Contents available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

International Diabetes Federation

Visceral adiposity index and lipid accumulation product as a predictor of type 2 diabetes mellitus: The Bogor cohort study of non-communicable diseases risk factors

Randy Nusrianto [a,1], *Gratcia Ayundini* [a,1], *Melly Kristanti* [b], *Cindy Astrella* [c], *Nida Amalina* [b], *Muhadi* [d], *Woro Riyadina* [e], *Dicky L. Tahapary* [b,c,1], *Pradana Soewondo* [b,c,*,1]

[a] *Department of Internal Medicine, Dr. Cipto Mangunkusumo National Referral Hospital, Faculty of Medicine Universitas Indonesia, Jl. Diponegoro No. 71, Central Jakarta 10430, Indonesia*

[b] *Division of Endocrinology, Department of Internal Medicine, Dr. Cipto Mangunkusumo National Referral Hospital, Faculty of Medicine Universitas Indonesia, Jl. Diponegoro No. 71, Central Jakarta 10430, Indonesia*

[c] *Metabolic, Cardiovascular and Aging Cluster, The Indonesian Medical Education and Research Institute, Faculty of Medicine Universitas Indonesia, Jl. Salemba Raya No VI, Central Jakarta 10430, Indonesia*

[d] *Division of Cardiology, Department of Internal Medicine, Dr. Cipto Mangunkusumo National Referral Hospital, Faculty of Medicine Universitas Indonesia, Jl. Diponegoro No. 71, Central Jakarta 10430, Indonesia*

[e] *National Institute of Health Research and Development, Ministry of Health Republic of Indonesia, Jl. Percetakan Negara No. 29, Central Jakarta 10560, Indonesia*

ARTICLE INFO

Article history:
Received 15 February 2019
Received in revised form
12 June 2019
Accepted 17 July 2019
Available online 19 July 2019

ABSTRACT

Objectives: Lipid accumulation product (LAP) index and Visceral Adiposity Index (VAI) are simple calculations to measure fat accumulation and visceral fat respectively. We aim to study the use of LAP index and VAI as diagnostic parameter and predictor of T2DM.

Methods: We analysed the baseline and longitudinal data from the Indonesian Ministry of Health Cohort Study of Non-communicable Diseases Risk Factors in West Java, comprising 846 men and 2437 women aged 25–65 years. At baseline, the odds ratio for the diagnosis of prediabetes and T2DM among subjects with high LAP Index and VAI was analysed using logistic regression analysis. In the longitudinal analysis, LAP index and VAI as predictor of prediabetes and T2DM was analysed with cox regression analysis.

Result: Worsening glycemia status was associated with an increased LAP index and VAI ($p < 0.001$). Subjects with high VAI had an increased OR of having T2DM in both men [OR, 95%CI, 2.29(1.15–4.56), $p = 0.018$] and women [1.95(1.49–2.54), $p < 0.001$)]. Association of high LAP with T2DM was found only in women [OR, 95%CI, 2.11(1.16–1.52), $p < 0.001$]. In terms of T2DM prediction, only women [RR, 95% CI, 2.59 (1.05–6.39), $p = 0.038$)], with high VAI had an increased risk of T2DM in the future. High LAP index was not associated with an in increased risk of T2DM in the future in both sexes.

* Corresponding author at: Division of Endocrinology, Department of Internal Medicine, Dr. Cipto Mangunkusumo National Referral Hospital, Faculty of Medicine Universitas Indonesia, Jl. Diponegoro No. 71, Central Jakarta 10430, Indonesia.
E-mail addresses: dicky.tahapary@ui.ac.id (D.L. Tahapary), pradana.soewondo@ui.ac.id (P. Soewondo).

[1] These authors have contributed equally.

https://doi.org/10.1016/j.diabres.2019.107798

Conclusion: High LAP index was associated with an increased risk of T2DM diagnosis in women but it could not predict the development of T2DM. High VAI was associated with an increased risk of T2DM diagnosis in both sexes, however, it could only predict the development of T2DM in women.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a global problem, as the incidence was escalating worldwide with doubled prevalence from 4.7% to 8.5% in the past few decades [1–2]. Evidence showed that obesity plays a major role in the development of T2DM [3,4]. Continuous positive energy balance in obesity contributes to increased deposition of both subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). In addition to lipid deposition in adipose tissue, obesity is also associated with lipid accumulation in ectopic tissues such as liver and skeletal muscle which further impair insulin function. Ectopic lipid deposition was found to be a mechanism that plays a role in organ injury in metabolic disease [5]. Thus, adipose tissue dysfunction, ectopic lipid deposition, and the release of adipokines which impair insulin sensitivity in tissues as well as causing lipotoxicity, will lead to abnormal glucose metabolism, hence T2DM in the future [6–9]. In the development of T2DM, VAT seems to play a relatively more important role than SAT [10].

The established measurements of obesity according the majority of existing guidelines were using Body Mass Index (BMI) and waist circumference (WC). However, both measurements might not completely represent the fat accumulation in the body. Not only that BMI could not differentiate between lean body mass and fat mass, it also could not characterize body fat distribution, a known determinant of metabolic risk [11,12]. While waist circumference, a better marker for central obesity, could not differentiate between VAT and SAT [13–15].

Other parameters of obesity that were postulated to be superior to traditional measurement of obesity were lipid accumulation product (LAP) and Visceral Adipose Tissue Index (VAI). LAP is an index of lipid accumulation, which is computed from WC and triglycerides (TG) of which the later represents increased lipotoxicity [7]. Ectopic lipid accumulation eventually leads to insulin resistance. Hence, LAP might be a better marker to predict the worsening of glycemic status such as T2DM. Other measurement that was considered as the gold standard to measure VAT was abdominal CT scan or MRI. However, such examinations are expensive and have limited availability, therefore difficult to be applied for population based studies or in general practice [13]. Alternatively, VAI is a mathematical model to estimate VAT using anthropometric and laboratory parameters by calculating linear equation of body fat distribution and corrected by High Density Lipoprotein-Cholesterol (HDL-C) and TG level [9,16]. VAI has been reported to be correlated with the surface area and volume of VAT, and with insulin resistance, an important pathogenesis in the development of T2DM [17].

