Clinical Usefulness of Lipid Ratios to Identify Subclinical Atherosclerosis in Perimenopausal/Menopausal Women

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Background: *Evidence shows that lipid ratios perform better than individual lipids in predicting cardiovascular risk. The lipid ratio serves as a quick and simple tool for identifying subclinical atherosclerosis. The population at risk especially perimenopausal and menopausal women should be monitoring to prevent cardiovascular disease in the future.*
Objective: *To examine the association between lipid ratios and subclinical atherosclerosis by carotid intima media thickness (CIMT) in perimenopausal/menopausal women.*
Material and Method: *A cross-sectional study was conducted with 130 participants aged 40 to 80 years between February 2015 and January 2016 in Suranaree University of Technology Hospital, Thailand. CIMTs were assessed using a high-resolution B mode ultrasound system. Traditional anthropometry, body mass index (BMI), waist circumference (WC), and parameters including blood pressure, fasting plasma glucose, lipid profile [Total cholesterol (TC), Triglyceride (TG), High-density lipoprotein cholesterol (HDL-C) and Low-density lipoprotein cholesterol (LDL-C)], and CIMT were assessed in all subjects. All lipid ratios were calculated.*
Results: *One hundred thirty perimenopausal/menopausal participants were included in this study. Of those participants, 41% were central obese phenotype and 22% had abnormal CIMT that can identify atherosclerosis. Age and systolic blood pressure in atherosclerosis group were higher than normal CIMT group; $p<0.01$ and $p<0.01$, respectively. Lipid ratio in normal CIMT was higher than atherosclerotic group but not statistically significance except TG/HDL-C ($p = 0.03$). All lipid ratios and single lipid parameters lacked prediction for the presence of early atherosclerosis.*
Conclusion: *All of lipid ratios, TC/HDL-C, TG/HDL-C, and LDL-C/HDL-C were not identified as early subclinical atherosclerosis among perimenopausal/menopausal women.*

Keywords: *Lipid ratio, Subclinical atherosclerosis, Perimenopausal women, Menopausal women*

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Cardiovascular disease (CVD) is the leading cause of mortality worldwide, especially menopausal women. Older age people are increasingly exposed to high levels of major CVD risk. Decreasing estrogen levels during the menopausal transition has been linked to endothelial dysfunction, larger vessel diameters, and markers of early adverse vascular changes including factors, a poor lipid profile, and weight gain[1-5]. Lipids profile (Total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)) are known to change in association with both age and the menopausal transition[6-8]. There is growing recognition of the heterogeneity in CVD risk due to change in body

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weight or individual central obesity phenotype[9,10]. Multiple studies have identified that lipid ratios perform better than individual lipids in predicting cardiovascular risk or identify early atherosclerosis in general Asian including Thai populations[11]. The lipid ratio is serve as a quick and simple tool for identifying subclinical atherosclerosis. The population at risk especially perimenopausal/menopausal women should be monitoring to prevent cardiovascular disease in the future. Simple and non-invasive technique for detecting carotid intima media thickness (CIMT) using B-mode carotid ultrasound.

The objective of this study is to analyze the lipid ratios, TC/HDL-C, TG/HDL-C, and LDL-C/HDL-C to identify subclinical atherosclerosis in peri-menopausal/menopausal women.

Material and Method

Study population

Between February 2015 and January 2016, we recruited 130 perimenopausal and menopausal participants underwent the annually health check in the Suranaree University of Technology Hospital, Thailand. Aged 40 to 80 years without history of hormonal replacement therapy were eligible and were enrolled when they participated in their annual health examination. All participants underwent a complete cardiovascular evaluation after 8 hours of fasting, including 1) medical history for acute myocardial infarction, congestive heart failure, previous stroke, end stage renal disease, hypertension, diabetes mellitus, dyslipidemia or smoking, 2) anthropometric measurement including weight, height, waist circumference (WC) and hip circumference (HC), 3) blood pressure evaluation, 4) serum glucose levels, 5) plasma lipids profile including TC, TG, HDL-C, and LDL-C level, and 6) evaluated lipid ratios of TC/HDL-C, TG/HDL-C, and LDL-C/HDL-C.

Study protocol

At the baseline visit, all participants completed self-administered questionnaires that included information on demographic and medication use, medical history, and family history of CVD and diabetes. Additionally, each participant underwent a physical examination that included anthropometric and blood pressure measurements, and collection of fasting blood specimens (after 8 hours or longer of fasting). The study protocol was approved by the ethics committee of Suranaree University of Technology code EC-58-02 and informed consent was signed by each participant.

