Lipid Accumulation Product and Index of Central Lipid Distributions for Subclinical Atherosclerosis in Perimenopausal/Menopausal Women

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Background: *Lipid accumulation product (LAP) is a novel biomarker of central lipid accumulation related to the risk of diabetes and cardiovascular disease (CVD). Consistent with physiologic observations, an alternative index uses waist circumference (WC) and fasting triglycerides (TG) concentrations to describe lipid over accumulation.*
Objective: *Explore the association of LAP with anthropometric parameters and subclinical atherosclerosis in perimenopausal/menopausal women with no evidence of established CVD.*
Material and Method: *The study was an observational cross-sectional study and included 130 perimenopausal/menopausal participants. The anthropometric parameters used were height, weight, and WC. Laboratory lipid profile and LAP were calculated. High-resolution B-mode ultrasonography was performed to measure carotid intima media thickness (CIMT) and to search for carotid atherosclerosis.*
Results: *One hundred thirty perimenopausal/menopausal women were studied. About 22.3% had an abnormal CIMT. The percentages of normal weight, generalized obesity, and central obesity among study participants were 30.7%, 14.0%, and 55.3%, respectively. LAP was not correlated with CIMT and atherosclerosis. WC and waist-hip ratio (WHR) were correlated with CIMT but were not correlated with atherosclerosis. The other parameters of LAP and body mass index were not predictive of carotid atherosclerosis. Systolic blood pressure, diastolic blood pressure, fasting blood sugar, TG, and high-density lipoprotein cholesterol were higher with LAP equal or greater than 34.5 than with LAP lower than 34.5. However, CIMT was not statistically different between the two LAP groups (p = 0.99).*
Conclusion: *Central lipid distribution in perimenopausal/menopausal women using anthropometric phenotype WC and WHR was correlated with higher CIMT values. Both LAP index and anthropometric phenotype were not helpful for identifying subclinical atherosclerosis defined by CIMT measurement equal or greater than 0.9 mm.*

Keywords: *Lipid accumulation product, Subclinical atherosclerosis, Perimenopausal women, Menopausal women*

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Perimenopausal and menopausal status are associated with an increase in total adiposity, preferentially in the visceral region. This is due to changes in hormone levels at menopause, in particular estrogen deficiency. The relationship between obesity and cardiovascular disease (CVD) depends not only on the amount of total body fat but also on its distribution[1]. Abdominal obesity is considered a fundamental pathology for metabolic syndrome (MS) development, which is associated with an increased risk of cardiovascular morbidity and mortality. Waist circumference (WC) and waist-hip ratio (WHR) are used to define abdominal obesity but these measurements cannot distinguish between visceral and subcutaneous

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adipose tissue[2,3]. Visceral fat accumulation particularly is closely associated with the development of MS.

Lipid accumulation product (LAP), a novel index of central lipid accumulation, is based on a combination of WC and plasma triglyceride (TG) levels. Regardless of if the over accumulation is marked by increasing waist size, by TG concentration, or by both, the calculated value of LAP will be elevated. In parallel with the LAP increments, excess lipid material will increasingly be deposited in non-adipose tissues where it may adversely modify cellular metabolism, accelerate apoptosis, and interfere with cardiovascular control[4,5]. Prior to 50 years of age, LAP appears to rise more slowly with age in women compared to men[6]. Subclinical atherosclerosis of the vascular walls is an early stage in the development of atherosclerotic disease. The damage is still minimal, and can still potentially be corrected. Carotid artery ultrasonography with measures of carotid intima media thickness (CIMT) may be useful in identifying patients who may benefit from more aggressive preventative therapy[7-9]. The application of CIMT as a screening tool for CVD provides a measurement that can place an individual into a higher or lower risk category, thus allowing for appropriate implementation of preventive strategies in menopausal women.

Therefore, the aim of this study was to determine the usefulness of LAP and traditional anthropometric measurements for predicting subclinical atherosclerosis using CIMT in asymptomatic perimenopausal and menopausal women.

Material and Method

Study population

Participants were recruited from Suranaree University of Technology Hospital in Thailand between February 2015 and January 2016. The study was approved by the Institutional Review Board of Suranaree University of Technology, and written informed consent was provided by all participants before enrollment. The study was observational and cross-sectional and included 130 perimenopausal/menopausal participants.

Study protocol

At the baseline visit, the women completed self-administered questionnaires that included information on demographics, medication use, medical history, and family history of CVD and diabetes. Additionally, each woman underwent a physical examination that included anthropometric and blood pressure measurements. Collection of fasting blood specimens (after 8 hours or longer of fasting) was also performed. The study protocol was approved by the ethics committee of Suranaree University of Technology and informed consent was signed by each participant.

