Atherosclerotic Index and Traditional Anthropometry for Predicting Carotid Intima Media Thickness in Perimenopausal/Menopausal Women

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Background: *Atherosclerosis is an important pathologic cause of cardiovascular disease (CVD) and a leading cause of morbidity and mortality worldwide. Menopause involves changes in hormonal status that are associated with an increased risk of developing CVD. The atherogenic index of plasma (AIP) has been used as a predictor of atherosclerosis. Atherosclerosis might also be assessed using a surrogate marker, the carotid artery wall intima media thickness (CIMT).*
Objective: *To assess the usefulness of AIP compared with traditional anthropometrics for predicting CIMT in perimenopausal and menopausal women.*
Material and Method: *This is a cross-sectional study involving perimenopausal and menopausal women voluntarily recruited. Lipid profiles, including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were assessed and AIP was calculated [log (TG/HDL-C)]. The anthropometric parameters of body mass index (BMI), waist circumference (WC), hip circumference (HC), and waist-hip ratio (WHR) were assessed. Pearson Chi-square for AIP and anthropometric parameters relationship to CIMT in perimenopausal and menopausal women.*
Results: *One hundred fourteen perimenopausal and menopausal women were included in this study. The novel atherosclerotic index of AIP and the anthropometric parameter of BMI were correlated with CIMT in both groups ($p<0.01$). There was no difference in AIP between perimenopausal and menopausal women. Neither WC nor WHR were different between the two groups. CIMT was significantly thicker in the menopausal compared with the perimenopausal group [0.78 ± 0.16 vs. 0.64 ± 0.09, respectively ($p<0.01$)].*
Conclusion: *AIP can add significant value when assessing the risk of developing the atherosclerosis marker of thickened CIMT in perimenopausal and menopausal women. A high AIP in menopause may indicate a higher risk of cardiovascular events in spite of no difference in common CVD risk factors such as lipid profile parameters.*

Keywords: *Atherogenic index of plasma, Carotid intima media thickness, Anthropometric parameters, Menopausal status*

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Atherosclerosis is an important pathologic cause of cardiovascular disease (CVD), which is a leading cause of morbidity and mortality worldwide. Preclinical or subclinical atherosclerosis has been related to higher rates of coronary artery disease (CAD). Carotid ultrasonography is more sensitive than the coronary artery calcification score (CACS) for the detection of subclinical atherosclerosis[1]. Hence, carotid intima media thickness (CIMT) may represent an accessible and reliable method to detect subclinical atherosclerosis[2]. Based on previous studies, menopausal women are at increased risk of developing CVD. It has been reported that there is a 49% increase in abdominal fat and a 22% increase in the subcutaneous fat of women in the postmenopausal stage compared to premenopausal women suggesting that menopause is associated with obesity linked traits such as a high proportion of the body fat mass and central adiposity[3]. Isolated elevation of triglycerides (TG) increases CAD risk more in women than men, but its effect can be counteracted by the levels of high-density lipoprotein cholesterol (HDL-C)[4] and the relationship between TG and HDL-C, and it has been shown that the ratio of TG to HDL-C is a strong

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predictor of myocardial infarction.

The atherogenic index of plasma (AIP), calculated as log (TG/HDL-C), has been successfully used as an additional index when assessing cardiovascular risk factors[5,6]. Indeed, it has been suggested that AIP values of -0.3 to 0.1 are associated with low, 0.1 to 0.24 with medium and above 0.24 with high cardiovascular risk[7]. The differences in AIP show statistically significant increases as time passes after menopause; the absolute values indicate that the first decade of menopause is associated with a low risk while the second decade is associated with a medium risk for CVD[8]. The cholesterol etherification rate in HDL-C plasma (FERHDL) has a strong relationship between lipoprotein particle sizes and thus can be considered as a functional risk marker for CVD. The logarithmetically transformed ratio of TG/HDL-C is the best determinant for FERHDL and thus a better predictor of cardiovascular risk than other previously used lipid parameters[9]. Furthermore, in situations where other atherogenic risk parameters appear normal, AIP may suggest an alternative diagnosis.

Therefore, the aim of this study was to investigate whether AIP and other anthropometric parameters are useful for assessing CIMT in perimenopausal/menopausal women.

Material and Method

Study population

This is a cross-sectional study involving 114 perimenopausal/menopausal participants, aged 40 to 80 years old, without history of hormonal replacement therapy who were recruited from the cardiovascular clinic and menopause clinic and underwent CIMT measurements in Suranaree University of Technology Hospital between August 2015 and January 2016. For the assessment of CIMT values, we excluded participants with any of the following overt CVD or cardiovascular equivalence conditions, history of stroke including cerebral infarction or transient ischemic attack, myocardial infarction, heart failure, and end stage renal disease. The study was approved by Institutional Ethical Committee.

