

LIPID ACCUMULATION PRODUCT AND METABOLICALLY UNHEALTHY RISK IN SUBCLINICAL ATHEROSCLEROTIC PERIMENOPAUSAL/MENOPAUSAL WOMEN

Pattama Tongdee^{1,*} and Porntip Nimkuntod²

Received: March 04, 2019; Revised: September 05, 2019; Accepted: September 11, 2019

Abstract

Background: The most profound metabolic abnormalities has related with central obesity that effect from fat distribution to abdominal. Central fat distribution has associated with an increased risk of atherosclerotic cardiovascular diseases (CVD). The alternative measurement as Lipid accumulation product (LAP) was index of lipid accumulation used waist circumference (WC) and fasting triglycerides (TG). **Objective:** To investigate whether LAP is related to metabolically unhealthy risk in perimenopausal/menopausal women. **Materials and Methods:** Perimenopausal/menopausal participants without history of CVD were enrolled in the present observational cross-sectional study from Suranaree University of Technology Hospital, Thailand from January 2015 to December 2015. Weight, body mass index (BMI), WC and hip circumferences, waist to hip ratio (WHR), serum levels of lipid and carotid intima media thickness (CINT) were measured. LAP was calculated. High resolution B-mode ultrasonography was performed to measured CINT. **Results:** Total 130 perimenopausal/menopausal women were studied: Metabolically unhealthy normal weight and metabolically unhealthy overweight/obese 16.15%, 83.84% respectively. Compared LAP<34.5 and LAP>34.5, LAP>34.5 group was associated with higher age, systolic blood pressure, diastolic blood pressure, BMI, WHR and lipid ratio ($p<0.01$). Pearson correlation analyses revealed that metabolic unhealthy normal weight and overweight/obese were significantly associated with LAP index but was negatively correlated with subclinical atherosclerosis. **Conclusions:** LAP index is a marker to differentiate metabolically unhealthy normal weight to metabolically unhealthy overweight/obesity in perimenopausal/menopausal women.

¹ School of Obstetrics and Gynecology, Institute of Medicine, Suranaree University of Technology, Nakhon Ratchasima 30000, Thailand. E-mail: pattama_t@sut.ac.th

² School of Medicine, Institute of Medicine, Suranaree University of Technology, Nakhon Ratchasima 30000, Thailand. E-mail: porntipnimk@sut.ac.th

* Corresponding author

Keywords: antioxidant enzyme gene, curcuminoid, fatty acid transport gene, slow-growing chicken, n-3 PUFA

Introduction

The perimenopausal/menopausal women are associated with increase in total and central or abdominal obesity. Estrogen deficiency in menopause is associated with an increase in total adiposity, preferentially at a visceral region. Abdominal accumulation of fat tissue produces the most profound metabolic abnormalities and is associated with an increased risk of atherosclerotic cardiovascular disease (CVD) (Nissen *et al.*, 2008). Accumulation of visceral fat is a major component of central obesity which is more important for the development of metabolic disorders including insulin resistance (Goodpaster *et al.*, 2003; Wagenknecht *et al.*, 2003; Tulloch-Reid *et al.*, 2004), type 2 diabetes (Boyko *et al.*, 2000; Kanaya *et al.*, 2004), and metabolic syndrome (MS) (Lemieux *et al.*, 2000).

Lipid accumulation product (LAP), a novel index of central lipid accumulation, based on a combination of waist circumference (WC) and plasma triglyceride (TG) levels. The marker of over accumulation was measured by TG concentration and/or waist size that effect to calculated value of LAP. In excess lipid material will increasingly be deposited in non-adipose parallel with the LAP increments which accelerated apoptosis, and interfered the cardiovascular control (Schaffer, 2003; Unger, 2003a). The LAP is raising slowly in women compare with men for age <50 years Prior to 50 years old (Kahn, 2005). The LAP (describing lipid over accumulation) performed better than BMI (describing weight over accumulation) for identifying adults at cardiovascular risk. Studies presented more discriminatory capacity of LAP 34.5 for the incidence of diabetes than BMI and similar to WC and waist to hip ratio (WHR). The odds of a diabetic individual having high LAP value was 3.91 times more as compared to a non-diabetic individual.