The participants' medical history, alcohol intake, and smoking habits were ascertained by a questionnaire. Alcohol intake and smoking habits were classified as current habitual use or not. Height and weight were measured, and body mass index (BMI) was calculated as weight in kilograms (kg) divided by the square of height in square meters (m^2) as an index of obesity. WC was measured at the level of the umbilicus in the standing position and waist-hip ratio (WHR) was calculated as WC divide by HC.

Laboratory measurement

Baseline serum specimens were measured for levels of fasting glucose and lipid profile. Serum glucose, TC, TG, HDL-C, and LDL-C level were measured by the central laboratories of Suranaree University of Technology Hospital. Diabetes was defined as self-reported diabetes treatment or a fasting glucose level $\geq$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 with menstrual period irregularity in the past 12 months. Menopausal status was defined as those with no menstrual period within the last 12 months.

Carotid intima media thickness (CIMT) measurement

The measurement was carried out according to a validated procedure, using a high-resolution B-mode ultrasonography with phased array transducer (PLT-704SBT 7.5 MHz, Toshiba). The study in the far wall of the common carotid artery, carotid bulb and internal carotid artery using the automated edge detection lumen intima and the media-adventitia interface at the far wall for CIMT. The mean CIMT of each of the six carotid segments was determined, and the average of these six mean measures was computed for the outcome variable in this analysis. According to the joint European Society of Hypertension (ESH)/ European Society of Cardiology (ESC) guidelines, we considered normal values as <0.9 mm. and abnormal CIMT >0.9 mm marker of atherosclerosis.

Anthropometrics measurement

BMI was calculated as weight in kg divided by height in m^2. WC was measured at the level of the natural waist, which waist narrowing was taken at the

smallest circumference in the area between the last ribs and the iliac crest at horizontal plane.

Statistical analysis

Statistical analyses were performed and continuous variables of the subjects at baseline were expressed as mean and standard deviation or median. Demographics, health history, median laboratory values were identified and compared among normal CIMT and atherosclerosis CIMT ≥0.9 mm, using the independent t-test. Correlation between mean CIMT and atherosclerosis was determined by using Pearson's correlation. All reported *p*-values were two tailed, and $p<0.05$ was considered statistically significant.

Results

Baseline characteristics of perimenopausal/menopausal participants are presented (Table 1).

One hundred thirty women with central obesity had higher incidence than generalized obesity participants (41% vs. 24%) and 22% (29/130) were identified subclinical atherosclerosis CIMT ≥0.9 mm. Age and systolic blood pressure (SBP) were higher in atherosclerotic than normal CIMT groups but there was no difference in anthropometric parameters and lipids. Only TG/HDL-C in normal CIMT was higher than CIMT ≥0.9 mm ($p = 0.03$). The other lipid ratios in normal CIMT were higher than subclinical atherosclerotic CIMT ≥0.9 mm but no statistical significance was found (Table 1).

In addition, the present study also observed that all single lipid and lipid ratios TC/HDL-C, TG/HDL-C, and LDL-C/HDL-C and found that they were not correlated with mean CIMT and atheros-clerosis CIMT ≥0.9 mm (Table 2).

Discussion

In the presenting perimenopausal/menopausal women, only 22% were identified as atherosclerosis. The correlation between lipid ratios and CIMT marker of early atherosclerosis was not found. This was reflected by higher levels of CIMT in perimenopausal/menopausal status when compared with female gender in general population from previous study in Thailand 0.74 mm and 0.67 mm, respectively[11]. Korean population has already reported normative CIMT values showing that mean CIMT was 0.63±0.11 mm[12]. In the study, mean CIMT of premenopausal women was not different (0.7 mm vs. 0.7 mm) but lower than postmenopausal women (0.7 mm vs. 0.8 mm) from previous studies in China population[13]. Our study confirms the results of previous investigations that menopause transition in women is associated with accelerated subclinical atherosclerosis.