Study protocol

A standardized questionnaire was administered that included a personal and family history of chronic disorders, gynecological anomalies, medication intake, physical activity, dietary information, alcoholism, and smoking status. Anthropometric measurements such as height, weight, waist circumference (WC), and hip circumference (HC) were taken. WC was measured at the midpoint at the bottom of the rib cage and the top of the lateral border of the iliac crest during minimal respiration. Body mass index (BMI) was calculated as weight (kilogram; kg) divided by the square of height (meter^2; m^2) as an index of obesity and waist-hip ratio (WHR) was calculated as WC divide by HC. WHR above 0.8 was considered as abdominal obesity.

Laboratory measurement

Fasting blood samples were collected by venipuncture from the antecubital vein into sterile plain tubes under aseptic conditions. The blood samples were allowed to clot and sent to the central laboratory unit of Suranaree University of Technology Hospital. The serum was used for the analysis of total cholesterol (TC), TG, HDL-C, and low-density lipoprotein cholesterol (LDL-C) levels. AIP calculated as log (TG/HDL-C).

Definition of terms

Perimenopausal/menopausal status

Participants were also asked about their menstrual bleeding patterns in the 12 months prior to recruitment and classified as 1) perimenopausal status age $\geq$40 years with menstrual period irregularity in the past 12 months, and 2) menopausal status age $\geq$40 years with no menstrual periods within the past 12 months.

Carotid artery measurement

Carotid artery scans were performed using a high-resolution B-mode scanner (Toshiba Apalio) and phased array transducer (PLT-704SBT 7.5 MHz). A single cardiologist who was blinded to the clinical characteristics measured CIMT. Both common carotid arteries were scanned from proximal to distal to the bifurcation. CIMT was measured at 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 and abnormal values as >0.9 mm, a marker of atherosclerosis.

Statistical analysis

Baseline characteristics were analyzed using descriptive techniques. Data for continuous variables were presented as the mean $\pm$ standard deviation (SD)

and proportions were presented as frequencies and percentages. Categorical data were reported in proportions and differences tested by Pearson's Chi-squared test. The correlation of AIP and plasma lipid ratio with CIMT was assessed by Pearson correlation. Test for significance was done using student's t-test, Chi-square test and analysis of variance (ANOVA) where applicable. The *p*-values less than or equal to 0.05 were considered as significant.

Ethics statement

All participants signed informed consent forms for participation in this study. This study has been reviewed and approved by the Ethics Committee for Research Involving Human Subjects, Suranaree University of Technology. The project code EC-58-36 approved by Institutional Ethical Committee.

Results

Mean and SD of demographic data and clinical characteristics of menopausal status both perimenopausal and menopausal women were analyzed. There were statistically significant increases ($p<0.01$) in CIMT in menopausal women. The AIPs were high risk in perimenopausal and menopausal women but there was no statistically significant difference between the two groups; 0.32 ± 0.26 and 0.27 ± 0.25, respectively ($p = 0.27$). There were no differences between the two groups in anthropometric parameters (BMI, WC and WHR) or lipid parameters (TC, TG, HDL-C, and LDL-C) levels (Table 1).

Pearson's Chi-square for prediction of CIMT by AIP and anthropometric parameters (BMI, WC and WHR) in different menopausal statuses; perimeno-pausal and menopausal women. Only AIP had a statistically significant correlation with both perimenopausal ($\chi^2 = 3{,}068.00$, $p<0.01$) and menopausal groups ($\chi^2 = 2{,}420.00$, $p<0.01$) for predicting CIMT. The traditional anthropometric parameter BMI was statistically significant in only menopausal groups for predicting CIMT ($\chi^2 = 2{,}323.75$, $p = 0.04$) (Table 2).

Discussion

This study compared the discriminative capability of different adiposity indices including AIP, as well as simple anthropometric indices (BMI, WC and WHR) for predicting preclinical atherosclerosis in perimenopausal and menopausal groups of women. Higher CIMT was associated with the development of menopausal status the same as in previous study[10]. Our results are in agreement with previous findings that AIP is a significant predictor of the atherosclerotic marker CIMT. However, there were no differences observed regarding lipids between the groups. These findings remind us that early prevention of atherosclerosis should start by looking for subclinical atherosclerosis to enable detection of an abnormal state of health. Our investigation suggests that menopausal women have increased CIMT compared with perimenopausal women. In this study, there was no significant difference in lipid profile parameters between perimenopausal and menopausal women.