Our primary focus in this study, therefore, was to assessed if LAP can outperform BMI, normal weight and

overweight/obese in predicting metabolically unhealthy risk in perimenopausal/menopausal women.

Materials and Methods

Study Population

Study subjects were individuals recruited from a physical examination center at Suranaree University of Technology Hospital in Thailand from January 2015 to December 2015. The study was approved by the Institutional Review Board of Suranaree University of Technology, and written informed consented was provided by all participants before enrollment.

Study Protocol

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

Laboratory Measurement

Baseline serum specimens (stored at the central repository) were measured for levels of glucose and lipid profile. Serum glucose, total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured by the central laboratories. Diabetes was defined as self-reported diabetes treatment or a fasting glucose level 126 mg/dL were measured or taking anti-diabetic medication from visiting

data in Suranaree University of Technology Hospital or medication from other hospital.

Definition of Terms

Perimenopausal/Menopausal Women

Participants were also asked about their menstrual bleeding patterns in the 12 months prior to recruitment. Perimenopausal status age ≥ 40 years around menopause and had menstrual period irregularity in the past 12 months. Menopausal status those with no menstrual periods within the last 12 months.

Carotid Intima Media Thickness Measurement

The measurement was carried out according to a validated procedure, using a high resolution B-mode ultrasonography with phased array 5-7 MHz transducer view of the far wall of the common carotid artery, carotid bulb, internal carotid artery using the automated edge detection lumen intima and the media adventitia interface at the far wall for carotid intima media thickness (CIMT) by one cardiologist to perform carotid intima media thickness. The mean CIMT of each of the six carotid segments was determined, and the average of these six mean measures in millimeters was computed for the outcome variable in this analysis.

Anthropometrics Measurement

Body mass index (BMI) was calculated as weight in kilograms divided by height in square meters. WC was measured at the level of the narrowest part of the torso that smallest horizontal circumference in the area between the ribs and the iliac crest. The LAP was proposed by Kahn (2005) as a simple and effective index for lipid over accumulation among adults. based on waist circumference and fasting concentration of circulating triglycerides. The LAP for women was calculated as $[\text{WC (cm)} - 58] \times [\text{TG concentration (mM)}]$.

Metabolically Unhealthy

Metabolically unhealthy is the health status that combination of obesity markers (BMI or WC) and cardiometabolic abnormalities. Define the subjects who are considered as

having large quantities of fat mass or body weight but exhibit a healthy metabolic profile from ATP III criteria > 3 criteria (Blood pressure, Fasting glucose, Triglyceride, HDL-C).

Statistical Analysis

Student's *t* test was used to compare mean values between LAP index, and simple correlations to investigate the association between the LAP and anthropometric parameters, blood pressure, CIMT measures, glucose, lipids, Quantitative variables are expressed as mean $\pm$ standard deviation (SD). All reported *p*-values were two tailed and $p < 0.05$ was considered statistically significant.

Results and Discussion

Overall 130 participants, 51.8% of the participants were perimenopausal women, and 48.2% were menopausal women. As expected, values for age, systolic blood pressure, diastolic blood pressure, BMI, WHR, fasting blood sugar and lipid ratio were significantly greater in LAP ≥ 34.5 group, while there were no LAP index differences in single lipid parameters and CIMT values (Table 1).

Cardio metabolic risk and LAP index, Pearson correlation analyses revealed that BMI, WC, WHR and lipid ratio were significantly associated with LAP index ($p < 0.01$) (Table 2).

Metabolic unhealthy and LAP index, metabolically unhealthy normal weight and metabolically unhealthy overweight/obese 16.15%, 83.84% respectively. Metabolic unhealthy overweight/ obese marked by BMI were associated with an increased risk of changes in LAP index ($p < 0.01$) and is not associated with CIMT (Table 3).

