narra j

Short Communication

Comparison of leptin and estrone levels between normal body mass index and obese menopausal women

Muhammad FG. Siregar[1,2*], Masakazu Terauchi[3], Rizka A. Sari[4], Cut A. Adella[1,2], Muhammad O. Prabudi[5,6], Melvin NG. Barus[7,8], Riza Rivany[1,2], Immanuel DL. Tobing[4,9] and Selly Azmeila[10]

[1]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [2]Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, H. Adam Malik General Hospital, Medan, Indonesia; [3]Department of Women's Health, Tokyo Medical and Dental University, Tokyo, Japan; [4]Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [5]Division of Fertility and Reproductive Endocrinology, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [6]Division of Fertility and Reproductive Endocrinology, Department of Obstetrics and Gynecology, H. Adam Malik General Hospital, Medan, Indonesia; [7]Division of Fetomaternal, Department of Obstetrics and Gynecology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia; [8]Division of Fetomaternal, Department of Obstetrics and Gynecology, H. Adam Malik General Hospital, Medan, Indonesia; [9]Department of Obstetrics and Gynecology, H. Adam Malik General Hospital, Medan, Indonesia; [10]Department of Physiology, Faculty of Medicine, Universitas Sumatera Utara, Medan, Indonesia

*Corresponding author: fgsiregar@gmail.com

Abstract

Postmenopausal women often experience hormonal changes and shifts in fat composition, affecting weight gain and obesity. Understanding the link between hormones, especially estrogen and leptin, is key to managing weight and lowering disease risk in menopausal women. The aim of this study was to compare the levels of leptin and estrone in menopausal women with normal weight and obesity. A cross-sectional study was conducted on menopausal women, either normal body mass index (BMI) or obese, at H. Adam Malik General Hospital, Medan, Indonesia. Blood samples were collected to measure leptin and estrone levels using the enzyme-linked immunosorbent assay (ELISA) method. The differences in leptin levels between groups were analyzed using the Wilcoxon test, while the correlation between BMI and leptin was examined using the Pearson correlation test. The disparity in estrone levels in both groups was analyzed using the Mann-Whitney test and the correlations between variables were assessed using the Spearman or Pearson correlation tests as appropriate. The mean leptin levels in normal BMI and obesity groups were 17.73±4.96 and 25.46±12.95 ng/mL, respectively, and were statistically different (p=0.006). The mean estrone levels in menopausal women with normal BMI and obesity were 943.23±391.79 and 851.38±282.23 ng/mol, respectively and were not statistically different (p=0.564). A significant positive correlation was found between BMI and leptin level (r=0.59; p<0.001), while BMI and estrone were not significantly correlated (r=0.083; p=0.559). In conclusion, leptin level was significantly different between BMI groups and had a strong positive correlation with BMI. This finding could be an important insight in body weight management and disease risk prevention in menopausal women.

Keywords: Obesity, BMI, menopausal women, leptin, estrone

Introduction

Menopause, as defined by the World Health Organization (WHO), refers to the permanent cessation of the menstrual cycle in women who have previously experienced monthly

https://narraj.org/

Received: March 3, 2024 - Accepted: May 16, 2024 - Published online: May 27, 2024

menstruation, with amenorrhea occurring consistently for the last 12 months and not attributable to a pathological condition [1-3]. Menopausal women experience shifts in muscle mass and estrogen levels due to follicle loss, leading to a decrease in ovarian estrogen secretion and dominance of estrone from theca cells and adrenal androgens [4]. These changes increase susceptibility to obesity compared to premenopausal women, as the disappearance of the menstrual cycle alters calorie intake and lowers metabolism, often resulting in weight gain [4]. Menopausal symptoms significantly affect women's quality of life and are influenced by various risk factors, including body mass index (BMI), nutritional status, and knowledge. The relationship between BMI and menopausal symptoms yields varied outcomes. A study suggests that advanced age contributes to increased obesity rates, persisting into later stages of life, such as at 60 years of age [3].

According to WHO report, post-menopausal women have a higher prevalence of obesity compared to the general female population, and overweight and obesity are significantly associated with increased risk of morbidity and mortality [5]. The WHO also reported that obesity affects over 10% of the world adult population, with nearly 300 million cases reported among women alone [5]. Based on the result of Indonesian *Riset Kesehatan Dasar (Riskesdas)* 2018, from 2007 to 2018, there was an increase in the prevalence of overweight (from 8.6% to 13.6%) and obesity (from 10.5% to 21.8) [6]. The prevalence is slightly higher among adult women compared to other groups in the country, with approximately 15.1% classified as overweight and 29.3% falling into the obese category [7].

