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Cut-off Levels of Visceral Adiposity Index for Determining Hyperandrogenemia in Women with Polycystic Ovary Syndrome

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ABSTRACT

Objectives: To evaluate the optimum cut-off values and AUC of visceral adiposity index (VAI) and lipid accumulation product (LAP) to predict hyperandrogenemia in Thai polycystic ovary syndrome (PCOS) women and to identify factors that associated with these values.

Materials and Methods: This prospective cross-sectional study recruited 102 Thai PCOS women, aged 18-45 years. All participants were measured for anthropometric data, lipid, carbohydrate and androgen profiles. VAI, LAP and free testosterone were calculated. The receiver operating characteristics (ROC) curve was performed to evaluate the optimum cut-off values of VAI and LAP in predicting hyperandrogenemia, and also to identify factors associated with VAI and LAP.

Results: The mean ± standard deviation of age was 26.9 ± 5.7 years. Prevalence of hyperandrogenemia was 49%. The optimal cut-off values of VAI and LAP in predicting hyperandrogenemia were ≥ 1 (AUC = 0.755) and ≥ 16.5 (AUC = 0.756) respectively. VAI was positively correlated with LAP, hip circumference (HC), waist-to-hip ratio (WHR), the waist-to-height ratio and low density lipoprotein-cholesterol. LAP was significantly correlated with HC, waist circumference, and WHR. Both LAP and VAI were significantly correlated with free testosterone and free androgen index (FAI), but not correlated with total testosterone and dehydroepiandiosterone sulfate.

Conclusion: Both VAI and LAP were significantly correlated with free testosterone and FAI. A VAI value of ≥1 and a LAP value of ≥ 16.5 were determined to be indicators for predicting hyperandrogenemia in PCOS women.

Keywords: hyperandrogenemia, lipid accumulation product, polycystic ovary syndrome, visceral adiposity index.

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การศึกษาค่าจุดตัดของ visceral adiposity index เพื่อทำนายภาวะฮอร์โมนเพศชายสูงในหญิงกลุ่มอาการถุงน้ำรังไข่หลายใบ

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บทคัดย่อ

วัตถุประสงค์: *เพื่อหาค่าจุดตัดที่เหมาะสมและค่า AUC ของ visceral adiposity index (VAI) และ lipid accumulation product (LAP) ในการทำนายภาวะฮอร์โมนเพศชายสูง ของหญิงไทยที่มีกลุ่มอาการถุงน้ำรังไข่หลายใบร่วมกับหาปัจจัยเสี่ยงที่สัมพันธ์กับค่าเหล่านี้*

วัสดุและวิธีการ: *การวิจัยแบบภาคตัดขวาง (cross section study)ในหญิงไทยที่มีกลุ่มอาการถุงน้ำรังไข่หลายใบจำนวน 102 คน ที่มีอายุ 18-45 ปี ผู้เข้าร่วมวิจัยจะได้รับการตรวจวัด ข้อมูลพื้นฐานและตรวจเลือดเพื่อนำมาใช้ในการคำนวณ VAI, LAP และฮอร์โมนเพศชายอิสระ (Free testosterone) และหลังจากนั้นนำมาคำนวณาจุดตัดที่เหมาะสม รวมถึงปัจจัยที่มีผลต่อ VAI และ LAP*

ผลการศึกษา: *อายุเฉลี่ยของผู้เข้าร่วมวิจัย 26.9 ± 5.7 ปี พบความชุกของภาวะฮอร์โมนเพศชายสูงร้อยละ 49 จุดตัดที่เหมาะสมของค่า VAI และ LAP ในการทำนายภาวะฮอร์โมนเพศชายสูง คือ ≥ 1 (AUC = 0.755) และ ≥ 16.5 (AUC = 0.756) ตามลำดับ การศึกษาพบว่าค่า VAI สัมพันธ์กับ LAP เส้นรอบสะโพก (hip circumference) สัดส่วนรอบเอวต่อรอบสะโพก (waist-to-height ratio) และค่าไขมันคลอเรสเตอรอลชนิด LDL นอกจากนี้ยังพบว่าค่า VAI และ LAP มีความสัมพันธ์อย่างมีนัยสำคัญกับระดับฮอร์โมนเพศชายอิสระและดัชนีฮอร์โมนเพศชายอิสระ (free androgen index)*