In our study, perimenopausal/ menopausal participants with abnormal LAP index exhibited higher prevalences of cardiometabolic risk factors than participants with normal LAP index. LAP has a noninvasive tool and low cost compare with

Table 1. Distribution of cardiovascular risk markers according to cut off value of the LAP index

Cardiovascular risk markers	LAP<34.5 n = 85	LAP≥34.5 n = 45	p-value
Age (years)	53.07±9.60	54.78±10.52	0.034*
Systolic blood pressure (mmHg)	123.37±16.95	130.84±15.51	0.015*
Diastolic blood pressure (mmHg)	67.43±9.61	72.84±9.34	0.03*
Body mass index (kg/m ²)	23.29±3.09	28.21±4.39	<0.01*
Waist to hip ratio	0.85±0.06	0.89±0.05	<0.01*
Fasting blood sugar (mg/dL)	95.51±13.54	110.71±27.74	<0.01*
Creatinine (mg/dL)	0.81±0.13	0.81±0.14	0.89
Total cholesterol; TC (mg/dL)	216.89±40.91	228.40±51.26	0.17
Triglyceride; TG (mg/dL)	98.07±38.17	169.38±72.04	<0.01*
High-density lipoprotein cholesterol; HDL-C (mg/dL)	61.25±11.99	53.87±23.83	0.02*
Low-density lipoprotein cholesterol; LDL-C (mg/dL)	131.48±35.62	138.47±48.99	0.36
TC/HDL-C	3.67±0.87	4.77±1.64	<0.01*
TG/HDL-C	1.72±0.79	3.68±2.13	<0.01*
LDL/HDL-C	2.23±0.69	2.93±1.21	<0.01*
Carotid intima media thickness (mm)	0.70±0.16	0.70±0.13	0.99

* Significant difference at $p < 0.05$.**Table 2. Correlation between LAP and cardiometabolic risk in metabolic unhealthy group**

Cardiometabolic risk parameters	LAP index	
	Pearson correlation (r)	p-value
Body mass index	0.510	<0.01*
Waist circumference	0.615	<0.01*
Waist to hip ratio	0.400	<0.01*
Fasting blood sugar	0.152	0.09
Total Cholesterol; TC	0.088	0.32
Triglyceride; TG	0.117	0.18
High-density lipoprotein cholesterol; HDL-C	0.064	0.47
Low-density lipoprotein cholesterol; LDL-C	0.038	0.67
TC/HDL-C	0.389	<0.01*
TG/HDL-C	0.757	<0.01*
LDL-C/HDL-C	0.279	<0.01*

* Significant correlation at $p < 0.05$.

other radiology imaging study for estimating the lipid burden in isolated tissues (Kahn, 2006). The cardiometabolic risk factors were overweight/obesity elevated systolic and diastolic blood pressure, fasting/postprandial hyperglycemia, and dyslipidemia (Vanuzzo *et al.*, 2008). Abdominal obesity was recognized as a clinically measurable in MS entity (Grundy *et al.*, 2004; Despres and Lemieux, 2006; Reaven, 2007). WC cannot distinguish visceral adiposity, an important correlate of metabolic abnormalities, from the amount of subcutaneous abdominal fat. The lipid over-accumulation lead to ectopic deposition of lipids in non- adipose tissues which effect to blood concentrations of lipids, then become chronically elevated referred to lipid over accumulation (Unger, 2003b).

The result of LAP index in previous studies when identifying characterized patient

with triad of atherogenic metabolic: fasting hyperinsulinemia, hyperapolipoprotein B and high proportion of small LDL-C may be used as a screening marker (Wiltgen *et al.*, 2009; Ioachimescu *et al.*, 2010). LAP index discriminatory to identify cardiometabolic risk profile in participants compared with National Cholesterol Education Program-Adult Treatment Panel III and International Diabetes Federation (NCEP, 2002) as low cost to identify people under higher cardiovascular risk. Results showed that perimenopausal and menopausal women with LAP and BMI <25 kg/m² were significantly different from those with BMI ≥25 kg/m² in body weight, BMI, WC, WHR and TG. The metabolic risk factors from adipose tissue are correlated with remains more strongly associated with an adverse metabolic risk profile even after accounting for

Table 3. Metabolic unhealthy normal weight and metabolic unhealthy overweight/obesity and LAP index

Metabolically Unhealthy		n	Mean $\pm$ SD	p-value	95% CI (Lower-Upper)
CIMT	Normal weight	21	0.69 $\pm$ 0.15	0.62	0.05-0.09
	Overweight/obesity	109	0.70 $\pm$ 0.15		
LAP	Normal weight	21	17.67 $\pm$ 6.80	<0.01*	8.48-28.99
	Overweight/obesity	109	36.39 $\pm$ 23.49		

* Significant correlation at $p < 0.05$.

standard anthropometric index (Fox *et al.*, 2007).