Obesity-related anthropometric parameters have been reported to be associated with increased cardiovascular risks. However, the conclusions of the studies in the literature are inconsistent. Higher CIMT correlates with obesity-related anthropometric parameters, including BMI, WC and WHR in general populations[11-13]. These contradictory findings suggest that obesity does not affect vascular parameters related to early atherosclerosis, including CIMT in women with minor cardiovascular risk factors[14].

Recent studies have reported CIMT may be a valuable marker for cardiovascular risk in the general population aged <45 years (CIMT 0.63 mm) who are not yet eligible for standard cardiovascular risk screening[15] and may be applicable for cardiovascular screening in the menopausal transition in low risk groups of perimenopausal women; mean age 45.27 ± 3.06 years and CIMT 0.64 ± 0.09 mm in the study. In a previous study, WHR was superior to the other anthropometric indices to predict carotid atherosclerosis in postmenopausal women[12,16]. These findings contradict our study and found that BMI was the best diagnostic anthropometric parameter for the initial stage of atherosclerosis in menopausal women while WC and WHR were not associated with atherosclerosis same as previous study but in a younger age group (<50 years) than our study[17]. The cutoff points of anthropometric variables for predicting incident CVD may be different between central obesity variables in other Asian populations[18-22].

In our study in a Thai population AIP and BMI appear to be better predictors of early atherosclerosis than WHR or WC. The findings of the current study provide support for the use of AIP for predicting atherosclerosis before the clinical manifestations of CVD. However, more studies with larger sample sizes are recommended.

Conclusion

AIP can significantly add value when

Table 1. Demographic and clinical characteristics of study subjects

Demographic and clinical characteristics	Perimenopausal women (n = 59)	Menopausal women (n = 55)	*p*-value
Age (years)	45.27±3.06	60.87±8.05	<0.01*
Systolic blood pressure (mmHg)	120.31±13.02	130.44±17.31	<0.01*
Diastolic blood pressure (mmHg)	69.69±10.49	68.65±8.91	0.57
Waist circumference (cm)	82.01±10.25	84.28±9.44	0.22
Waist-hip ratio	0.85±0.05	0.87±0.06	0.03*
Body mass index (kg/m^2)	25.22±4.34	24.54±4.13	0.39
Fasting plasma glucose (mg/dL)	99.10±17.98	101.78±20.80	0.46
Creatinine	0.81±0.13	0.82±0.13	0.52
Total cholesterol (mg/dL)	223.85±46.24	218.33±46.04	0.53
Triglyceride (mg/dL)	128.44±61.70	116.42±66.83	0.32
High-density lipoprotein cholesterol (mg/dL)	57.32±13.94	58.33±13.51	0.70
Low-density lipoprotein cholesterol (mg/dL)	140.92±37.14	129.18±42.79	0.12
Atherosclerotic index of plasma	0.32±0.26	0.27±0.25	0.27
Carotid intima media thickness (mm)	0.64±0.09	0.78±0.16	<0.01*

* Significant difference at $p<0.05$

Table 2. AIP compared to anthropometric parameter in perimenopausal and menopausal status for predicting CIMT

Atherosclerosis	Atherosclerotic index of plasma		Body mass index		Waist circumference		Waist-hip ratio	
	χ^2	*p*-value	χ^2	*p*-value	χ^2	*p*-value	χ^2	*p*-value
Perimenopausal women	3,068.00	<0.01*	3,068.00	0.10	841.17	0.22	998.25	0.35
Menopausal women	2,420.00	<0.01*	2,323.75	0.04*	729.25	0.07	921.71	0.06
Total	10,326.50	<0.01*	10,203.00	<0.01*	1,746.55	0.37	2,246.61	0.02*

χ^2 = Chi-square
* Correlation is significant at the 0.05 level

assessing the risk of developing the atherosclerosis marker CIMT in perimenopausal and menopausal women. AIP which can easily be calculated from the standard lipid profile can act as an adjunct that significantly adds predictive value beyond the traditional anthropometric parameters.

What is already known on this topic?

The present study is not the first report comparing AIP with lipid ratio and CIMT values in Asian populations but previous studies cannot be directly applied to the menopausal transition between perimenopausal and menopausal specific subgroups in the Thai population because of differences in ethnic groups and environmental factors.

What this study adds?

AIP, in our study, will allow the application of CIMT marker for early atherosclerosis measurement in specific perimenopausal and menopausal participants from the Thai population.

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Potential conflicts of interest

None.