สรุป: *ค่า VAI และ LAP สัมพันธ์กับกับระดับฮอร์โมนเพศชายอิสระและดัชนีฮอร์โมนเพศชายอิสระ (free androgen index) อย่างมีนัยสำคัญและค่า VAI ที่ตั้งแต่ 1 ขึ้นไปและ LAP ตั้งแต่ 16.5 ขึ้นไป สามารถทำนายภาวะ ฮอร์โมนเพศชายสูงในหญิงไทยที่มีกลุ่มอาการถุงน้ำรังไข่หลายใบ*

คำสำคัญ: *ภาวะไขมันในเลือดสูง, lipid accumulation product, กลุ่มอาการถุงน้ำรังไข่หลายใบ, visceral adiposity index*

Introduction

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders among women of reproductive age, approximately 10-15% worldwide[1]. Clinical manifestations of PCOS are irregular menstruation, anovulation, hirsutism, acne, male pattern alopecia and infertility[2]. Furthermore, PCOS is strongly associated with central obesity, insulin resistance and metabolic syndrome, all of which increase metabolic cardiovascular risk[3].

Among the diagnostic criteria, hyperandrogenism is a key feature of PCOS[2]. An androgen excess in PCOS is primarily produced by ovaries; other causes are the adrenal glands and peripheral conversion. The mechanism of androgen excess results from an increase in LH pulse frequency, leading to an increase in theca cell volume and androgen synthesis. In addition, insulin and abdominal visceral adiposity contribute to the development of androgen excess in PCOS by increasing lipolysis of visceral adiposity, followed by the release of more free fatty acids and the production of more adipocytokines. The deterioration in insulin sensitivity causes hyperinsulinemia and, eventually, increases ovarian androgen production and decreases hepatic sex hormone-binding globulin production. Furthermore, in PCOS the insulin receptor increases phosphorylation of serine, which inhibits the insulin signaling pathway, causing insulin resistance. Elevated levels of serum free fatty acids also cause androgen overproduction by increasing in serine phosphorylation of P450c17. Consequently, chronic androgen excess results in abdominal visceral obesity in a vicious cycle[1, 3-5].

Abdominal visceral fat surrounds internal abdominal organs such as the liver, pancreases and intestines[6, 7]. Abdominal visceral fat has been found to be associated with several metabolic conditions, including impaired glucose, insulin resistance, poor lipid metabolism, metabolic syndrome, and hyperandrogenism in PCOS[3]. The gold standard to directly evaluate visceral and subcutaneous adipose tissue is by imaging, including computerized tomography (CT) and magnetic resonance imaging (MRI); nevertheless, imaging is not recommended as a routine procedure due to its high cost and complicated, technical nuances. As a result, indirect methods have been progressively introduced to determine visceral adipose tissue. They include anthropometric data (body mass index (BMI), waist circumference (WC) and waist-to-hip ratio (WHR)), the visceral adiposity index (VAI), and the lipid accumulation product (LAP). While BMI and WC cannot distinguish between subcutaneous and visceral fat[6-9]. VAI and LAP are reliable indirect methods for determining abdominal visceral tissue.

In the recent years, many studies have investigated the association between VAI and various features of PCOS, such as the severity of anovulation, insulin resistance, hyperandrogenemia and metabolic syndrome in PCOS women[10-13]. Aboelnaga et al[14] studied the correlation of VAI with the Rotterdam criteria in Egyptian PCOS women. They reported that total testosterone was significantly correlated with VAI, WC, BMI and weight. Furthermore, Androulakis et al in 2014[12], reported that VAI correlation with free testosterone level was significantly positive.

Currently, there is insufficient evidence to established definitive values for hormonal levels or clinical presentations of hyperandrogenism in case of hyperandrogenemia. Accurate methods of free testosterone measurement (such as equilibrium dialysis, gas or liquid chromatography-mass spectrometry) are technically complex, costly and not widely available[2]. In this study, we set out to establish measurements that could be easily and cost-effectively used to screen for hyperandrogenemia in Thai PCOS women. Accordingly, the aim of the study was to ascertain the cut-off points for VAI and LAP values that could be used to predict hyperandrogenemia in Thai PCOS women, and to identify factors that are significantly associated with those values in the PCOS population. Data from this study will improve screening; in turn, this will result in an increase in definite diagnoses of hyperandrogenemia and a reduction in healthcare costs related to using the testosterone cut-off.

Materials and Methods

This prospective cross-sectional study was performed from October 2019 to February 2020 at the Gynecologic Endocrinology Clinic, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj hospital, Mahidol University, Thailand. The study was conducted in accordance with the principle of the International Conference on Harmonization in Good Clinical Practice (ICH-GCP), Declaration of Helsinki, the Belmont Report and The Council for International Organizations of Medical Sciences (CIOMS) Guidelines. The protocol of this study was approved by the Siriraj Institutional Review Board (SIRB No.561/2562). All participants were informed and written consent to participate in this study was obtained.