Laboratory measurement

Baseline serum specimens (stored at the central repository) were measured for serum fasting glucose, total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) by the central laboratory. Diabetes was defined as self-reported diabetes treatment or a fasting glucose level greater than or equal to 126 mg/dL.

Definition of terms

Perimenopausal/menopausal women

Participants were also asked about their menstrual bleeding patterns in the 12 months prior to recruitment. Perimenopausal status was defined as age $\geq$40 years (around menopause) with menstrual period irregularity in the past 12 months. Menopausal status was defined as age $\geq$40 years with no menstrual periods within the last 12 months.

Carotid intima media thickness measurement

The CIMT measurement was carried out according to a validated protocol, using high resolution B-mode ultrasonography with phased array transducer (PLT-704SBT 7.5 MHz, Toshiba). Both common carotid arteries were scanned proximal to distal to the bifurcation. CIMT was measured from the far wall of both common carotid arteries approximately 1 cm proximal to the carotid bulb. CIMT was defined as the mean of the maximal intima media thickness of each carotid artery. According to the joint European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines we considered normal values as <0.9 mm, abnormal CIMT as values ranging from 0.9 mm to 1.5 mm and asymptomatic carotid plaque (ACP) values as >1.5 mm.

Anthropometrics measurement

Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. WC was measured with the participant in nonrestrictive undergarments, at the level of the natural waist, defined as the narrowest part of the torso as seen from the

Table 1. Demographic data of the participants

Demographic data (n = 130)	Mean ± SD
Age (years)	53.75±9.93
Waist circumference (cm)	83.11±9.89
Waist-hip ratio	0.86±0.06
Body mass index (kg/m^2)	24.89±4.23
Systolic blood pressure (mmHg)	125.88±16.76
Diastolic blood pressure (mmHg)	69.22±9.85
Fasting blood sugar	101.00±20.91
Total cholesterol; TC	221.24±44.92
Triglyceride; TG	123.26±62.25
High-density lipoprotein cholesterol; HDL-C	58.58±17.32
Low-density lipoprotein cholesterol; LDL-C	134.25±40.76
TC/HDL-C	4.02±1.28
TG/HDL-C	2.35±1.65
LDL-C/HDL-C	2.46±0.94
Carotid intima media thickness (mm)	0.70±0.15
Lipid accumulation product	33.35±22.73

anterior aspect. For cases in which waist narrowing was difficult to determine, the measure was taken at the smallest horizontal circumference in the area between the ribs and the iliac crest.

Definition of terms

The LAP was calculated as (waist circumference [cm] -65) x (triglyceride concentration [mmol/L]) for men, and (waist circumference [cm] -58) x (triglyceride concentration [mmol/L]) for women. The formula includes the minimum sex-specific waist circumference values of 65 and 58 cm, for men and women, respectively. The LAP cut-off point was 34.5 cm.mmol/L.

Statistical analysis

Data were presented as mean and standard deviation (SD) or counts and percentage, as appropriate. Independent sample t-tests were conducted to assess the relationship between the LAP index and the studied variables. Group comparisons were performed using the Chi-square test (categorical variables) and the analysis of variance (ANOVA) test (continuous variables). All reported *p*-values were two tailed, and $p<0.05$ was considered statistically significant.

Results

There were 130 perimenopausal and menopausal participants. The mean age of the participants was 53.75±9.93 years. The women were perimenopausal and menopausal at 51.8% and 48.2%, respectively. Hypertension and hyperlipidemia were 26.9% and 47.0%, respectively. Abnormal CIMT was 22.3%. The mean LAP of the participants was 33.35±22.73. The prevalence of perimenopausal/menopausal women with an LAP index ≥34.5 cm.mmol/L was 35.4% (Table 1 and Table 2).

Table 2. Behavioral characteristics of the participants

Behavioral characteristics (n = 130)	%
Menopausal status	48.2
Diabetes mellitus	6.1
Essential hypertension	26.9
Dyslipidemia	47.0
Central obesity by waist to hip ratio	60.5
Generalized obesity by body mass index	24.6
Abnormal carotid intima media thickness	22.3
Abnormal lipid accumulation product	35.4

Mean values (±SD) of the studied variables were compared for participants with normal LAP and abnormal LAP. The test showed that, except for HDL-C, all cardiovascular risk markers had a higher chance of being worse when the LAP was above the cutoff value of 34.5 cm.mmol/L (Table 3).

Significant correlations were found between WC, WHR, and CIMT values in perimenopausal/

Table 3. Relationship between the LAP index and the studied variables

Anthropometric parameter		Normal LAP, n = 84	Abnormal LAP, n = 46	*p*-value
Generalized obesity	Body weight	56.13±8.80	68.60±12.46	<0.01*
	Body mass index	23.29±3.09	28.21±4.39	<0.01*
Central obesity	Waist circumference	79.30±8.27	91.02±8.19	<0.01*
	Waist-hip ratio	0.85±0.06	0.89±0.05	<0.01*

* Significant difference at $p<0.01$

Table 4. The correlation of LAP index, anthropometric parameters and CIMT.