Our study also reported lipid ratios of individuals have lower ratio, but HDL-C higher than

Table 1. Demographic and metabolic characteristics of the study population

Parameters	CIMT <0.9 mm (n = 101)	CIMT ≥0.9 mm (n = 29)	*p*-value
Age, years	51.25±8.42	62.45±10.00	<0.01*
Systolic Blood Pressure, mmHg	123.57±15.69	133.90±18.16	<0.01*
Diastolic Blood Pressure, mmHg	69.37±10.42	68.72±7.67	0.72
Body weight, kg	61.09±12.21	58.07±9.97	0.18
Waist Circumference, inch	32.57±4.05	33.08±3.26	0.48
Hip circumference, inch	38.09±3.69	38.00±2.75	0.89
BMI, kg/m^2	25.16±4.36	23.90±3.65	0.16
WHR	0.86±0.06	0.87±0.04	0.22
Glucose, mg/dL	99.75±19.36	105.35±25.52	0.28
Total Cholesterol, mg/dL	219.05±43.35	228.86±50.05	0.34
Triglyceride mg/dL	126.97±66.08	110.34±45.16	0.12
LDL-C mg/dL	133.87±38.53	135.59±48.46	0.37
HDL-C mg/dL	57.92±18.05	60.86±14.51	0.86
TC/HDL-C	4.05±1.36	3.92±0.94	0.59
TG/HDL-C	2.48±1.77	1.88±1.00	0.03*
LDL-C/HDL-C	2.50±0.97	2.32±0.87	0.39
Mean CIMT	0.64±0.08	0.91±0.13	<0.01*

* Correlation is significant at the 0.05 level

Table 2. Lipid parameters and atherosclerosis

Parameters		Mean CIMT		Atherosclerosis	
		r	*p*-value	r	*p*-value
Traditional lipid parameter	TC	0.16	0.08	0.09	0.30
	TG	-0.09	0.31	-0.11	0.21
	HDL-C	-0.00	0.98	0.07	0.42
	LDL-C	0.06	0.51	0.02	0.84
Lipid ratio	TC/HDL-C	0.04	0.66	0.04	0.66
	TG/HDL-C	-0.11	0.26	-0.15	0.12
	LDL-C/HDL-C	-0.05	0.62	-0.08	0.42

* Correlation is significant at the 0.05 level

previous studies. The study was suggested that the protective effects of HDL-C on CIMT may diminish over time in middle aged women[14]. The lipid ratio in normal CIMT study is higher than atherosclerotic group but is not statistically significant that except TG/HDL-C may affect to mean CIMT and atherosclerosis. In current study participants who had coronary atherosclerosis, which showed that CIMT was 0.91±0.13 mm. The authors define abnormal CIMT ≥0.9 mm due to correlation with marker of atherosclerosis[15]. Although lipid ratio in this study was not statistically to identify subclinical atherosclerosis same as previous study in general population of LDL-C/HDL-C ratio <2.5 in both normal and abnormal CIMT that lower than other studies such as the Helsinki and PROCAM observational study[16-18].

In this study, the age of participants in atherosclerosis is higher than normal CIMT at 11.20 years with statistical significance (62.45 years vs. 51.25 years). Other parameters such as systolic blood pressure in atherosclerosis group was higher than normal group at approximately 10.33 mmHg (133.90 mmHg vs. 123.57 mmHg) may affect to mean CIMT or atherosclerosis CIMT ≥0.9 mm. Previous study, all parameters of age, gender and geographical origin may be affected to intima media thickness of carotid artery in Atherosclerosis Risk in Communities (ARIC) study[19]. However, the potential association of lipid ratio and menopausal duration with the formation of CIMT progression has not yet been examined in those studies, particularly for Thai women population. Therefore, the results presented in this study further extends the findings of previous investigations by including not only mean CIMT, but also carotid plaque that demonstrate associations with menopause and lipid parameters.

The results of this study need to be interpreted in light of certain limitations. Our cross-sectional analysis cannot be used to determine causation. As our cohort consisted of women in perimenopausal/menopausal status, the results may not be generalizable to younger women or men.

Conclusion

All lipid ratios TC/HDL-C, TG /HDL-C, and LDL-C/HDL-C could not have predicted subclinical atherosclerosis in perimenopausal/menopausal women. However, they may be act as an adjunct that significantly adds predictive value beyond that of the individual lipids in future high risk group of the study.

What is already known on this topic?

The present study is not the first report of lipid ratio and CIMT values in but previous studies cannot be directly applied to perimenopausal/menopausal specific subgroup in Thai population because of differences in ethnic groups and environmental factors provided for cardio-metabolic risks and CIMT in our study.

What this study adds?

Correlation between lipid ratios and CIMT risk of developing subclinical atherosclerosis in non-overt CVD was study. That is the great significance to reducing the incidence of CVD among perimenopausal/menopausal women in future.

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Potential conflicts of interest

None.