Taken together, LAP index, and VAI might be better associated with T2DM or even predict the development of T2DM in the future than conventional anthropometric measures. However, both LAP index and VAI were developed from Caucasian population, hence, the use of LAP index and VAI for Asian population with a generally higher VAT at a lower BMI must be further evaluated. To the best of our knowledge studies on Asian population were limited, if anything, most studies were performed among Chinese population. This study aims to assess whether LAP index and VAI can be used as a predictor of T2DM in Indonesia with majority of Malay ethnicity.

2. Materials and methods

2.1. Subjects

We analyzed secondary data from the ongoing Bogor Non-communicable Diseases Cohort Study from 2011 to 2015 [18]. The Bogor Non-communicable Diseases (NCDs) Risk Factors Cohort Study was a population based prospective cohort study held by the Ministry of Health Republic of Indonesia that was aimed to assess the predictive value of certain risk factor for the development of NCDs such as T2DM, hypertension, cardiovascular disease and stroke in Bogor. However, this study particularly assess T2DM. This study has been approved by the Ethical Committee Board Faculty of Medicine Universitas Indonesia (No 1293/UN2.F1/ETIK/2018). The studied subjects were adult population aged 25–65 years old who lived in five villages in Bogor, West Java. Subjects with uncomplete data throughout the four years follow up were excluded.

2.2. Measurements

Baseline demographic information such as age, gender, diabetes status, hypertension status, family history of diabetes, smoking status and physical activity state were obtained at the community clinics using standardized questionnaire. The anthropometric measurements included body weight, body height, WC and blood pressure. Body weight and height were measured by standard methods and recorded to the nearest of 0.1 kg and 0.1 cm, respectively whereas BMI was calculated as the weight in kilograms divided by the square of the height in meters. WC was measured twice at one cm above the umbilicus level during minimal respiration. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were examined three times at 30-second intervals by trained doctors, using a standardized mercury sphygmomanometer on both arms after resting for five minutes in a sitting position. Laboratory examinations including fasting plasma glucose

(FPG), post oral glucose tolerance test (OGTT), total cholesterol, high density lipoprotein cholesterol (HDL-C), Low density lipoprotein cholesterol (LDL-C), TG and serum creatinine were performed. Blood samples were collected in the morning after at least eight hours of overnight fasting. Laboratory tests were conducted in qualified and standardized laboratories using commercial reagents.

During the four years observation, the incidence of prediabetes and T2DM was recorded. T2DM was diagnosed based on the American Diabetes Association 2018 criteria which are FPG $\geq$ 126 mg/dl and or OGTT $\geq$ 200 mg/dL, or if the subjects have been previously diagnosed with diabetes by certified physician [19]. The diagnosis of prediabetes was established if the subjects had 2 h plasma glucose post 75 g glucose load of 140–199 mg/dl (impaired glucose tolerance) and or fasting glucose of 100–125 mg/dl (impaired fasting glucose).

The status of obesity and central obesity was determined based on WHO Asia Pacific criteria. Obesity was defined as BMI $\geq$ 25 kg/m^2 and overweight was defined as BMI 23–24.9 kg/m^2. Central obesity was defined as waist circumference $\geq$ 80 cm for women, and WC $\geq$ 90 for men [11]. Hypertension was defined if the subjects consume any anti-hypertensive drug and/or systolic blood pressure $\geq$ 130 and/or diastolic blood pressure $\geq$ 80 mmHg [20]. The study participants were grouped based on age: 24–44, 45–54, and 55–65 years old according to the Ministry of Health Republic of Indonesia Health Report 2009 [21]. Data on anti-hypertensive agents, ACE inhibitor and statin consumption were also recorded in this study.

2.3. Definition of LAP and VAI

The LAP index was calculated using fasting triglycerides (TG) level and waist circumference (WC) as follows [22]:

$$\textbf{Men LAP} : \text{TG (mmol/L)} \times [\text{WC (cm)} - 65)]$$

$$\textbf{Women LAP} : \text{TG (mmol/L)} \times [\text{WC (cm)} - 58)]$$

The VAI score was calculated by using the published formula; both TG and HDL-C levels are expressed in mmol/l: [17]

$$\textbf{Men VAI} : \left[\frac{WC\,(cm)}{\{39.68+(1.88x\text{BMI}(\frac{kg}{m2}))\}}\right] \times \left[\frac{\text{TG(mmol/l)}}{1.03}\right] \times \left[\frac{1.31}{HDL(\text{mmol/l})}\right]$$

$$\textbf{Women VAI} : \left[\frac{WC\,(cm)}{\{36.58+(1.89x\text{BMI}(\frac{kg}{m2}))\}}\right] \times \left[\frac{\text{TG(mmol/l)}}{0.81}\right] \times \left[\frac{1.52}{\text{HDL(mmol/l)}}\right]$$

2.4. Statistical analysis

All statistical analyses were performed using SPSS version 20 for Windows. Variables with normal distribution were presented as mean with standard deviation (SD) and skewed variables were presented as the median with interquartile range (IQR). All analyses were performed separately for men and women.

In the first part of this study we analysed the baseline data cross-sectionally. The trends of VAI, LAP, BMI and WC among normal, prediabetes and T2DM groups were analysed using linear regression analysis. A receiver-operating characteristic (ROC) analysis was performed to examine the optimal cut-off point for LAP and VAI for the diagnosis of prediabetes and T2DM. Several parameters were compared based on high versus low LAP index and high versus low VAI in men and women using independent sample T-test for variable with normal distribution and Mann Whitney for skewed distribution. Logistic regression analysis with adjustment of age as the confounding factor was performed to obtain the odds ratios for prediabetes and T2DM among subjects with high LAP and VAI index that was defined according to the cut-off values determined in this study.

In the second part of the study, we analysed the longitudinal data to assess whether LAP index or VAI can be used to predict the development of prediabetes and T2DM. For this phase of analysis we excluded subjects with T2DM at baseline for the prediction of T2DM and we further exclude prediabetes subjects for the prediction of prediabetes. The VAI and LAP index was categorized based on the cut-off points obtained with the baseline ROC analysis and analysed for the relative risk of prediabetes and T2DM using cox regression analysis with adjustment of confounding variables such as age, hypertension, family history of TD2DM, smoking status, consumption of ACE-inhibitor and other anti-hypertensive drugs, consumption of statin. Additional adjustment for pre-diabetes status was also added for analysis of T2DM prediction. All p-values were two-tailed and statistical significance was defined as $p < 0.05$.