Parameters	Carotid intima media thickness	
	Pearson correlation (r)	*p*-value
Weight	0.01	0.94
Body mass index	0.03	0.74
Waist circumference	0.20	0.04*
Waist-hip ratio	0.25	0.01*
Lipid accumulation product	0.05	0.55

* Significant correlation at $p<0.05$

menopausal women. In contrast, LAP index was not related to measures of CIMT values, a marker of subclinical atherosclerosis (Table 4).

No significant differences were found between any of the LAP index, WC, WHR anthropometric parameters, and values for discriminating a CIMT range useful for identifying atherosclerosis, although WC and WHR showed a trend towards significance with the CIMT value (Table 4 and Table 5).

Discussion

The present study provided important evidence increased WC and WHR in perimenopausal/menopausal women without history of CVD that represented for central fat accumulation was associated with CIMT value. LAP were not significantly higher than other anthropometric measures for predicting subclinical atherosclerosis. A previous study demonstrated the relationship between carotid atherosclerotic marker and difference obesity phenotype[10-13]. However, studies evaluating the associations between an index of central fat distribution by using the anthropometric parameters WHR or LAP and CIMT in perimenopausal/menopausal women are limited.

A meta-analysis in the Asia-Pacific region showed that the serum TG level is an important and independent predictor of CVD risk[14,15]. LAP is based on a combination of WC and TG. The components of LAP tend to increase with age[16]. The single components of LAP have been associated with risk for CVD, type 2 diabetes, polycystic ovary syndrome, and MS[17,18]. WC, a simple measure of truncal fat that reflects both abdominal subcutaneous adipose tissue and, especially, visceral adipose tissue, is a robust predictor for cardiometabolic risk, and represents the main component of MS[19]. TG, also, is a reliable predictor for these cardiometabolic syndromes.

In patients at high risk of CVD without diabetes LAP can predict both mortality and increased risk of future stroke[20,21]. High LAP values are predictive of mortality independently of other cardiovascular risk factors in normal weight and diabetic postmenopausal women but not in men[22]. Obesity is an independent risk factor of CVD, and in our study the prevalence of central obesity was 60.5% among perimenopausal/menopausal women. Another already established risk factor for CVD is HDL-C levels below the recommended limit, irrespective of LDL-C values[23]. The most common dyslipidemia components in our study were an increase in TC, which includes LDL-C but also higher levels of HDL-C than recommended. Therefore, the use of anthropometric indices for the diagnostic evaluation of central obesity WC and WHR seems to be more adequate for correlating with atherosclerosis in perimenopausal/menopausal women. Using the cut off identified here, the LAP index appears to be a less accurate tool to identify preclinical atherosclerosis in women with perimenopausal/menopausal status and should not be adopted in clinical practice.

The present study has some limitations. Due to the cross-sectional study design our findings could not prove causal relationships between central fat accumulation and elevated CIMT. In addition, the study had a small sample size and a narrow population of

Table 5. LAP and anthropometric parameters in CIMT range (<0.9 mm, ≥0.9 mm) (ANOVA)

Index	Parameters	F	*p*-value
Central lipid accumulation	Lipid accumulation product	0.96	0.33
Central lipid distributions	Waist circumference	0.19	0.66
	Waist-hip ratio	1.52	0.22
General lipid distribution	Weight	4.30	0.04*
	Body mass index	4.83	0.03*

* Significant correlation at $p<0.05$

those attending a menopause clinic and cardiovascular clinic. Participants in this study were perimenopausal/menopausal women in Thailand, limiting generalizability of our findings to other ethnicities and limiting the age groups.

Conclusion

In our study LAP was not significantly better than traditional anthropometric measures for predicting CIMT value. Neither LAP, WC, nor WHR can be used in identifying perimenopausal/menopausal women at risk of subclinical atherosclerosis by abnormal CIMT (≥0.9 mm).

What is already known on this topic?

The present study is not the first to report about the LAP and adiposity index correlation with early atherosclerosis CIMT values, however previous studies cannot be directly applied to the perimenopausal/menopausal specific subgroup in the Thai population because of differences in ethnic groups and environmental factors provided for cardiometabolic risks.

What this study adds?

LAP, in our study, does not demonstrate a more useful application as a marker of increased risk for early atherosclerosis (measured by CIMT) in perimenopausal/menopausal participants than anthropometrics in the Thai population.

Acknowledgement

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Potential conflicts of interest

None.