The longitudinal relationship between leptin and the development of menopause has previously been investigated in several studies, showing that body adiposity is a major contributor to leptin levels [8-11]. Leptin has a central role in energy homeostasis and high leptin level (hyperleptinemia) is found in obese patients, where leptin concentrations are strongly correlated with BMI and body fat percentage [8]. Increased obesity in postmenopausal women increases leptin, contributing to insulin resistance [12].

Contrasting estrone and estradiol provides insight into postmenopausal estrogen production. Estrone partly arises from androstenedione conversion, while estradiol may derive from estrone conversion. It is suggested that androstenedione aromatization to estrone is associated with body weight, especially excess fat, in postmenopausal women [8]. Therefore, the aim of this study was to compare the leptin and estrone levels in menopausal women with normal BMI and obesity.

Methods

Study design and patients

A cross-sectional study was conducted on menopausal women at H. Adam Malik General Hospital, Medan, Indonesia, in August 2023. Non-probability sampling was employed along with the consecutive sampling strategy. The minimum sample size of 26 was determined for each group (normal and obese). This study included menopausal women (spontaneous cessation of menstruation for at least 12 consecutive months) with either a normal body mass index (BMI: 18.5–22.9 kg/m^2) or obese (BMI: ≥25 kg/m^2). Patients should not have any history of cardiovascular disease, chronic kidney disease, hepatitis, malignancy, diabetes mellitus, hypothyroidism, hyperthyroidism, autoimmune disease, insulin or corticosteroid uses, ongoing hormonal therapy, oophorectomy, or hysterectomy. Patients who withdrew and those with damaged blood samples were excluded from the study.

Data collection

Anamnesis was carried out on the patients to obtain the patient's characteristic data, such as age, parity, and duration of menopause. Anthropometric measurements (weight and height) and blood samples were performed individually by doctors and laboratory officers at the patient's house or workplace. A total of 6 mL of blood was drawn from the median cubital vein and the blood sample was then divided in half and put into two tubes to measure leptin and estrone levels. Leptin and estrone level examination employed the enzyme-linked immunosorbent assay (ELISA) method conducted at H. Adam Malik General Hospital, Medan, Indonesia.

Statistical analysis

Data were analyzed descriptively to display the frequency distribution of the patient's characteristics. Differences in leptin and estrone levels between the two groups (normal and obese) were assessed using the independent t-test for normally distributed data or the Mann-Whitney test for non-normally distributed data. Correlation analysis between leptin and estrone levels in the normal and obese groups involved using the Pearson test for normally distributed data and the Spearman test for non-normally distributed data. A *p*-value of <0.05 was considered statistically significant. All statistical analyses were performed on SPSS version 25 (SPSS Inc., Chicago, USA).

Results

Characteristics of the patients

A total of 52 menopausal women (26 normal and 26 obese) were included in the study, as presented in **Table 1**. The average age of the women was 57 years old (**Table 1**). Among the groups, the majority had a menopause duration of less than five years and were multiparous. The BMI of the normal and obese groups were 21.99±1.22 and 28.78±3.36 kg/m^2, respectively. No significant differences were observed among the characteristics (p>0.05).

Table 1. Characteristics of menopausal women

Characteristics	Menopausal women		*p*-value
	Normal	Obese	
Age (mean±SD)	57.46±7.14	54.53±3.82	0.127
Duration of menopause			0.212
<5 years	10 (43.5%)	13 (56.5%)	
5–10 years	11 (47.8%)	12 (52.2%)	
>10 years	5 (83.3%)	1 (16.7%)	
Parity			0.353
Nulliparous	0 (0%)	1 (100%)	
Primiparous	3 (75%)	1 (25%)	
Multiparous	16 (44.4%)	20 (55.6%)	
Grand multiparous	7 (63.6%)	4 (36.4%)	
Body mass index (BMI) (mean±SD), kg/m^2	21.99±1.22	28.78±3.36	0.392

Comparison of leptin and estrone levels between normal and obese menopausal women

The normal group had a mean leptin level of 17.73±4.96 ng/mL, which was significantly lower than the mean of 25.46±12.95 ng/mL observed in the obesity group (p=0.006). However, estrone levels did not significantly differ between the two groups, with the mean values reported in the normal and obese groups being 943.23±391.79 ng/mol and 851.38±282.23 ng/mol (p=0.564), respectively (**Table 2**).

