Association of Lipid Accumulation Product with Cardio-Metabolic Risk Factors in Postmenopausal Women

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Abstract- The lipid accumulation product is a novel, safe and inexpensive index of central lipid over accumulation based on waist circumference and fasting concentration of circulating triglycerides. This study was designed to investigate the ability of lipid accumulation product to predict Cardio-metabolic risk factors in postmenopausal women. In this Cross-sectional study, 264 postmenopausal women by using convenience sampling method were selected from menopause clinic in Tehran. Cardio-metabolic risk factors were measured, and lipid accumulation product (waist-58×triglycerides [nmol/L]) was calculated. Optimal cut-off point of lipid accumulation product for predicting metabolic syndrome was estimated by ROC (Receiver-operating characteristic) curve analysis. Metabolic syndrome was diagnosed in 41.2% of subjects. Optimal cut-off point of lipid accumulation product for predicting metabolic syndrome was 47.63 (sensitivity:75%; specificity:77.9%). High lipid accumulation product increases risk of all Cardio-metabolic risk factors except overweight, high Total Cholesterol, high Low Density Lipoprotein Cholesterol and high Fasting Blood Sugar in postmenopausal women. Our findings show that lipid accumulation product is associated with metabolic syndrome and some Cardio-metabolic risk factors Also lipid accumulation product may have been a useful tool for predicting cardiovascular disease and metabolic syndrome risk in postmenopausal women.

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Keywords: Lipid accumulation product; Menopause; Metabolic syndrome; Cardio-metabolic syndrome

Introduction

Menopause status has been associated with changes in body composition resulting to an increase in central adiposity specially visceral fat (1,2). Central adiposity in postmenopausal women has been recognized as an independent risk for developing metabolic syndrome, dyslipidemia, and cardiovascular diseases (CVD) (3). Elevated plasma triglycerides (TG) levels have also been associated with a higher risk of CVD (4,5).

The lipid accumulation product (LAP), is a novel, safe, and inexpensive index of central lipid over accumulation which was first explained by Kahn (2005), based on waist circumference and fasting concentration of circulating triglycerides: [LAP=(WC-65)×TG for men and (WC-58)×TG for women] (6).There are reports of different cut-off points at 34.5 and 44.1 for LAP as a simple screening tool for insulin resistance, metabolic, and cardiovascular risk in young men with polycystic ovary syndrome (PCOS) (7,8).

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This study aimed to investigate the ability of LAP in predicting metabolic and cardiovascular risks in postmenopausal women. Our other objective was to recognize the reliability of LAP as a simple, cost benefit index to estimate the prevalence of metabolic syndrome (MetS) and cardiovascular risk factors.

Materials and Methods

All menopausal women above 40 years of age who have come to the menopause clinic were included in the study, which the lack of missed period within a year or FSH≥40 was defined as menopause. Those who had been under the treatment of drugs specifically lipid lowering drugs or have had a history of weight loss surgeries or any other kind of procedure that caused waist circumference reduction like lipolysis, liposuction, abdominoplasty or with a history of coronary heart diseases, kidney, and liver diseases have been excluded from the study.

We conducted a cross-sectional study on women consulting for climacteric symptoms at the menopause clinic of Tehran women general hospital, Tehran, Iran. The study was performed from January 2011 to April 2013 among 264 postmenopausal women in menopause clinic. A checklist was completed for each patient; it included demographic information, menopausal status, medical history, reproductive history, drug history, family history, physical examination, and clinical laboratory data. Body Mass Index (BMI) was calculated by dividing weight (in kilograms) by the square of the height (in meters). Waist circumference (WC) was measured at a level midpoint between the lower rib margin and the top of the iliac crest. Blood pressure (BP) was measured twice with a standard sphygmomanometer in a sitting position, and the average blood pressure had been documented in the sheets. After twelve-hour fasting period fasting blood glucose (FBG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and low- density lipoprotein cholesterol (LDL-C), and TG levels were determined using an auto-analyzer (Hitachi, 902, Japan).