In all, the study recruited 102 Thai PCOS women, who had been diagnosed using the 2003 Rotterdam criteria[15]. Eligible participants were registrants who were 18-45 years of age; were not pregnant; and during the 3 months preceding their participation, had not taken any hormones, hormonal contraceptive drugs, steroids, or other medications which could interfere with their serum lipid profiles or insulin and androgen levels (for example, niacin, corticosteroid, beta-blockers, calcium channel blocker, and lipid-lowering medications). Patients were excluded if they had a severe medical disease, such as a liver or renal disease, that may cause an abnormal liver function. After the diagnosis of PCOS was made, all patients were registered to this project. After their written informed consent was obtained, their personal and medical history was obtained in a structured interview. Their medical history records in the hospital database were also reviewed by the investigators to see if any of the exclusion criteria were met. Baseline characteristics were collected and recorded in case record form. Physical examinations measured height (cm), weight (kg), waist and hip circumference (WC and HC; cm), and blood pressure (mmHg). The values were subsequently used to calculate BMI, WHR, and waist-to-height ratio (WHtR). The following were also recorded: signs of clinical hyperandrogenism using modified Ferriman-Gallwey score (mFG), carbohydrate metabolic profiles (fasting glucose and insulin, 2-hr glucose and insulin post 75-gram oral glucose loading or oral glucose tolerance tests (OGTT), and calculated homeostatic measurement assessment-insulin resistance or homeostatic model assessment for insulin resistance (HOMA-IR), lipid profiles (total cholesterol, triglyceride (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C)) and androgens (dehydroepiandrosterone sulfate (DHEAS); total testosterone and calculated free testosterone) were recorded. Details of measurements and biochemical assays were present in our previous report[13].

Laboratory assays

All laboratory assays for carbohydrate profiles were performed using automatic analyzers, Cobas 8000 with ISO 15189 certification. Serum total testosterone was measured using electrochemiluminescence immunoassay (ECLIA) on a Roche Cobas 8000 c602 instrument (Roche Diagnostic, Germany) with intra-assay coefficient of variation (CV) of 1.57% - 2.26%, and inter-assay CV of 2.92% - 4.32%. DHEA-S and sex hormone binding globulin (SHBG) were analyzed by measured using ECLIA on a Roche Cobas 8000 modular analyzer.

Visceral adiposity index (VAI) and Lipid accumulation product (LAP)[8, 9]

VAI is a gender specific, mathematical model which combines anthropometric data (BMI and WC) and functional parameter (TG and HDL-C). VAI was calculated by using the following formula.

VAI (women) = WC/[(36.58+(1.89×BMI)]× TG/0.81×1.52/HDL

LAP is a simple, sex specific formula that combines waist circumference and triglyceride concentration. LAP was calculated by using the following formula.

LAP women = (WC-58) x TG concentration

WC is expressed in centimeter, BMI in kg/m^2, TG in mmol/L and HDL-C in mmol/L.

Definition of hyperandrogenemia

Clinical hyperandrogenism was diagnosed when a modified Ferriman-Gallwey score ≥ 8[16]. Hyperandrogenemia was diagnosed when the serum level of least one androgen was higher than the recommended cutoff, namely, total testosterone > 0.8 ng/mL; free testosterone > 0.006 ng/mL; or DHEAS > 350 µg/dL[17]. Free testosterone level was calculated using method described by Vermeulen et al[18] which includes total testosterone, SHBG and albumin level in the calculation.

Definition of metabolic syndrome

Metabolic syndrome was defined according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III criteria, in Asian[19], metabolic syndrome is present if three or more of the following five criteria are met included WC ≥ 80 cm, elevated blood pressure (systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥ 85 mmHg), fasting TG level ≥ 150 mg/dL, fasting HDL-C level < 50 mg/dL and impaired glucose tolerance (fasting plasma glucose ≥ 100 mg/dL).

Statistical analysis

From the previous study by Hossein et al[20], the optimal cut-off point of anthropometric measurement to predict insulin resistance has an area under the curve (AUC) of 0.75. Since there is no previous study that assesses the cut-off point for VAI and LAP to predict hyperandrogenemia in PCOS patients, we hypothesized that VAI could predict hyperandrogenemia with sensitivity at 75%. At the error level of 12%, the calculation formula with p = 0.75 and α = 0.05 was applied. We need 51 PCOS with hyperandrogenemia to test this hypothesis. According to statistic records at the Gynecologic Endocrinology Clinic, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, the prevalence of hyperandrogenemia was found to be 50%. Therefore, we needed a total 102 patients to be enrolled in our study.