Table 2. Comparison of leptin and estrone levels between study groups

Group	Leptin serum (ng/mL)	*p*-value	Estrone serum (ng/mol)	*p*-value
	Mean±SD		Mean±SD	
Normal	17.73±4.96	0.006[a]	943.23±391.79	0.564[b]
Obese	25.46±12.95		851.38±282.23	

[a] Analyzed with independent Student t-test
[b] Analyzed with Mann-Whitney test

Correlation between leptin and estrone levels with normal BMI and obesity in menopausal women

The analysis revealed a moderate positive correlation between leptin and BMI, which was statistically significant (p<0.05). Additionally, there was a very weak positive correlation between estrone levels and BMI; however, this relationship was not statistically significant (**Table 3**).

Table 3. Correlation between BMI with leptin and estrone levels

Variable	Leptin serum (ng/mL)		Estrone serum (ng/mL)	
	r	*p*-value	*r*	*p*-value
Body mass index (BMI)	0.590	<0.001[a]	0.083	0.559[b]

[a] Analyzed with Pearson test
[b] Analyzed with Spearman test

Leptin and estrone levels based on the duration of menopause

The group with a menopause period of more than 10 years exhibited the lowest mean leptin levels (18.17±3.87), while the highest levels were observed in the 5–10 years group (22.74±11.67). Meanwhile, the average estrone levels were based on the length of menopause. The lowest estrone levels were in the group with a menopause duration of 5–10 years and the highest were in the group with a menopause duration of less than five years (931.00±416.67). However, the duration of menopause did not have any significant impact on the difference between leptin and estrone levels (p>0.05) (**Table 4**).

Table 4. Mean of leptin and estrone levels based on duration of menopause

Duration of menopause	Leptin (ng/mL)	*p*-value	Estrone (ng/mol)	*p*-value
<5 years	21.35±10.48	0.637	931.00±416.67	0.749
5–10 years	22.74±11.67		856.26±291.74	
>10 years	18.17±3.87		925.50±188.17	

Discussion

Our study revealed that the mean leptin levels in menopausal women with normal BMI (17.73±4.96 ng/mL) was significantly lower compared to the menopausal women with obese BMI (25.46±12.95 ng/mL). This aligns with a previous study that found a notable distinction in leptin levels between normal and abnormal BMI groups (p<0.0001), with higher levels observed in the obese group compared to the non-obese, thereby establishing a significant association between leptin levels and obesity [10]. The result was also similar to a study that found the levels of leptin and free leptin had a significant relationship with body weight, and the leptin levels were different between obese and the non-obese groups [11]. However, a study on postmenopausal women with osteoporosis showed that plasma leptin levels were correlated with BMI in both the control and patient groups, but the mean plasma leptin concentration in both groups was not significantly different [14]. Leptin secretion is directly proportional to the amount of body fat and it is synthesized as a marker of adequate energy production. Leptin will act on the infundibulum/arcuate nucleus by modulating the expression of various anorexigenic neuropeptides such as pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript (CART) and binding to soluble leptin receptor (sOBR) to maintain bioavailability and reduce its concentration [8]. The sOBR plays an important role in optimizing leptin function and has been known to be associated with adiposity and obesity [8]. This is due to the proportional distribution of subcutaneous fat [8]. While leptin decreases appetite and body weight, the paradoxical relationship of obesity will lead to leptin resistance. Post-menopause hormonal activity is believed to have an effect on leptin resistance as part of the aging process, affecting energy homeostasis in the hypothalamus, which is mediated by various neurons such as orexigenic agouti-related peptide (AgRP), neuropeptide Y (NPY), and anorexigenic pro-opiomelanocortin as well as the long isoform of the leptin receptor (LERP-B) [13,15]. Apart from that, a sedentary lifestyle can also increase the incidence of obesity [16].

This present study found no significant differences in serum estrone levels between normal and obese groups. The findings are supported by a different study that reported there was no significant correlation between estrone and BMI in patients receiving letrozole therapy [17]. Letrozole, an aromatase inhibitor, is utilized to treat estrogen receptor-positive breast cancer in postmenopausal women. However, in cases of obesity or metabolic syndrome, standard doses of letrozole (2.5 mg/day) may not effectively suppress estradiol and estrone due to increased levels of free estrogen from peripheral aromatization of fatty tissue, highlighting the potential limitations of aromatase inhibitors in patients with excessive BMI [17]. Our study result differ from those of Silva *et al.* [18] and Oh *et al.* [19], which showed that increasing BMI had a

significant correlation with estrone. Our data indicated that the estrone level was higher in the obese group, although it was not correlated with BMI. This may be due to estrone's ability to act as a compensatory mechanism to protect organ systems that cause metabolic changes [18,19]. Following menopause, when the ovaries stop producing estrogen, adipose tissue becomes the primary site for estrogen synthesis through aromatization, converting androstenedione into estradiol and estrone [20]. Consequently, the correlation between BMI and the levels of circulating total estradiol and free estradiol in postmenopausal women can be attributed to the higher fat mass, which promotes increased estrogen production. Estrone continues to be produced through peripheral aromatization, while the levels of estradiol, typically produced by the ovaries, decline [21,22].