3. Results

3.1. Baseline characteristics

A total of 1997 men and 3686 women were recruited in this study, of which 2382 participants were excluded due to incomplete data, yielding a total of 3283 participants (846 men and 2437 women) analysed in the first part of this study (Fig. S1). The study population was dominated with younger women (Table 1). More than half of the women were obese (55.9%) while more than half of the men had normal BMI (51.5%). Women had significantly higher proportion of hypertension, family history of T2DM, central obesity, and prediabetes and T2DM, whereas men had significant higher proportion of smoking, low physical activity and T2DM. In addition, women had significantly higher total cholesterol and HDL-C, but significantly lower triglyceride level compared to men. The FPG level of men was significantly higher but the OGTT level was significantly lower compared to women. Interestingly, only a few numbers of subjects with hypertension consumed anti-hypertensive agents.

The LAP index was higher in female compared to male [median (IQR), 22.49(12.30–38.53) vs 17.61(7.39–34.98)] but the median of VAI index was lower [median (IQR), 0.69(0.48–1.05) vs 1.31 (0.92–2.11), respectively] (Table 1). All subjects with higher LAP index and VAI had significantly more hyper-

Table 1 – Baseline characteristics of study participants.

Parameter	Men (n = 846)	Women (n = 2437)	Total (n = 3283)	p-value
Age (years, median, IQR)	47.00 (38–54)	43.00(36–51)	44.00 (36–52.0)	<0.001
25–44 years old (n, %)	353(41.7%)	1 320 (54.2%)	1 673 (51.0%)	
45–54 years old (n, %)	297 (35.1%)	741 (30.4%)	1 038 (31.6%)	
55–65 years old (n, %)	196 (23.2%)	376 (15.4%)	572 (17.4%)	
Hypertension (n, %)	213 (25.2%)	765 (31.4%)	978 (29.8%)	0.001
Smoking (n, %)	569 (67.3%)	352 (14.4%)	921 (28.1%)	<0.001
Low physical activity (n, %)	49 (5.8%)	18(0.7%)	67 (2.0%)	0.001
Family History of T2DM (n, %)	105 (12.4%)	405 (16.6%)	510 (15.5%)	0.004
BMI (kg/m^2, median, IQR)	23.39(20.73–26.23)	25.51(22.51–28.44)	24.91(21.86–27.98)	<0.001
Normal (n, %)	436 (51.5%)	673 (27.6%)	1 109 (33.8%)	
Overweight (n, %)	142 (16.8%)	400 (16.4%)	542 (16 0.5%)	
Obesity (n, %)	267 (31.6%)	1 362 (55.9%)	1 629 (49.6%)	
Waist Circumference (cm, median, IQR)	80.10(71.00–89.00)	80.50(72.00–88.00)	80.40(72.0–88.0)	0.383
Central Obesity (n, %)	197 (23.3%)	1 391 (57.1%)	15 88 (48.4%)	<0.001
LAP (median, IQR)	17.61(7.39–34.98)	22.49(12.30–38.53)	21.34(10.97–37.80)	<0.001
VAI (median, IQR)	1.31 (0.92–2.11)	0.69(0.48–1.05)	0.81(0.54–1.31)	<0.001
Total Cholesterol (median, IQR) mg/dl	198.00 (222.00–177.00)	202 (180–228)	201(179.00–227.00)	0.002
HDL-C (median, IQR) mg/dl	44(38.00–50.00)	52(46–60)	50(43–58)	<0.001
LDL-C (median, IQR) mg/dl	128.00 (110–147)	128 (108–151)	128(108–149)	0.599
Triglyceride (median, IDR)) mg/dl	113.00(83.75–155.25)	90.00 (67.00–123.00)	96(70–132)	<0.001
FBG (median, IQR) mg/dl	86.00 (80.00–93.00	84.00(78.00–91.00)	84.00(79.00–91.00)	<0.001
OGTT (median, IQR) mg/dl	112.00(94.00–138.00)	121.00(103.00–143.00)	118(101–142)	<0.001
Glycemic Status (%)				
T2DM (n, %)	59 (7.0%)	145 (5.9%)	204 (6.2%)	<0.001
Prediabetes (n, %)	130(15.4%)	522(21.4%)	652 (19.9%)	
Normal (n, %)	657 (77.7%	1,770 (72.6%)	2,427 (73.9%)	

Data was presented in percentage for categorical variable and median (IQR) for abnormally distributed numerical variable. Chi-square analysis was used to assess the differences of categorical variables between genders while Man Whitney analysis was performed for abnormally distributed numerical variable. p-value of <0.05 was considered significant. T2DM (type 2 diabetes mellitus), LAP (Lipid Accumulation Product), VAI (Visceral Adiposity Index), BMI (Body Mass Index), HDL-C (high density lipoprotein cholesterol), LDL-C (low density lipoprotein cholesterol), FBG (fasting blood glucose), OGTT (post-oral glucose tolerance testglucose).

tension compared to those with low LAP index and VAI. Men and women with high LAP index and VAI index had significantly higher FPG and OGTT level but lower serum creatinine compared to men and women with lower LAP index and VAI. Women with higher LAP index and VAI had significantly higher BMI, total cholesterol, LDL-C and TG compared to women with lower LAP index and VAI. On the opposite, HDL-C level was significantly higher in women with lower LAP index and VAI (Table 2).

We further categorized LAP index, VAI, BMI and waist circumference based on age group. Among women, we observed a significant increase of LAP, VAI, BMI, and waist circumference along with increasing age. Among men, similar trend was observed for LAP. We observed no effect of age on VAI. In contrast, we observed that both BMI and waist circumference in men were significantly reduced with increasing age (Table S1).