Descriptive characteristics were presented in mean and standard deviation (SD), median and interquartile range (IQR), number (n) and percent (%), or odds ratio (OR) and 95% confidence interval (CI). Pearson correlation coefficient (r) was used to analyze factors associated with VAI and LAP. Comparisons between hyperandrogenemia and non-hyperandrogenemia, also metabolic and non-metabolic syndrome groups were used student's t-test or Mann-Whitney U test for continuous data and chi-square test or Fisher's exact test for categorical data. All tests were two-sided, and the cut-off levels of VAI and LAP for determining hyperandrogenemia were used in receiver operating characteristics (ROC) curve analysis. All statistical analysis was performed using SPSS version 22.0. A p value < 0.05 was considered to be statistically significant.

Results

In all, 102 PCOS women were enrolled. Their baseline characteristics are detailed in Table 1 and 2. The mean age was 26.9 ± 5.7 years; the mean BMI was 26.1 ± 6.7 kg/m^2. Among the participants, 41.2 % were classified as normal weight, while 33.3% were categorized as being overweight according to Asian BMI reference. Clinical hyperandrogenism was found in 15.7% of the participants. The median level of TG was 73 (54-102.3) mg/dL, and 11% of all were defined as having hypertriglyceridemia. The mean HDL-C was 61.3 ± 16.1 mg/dL, with 17.6% of the participants having an HDL-C levels less than 50 mg/dL. Metabolic syndrome was diagnosed in 17.6% of the 102 participants. The prevalence of hyperandrogenemia (defined by an excess of total testosterone, free testosterone, or DHEAS) was 49% (50/102). In the hyperandrogenemia PCOS group, free testosterone was > 0.006 ng/mL for 98% of the group (49/50), serum total testosterone was > 0.8 ng/mL for 10% (5/50) and DHEAS was > 350 µg/mL for 22% (11/50).

Table 1. Characteristics of Thai women with polycystic ovary syndrome.

Characteristics	mean ± SD or n (%) or median [interquartile range]
Age (years)	26.9 ± 5.7
Body mass index (kg/m^2)	26.1 ± 6.7
≥ 23.5	60 (58.8%)
≥ 30	26 (25.5%)
Hip circumference (cm)	100.6 ± 12.4
Waist circumference (cm)	84.4 ± 14.6
≥ 80	63 (61.8%)
Waist/hip ratio	0.84 ± 0.06
Waist/height ratio	0.53 ± 0.09
Systolic blood pressure (mmHg)	118 ± 13
≥ 130	24 (23.5%)
Diastolic blood pressure (mmHg)	73 ± 10
≥ 85	15 (14.7%)
Modified Ferriman-Gallwey score	4.0 [3.0-6.0]
≥ 3	83 (81.4%)
≥ 8	16 (15.7%)

Data are mean ± SD, or median [interquartile range], or number (%), Data were analyzed using Student t-test or Mann-Whitney U test for continuous data, or Chi-square test or Fisher's exact test for categorical data. WC: waist circumference

Table 2. Biochemical laboratory assays of Thai polycystic ovary syndrome women.

Laboratory	mean ± SD or n (%) or median [interquartile range]
Carbohydrate profiles	
Fasting blood glucose	87.8 ± 25
≥ 100 mg/dL	5 (4.9%)
Fasting insulin	10.8[6.9-19.5]
2-hour 75 gm OGTT	120 ± 53
≥ 140 mg/dL	21(20.6%)
Fasting glucose/insulin ratio	8.1 [4.7-12.2]
HOMA-IR	1.36 [0.86-2.44]
Lipid profiles	
Triglyceride	73 [54-102.3]
≥ 150 mg/dL	11 (10.8%)
HDL-C	61.3 ± 16.1
< 50 mg/dL	76 (74.5%)
Metabolic syndrome	18 (17.6%)
Androgens	
Total testosterone (ng/mL)	0.41 ± 0.19
> 0.8	5 (4.9%)
Free testosterone (ng/mL)	0.0056[0.0034-0.0099]
> 0.006	49 (48%)
DHEAS (µg/dL)	227.0 ± 100.3
> 350	11 (10.8%)
Free androgen Index	0.97 [0.5-1.86]
Hyperandrogenemia*	50 (49%)
VAI	0.96 [0.6-1.67]
LAP	19.02 [10.28-38.85]