This study revealed that the highest mean of leptin levels was observed in women with a menopause duration of 5–10 years. However, the duration of menopause did not have any significant impact on the difference between leptin and estrone levels. A study examining the correlation between menopausal symptoms with ghrelin and adipokines in women categorized as early post-menopause (<10 years since menopause) and late post-menopause (>10 years since menopause) found no association between adipokine levels (leptin, adiponectin, and resistin) and menopause duration [23]. The study divided leptin levels into three groups (9.7–16 ng/mL, 17–26.5 ng/mL, and >26.5 ng/mL) and revealed no significant relationship with the duration of menopause (<10 years, p=0.33; >10 years, p=0.35) [23]. Another study also showed that serum leptin levels were not related to estradiol and estrone levels [24]. Leptin plays a role in improving menopausal symptoms by causing changes in the brain's appetite and energy expenditure. Elevated leptin levels also have a role in increasing core body temperature and the symptoms of hot flashes in post-menopausal women worsen as a result of this rise in temperature [25].

Based on menopause duration, we found that the mean estrone levels were 931.00±416.67 ng/mol for under five years, 856.26±291.74 ng/mol for 5–10 years, and 925.50±188.17 ng/mol for over 10 years. Although there is no previous study similar to these findings, a study in 2021 analyzed estrogen (estradiol) levels based on menopause duration [26]. The study found that the median estradiol level in the early menopause group (less than six years of menopause) was 46.0 pg/mL, whereas in the late menopause group (more than 10 years of menopause), it was 45.0 pg/mL and there was no significant difference between the groups [26]. Menopause is associated with various hormonal changes, most notably a decrease in circulating estrogen levels. This decline leads to several physiological changes, such as genital atrophy, loss of urogenital tissue support, and bone loss [27,28]. However, while estradiol levels produced by the ovaries decrease, estrone production continues through peripheral aromatization [21,22].

Conclusion

Our study found that BMI was associated with the levels of leptin and estrone in menopausal women. Future research should explore additional factors that may contribute to obesity in menopausal women to help identify prevention and treatment strategies and reduce the impact of obesity-related morbidity and mortality.

Ethics approval

This study has been approved by the Ethics and Legal Committee for Conducting Health Research of Universitas Sumatera Utara, Medan, Indonesia (936/KEPK/USU/2023).

Acknowledgments

The authors would like to acknowledge all of the people who helped with the research.

Competing interests

All authors affirm that they have no conflicts of interest.

Funding

This study received no external funding.

Underlying data

Data derived to support the conclusions of this study can be obtained by contacting the corresponding author upon request.

How to cite

Siregar MFG, Terauchi M, Sari RA, *et al.* Comparison of leptin and estrone levels between normal body mass index and obese menopausal women. Narra J 2024; 4 (2): e745 - http://doi.org/10.52225/narra.v4i2.745.