Our study found a similar associated novel index of central lipid accumulation calculated as LAP index with metabolically unhealthy risk in a perimenopausal/menopausal women, Thai populations. The same finding has been previously reported impacts of visceral adipose tissue on metabolic risk factors with dominant impacts on TG concentrations in middle-aged Japanese (Oka *et al.*, 2010). We may conclude that the LAP index is a marker to differentiate metabolically unhealthy normal weight to metabolically unhealthy overweight/obesity without overt CVD.

The study of routine referred to coronary angiogram in high LAP values of postmenopausal women are predictive of mortality independently of other cardiovascular risk factors in normal weight and diabetic postmenopausal women were routinely referred to coronary angiography (Bozorgmanesh *et al.*, 2010; Wehr *et al.*, 2011). Early detection and intervention of risk factors of CVD are the key points for prevention and delay of CVD development. The cross-sectional study design, our findings could not prove causal relationships between lipid accumulation products and elevated CIMT and subgroup of metabolically unhealthy measurement had a relatively small sample size.

Strength of the Study

The present study is not the first report of LAP and adiposity index correlation with cardiometabolic risk but previous studies cannot be directly applied to metabolic unhealthy risk of perimenopausal/menopausal

specific subgroup in Thailand. LAP in our study, will allow the application of LAP index to discrimination of metabolically unhealthy risk measurement in individual specific perimenopausal/menopausal participants from the Thai populations.

Limitation of Study

The sample size is not cover all region of Thailand and not include other vascular diseases may be less reflected.

Future Recommendations

However, it is important to evaluation a correlation between LAP and CIMT risk of developing subclinical atherosclerosis and other vascular diseases in Thai and Asian populations.

Conclusions

Our study LAP an inexpensive and simple risk profiling that may allow to identifying metabolically unhealthy that risk to subclinical atherosclerosis in perimenopausal/menopausal women.

Disclosures

The authors declare that they have no competing interests.

Acknowledgement

We thank all who participated in the study, the staff at cardiovascular clinic and menopause clinic of Suranaree University of Technology Hospital who assisted the study.