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ประโยชน์ทางคลินิกของอัตราส่วนไขมันเพื่อวินิจฉัยภาวะหลอดเลือดแดงตีบแบบไม่แสดงอาการในสตรีวัยใกล้หมดประจำเดือน/วัยหมดประจำเดือน

ปัทมา ทองดี, ไรอัน เอ ลอยด์, สุชสันต์ กนกศิลป์, จันทกานต์ กาญจนเวทางค์, เกษตร วิณวันก์, พรทิพย์ นิ่มขุนทด

ภูมิหลัง: *หลักฐานที่แสดงให้เห็นว่าอัตราส่วนของไขมันมีประสิทธิภาพสูงกว่าไขมันแบบเดี่ยวในการทำนายความเสี่ยงโรคหัวใจและหลอดเลือด พบว่าการใช้อัตราส่วนไขมันเป็นเครื่องมือทำได้รวดเร็วและง่ายสำหรับการวินิจฉัยภาวะหลอดเลือดแดงตีบแบบไม่แสดงอาการ และใช้ในการตรวจติดตามในประชากรที่มีความเสี่ยงต่อหัวใจและหลอดเลือด โดยเฉพาะสตรีวัยใกล้หมดประจำเดือนและวัยหมดประจำเดือน*

วัตถุประสงค์: *เพื่อหาความสัมพันธ์ระหว่างอัตราส่วนไขมันและภาวะหลอดเลือดแดงตีบแบบไม่แสดงอาการจากการวัดความหนาของไขมันที่หลอดเลือดแดงคอคาร์โรติดในกลุ่มประชากรที่เฉพาะเจาะจงในสตรีวัยใกล้หมดประจำเดือนและหมดประจำเดือน*

วัสดุและวิธีการ: *การศึกษาแบบตัดขวางมีผู้เข้าร่วมการศึกษา 130 คน อายุระหว่าง 40-80 ปี ตั้งแต่เดือนกุมภาพันธ์ พ.ศ. 2558 ถึงเดือนมกราคม พ.ศ. 2559 ของโรงพยาบาลมหาวิทยาลัยเทคโนโลยีสุรนารี ประเทศไทย การวัดความหนาของไขมันชั้นในของหลอดเลือดแดงคอคาร์โรติดวัดโดยใช้คลื่นเสียงความถี่สูง การวัดสัดส่วนของร่างกายแบบดั้งเดิม ได้แก่ ดัชนีมวลกาย และรอบเอว ตัวแปรต่าง ๆ ได้แก่ ความดันโลหิต ระดับน้ำตาลในเลือด ไขมันเดี่ยว (โคเลสเตอรอล ไตรกลีเซอไรด์ เอชดีแอล และแอลดีแอล) และการวัดความหนาของไขมันชั้นในของหลอดเลือดแดงคอคาร์โรติด ทุกคนได้รับการประเมินอัตราส่วนไขมัน*

ผลการศึกษา: *ข้อมูลจากผู้เข้าร่วมวิจัยสตรีวัยใกล้หมดประจำเดือนและวัยหมดประจำเดือนทั้งหมด 130 คน พบว่าร้อยละ 41 มีภาวะอ้วนลงพุง และร้อยละ 22 มีความหนาของไขมันชั้นในของหลอดเลือดแดงคอคาร์โรติดผิดปกติที่ระบุว่ามีภาวะหลอดเลือดแดงตีบแบบไม่แสดงอาการ อายุและความดันโลหิตซิสโตลิก ในกลุ่มที่มีภาวะหลอดเลือดแดงตีบแบบไม่แสดงอาการสูงกว่ากลุ่มปกติ $p<0.01$ และ $p<0.01$ ตามลำดับ อัตราส่วน ไขมันในกลุ่มปกติสูงกว่ากลุ่มที่มีภาวะหลอดเลือดแดงตีบแบบไม่แสดงอาการแต่ไม่มีนัยสำคัญทางสถิติ ยกเว้นไขมันไตรกลีเซอไรด์ต่อเอชดีแอล ($p = 0.03$) ค่าอัตราส่วนไขมันและไขมันเดี่ยวไม่สามารถทำนายการเกิดหลอดเลือดแดงตีบแบบไม่แสดงอาการได้*

สรุป: *ค่าอัตราส่วนไขมันทั้งอัตราส่วนไขมันโคเลสเตอรอลต่อเอชดีแอล ไขมันไตรกรีเซอไรด์ต่อเอชดีแอลและไขมันแอลดีแอลต่อเอชดีแอลไม่สามารถใช้เพื่อทำนายหลอดเลือดแดงตีบระยะเริ่มต้นแบบไม่แสดงอาการในสตรีวัยใกล้หมดประจำเดือนและวัยหมดประจำเดือนได้*