MetS was defined according to the National Cholesterol Education Program, Adult Treatment Panel III (ATPIII) criteria, i.e. having three or more of the following components (4):

1) Abdominal obesity: WC≥88 cm

2) High TG: serum TG level≥150 mg/dl

3) Low HDL-C: HDL-C<50 mg/dl

4) High BP: systolic BP (SBP)≥130 mmHg and/or diastolic BP (DBP)≥85mmHg or being on treatment for hypertension

5) High FBG: serum glucose level≥100 mg/dl or being on treatment for diabetes

High TC and High LDL-C were considered as other cardio-metabolic risk factors and were defined based on ATP III Classification.

LAP (waist-58×TG [nmol/L]) was calculated after the clinical and laboratory evaluations.

To determine the optimal threshold for predicting MetS risk, the receiver operator characteristic (ROC) curve analysis was plotted with an estimation of the variables' sensitivity, specificity. Optimal threshold for cardiovascular and metabolic risk factors were assessed by the minimum value of $\sqrt{(1-\text{sensitivity})^2+(1-\text{specificity})^2}$ (9), which represented the maximum sum of sensitivity and specificity.

The area under curve (AUC) relates to the overall ability of using the LAP as diagnostic test for predicting of cardiovascular and metabolic risks. An AUC value range is between0 to 1. The AUC can be interpreted according to the following principles: test equal to chance (AUC=0.5), less accurate (0.5<AUC≤0.7), moderately accurate (0.7<AUC≤0.9), highly accurate (0.9<AUC≤1.0), and perfect performance tests (AUC=1.0) 10.

The normality distribution of data was tested by Kolomogrov test. Results are shown as means±standard deviation (SD) or median and inter quartile range (IQR). Mean of baseline characteristics and MetS component according to LAP optimal cutoff point was assessed by t-test and Mann–Whitney U test. Spearman's rank or Pearson's correlation coefficient was calculated between variables using a 2-tailed significance test. All data were analyzed by SPSS version 16.0 (SPSS Inc, Chicago, IL, USA). $P<0.05$ was considered as statistically significant.

Results

The mean age of participants was 53.98 (SD:5.57) years, the mean (SD) age at menopause was 47.23 (5.25) years, and the median time since menopause was 5 (IQR:6) years. MetS was diagnosed in 41.2% of individuals.

ROC curve analysis showed that the AUC was 82.7 (95%CI:77.5-87.9), and the optimal cut-off point for LAP to diagnose MetS risk was 47.63 (sensitivity: 75%; specificity:77.9%). Figure 1 shows the ROC of LAP index as marker for diagnosing MetS.

Table 1 shows mean of clinical, anthropometric and MetS components according to LAP optimal cut-off

point (47.63). As presented in this Table, those individuals with higher LAP levels (>47.63) had higher WC, hip circumference, SBP; DBP, and TG levels and lower HDL-C.

Table 1. Mean (SD) of Baseline characteristics & Cardio metabolic risk factors according to LAP categories in postmenopausal women

	All	LAP<47.63	LAP≥47.63	*P*.value
LAP	53.35(36.13)	30.22(10.22)	83.31(35.66)	<0.001
Age(years)	53.98(5.57)	53.27(5.49)	55(5.59)	0.01
Time since menopause (years)	6.79(6.23)	6.22(5.51)	7.21(6.35)	0.17
Menopause age(years)	47.23(5.25)	47.03(5.03)	47.78(4.57)	0.21
BMI(kg/m^2)	28.66(44.47)	27.36(4.01)	30.33(4.51)	<0.001
WC(cm)	91.70(13.19)	86.02(9.29)	98.87(13.87)	<0.001
HC(cm	107.51(11.06)	103.56(9)	112.49(11.46)	<0.001
TC(mg/dl)	206.24(48.55)	203.75(48.21)	207.83(47.76)	0.49
HDL-c(mg/dl)	55.20(14.88)	59.37(15.28)	50.07(10.57)	0.07
LDL-c(mg/dl)	127.41(60.74)	128.87(75..55)	124.55(32.55)	0.56
SBP(mmHg)	119.86(18.83)	117.06(20.28)	123.56(16.20)	0.005
DBP(mmHg)	80.39(12.83)	78.37(12.57)	83(12.80)	0.004
FPG(mg/dl)	101.70(27.74)	99.97(25.68)	102.81(27.70)	0.38
TG(mg/dl)	139.63(72.38)	102.04(40.29)	188.02(75.91)	<0.001