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ดัชนีหลอดเลือดแดงแข็งกับสัดส่วนร่างกายแบบดั้งเดิมสำหรับทำนายความหนาของไขมันเกาะหลอดเลือดแดงคาโรติดในสตรีวัยใกล้หมดประจำเดือนและวัยหมดประจำเดือน

พรทิพย์ นิ่มขุนทด, ปัทมา ทองดี

ภูมิหลัง: *หลอดเลือดแดงแข็งเป็นสาเหตุทางพยาธิวิทยาที่สำคัญที่ทำให้เกิดโรคหัวใจและหลอดเลือด ซึ่งเป็นสาเหตุทำให้ทุพพลภาพและเสียชีวิตอย่างกว้างขวาง วัยหมดประจำเดือนมีการเปลี่ยนแปลงระดับฮอร์โมนเพิ่มความเสี่ยงต่อโรคหัวใจและหลอดเลือด ค่าดัชนีหลอดเลือดแข็งของพลาสม่าถูกนำมาใช้ในการทำนายการเกิดหลอดเลือดแดงตีบโดยใช้ความหนาของไขมันเกาะหลอดเลือดแดงคาโรติดเป็นตัวบ่งชี้การเกิดหลอดเลือดแดงตีบระยะเริ่มต้น เป็นตัวทำนายที่น่าเชื่อถือในการเกิดโรคหัวใจ และหลอดเลือดในอนาคต*

วัตถุประสงค์: *เพื่อเปรียบเทียบการใช้ดัชนีหลอดเลือดแดงแข็งกับสัดส่วนร่างกายแบบดั้งเดิมในการทำนายความหนาของไขมันที่หลอดเลือดแดงคาโรติดในสตรีวัยใกล้หมดประจำเดือนและหมดประจำเดือน*

วัสดุและวิธีการ: *การศึกษาแบบตัดขวางประกอบด้วยสตรีวัยใกล้หมดประจำเดือนและหมดประจำเดือนที่สมัครใจเข้าศึกษา วัดระดับไขมัน โคเลสเตอรอล ไตรกลีเซอไรด์ เอชดีแอล และแอลดีแอล คำนวณเป็นค่าดัชนีหลอดเลือดแข็ง log (ไตรกลีเซอไรด์ต่อเอชดีแอล) วัดสัดส่วนร่างกายแบบดั้งเดิม ดัชนีมวลกาย รอบเอว รอบสะโพก และสัดส่วนรอบเอว ต่อรอบสะโพก ใช้เพียร์สันไคสแควร์สำหรับการเปรียบเทียบค่าดัชนีหลอดเลือดแข็งกับสัดส่วนร่างกายแบบดั้งเดิม เพื่อใช้ในการทำนายความหนาของไขมันที่เกาะบริเวณหลอดเลือดแดงคาโรติด*

ผลการศึกษา: *สตรีวัยใกล้หมดประจำเดือนและหมดประจำเดือนทั้งหมด 114 คน ดัชนีหลอดเลือดแดงแข็งตัว และสัดส่วนร่างกายแบบดั้งเดิมเพียงเฉพาะดัชนีมวลกายสามารถใช้ในการทำนายความหนาของไขมันที่เกาะบริเวณหลอดเลือดแดงคาโรติดทั้ง 2 กลุ่ม ($p<0.01$) ไม่พบความแตกต่างของดัชนีหลอดเลือดแดงแข็งในสตรีวัยใกล้หมดประจำเดือนและหมดประจำเดือน ทั้งค่ารอบเอวและสัดส่วนรอบเอวต่อรอบสะโพกไม่มีความแตกต่างใน 2 กลุ่ม ค่าความหนาของไขมันที่เกาะบริเวณหลอดเลือดแดงคาโรติดในสตรีวัยหมดประจำเดือนมากกว่าวัยใกล้หมดประจำเดือน 0.78±0.16 vs. 0.64±0.09 มิลลิเมตร ตามลำดับ ($p<0.01$)*

สรุป: *ดัชนีที่มีฐานจากค่าไขมันไตรกรีเซอไรด์ดังค่าดัชนีหลอดเลือดแดงแข็ง สามารถเสริมในการประเมินความเสี่ยงในการเกิดหลอดเลือดแดงตีบในสตรีวัยใกล้หมดประจำเดือนและหมดประจำเดือน ค่าดัชนีหลอดเลือดแข็งที่สูงในช่วงวัยหมดประจำเดือนอาจจะมีความสี่ยงในการเกิดภาวะทางหัวใจและหลอดเลือดในอนาคต แม้ว่าจะไม่มีความแตกต่างของปัจจัยเสี่ยงของหัวใจและหลอดเลือดเช่นเดียวกับค่าไขมันก็ตาม*