3.1.1. *The association between LAP Index, VAI, and dysglycemia*

At the baseline, the number of normoglycemic, pre-diabetes and diabetes subjects were 2427 (73.9%); 652 (19.9%) and 204 (6.2%) respectively. In men, worsening of glycaemic status was associated with progressive increase in LAP index [median, IQR, 12.76 (6.19–29.42) vs 24.79 (15.65–38.56) vs 38.26 (18.55–65.77), for normoglycemia, prediabetes, and diabetes respectively, p-value for trend < 0.001] (Fig. 1A). Similar trends was observed in women with higher LAP [18.97 (10.97–32.56) vs 30.12 (16.64–48.47) vs 39.52 (25.34–67.48), for normoglycemia, prediabetes, and diabetes respectively, p-value for trend < 0.001] (Fig. 1B). In term of VAI, we also observed similar trends for men [1.23 (0.87–1.86) vs 1.47 (1.12–2.26) vs 2.18 (1.18–3.20), for normoglycemia, prediabetes, and diabetes respectively, p-value for trend < 0.001] (Fig. 1C) and women [0.64 (0.45–0.93) vs 0.81 (0.57–1.33) vs 1.01 (0.68–1.56), for normoglycemia, prediabetes, and diabetes respectively, p-value for trend < 0.001] (Fig. 1D). Simple anthropometric measures, such as BMI (Fig. 1E and F) and WC (Fig. 1G and H) also showed significant upward trend towards worsening dysglycemic status. In general, worsening of glycemic status was associated with increasing LAP index, VAI, BMI, and WC (Fig. 1A–H).

3.1.1.1. *OGTT.*

3.1.1.1.1 *LAP index and VAI for the diagnosis of prediabetes.*

Based on the ROC analysis, LAP index, VAI as well as BMI and waist circumference were all inferior in diagnosing prediabetes in both sexes as all of the AUC values did not pass the reference line of 0.7. The AUC value of LAP index, VAI, BMI and waist circumference for diagnosing prediabetes in men were 0.43, 0.48, 0.46 and 0.46 respectively. Whereas the AUC value of LAP index, VAI, BMI and waist circumference for diagnosing prediabetes in women were 0.42, 0.44, 0.45 and 0.43 respectively (Fig. S2).

The cut-off point of LAP index for the diagnosis prediabetes was 8.07 (67.5% specificity and 72.3% for sensitivity)

Table 2 – Baseline clinical data of subjects with low vs high LAP index and low vs high VAI.

Paramater	Men (n = 846)						Women (n = 2437)					
	High LAP (n = 406)	Low LAP (n = 440)	p-value	High VAI (n = 368)	Low VAI (n = 478)	p-value	High LAP (n = 1058)	Low LAP (n = 1379)	p-value	High VAI (n = 1194)	Low VAI (n = 1243)	p-value
Age (years, median, IQR)	47 (38.7–54.0)	46.0(38.0–53.0)	0.451	46.0(38.0–54.0)	47.0(38.00–54.0)	0.452	46.0 (39.0–53.00)	41 (34–49)	<0.001	45 (38–53)	41(34–49)	<0.001
Hypertension (n, %)	145(35.7)	68 (15.5)	<0.001	105 (28.5)	108(22.6)	0.049	435 (41.1)	330 (23.9)	<0.001	425 (35.6)	340 (27.4)	<0.001
Smoking (n, %)	260 (64.0)	309(70.4)	0.049	241 (65.5)	328 (68.8)	0.314	177 (16.8)	175 (12.7)	0.005	190 (15.9)	162 (13.0)	0.041
Low physical activity (n, %)	28 (6.9)	21 (4.8)	0.186	23 (6.2)	26 (5.4)	0.617	11 (1.0)	7(0.5)	0.128	11 (-0.9)	7 (0.6)	0.302
Family History of T2DM (n, %)	47 (11.6)	58(13.2)	0.471	42 (11.4)	63(13.2)	0.433	186 (17.6)	219 (15.9)	0.255	195 (16.4)	210 (16.9)	0.723
BMI (kg/m^2, median, IQR)	23.27(20.54–26.40)	23.45(20.87–25.86)	0.893	23.24 (20.77–26.62)	23.44(20.66–25.84)	0.428	28.24 (25.86–31.13)	23.3(20.96–25.73)	<0.001	27.00(24.23–29.94)	23.87(21.23–26.79)	<0.001
Waist Circumference (cm, median, IQR)	80.1 (70.7–90.0)	80.2(73.0–87.0)	0.577	80.1(70.9–90.0)	80.15(72.00–87.00)	0.770	88.0(83.00–94.00)	74(70–80)	<0.001	85 (79–91)	76 (70.2–83.0)	<0.001
Central Obesity (n, %)	106 (26.1)	91 (20.7)	0.037	100 (27.2)	97 (20.3)	0.012	979 (92.5)	412 (30.1)	<0.001	890 (74.5)	501 (40.7)	<0.001
Total Cholesterol (median, IQR) mg/dl	201.0 (38.74)	199.4 (32.74)	0.382)	199.3 (37.47)	200.9 (34.4)	0.520	217(196–243)	192 (171–214)	<0.001	214(191–240)	192(172–215)	<0.001
HDL-C (median, IQR) mg/dl	43.0(38.0–50.0)	44.0(38.0–50.0)	0.319	43.0(38.0–50.0)	44.0(38.0–50.0)	0.268	43(49–56)	55 (48–63)	<0.001	47 (42–53)	58 (51–65)	<0.001
LDL-C (median, IQR) mg/dl	127.9 (33.06)	129.8(28.43)	0.515	127.44(31.5)	130.1 (30.15)	0.213	138 (119–162)	120 (101–139)	<0.001	137 (117–160)	119 (101–138)	<0.001
Triglyceride (median, IDR)) mg/dl	115.0(82.75–172.0)	109.0(85.25–149.7)	0.154	117.5(84.0–164.0)	107.0(83–151)	0.091	125(103–161)	71 (58–88)	<0.001	124(102–159)	68 (57–80)	<0.001
FPG (median, IQR) mg/dl	87.0(80.0–96.0)	85.0(80.0–91.0)	0.001	87.0(81.00–94.0)	85.0(79.0–91.0)	<0.001	85.00(80.00–94.00)	83(77–89)	<0.001	85(80–93)	83 (77–89)	<0.001
OGTT (median, IQR) mg/dl	120.5 (97.7–154.3)	107.0(90.25–123.75)	<0.001	115.0(95.0–150.0)	109.0(92.75–130)	<0.001	132(113–156)	112 (98–133)	<0.001	128 (109–153)	113 (99–134)	<0.001
Glycemic Status (%)												
T2DM (n, %)	45 (11.1)	14 (3.2)	<0.001	39 (10.6)	20 (4.2)	<0.001	109 (10.3)	36 (2.6)	<0.001	105 (8.8)	40 (3.2)	<0.001
Prediabetes (n,%)	87 (21.4)	43 (9.8)		62(16.8)	68 (14.2)		298 (28.2)	224 (16.2)		313 (26.2)	209 (16.8)	
Normal (n, %)	274 (67.5)	383 (87.0)		267 (72.6)	390 (81.6)		651 (61.5)	1119 (81.1)		776 (65.0)	994 (80.0)	
Creatinine	0.96 (0.85–1.08)	1.10 (1.0–1.30)	<0.001	1.00(0.88–1.14)	1.10(0.92–1.20)	<0.001	0.72(0.64–0.81)	0.90(0.80–1.00)	<0.001	0.77(0.68–0.90)	0.90 (0.80–1.00)	<0.001