Data are mean ± SD, or median [interquartile range], or number (%), Data were analyzed using Student t-test or Mann-Whitney U test for continuous data, or Chi-square test or Fisher's exact test for categorical data. OGTT: oral glucose tolerance test, HOMA-IR: Homeostatic Model assessment approximates insulin resistance, HDL-C: high density lipoprotein cholesterol, DHEAS: dehydroepiandrosterone sulphate, VAI: visceral adiposity index, LAP: lipid accumulation product. * Hyperandrogenemia was defined as serum of at least 1 of androgen higher than recommended cut-off (Total testosterone > 0.8 ng/mL, Free testosterone > 0.006 ng/mL, DHEAS > 350 µg/dL)

Factors associated with VAI and LAP in Thai PCOS women are demonstrated in Table 3. A significantly strong positive correlation was revealed between VAI and LAP ($r = 0.885$, $p < 0.001$). VAI was also found to positively correlate with HC, WHR, WHtR, blood pressure, fasting blood sugar, 75-gm oral glucose tolerance test, fasting insulin, HOMA-IR, LDL-C, free testosterone, and free androgen index (FAI). On the other hand, VAI was not correlated with total testosterone, DHEA-S, or mFG score. LAP was significantly and strongly correlated with HC, WC, WHR, fasting insulin, and HOMA-IR. Both LAP and VAI were significantly correlated with free testosterone and FAI, but not with total testosterone or DHEA-S.

Table 3. Factors associating with visceral adiposity index and lipid accumulation product in Thai polycystic ovary syndrome women.

Characteristics	VAI		LAP	
	r	p value	r	p value
VAI	1		0.885	< 0.001
LAP	0.885	< 0.001	1	
Clinical				
Age (years)	0.124	0.216	0.130	0.194
Body mass index (kg/m^2)	N/A	N/A	0.813	< 0.001
Hip circumference (cm)	0.533	< 0.001	0.791	< 0.001
Waist circumference (cm)	N/A	N/A	N/A	N/A
Waist/hip ratio	0.447	< 0.001	0.589	< 0.001
Waist/height ratio	0.583	< 0.001	0.830	< 0.001
Systolic blood pressure (mmHg)	0.405	< 0.001	0.471	< 0.001
Diastolic blood pressure (mmHg)	0.380	< 0.001	0.427	< 0.001
Modified Ferriman-Gallwey score	0.177	0.076	0.207	0.037
Carbohydrate profiles				
Fasting blood glucose	0.422	< 0.001	0.522	< 0.001
Fasting insulin	0.679	< 0.001	0.773	< 0.001
2-hour glucose	0.480	< 0.001	0.468	< 0.001
Fasting glucose/insulin ratio	- 0.642	< 0.001	- 0.730	< 0.001
HOMA-IR	0.688	< 0.001	0.787	< 0.001
Lipid profiles				
Triglyceride	N/A	N/A	N/A	N/A
HDL-C	N/A	N/A	-0.684	< 0.001
Cholesterol	0.170	< 0.001	0.202	0.042
LDL-C	0.345	< 0.001	0.340	< 0.001
Androgens				
Total testosterone	0.039	0.693	0.064	0.521
Free testosterone (ng/mL)	0.407	< 0.001	0.443	< 0.001
Free androgen index	0.502	< 0.001	0.532	< 0.001
DHEAS (µg/dL)	0.007	0.947	0.021	0.835

Data were analyzed using Pearson correlation, N/A = not applicable. VAI: visceral adiposity index, LAP: Lipid accumulation product, WC: waist circumference, OGTT: oral glucose tolerance test, HOMA-IR: Homeostatic Model assessment approximates insulin resistance, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol DHEAS: dehydroepiandrosterone sulphate

Table 4 details the factors associated with hyperandrogenemia in Thai PCOS women. There were significant differences in the median VAI and LAP levels of the hyperandrogenemia and non-hyperandrogenemia groups (VAI = 0.72, with 95% CI of 0.55–1.04; and LAP = 1.23, with 95% CI of 0.83-2.28, $p < 0.001$). There were also significant statistical differences in the 2 groups' values for other laboratory data: fasting insulin, 75-gm oral glucose tolerance test, fasting glucose/insulin ratio, HOMA-IR, TG, and HDL-C. This is consistent with their respective prevalences of metabolic syndrome. The

hyperandrogenemia women were also significantly different from the non-hyperandrogenemia women by way of a younger mean age, a higher mean BMI, and a higher WC ($p < 0.001$). Moreover, some components of metabolic-diastolic blood pressure, WC, and TG-were significantly higher in the hyperandrogenemia group than in the non-hyperandrogenemia group ($p < 0.05$ for each component).