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ผลิตภัณฑ์ไขมันสะสมและดัชนีไขมันสะสมกระจายส่วนกลางสำหรับโรคหลอดเลือดแดงตีบแบบไม่มีอาการในสตรีวัยใกล้หมดประจำเดือน/วัยหมดประจำเดือน

ปัทมา ทองดี, ธีธัช อนันต์วัฒนสุข, เฟื่องฟ้า เบญจโอฬาร, กิติรัตน์ รัตนถาวรกิติ, จิตรวดี หอพิบูลสุข, พรทิพย์ นิ่มขุนทด

ภูมิหลัง: ผลิตภัณฑ์ไขมันสะสมเป็นดัชนีใหม่ของไขมันสะสมกระจายส่วนกลางมีความสัมพันธ์กับการเกิดโรคเบาหวานและโรคหลอดเลือดหัวใจ จากการสังเกตทางสรีรวิทยาพบว่าดัชนีอันใหม่ได้จากการใช้รอบเอวและค่าไขมัน ไตรกรีเซอไรด์ เพื่อใช้อธิบายไขมันสะสมมากกว่าปกติ

วัตถุประสงค์: เพื่อประเมินความสัมพันธ์ของผลิตภัณฑ์ไขมันสะสมและขนาดรูปร่างกับการเกิดหลอดเลือดแดงแข็งแบบไม่มีอาการทางคลินิกในสตรีวัยใกล้หมดประจำเดือนและวัยหมดประจำเดือนที่ไม่มีโรคทางหัวใจและหลอดเลือด

วัสดุและวิธีการ: การศึกษาแบบสังเกตแบบภาคตัดขวางในสตรีวัยใกล้หมดประจำเดือนและวัยหมดประจำเดือนจำนวน 130 คน โดยวัดขนาดรูปร่างของร่างกายได้แก่ ส่วนสูง น้ำหนัก และรอบเอว การตรวจทางห้องปฏิบัติการได้แก่ ระดับไขมันในเลือด การใช้คลื่นเสี่ยงความถี่สูงในการวัดความหนาของไขมันเกาะที่หลอดเลือดแดงคาร์โรติด

ผลการศึกษา: สตรีวัยใกล้หมดประจำเดือนและวัยหมดประจำเดือน 130 คน พบความผิดปกติของไขมันที่หลอดเลือดแดงคาร์โรติด 22.3% พบว่ามีน้ำหนักปกติ อ้วนทั้งตัว และอ้วนลงพุง 30.7%, 14% และ 55.3% ตามลำดับ ผลิตภัณฑ์ไขมันสะสมไม่มีความสัมพันธ์กับค่าความหนาของไขมันเกาะบริเวณหลอดเลือดแดงคาร์โรติดและหลอดเลือดแข็ง ค่ารอบเอวและสัดส่วนรอบเอวต่อรอบสะโพกมีความสัมพันธ์กับค่าความหนาของไขมันเกาะบริเวณหลอดเลือดแดงคาร์โรติด แต่ไม่สามารถทำนายหลอดเลือดแข็ง ค่าผลิตภัณฑ์ไขมันสะสม ค่ารอบเอว และสัดส่วนรอบเอวต่อรอบสะโพกไม่สามารถทำนายภาวะหลอดเลือดแข็งได้ ค่าความดันโลหิตขณะหัวใจบีบตัวและคลายตัว น้ำตาลในเลือด ไขมันไตรกรีเซอไรด์ และเอชดีแอลในกลุ่มที่มีค่าผลิตภัณฑ์ไขมันสะสมมากกว่า ≥34.5 มีค่าสูงกว่ากลุ่มที่มีค่าผลิตภัณฑ์ไขมันสะสมมากกว่า <34.5 ความหนาของไขมันที่เกาะบริเวณหลอดเลือดแดงคาร์โรติดไม่มีความแตกต่างกันทางสถิติในการแยกกลุ่มของผลิตภัณฑ์ไขมันสะสม ($p = 0.99$)

สรุป: การกระจายตัวของไขมันในสตรีวัยใกล้หมดประจำเดือนและวัยหมดประจำเดือนโดยใช้ขนาดรูปร่างจากรอบเอวและสัดส่วนรอบเอวต่อรอบสะโพกพบว่ามีความสัมพันธ์กับค่าความหนาของไขมันเกาะบริเวณหลอดเลือดแดงคาร์โรติดทั้งค่าผลิตภัณฑ์ไขมันสะสมและขนาดรูปร่าง ไม่สามารถแยกกลุ่มที่มีความหนาของไขมันที่เกาะบริเวณหลอดเลือดแดงคาร์โรติดที่ปกติและผิดปกติออกจากกันได้เพื่อทำนายการเกิดหลอดเลือดตีบที่ไม่มีอาการทางคลินิก