References

1. Indah W, Aurora D, Kusdiyah E, Mulyadi D. Hubungan antara indeks massa tubuh dan kadar kalsium dalam darah sebagai deteksi osteoporosis pada wanita usia 40-60 tahun di Kota Jambi. JMJ, Spec Issues, JAMHESIC 2021;10(2):299-305.
2. World Health Organization. Menopause. Available from: https://www.who.int/news-room/fact-sheets/detail/menopause (2022). Accessed: 19 April 2024.
3. Zulfi OE, Dwiningsih SR, Krisnana I. The body mass index (BMI) related to menopause symptoms. Indones Midwifery Heal Sci J 2021;5(1):73-87.
4. Yulizawati, Yulika M. Mengenal fase menopause edisi pertama. Sidoarjo: Indomedia Pustaka; 2022.
5. World Health Organization. Obesity and overweight. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight (2024). Accessed: 19 April 2024.
6. Kementrian Kesehatan Republik Indonesia. Badan Penelitian dan Pengembangan Kesehatan. Laporan Nasional Riskesdas 2018. Jakarta: Lembaga Penerbit Badan Penelitian dan Pengembangan Kesehatan (LPB); 2018.
7. UNICEF. Analisis lanskap kelebihan berat badan dan obesitas di Indonesia. Available from: https://www.unicef.org/indonesia/id/laporan/analisis-lanskap-kelebihan-berat-badan-dan-obesitas-di-indonesia (2019). Accessed: 19 April 2024.
8. Fitri Y, Tann G, Rusdiana. Estradiol and leptin in women with obesity, overweight, and normal body weight. Indones J Med 2017;2(1):35-40.
9. Sowers MFR, Wildman RP, Mancuso P, *et al.* Change in adipocytokines and ghrelin with menopause. Maturitas 2008;59(2):149-157.
10. Kumar R, Mal K, Razaq MK, *et al.* Association of leptin with obesity and insulin resistance. Cureus 2020;12(12):19-22.
11. Hestiantoro A, Astuti BPK, Muharam R, *et al.* Dysregulation of kisspeptin and leptin, as anorexigenic agents, plays role in the development of obesity in postmenopausal women. Int J Endocrinol 2019;2019:1347208.
12. Proietto J. Obesity and weight management at menopause. Aust Fam Physician 2017;46(6):368-370.
13. Hestiantoro A, Astuti BPK, Muharam R, *et al.* Dysregulation of kisspeptin and leptin, as anorexigenic agents, plays role in the development of obesity in postmenopausal women. Int J Endocrinol 2019;2019:1347208.
14. Koçyiğit H, Bal S, Atay A, *et al.* Plasma leptin values in postmenopausal women with osteoporosis. Bosn J Basic Med Sci 2013;13(3):192-196.
15. Hajiahmadi M, Shafi H, Delavar MA. Impact of parity on obesity: A cross-sectional study in Iranian women. Med Princ Pract 2015;24(1):70-74.
16. Shih YL, Shih YH, Huang TC, *et al.* Association between sedentary time and plasma leptin levels in middle-aged and older adult population in Taiwan: A community-based, cross-sectional study. Front Cardiovasc Med 2023;9:1057497.
17. Elliott MJ, Ennis M, Pritchard KI, *et al.* Association between BMI, vitamin D, and estrogen levels in postmenopausal women using adjuvant letrozole: A prospective study. NPJ Breast Cancer 2020;6:22.
18. Silva TCBF, Barrett-Connor E, Ramires JAF, Mansur AP. Obesity, estrone, and coronary artery disease in postmenopausal women. Maturitas 2008;59(3):242-248.
19. Oh H, Coburn SB, Matthews CE, *et al.* Anthropometric measures and serum estrogen metabolism in postmenopausal women: The women's health initiative observational study. Breast Cancer Res 2017;19(1):1-17.
20. Knight MG, Anekwe C, Washington K, *et al.* Weight regulation in menopause. Menopause 2021;28(8):960-965.
21. Lizcano F, Guzmán G. Estrogen deficiency and the origin of obesity during menopause. Biomed Res Int 2014;2014:757461.
22. Diaz-Ruano AB, Martinez-Alarcon N, Perán M, *et al.* Estradiol and estrone have different biological functions to induce NF-κB-driven inflammation, EMT and stemness in ER+ cancer cells. Int J Mol Sci 2023;24(2):1-19.

23. Karim R, Dang HM, Hodis HN, *et al*. Association of hot flushes with ghrelin and adipokines in early versus late postmenopausal women. Menopause 2020;27(5):512-518.
24. Castracane VD, Kraemer GR, Ogden BW, Kraemer RR. Interrelationships of serum estradiol, estrone, and estrone sulfate, adiposity, biochemical bone markers, and leptin in post-menopausal women. Maturitas 2006;53(2):217-225.
25. Alexander C, Cochran CJ, Gallicchio L, *et al*. Serum leptin levels, hormone levels, and hot flashes in midlife women. Fertil Steril 2010;94(3):1037-1043.
26. Sriprasert I, Kono N, Karim R, *et al*. Factors associated with serum estradiol levels among postmenopausal women using hormone therapy. Obs Gynecol 2020;136(4):675-684.
27. Talaulikar V. Menopause transition: Physiology and symptoms. Best Pract Res Clin Obstet Gynaecol 2022;81:3-7.
28. Monteleone P, Mascagni G, Giannini A, *et al*. Symptoms of menopause - Global prevalence, physiology and implications. Nat Rev Endocrinol 2018;14(4):199-215.