Table 4. Factors associating with hyperandrogenemia in polycystic ovary syndrome Thai women.

Characteristics	Hyperandrogenemia mean ± SD or n (%) or median [interquartile range]		p value
	No n = 52	Yes n = 50	
VAI	0.72 [0.55-1.04]	1.23 [0.83-2.28]	< 0.001
LAP	13.86 [6.81-21.42]	31.67 [17.41-54.0]	< 0.001
Clinical			
Age (years)	28.3 ± 5.7	25.5 ± 5.3	0.013
Body mass index (kg/m^2)	23.9 ± 6.4	28.4 ± 6.4	0.001
≥ 23.5	21 (40%)	39 (78%)	< 0.001
≥ 30	8 (15%)	18 (36%)	
Hip circumference (cm)	96.4 ± 11.8	105 ± 11.5	< 0.001
Waist circumference (cm)	79.4 ± 13.4	89.6 ± 14.1	< 0.001
≥ 80	22 (42.3%)	41 (82%)	< 0.001
Waist/hip ratio	0.82 ± 0.07	0.85 ± 0.06	0.026
Waist/height ratio	0.49 ± 0.08	0.56 ± 0.09	< 0.001
Systolic blood pressure (mmHg)	116 ± 12	120 ± 14	0.057
≥ 130	10 (19.2%)	14 (28%)	0.350
Diastolic blood pressure (mmHg)	71 ± 10	75 ± 10	0.037
≥ 85	6 (11.5%)	9 (18%)	0.411
MFG	3 [2-5]	5 [4-8]	< 0.001
≥ 3	37 (71.2%)	46 (92%)	0.01
≥ 8	1 (1.9%)	15 (30%)	< 0.001
Carbohydrate profiles			
Fasting blood glucose	83.3 ± 8.9	92.6 ± 34.1	0.062
≥ 100 mg/dL	1 (1.9%)	4 (8%)	0.200
Fasting insulin	7.15 [5.59-10.68]	15.39 [10.83-22.43]	< 0.001
2-hour 75 gm OGTT	105.5 ± 27.6	136.9 ± 66.4	0.002
≥ 140 mg/dL	5 (9.6%)	16 (32%)	0.007
Fasting glucose/insulin ratio	10.98 [8.12-14.44]	5.59 [3.94-8.08]	< 0.001
HOMA-IR	0.90 [0.71-1.36]	2.01 [1.38-2.92]	< 0.001
Lipid profiles			
Triglyceride	63 [51.3-76.75]	85 [59.5-130.25]	0.001
≥ 150 mg/dL	2 (3.8%)	9 (18%)	0.027
HDL-C	68.5 [57.25-82]	54 [45-60]	< 0.001
< 50 mg/dL	44 (84.6%)	32 (64%)	0.023
Metabolic syndrome	4 (7.7%)	14 (28%)	0.009

Data are mean ± SD, or median [interquartile range], or number (%). * Data were analyzed using Student t-test or Mann-Whitney U test for continuous data, or Chi-square test or Fisher's exact test for categorical data. MFG: modified Ferriman-Gallwey score, OGTT: oral glucose tolerance test, HOMA-IR: Homeostatic Model assessment approximates insulin resistance, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol DHEAS: dehydroepiandrosterone sulphate

The ROC curve analyses for the optimal VAI and LAP levels needed to predict hyperandrogenemia in PCOS are presented in Table 5. The VAI cut-off value yielding the highest sensitivity (74%), the highest negative predictive value (75%), and the highest accuracy (74.5%) was 1 or more. The prevalence of

hyperandrogenemia using VAI ≥ 1 was 74% (37/50), and the AUC was 0.755 (95% CI, 0.66–0.85) (Fig. 1). As to the optimal cut-off point of LAP, it was 16.5; the prevalence and AUC were 66.7% and 0.756 (95% CI, 0.66–0.85). Diagnostic performances for the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of LAP were 80%, 61.5%, 66.7%, 76.2%, and 70.5%, respectively (Fig. 2).

Table 5. Diagnostic performance of visceral adiposity index and lipid accumulation product in predicting hyperandrogenemia in polycystic ovary syndrome.