References

- Boyko, E.J., Fujimoto, W.Y., Leonetti, D.L., and Newell-Morris, L. (2000). Visceral adiposity and risk of type 2 diabetes: A prospective study among Japanese Americans. *Diabetes Care.*, 23:465-471.
- Bozorgmanesh, M., Hadaegh, F., and Azizi, F. (2010). Predictive performances of lipid accumulation product vs. adiposity measures for cardiovascular diseases and all-cause mortality, 8.6-year follow up: Tehran lipid and glucose study. *Lipids Health Dis.*, 9:100.
- Despres, J.P. and Lemieux, I. (2006). Abdominal obesity and metabolic syndrome. *Nature.*, 444:881-887.
- Fox, C. S., Massaro, J. M., Hoffmann, U., Pou, K. M., Maurovich-Horvat, P., Liu, C. Y., Vasan, R. S., Murabito, J. M., Meigs, J. B., Cupples, L. A., D'Agostino, R. B. Sr., and O'Donnell, C. J. (2007). Abdominal visceral and subcutaneous adipose tissue compartments: association with metabolic risk factors in the Framingham Heart Study. *Circulation.*, 116(1):39-48.
- Goodpaster, B.H., Krishnaswami, S., Resnick, H., Kelley, D. E., Haggerty, C., Harris, T. B., Schwartz, A. V., Kritchevsky, S. and Newman, A.B. (2003). Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. *Diabetes Care.*, 26:372-379.
- Grundey, S. M., Brewer, H. B. Jr., Cleeman, J. I., Smith, S. C. Jr., and Lenfant, C. (2004). Definition of metabolic syndrome: Report of the National Heart, Lung, and Blood Institute/ American Heart Association conference on scientific issues related to definition. *Circulation.*, 109:433-438.
- Ioachimescu, A. G., Brennan, D. M., Hoar, B. M., and Hoogwerf, B. J. (2010). The lipid accumulation product and all-cause mortality in patients at high cardiovascular risk: a PreCIS database study. *Obesity (Silver Spring).*, 18(9):1,836-1,844.
- Kahn, H. S. (2005). The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. *BMC Cardiovascular Disorders.*, 5:26.
- Kahn, H.S. (2006). The lipid accumulation product is better than BMI for identifying diabetes: a population-based comparison. *Diabetes care.*, 29:151-153.
- Kanaya, A.M., Harris, T., Goodpaster, B.H., Tylavsky, F., and Cummings, S.R. (2004). Health, Aging, and Body Composition (ABC) Study: Adipocytokines attenuate the association between visceral adiposity and diabetes in older adults. *Diabetes Care.*, 27:1,375-1,380.
- Lemieux, I., Pascot, A., Couillard, C., Lamarche, B., Tchernof, A., Alméras, N., Bergeron, J., Gaudet, D., Tremblay, G., Prud'homme, D., Nadeau, A. and Després, J.P. (2000). Hypertriglyceridemic waist: A marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapolipoprotein b; small, dense ldl) in men? *Circulation.*, 102:179-184.
- National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). (2002). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation.*, 106(25):3,143-3,421.
- Nissen, S.E., Nicholls, S.J., Wolski, K., Rodés-Cabau, J., Cannon, C.P., Deanfield, J.E., Després, J.P., Kastelein, J.J., Steinhilb, S.R., Kapadia, S., Yasin, M., Ruzyllo, W., Gaudin, C., Job, B., Hu, B., Bhatt, D. L., Lincoff, A. M. and Tuzcu, E. M. (2008). STRADIVARIUS Investigators: Effect of rimonabant on progression of atherosclerosis in patients with abdominal obesity and coronary artery disease: The Stradivarius randomized controlled trial. *JAMA.*, 299:1,547-1,560.
- Oka, R., Miura, K., Sakurai, M., Nakamura, K., Yagi, K., Miyamoto, S., Moriuchi, T., Mabuchi, H., Koizumi, J., Nomura, H., Takeda, Y., Inazu, A., Nohara, A., Kawashiri, M. A., Nagasawa, S., Kobayashi, J. and Yamagishi, M. (2010). Impacts of visceral adipose tissue and subcutaneous adipose tissue on metabolic risk factors in middle- aged Japanese. *Obesity (Silver Spring).*, 18(1):153-160.
- Reaven, G. M. (2007). The individual components of the metabolic syndrome: is there a raison d'être? *J Am Coll Nutr.*, 26:191-195.
- Schaffer, J.E. (2003). Lipotoxicity: when tissues overeat. *Curr Opin Lipidol.*, 14:281-287.
- Tulloch- Reid, M. K., Hanson, R. L., Sebring, N. G., Reynolds, J.C., Premkumar, A., Genovese, D.J. and Sumner, A. E. (2004). Both subcutaneous and visceral adipose tissue correlate highly with insulin resistance in African Americans. *Obes Res* 12:1,352-1,359.
- Unger, R.H. (2003a). Lipid overload and overflow: metabolic trauma and the metabolic syndrome. *Trends Endocrinol Metab.*, 14:398-403.
- Unger, R.H. (2003b). Weapons of lean body mass destruction: the role of ectopic lipids in the metabolic syndrome. *Endocrinology.*, 144:5,159-5,165.
- Vanuzzo, D., Pilotto, L., Mirolo, R., and Pirelli, S. (2008). Cardiovascular risk and cardiometabolic risk: an epidemiological evaluation. *G Ital Cardiol (Rome).*, 9(4 Suppl 1):6S-17S.
- Wagenknecht, L. E., Langefeld, C. D., Scherzinger, A. L., Norris, J. M., Haffner, S. M., Saad, M. F. and Bergman, R.N. (2003). Insulin sensitivity, insulin secretion, and abdominal fat: The insulin resistance atherosclerosis study (iras) family study. *Diabetes*, 52:2490-2496.
- Wehr, E., Pilz, S., Boehm, B.O., März, W., and Obermayer-Pietsch, B. (2011). The lipid accumulation product is associated with increased mortality in normal weight postmenopausal women. *Obesity (Silver Spring).*, 19(9):1,873-1,880.
- Wiltgen, D., Benedetto, I.G., Mastella, L.S., and Spritzer, P.M. (2009). Lipid accumulation product index: a reliable marker of cardiovascular risk in polycystic ovary syndrome. *Hum Reprod.*, 24(7):1,726-1,731.