Data was presented in percentage for categorical variable and median (IQR) for abnormally distributed numerical variable. Chi-square analysis was used to assess the differences of categorical variables between genders while Man Whitney analysis was performed for abnormally distributed numerical variable. p-value of <0.05 was considered significant. T2DM (type 2 diabetes mellitus), LAP (Lipid Accumulation Product), VAI (Visceral Adiposity Index), BMI (Body Mass Index), HDL-C (high density lipoprotein cholesterol), LDL-C (low density lipoprotein cholesterol), FPG (fasting plasma glucose), OGTT (post-oral glucose tolerance test).

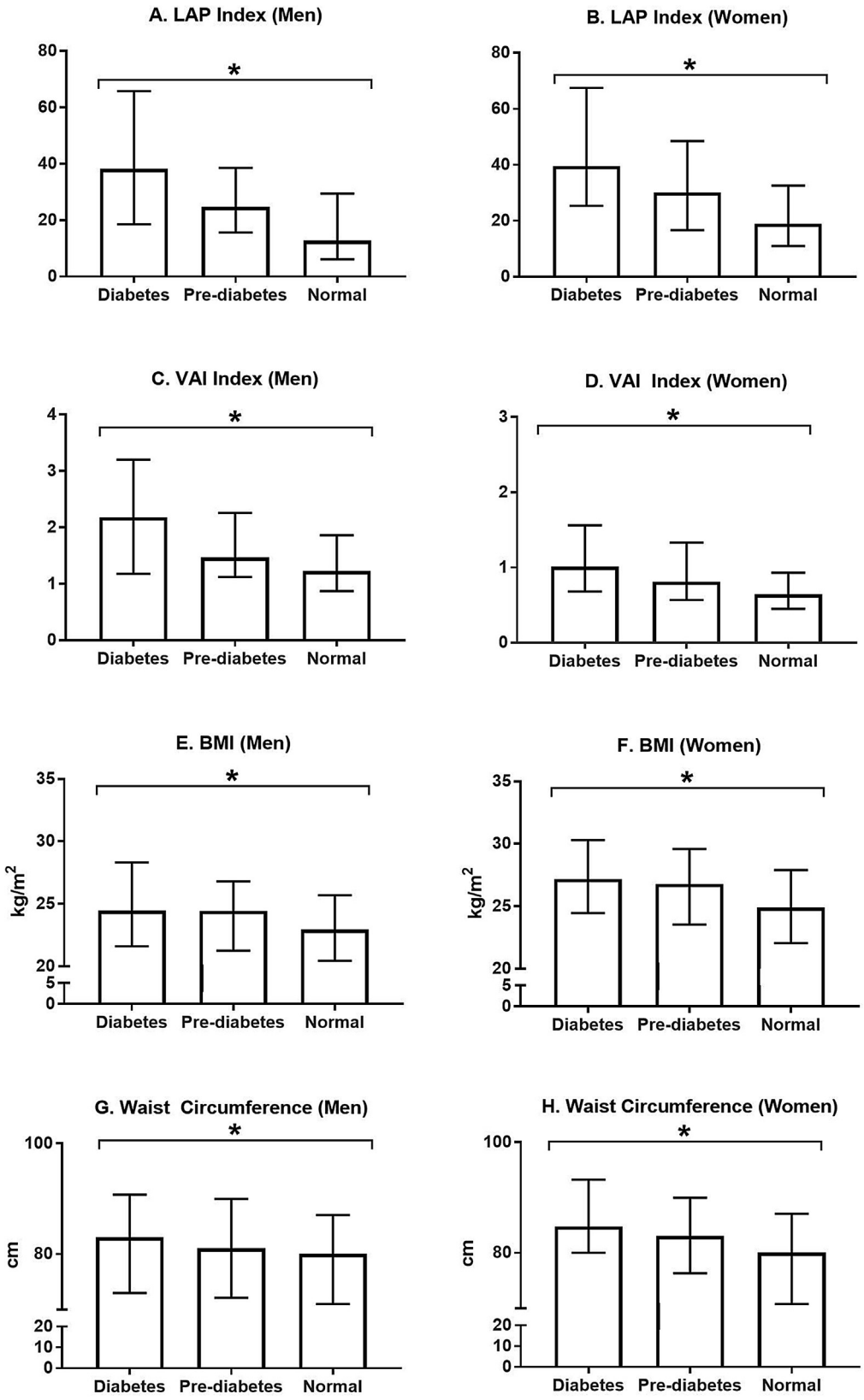

Fig. 1 – The association between LAP index, VAI index, BMI and WC and spectrum of dysglycemia. **The trend of Lipid Accumulation Product (LAP), Visceral Adipose Tissue Index (VAI), Body Mass Index (BMI) and Waist Circumference (WC) among diabetes, pre-diabetes and normal subjects based on gender were all analyzed using linear regression analysis. The graph was displayed in median (IQR). (*) resembles p-value < 0.001.**

for men and 12.41 (68.5% specificity and 75.1% sensitivity) for women. Whereas the cut-off point of VAI for the diagnosis prediabetes was 1.05 (62.3% specificity and 66.9% sensitivity) for men and 0.52 (64.5% specificity and 72.1% sensitivity) for women.