Androgen, cut-off point	Prevalence (n(%))	Performance (%)					ROC-AUC (95% CI)
		Sens.	Spec.	PPV	NPV	Acc.	
VAI							
≥ 1	37/50 (74%)	74	75	74	75	74.5	0.755 [0.66-0.85]
≥ 0.8	41/64 (64%)	82	55.8	64	76	68.6	
≥ 0.73	43/67 (64%)	86	53.8	64.2	80	69.6	
LAP							
≥ 12.5	43/70 (61.4%)	86	48.1	61.4	78.1	66.7	0.756 [0.66-0.85]
≥ 16.5	40/60 (66.7%)	80	61.5	66.7	76.2	70.5	
≥ 17.5	38/56 (67.9%)	76	65.4	67.9	73.9	70.6	

VAI: visceral adiposity index, LAP: lipid accumulation product, Acc: accuracy, NPV: negative predictive value, PPV: positive predictive value, ROC- AUC: receiver operator characteristics area under the curve, Sens: sensitivity, Spec: specificity, CI: confidence interval

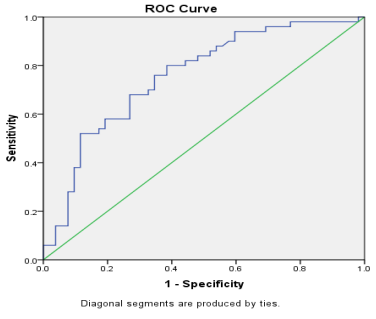

Fig. 1. Receiver operating characteristics curve of visceral adiposity index in predicting hyperandrogenemia in polycystic ovary syndrome.

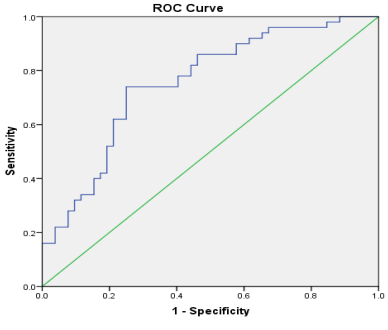

Fig. 2. Receiver operating characteristics curve of lipid accumulation product in predicting hyperandrogenemia in polycystic ovary syndrome.

Both VAI and LAP were found to be significantly associated with metabolic syndrome ($p < 0.01$) (Table 6). Furthermore, we found that 78% of the participants diagnosed with metabolic syndrome also had hyperandrogenemia; this was significantly different from the situation for the non-metabolic syndrome group.

Table 6. Factors associating with metabolic syndrome in polycystic ovary syndrome Thai women.

Characteristics	metabolic syndrome mean ± SD or n (%) or median [interquartile range]		p value
	No n = 84	Yes n = 18	
VAI	0.83 [0.58-1.20]	2.53 [1.64-4.54]	< 0.001
LAP	16.61 [8.13- 26.35]	58.39 [40.04-76.63]	< 0.001
Hyperandrogenemia**	36 (43%)	14 (78%)	0.007
Clinical			
Age (years)	26.7 ± 5.59	28.0 ± 6.07	0.380
Body mass index (kg/m^2)	24.7 ± 6.00	32.3 ± 6.53	< 0.001
≥ 23.5	43 (51%)	17 (94%)	< 0.001
≥ 30	15 (18%)	11 (61%)	
Hip circumference (cm)	98.6 ± 11.89	110.3 ± 10.21	< 0.001
Waist circumference (cm)	81.6 ± 13.42	97.7 ± 12.76	< 0.001
≥ 80	45 (54%)	18 (100%)	< 0.001
Waist/hip ratio	0.83 ± 0.06	0.88 ± 0.06	< 0.001
Waist/height ratio	0.51 ± 0.08	0.61 ± 0.78	0.001
MFG	4 [3-6]	4 [3.75-7.25]	0.181
≥ 3	65 (77%)	18 (100%)	0.025
≥ 8	12 (14%)	4 (22%)	0.401

Data are mean ± SD, or median [interquartile range], or number (%)

* Data were analyzed using Student t-test or Mann-Whitney U test for continuous data, or Chi-square. Test or Fisher's exact test for categorical data.

