 24-29).

**Tabel 3. Correlation Between Leptin Serum Level on Menopausal Women With and Without Hot Flash**

Serum	Hot Flash	Without Hot Flash	p value*
	Mean ± SD	Mean ± SD	
Leptin	25.87 ± 1.23	23.86 ± 0.75	.000*

\* *T Test Independent*

To assess the relationship of serum leptin levels in postmenopausal women with symptoms of hot flash and without symptoms of hot flash, independent t tests were performed and the results obtained p value = .000 (p <0.001) which showed significant differences in serum leptin levels in menopausal women with hot flash symptoms and without symptoms of hot flash.

**Table 4. Correlation Between Serum Estradiol Level on Menopausal Woman With and Without Hot Flash**

Serum	Hot Flash	Without Hot Flash	P value
	Mean ± SD	Mean ± SD	
Estradiol	25.52 ± 2.85	26.12 ± 1.45	.922**

\*\* *Mann Whitney Test*

For estradiol levels, a Mann Whitney Test was performed and p-value = .922 (p > 0.05) was obtained which showed no significant difference in serum estradiol levels in menopausal women with or without symptoms of hot flash.

**Table 5. Correlation between leptin serum level and estradiol serum level on menopausal woman with hot flash**

Serum	Correlation coefisien*	P value
Correlation between leptin and estradiol serum level on menopausal woman with hot flash	-0.294	.154

\**Spearman Test*

To find the correlation between leptin and estradiol serum level on hot flash, a spearman test was performed and a correlation coefficient = -0.294 was obtained which indicates a negative correlation

with a weak strength between serum levels of leptin and estradiol in menopausal women with symptoms of hot flash. This suggests that the higher the leptin serum level, the lower the estradiol serum levels.

## Discussion

In this study it was found that based on the degree of hot flash it appeared the majority of women were 16 people (64%) with mild degrees (1-6) and the remaining 9 people (36%) with moderate degrees (7-12). Whereas a study by Nakano showed that of 388 women, 274 (70.6%) reported having experienced hot flashes. Nearly half (49.0%) of these samples reported experiencing hot flashes in the last 30 days, and 63.1% reported that most of the hot flashes were included in moderate or severe intensity.<sup>15</sup> Research in India showed 88 women (68.8% ) had severe symptoms, followed by 18.7% suffering from moderate symptoms and 16 (12.5%) of them with very severe symptoms. Among these are some of the symptoms, a high average score found in the symptoms of hot flash and excessive sweating.<sup>16</sup>

The relationship between hot flash and reproductive history variables, including age at menarche, age at first and last pregnancy, and parity, is still unclear. Among women aged 40-65 years who were enrolled in a large prospective study in France, parity was associated with a reduced risk of menopausal symptoms, including hot flashes. In addition, the reduced risk of hot flashes is also associated with a higher number of live births observed in a prospective community-based study of Japanese women. In this study, for a history of parity of menopausal women who experience hot flashes found 22 women (88%) multiparous (2-4x giving birth) and the remaining 3 women (12%) grandemultiparous ( $\geq 5x$  giving birth). In contrast to the results of the study by Nakano, the majority (86.1%) of the study sample reported at least one pregnancy. More than three-quarters of women (77.8%) have one or more live births. The mean age at first live birth was  $26.8 \pm 145.7$  years, with 52.6% of participants experiencing their first live birth when they were 29 years old. In line with this study, research in India showed the mean age of menarche was  $13.19 \pm 1.95$  with a majority of 62 women (48.4%) with a history of multiparous parity, and most of the sample ie 63 people (49.2%) reached menopause within 1-2 years.<sup>16</sup> Slower oocyte atresia or continued circulation of normal estrogen levels have the potential to delay or prevent fluctuating estrogen levels associated with the menopausal transition and thermoregulation which cause dysfunction that manifests as hot flashes and night sweats.<sup>15</sup>

In this study the mean serum leptin levels in menopausal women with symptoms of hot flash were  $25.87 \pm 1.23$  (95% Confident Interval: 25.36, Min-Max: 24.2 - 28.3). Then, the mean serum estradiol level was  $25.52 \pm 2.85$  (95% Confident Interval: 24.34, Min-Max: 18-29). In contrast to this study, Huang's research showed that the average level of leptin in mild to moderate hot flashes was 10.2 ng / mL and in severe hot flash symptoms was 16.2 ng / mL. As for the estradiol levels in all menopausal women both hot flash and without symptoms, all estradiol levels  $<20$  pg / mL.<sup>14</sup>