High VAI was significantly associated with prediabetes for men [OR, 95% CI 2.697 (1.799–4.043), $p < 0.001$] and women [1.901 (1.524–2.372), $p < 0.001$] respectively. High LAP index was only associated with increased OR of having prediabetes in women [OR, 95% CI 1.962(1.546–2.490), $p < 0.001$] but not in men. No association of obesity defined by BMI and increased risk diagnosis of prediabetes found among both sexes. Central obesity was significantly associated with increased risk of prediabetes diagnosis only in women [OR, 95% CI 1.795 (1.475–2.185), $p < 0.001$] but not in men (Fig. 2A and B).

When we further stratified based on age group, The OR of having prediabetes in men with higher LAP index, higher VAI, general obesity and central obesity were highest in the age group of 25–45 years old. While for women, the risk of having prediabetes were highest among age group of 45–55 years old for higher LAP index, higher VAI and obesity, whereas the highest risk of having prediabetes were found among women aged > 55 years old (Table S2).

3.1.1.1.2 LAP index and VAI for the diagnosis of T2DM.

From the ROC analysis, both LAP index and VAI were superior in diagnosing T2DM with AUC values of 0.752 and 0.720 respectively compared to BMI and WC [AUC values 0.639 for BMI and 0.622 for WC] among women. LAP index also remained superior in the diagnosis of T2DM among men with AUC value of 0.747. Interestingly, the AUC value of VAI for diagnosis of T2DM in men was the lowest (AUC value 0.641) compared to BMI and WC [AUC values 0.734 for BMI and 0.738 for waist circumference] (Fig. S3). Based on the ROC analysis, the cut-off points of LAP index for the diagnosis of T2DM were 18.51 (76.2% sensitivity and 58.3% specificity) and 25.55 (75.7% sensitivity and 37.3 specificity) for men and women respectively. While, the cut-off value of VAI for the diagnosis of T2DM was 1.48 (66.1% sensitivity and 59.2% specificity) and 0.705 (72.9% sensitivity and 44.4% specificity) for men and women respectively.

Using the cut-off points above, our study reported that women with higher LAP had significantly higher chance to be diagnosed with T2DM compared to women with lower LAP [OR, 95% CI, 2.11 (1.16–1.52), $p < 0.001$]. However, high LAP index in men was not associated with increased risk of T2DM diagnosis. Men with high VAI had significantly 2.29

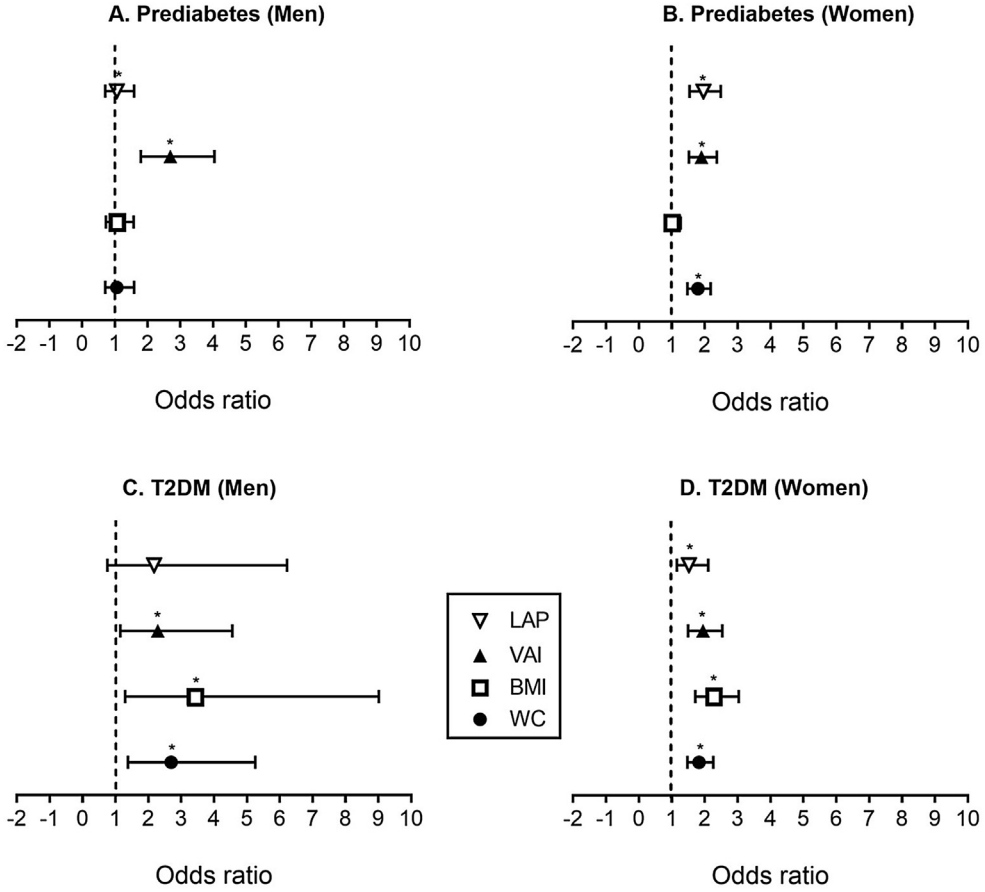

Fig. 2 – Comparison between LAP index, VAI, BMI and WC for Prediabetes and T2DM Diagnosis. **The odds of having prediabetes or T2DM among subjects with high Lipid Accumulation Product (LAP), high Visceral Adiposity Index (VAI), obesity and central obesity obtained during the baseline period was calculated using logistic regression analysis with adjustment of age. The forest plot was displayed in odds ratio and 95% confidence interval. (*) resembles p-value < 0.05. Inverted white triangle represents high LAP Index, black triangle represents high VAI, white box represents BMI ≥ 23 kg/m^2 and black dot represents Waist Circumference (WC) ≥ 80 cm for women and ≥ 90 for men.**

times higher chance to be diagnosed as T2DM compared to men with lower VAI [OR, 95% CI, 2.29 (1.15–4.56), p = 0.018]. Similar result was found in women [1.95 (1.49–2.54), p < 0.001)]. General obesity was associated with significantly higher risk of T2DM in both men [OR, 95% CI, 3.42 (1.30–9.02), p = 0.013] and women [2.283 (1.715–3.039), p < 0.001]. Central Obesity was also associated with significantly higher risk of T2DM in both men [OR, 95% CI, 2.69 (1.39–5.26), p = 0.004] and women [1.83 (1.48–2.26), p < 0.001] (Fig. 2C and D).