LAP: lipid accumulation product; BMI: Body mass index; HDL-c: high density lipoprotein cholesterol; LDL-c: LDL: low density lipoprotein cholesterol; TC: Total Cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; WC: Waist circumference; HC: Hip circumference; TG: triglyceride;

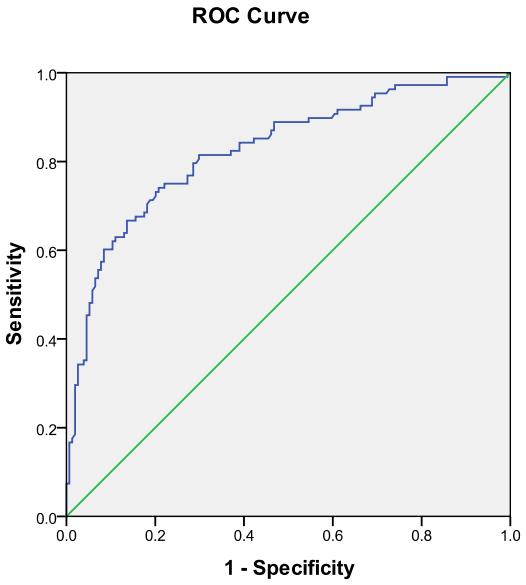

Figure 1. Roc curve for LAP index as marker for diagnosing MS

LAP was associated significantly with all cardio-metabolic risk factors except high TC, high LDL-C and high FBS (Table 2).

Table 3 shows association of LAP with cardio-metabolic risk factors in logistic regression model. As presented in this Table high LAP increase risk of all cardio-metabolic risk factors except overweight, high TC, high LDL-C and high FBS.

A negative correlation was seen between LAP and HDL-C levels which is in accordance with Maturana *et al*., findings (11). All these single components, both WC and TG levels are associated with dysfunctional and highly lipolytic adipose tissue, which is strongly associated with MetS, CVD, and type 2 diabetes (12). As we reported, a negative correlation existed between LAP, TG levels, and WC that shows LAP can well reflect the over accumulation of lipids in body, which is a major risk factor for cardio-metabolic diseases. E Jike *et al*. also implied that using LAP as a reliable index to evaluate cardio-metabolic risks in population is logically acceptable because LAP captured both anthropometric and metabolic dimensions of visceral fat over accumulation (13).

A positive correlation was seen between WC and DBP, which are all important values in cardio metabolic diseases. Kahn et Valdez reported a strong association between Glucose and blood pressure with EWET index (elevated waist circumference and elevated TG levels), which are all risk variables for MetS and CVD (14). Siani *et al*. also reported a positive association between increase in central adiposity (WC) and FBG, serum TG levels, which again confirm that simple values like WC could be of practical relevance in the assessment of the risk associated with the different components of the MetS and cardiovascular risk (15). Furthermore, it has been reported that WC has a high sensitivity and specificity to predict diabetes and cardiovascular events, as WC is an indicator of visceral adipose tissue

associated with increase in plasma free fatty acid, leading to hyperinsulinemia and other cardio-metabolic risks that could be simply measured (16,17). All these evidences show that LAP and WC (as a value measured in LAP) are simple, inexpensive and reliable indicators of MetS and CVD that could be considered as a useful index for CVD risk screening in postmenopausal women.

Table 2. Prevalence of cardio metabolic risk factors according to LAP categories in postmenopausal women

Cardio metabolic risk factors		All n=264	LAP<47.63 n=149(55.4%)	LAP≥47.63 n=115(42.8%)	*P*.value
BMI	Normal	53(20.2)	47(31.8)	6(5.3)	<0.001
	Overweight	120(45.8)	67(45.3)	53(46.5)	
	Obese	89(34)	34(23)	55(48.2)	
Abdominal obesity		173(65.5)	69(46.3)	104(90.4)	<0.001
High TG		92(34.8)	20(13.4)	72(62.6)	<0.001
Low HDL		103(39.2)	45(30.4)	58(50.4)	0.001
High SBP		82(31.2)	36(24.31)	46(40)	0.006
High DBP		80(30.5)	31(21.1)	49(42.6)	<0.001
High BP		106(40.3)	47(31.8)	59(51.3)	0.001
High FPG		121(45.8)	61(40.9)	60(52.2)	0.07
MetS		108(41.2)	27(18.4)	81(70.4)	<0.001
Number component of MetS	0	19(7.3)	19(12.9)	0(0)	<0.001
	1	56(21.4)	48(32.7)	8(7.8)	
	2	79(30.2)	53(36.1)	26(22.6)	
	3	65(24.8)	23(15.6)	42(36.5)	
	4	32(12.2)	4(2.7)	28(24.3)	
	5	11(4.2)	0(0)	11(9.6)	
High TC		188(62.5)	92(62.2)	73(63.5)	0.82
High LDL		132(49.1)	57(49.6)	57(49.6)	0.96