Leptin is a cytokine-like protein that regulates energy balance through its action in the brain against appetite and energy expenditure and can cause thermoregulatory dysfunction. Leptin levels will increase from the premenopausal stage to the postmenopausal stage. Changes in reproductive hormone

levels, including decreased estrogen concentrations, have long been regarded as etiological factors for hot flashes. In this study, an independent t test was performed and the results obtained p value = .000 ( $p < 0.001$ ) which showed significant differences in serum leptin levels in menopausal women with hot flash symptoms and without hot flash symptoms. In line with this study, Alexander found a significant relationship between leptin levels and the occurrence of hot flashes ( $p = 0.04$ ). Leptin levels were associated with experiences of experiencing hot flashes ( $p = 0.04$ ), hot flashes in the last 30 days, ( $p = 0.03$ ), and duration of hot flashes ( $> 1$  year,  $p = 0.03$ ). In addition, Alexander's study found leptin levels were positively correlated with free estrogen index (free estrogen index / FEI) levels ( $p < 0.0001$ ). However, it was found that although leptin levels were associated with hot flashes, leptin levels did not correlate with levels of estradiol and estrone.<sup>13</sup> In contrast to this study, research by Tomaseli showed no significant difference in leptin levels between the control group and the group with vasomotor symptoms. This is because hypoestrogenism induced by GnRH analogues (GnRHa) does not seem to affect leptin levels in normal women and menopausal women.<sup>17</sup>

In this study, to assess differences in estradiol levels between the two groups the Mann Whitney Test was performed and the results obtained  $p = .922$  ( $p > 0.05$ ) which showed no significant difference in serum estradiol levels in menopausal women with or without hot flash symptoms. Research by Arizanovic showed the mean levels of estradiol in postmenopausal women with hot flash was  $31.68 \pm 14.52$  and it was found that women with hot flashes had lower estradiol levels during the day and night ( $28.17 \pm 10.06$  vs.  $30.63 \pm 13.56$  during the day;  $24.69 \pm 12.86$  vs  $30.09 \pm 12.35$  at night) compared to women without hot flashes, but there was no statistically significant difference. This result is explained by the hot flash occurring as a result of changes in the concentration of sex hormones that occur during menopause. Increased concentrations of FSH and LH accelerate the depletion of follicular numbers and reduce estrogen and inhibin synthesis, leading to vasomotor instability and the appearance of hot flashes.

In addition, to assess the correlation between serum levels of leptin and estradiol in hot flash events, the Spearman correlation test was conducted in this study and a correlation coefficient =  $-0.294$  was obtained which indicates the inverse correlation with the weak strength between serum levels of leptin and estradiol in menopausal women with symptoms hot flash. Research by Alexander who also used the Spearman rank test, showed leptin levels were associated with hot flashes, did not correlate with levels of estradiol or estrone. Leptin is known to mediate the formation of estrogen from circulating androgen precursors and to influence thermoregulation. In a study using mice, leptin destroyed the sensitivity effect of insulin-like-growth factor-1 (IGF-1) to the synthesis of follicle stimulating hormone (FSH) -dependent estradiol by granulosa cells. Although the study did not show a correlation between leptin and estradiol, changes in reproductive hormone levels, including decreased estrogen concentrations, have long been regarded as etiological factors in hot flashes.<sup>13</sup>

## Conclusion

Based on this study there is a relationship between serum leptin levels in menopausal women with symptoms of hot flash and without hot flash with  $p = .000$  ( $p < 0.001$ ). However, no association was

found between serum estradiol levels in menopausal women with symptoms of hot flash and without symptoms of hot flash with  $p = .922$  ( $p > 0.05$ ). Then the correlation between serum levels of leptin and estradiol was obtained in the event of hot flash =  $-0.294$ , which indicates a negative correlation with the weak strength between serum levels of leptin and estradiol in menopausal women with symptoms of hot flash. This suggests that the higher the leptin, the lower the estradiol levels.

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