When we further stratified based on age group, the risk of having T2DM in men was the highest among age group of 45–55 years old for men with higher VAI and general obesity whereas the risk of having T2DM was the highest among age group >55 years old for men with higher LAP index and central obesity. Similar pattern was also observed among women with the highest risk of having T2DM was spotted among age group of 45–55 years old for higher VAI and central obesity, whereas the risk of having T2DM was the highest among age group > 55 years old for women with higher LAP index and central obesity (Table S2).

3.1.2. *Association between LAP index and VAI for the prediction of prediabetes and T2DM*

A total of 705 incidence of prediabetes occurred in four years follow up which consisted of 221 (33.6%) men and 484 (27.3%) women. A total of 27 new cases of T2DM occurred throughout the four years follow up with 19 male subjects (2.4%) and 8 female subjects (0.3%).

After four years follow up, both sexes showed increased of FPG level compared to baseline while the OGTT level increased significantly. The proportion of prediabetes and T2DM also increased significantly within follow up by 21.4% for prediabetes and 0.8% for T2DM in both sexes (Table S3).

3.1.2.1. Association between LAP index and VAI for the prediction of prediabetes. The relative risk (RR) of developing prediabetes and T2DM using LAP index, VAI, BMI, and WC were summarized in Fig. 3.

LAP index, VAI, BMI and waist circumference were all inferior to predict the incidence of prediabetes (Fig. 3A and B).

When we further stratified into age group, the highest RR of having prediabetes in men was found among men aged 25–45 years old with higher VAI, men age 45–55 years old with higher LAP index and general obesity, and men aged >55 years old with central obesity. Among women, the highest RR of having prediabetes were all found among age group of 45–55 years old for women with higher LAP index, VAI, general obesity and central obesity (Table S4).

3.1.2.2. Association between LAP index and VAI for the prediction of T2DM. Men with higher LAP index, higher VAI, and general obesity were not associated with increased RR of having T2DM, even after adjustment for confoundings [RR, 95% CI, 1.74 (0.87–3.47), p = 0.118)]vs [RR, 95% CI, 1.71 (0.92–3.20), p = 0.091))] vs [RR, 95% CI, 1.95 (0.73–5.19), p = 0.183)] for higher LAP index, higher VAI and general obesity respectively]. Only men with central obesity had an increased RR of having T2DM [RR, 95% CI, 2.06 (1.06–4.01), p = 0.033)] (Fig. 3C).

On the opposite, women with higher VAI index, general obesity and central obesity had an increased RR of having T2DM, even after adjustment for confoundings [RR, 95% CI, 2.59 (1.05–6.39), p = 0.038)], [RR, 95% CI, 2.02 (1.17–3.49), p = 0.012) and [RR, 95% CI, 1.65 (1.07–2.55), p = 0.024)] for higher VAI index, general obesity and central obesity respectively)] (Fig. 3D).

When we further stratified into age group, the highest RR of having T2DM in men was found among men aged 25–45 years old with higher LAP index, general obesity and central obesity, whereas men with higher VAI aged >55 years old had the highest RR of having T2DM. Among women, the highest RR of having prediabetes were found among age group of 25–45 years old for women with higher VAI index and general obesity, age 45–55 years old for women with central obesity and age >55 years old for women with higher LAP index (Table S4).

4. Discussion

Our study observed that worsening glycemic status was associated with higher LAP index and VAI. VAI index had significant association with the diagnosis of prediabetes and T2DM in both sexes. LAP index only showed significant association with the diagnosis of prediabetes and T2DM in women, but not in men. Higher VAI was also associated with a higher chance to develop T2D but only in women.

Lifestyle changes towards sedentary lifestyle and consumption of high calorie diet which are increasing, especially in low to middle income countries have mainly driven to the increase of obesity [1,23]. In Asian countries with rapid economy growth, urbanization and globalization, there was a dramatic shift from Asian diet that is mostly dominated with staple food to Westernized diet that is dominated with meat and poultry dairy product, fats and oil, which are higher in calorie [24]. Similar health problem was also faced in Indonesia as modernized diet was more popular nowadays, particularly in the urban area. Hence, the increased prevalence of obesity had contributed to the development and increased incidence of T2DM [3,4]. In most population-based studies, the common measurement of obesity such as BMI and WC might not completely represent the dysfunctional adipose tissue [25,26]. BMI may not distinguish between weight associated fat mass and fat free mass whereas WC cannot differ between visceral and subcutaneous fat [11–15]. Simple calculation of LAP index to measure lipid accumulation and VAI to assess visceral adiposity were suggested to be more superior and can be used as a surrogate marker for the diagnosis of dysglycemia as well as the predictor in the development of T2DM. Previous evidence showed that VAI has been a surrogate index for insulin sensitivity and cardiometabolic risk including coronary heart disease, myocardial infarction and stroke among Caucasian [9,27]. These surrogate ability of VAI was also in accordance with MRI and euglycemic clamp procedure [9]. On the other hand, LAP index was also found to be independently associated with the metabolic profile of hospitalized patients in Brazil [28]. Our study indeed observed that worsening glycemic status was associated with higher LAP index and VAI, suggested that these two simple calculated measures of obesity indeed correlated with the patho-