VAI: visceral adiposity index, LAP: lipid accumulation product, MFG: modified Ferriman-Gallwey score, DHEAS: dehydroepiandrosterone sulphate. **Hyperandrogenemia was defined as serum of at least 1 of androgen higher than Recommended cut-off (Total testosterone > 0.8 ng/mL, Free testosterone > 0.006 ng/mL, DHEAS > 350 µg/dL)

Discussion

Hyperandrogenism can be defined by either clinical (e.g., hirsutism, acne, or male pattern alopecia) or biochemical manifestations (serum testosterone, free testosterone, or FAI). In the case of the clinical manifestation of hyperandrogenism, the mFG score is the most widely used tool to assess terminal hairs in order to diagnose hirsutism[2]. In our study, we found that the prevalence of clinical and biochemical hyperandrogenism did not correlate with biochemical hyperandrogenism (15.6% and 49%, respectively). This finding was consistent with other studies that reported that there was no correlation between clinical and biochemical hyperandrogenism[21, 22]. It could be that the development of hirsutism might depend on not only the level of circulating androgen, but also the concentration of the hormone and the degree of androgen exposure to androgen receptors at the target organ. Although the mFG score is the most common visual assessment tool for the evaluation of terminal hairs, it may not be applicable due to variation in ethnicity or overestimation. It is also a subjective assessment tool: bias needs to be considered. For the present study, we therefore decided to evaluate the cut-off values of VAI and LAP to predict hyperandrogenemia, not hyperandrogenism, since those cut-off values were deemed likely to be more objective and reliable.

Previous studies have reported that obesity, insulin resistance, metabolic syndrome, and an excessive accumulation of abdominal visceral fat influence the development of hyperandrogenism in PCOS women[11-13]. Similar to this study, the

hyperandrogenemia PCOS group had a larger waist circumference, a higher BMI, lower insulin sensitivity, a greater degree of dyslipidemia and higher median VAI, and LAP than the non-hyperandrogenemia PCOS group.

VAI is a gender-specific, mathematical model which combines anthropometric data (BMI and WC) and functional parameters (TG and HDL-C). LAP is a simple, sex-specific formula that combines waist circumference and triglyceride concentration. Abdominal visceral fat was found associated with metabolic syndrome and its components including obesity, impaired glucose, insulin resistance, and abnormal lipid metabolism. While VAI and LAP are the specific mathematical formula that uses anthropometric data and lipid parameter. Therefore, the two models were the indirect methods to identify abdominal visceral tissue and the differences in anthropometric data and functional laboratory parameters may affect VAI and LAP values. The mean VAI (0.96 [0.6-1.67]) revealed in the present study was lower than the value of 4.05 ± 3.59 reported for Thai PCOS women by Techatraisak et al in 2015[13]. These differences might be explained by the higher prevalence of metabolic syndrome in our population, which had lower WC and TG levels and a higher HDL value-all components of the VAI formula-than the cohort investigated by Techatraisak and colleagues.

VAI and LAP in the present study were significantly and positively correlated with free testosterone and FAI (VAI: r = 0.4 and 0.5, respectively, with $p < 0.001$; LAP: r = 0.4 and 0.5, respectively, with $p < 0.001$), but total testosterone and DHEAS were not correlated with either VAI or LAP. However, these results were consistent with those of another study[14], which also reported that no correlation between VAI and total testosterone was demonstrated in a regression model. Total testosterone is comprised of bound and free forms, which could interfere with many factors; free testosterone interferes less than total testosterone and might therefore be more representative of the actual action of testosterone[4]. However, hyperandrogenemia in this study was mainly diagnosed by high levels of free testosterone.

This is the first study to evaluate the optimal cut-off values for VAI and LAP to predict hyperandrogenemia in PCOS women. From our findings, we suggest that VAI ≥ 1 (AUC = 0.755, p = 0.66-0.85) is the most appropriate point to use to predict hyperandrogenemia in PCOS. Due to the best accuracy and proper sensitivity, specificity, NPV, and PPV (74.5%, 75%, 75%, and 74% respectively) for LAP, we selected LAP ≥ 16.5 as the optimal cut-point value. Although LAP value of ≥ 17.5 showed the best accuracy, LAP ≥ 16.5 was better in terms of sensitivity and NPV, which are more important in terms of clinical screening.

Our strength of this study was the homogenous Asian population; its results may therefore reflect the Thai or Asian population. In addition, we compared VAI and hyperandrogenemia, which is a biochemical presentation that can avoid some bias or variations from ethnicity and over/under-estimation of hyperandrogenism. The limitation of our study was that it was conducted at a single center, which meant that it could not represent all of Thai PCOS population. A further multicenter study would be able to confirm the cut-off levels that we have proposed for use with the Thai PCOS population.

Conclusion

Both VAI and LAP significantly and positively correlated with free testosterone and the FAI. A VAI ≥ 1 or an LAP ≥ 16.5 can be used to predict hyperandrogenemia in PCOS women at Siriraj Hospital. In addition, the change of those values may be used to monitor responsiveness to treatment for hyperandrogenemia in PCOS women.

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Potential conflicts of interest

The authors declare no conflicts of interest.

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