LAP: lipid accumulation product; BMI: Body mass index; TG: triglyceride; HDL-c: high density lipoprotein cholesterol; LDL-c: low density lipoprotein cholesterol; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; MetS: Metabolic Syndrome; TC: Total Cholesterol;

Table 3. Association between LAP and cardio metabolic risk factors in logistic regression analysis

Cardio metabolic risk factors	LAP(>47.63/<47.63)	
	OR $_{adjusted}$* (95%CI)	*P*.Value
High SBP	1.84(1.1-3.21)	0.02
High DBP	2.68(1.55-4.64)	<0.001
HTN	2.07(1.24-3.47)	0.005
Low HDL	2.38(1.42-3.99)	0.001
Overweight	1.06(0.65-1.74)	0.81
Obesity	3.12(1.82-5.34)	<0.001
High FBS	1.55(0.95-2.55)	0.08
High TC	0.98(0.59-1.64)	0.95
High LDL	0.97(0.59-1.59)	0.96
MetS	10.45(5.83-18.75)	<0.001

LAP: lipid accumulation product; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HDL-c: high density lipoprotein cholesterol; FPG: Fasting plasma glucose; LDL-c: low density lipoprotein cholesterol; TC: Total Cholesterol; MetS: Metabolic Syndrome
*adjusted for age

Discussion

In this study, MetS was more prevalent in individuals with higher LAP; moreover, those with higher LAP had more adverse metabolic components in comparison with subjects with lower LAP. Different studies have shown an association between LAP level, metabolic and cardiovascular risk factors (6,11,18).

Previous studies show that higher WC and elevated TG levels can be a predictor of higher metabolic and CVD risks (12,14,19). Others showed an association between menopausal status and central adiposity, which is a great risk for cardiovascular events and metabolic disturbances (20,21). LAP was first explained by Kahn. in a study using data from NHANES ΠI database in 2005, which was a comparison between LAP and BMI to predict CVD, MetS, and diabetes risk. This study showed that LAP might be a better predictor of the incidence of CVD (6). Also, an increased risk of mortality with higher LAP was reported in a study on postmenopausal healthy women (8). Our findings also show an association between higher LAP and the prevalence of MetS and other metabolic and cardiovascular risks as higher WC, elevated TG and lower HDL-C levels. These suggest that LAP may have clinical application, to be a useful tool for CVD risk screening especially in postmenopausal women with obesity. Taverna *et al.,* also have shown that LAP could be an accurate predictor of the MetS in adults (18).

We showed a cut-off point of 48.61 as a reliable point to diagnose in postmenopausal women. To the best of our knowledge, no previous report about the best cut-off point of LAP for predicting in postmenopausal women. Wiltgen *et al*., report a cut-off point of 34.5 as a useful, cost benefit tool to screen CVD risk in young women with PCOS (7). In another study, Wehr *et al*. suggested a cut-off point of 44.1 for screening the risk of impaired glucose tolerance in PCOS women (22). Taverna *et al*., also used a cut-off value of 48.09 in men and 31.77 in women, for risk assessment of MetS in healthy population (18).

This study has some limitations; first small population study might influence our results. Furthermore, this study has been performed only on a limited population in Tehran, which may not be contributable to other regions of country or other ethnicities.

This study shows that LAP index is associated with MetS in postmenopausal women. Individuals with higher LAP index had an increased risk of metabolic disorders compared to those with lower LAP. This index may be a strong, reliable and low cost tool for screening metabolic syndrome in postmenopausal population.

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