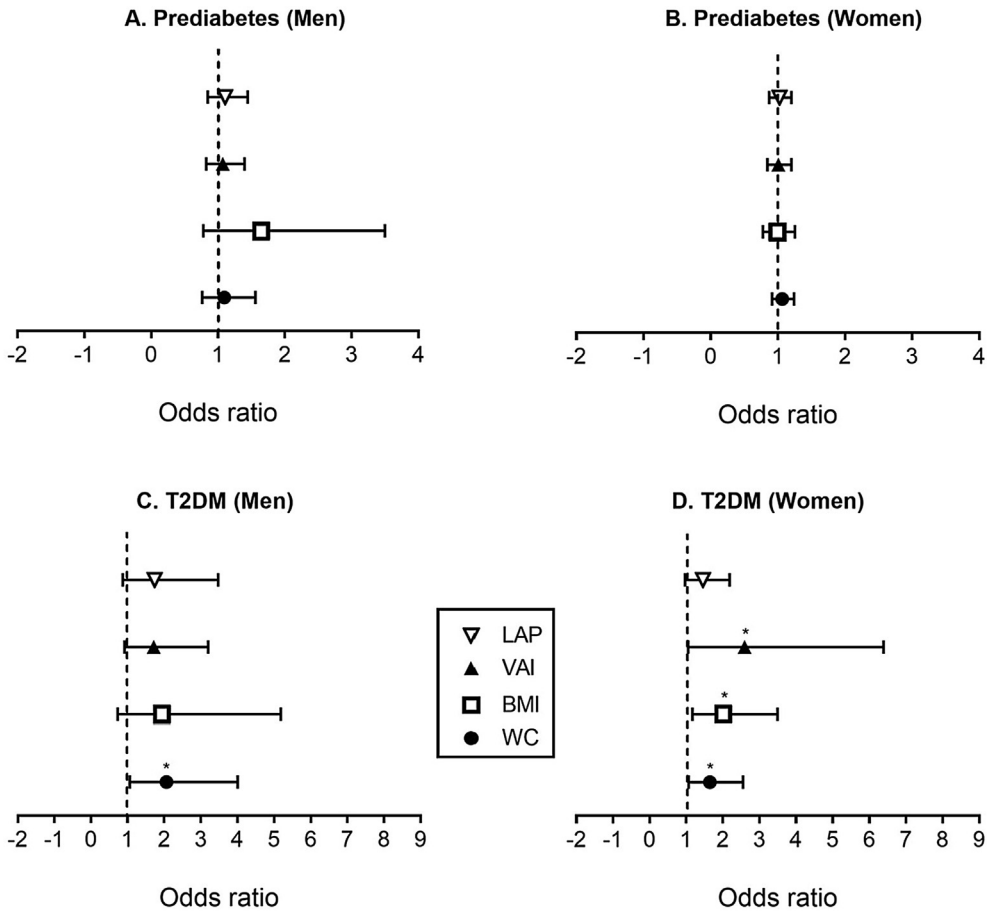

Fig. 3 – Comparison between LAP index, VAI, BMI and WC for Prediabetes and T2DM Predictor. **The relative risk of subjects with high Lipid Accumulation Product (LAP), obesity and central obesity to develop prediabetes or T2DM was analyzed using cox regression analysis with adjustment of age, hypertension, family history of TD2DM, smoking status, consumption of ACE-inhibitor and other anti-hypertensive drugs and consumption of statin. Additional adjustment for baseline prediabetes was performed for prediction of T2DM. The forest plot was displayed in relative risk and 95% confidence interval. (*) resembles p-value < 0.05. Inverted white triangle represents high LAP Index, black triangle represents high VAI, white box represents BMI ≥ 23 kg/m^2 and black dot represents Waist Circumference (WC) ≥ 80 cm for women and ≥ 90 for men.**

genesis of T2DM. If anything, the changes in LAP index and VAI with worsening glycemic status seemed to be more pronounced in comparison to changes in BMI and WC. This suggested that both LAP index and VAI might better represent the fat accumulation. Strong association of LAP index with worsening of glycemic status were in agreement with the result of previous studies reported by Kahn (2006), Bozorgmanesh et al (2010), Wakabayashi et al (2014) and Dev et al (2016) [22,29–31] which we have previously summarized [32].

Our study found that high VAI was better in diagnosing prediabetes and T2DM in both sexes while high LAP was superior in diagnosing prediabetes among women among Asian-Malay ethnicity in Indonesia. Similar strong association of higher VAI with pre-diabetes and diabetes also reported in study by Liu et al. [33]. Liu et al (2016) found that the odds of male patients with VAI index ≥ 2.78 to develop T2DM was 2.176 (95%CI = 1.404–3.374, p = 0.001). In addition, the odds ratio of female patients with VAI index ≥ 1.75 to develop T2DM was even higher with 7.630 (95%CI = 2.502–23.268, p < 0.001) [33]. Indeed, we have also previously summarize that VAI might be used as a predictor of T2DM in Asian population [34].

Our study found that both LAP index and VAI were not sufficient to predict he development of prediabetes among normal population in both sexes. These findings were opposite to a prospective cohort study with 5 years follow up by Wu et al. which evaluated the predictor of VAI index that was modified for Chinese population with higher body fat. Wu et al. found that the highest quartile of Chinese Visceral Adiposity Index (CVAI) was the strongest predictor among other obesity indices such as VAI, BMI, WC, WHR and WHtR after adjustment of confounding factors with OR 1.6(95% CI 1.16–2.2), p = 0.05 [35]. The differences of the study findings were probably caused the formula used in Wu et al study was modified for Chinese population while our study still used VAI formula that was developed among Caucasian population.

Other studies have reported that VAI were more superior as a predictor of T2DM compared to BMI and WC, but not

for LAP index. This was different with the previous longitudinal study demonstrated that individuals with high LAP index had an increased risk of diabetes as compared with those with low LAP index, but the predictive value of the LAP and other central obesity marker were similar [29]. In addition, sex hormones such as estrogen, was suspected to be involved in the stronger association observed between LAP and diabetes, also though the exact reason for the gender difference remains to be elucidated. Previous evidence showed that estrogen deficiency which is found on menopause women was associated with increased risk of cardiovascular disease, T2DM and metabolic syndrome [36]. As the average age of post-menopause in Asia and particularly in Indonesia ranged between 50 and 51 years old [37–39]. Hence, women aged >45 years old in our study can be considered as perimenopause population. Women going through menopausal transition was correlated with increased adiposity by the changes of inflammatory marker and adipokines which be the cause of increased risk of metabolic disease among this population [40]. Previous cross sectional study by Shabestari et al. which found that LAP index was associated with increased risk of having elevated FPG [OR, 95% CI 1.55 (0.95–2.55); p = 0.08] among post-menopausal women [41]. Our study did not find the increased OR or RR of having prediabetes or T2DM among peri and post-menopausal age with higher LAP or VAI as well as BMI and waist circumference.

Age factor may also contributes with higher lipid accumulation as previous evidence showed that aging is associated with increase of adiposity, redistribution of body fat and also ectopic fat deposition [40]. This evidence also in line with our study results as generally the LAP index and VAI index among men and women aged above 55 years old were higher compared to the younger ones.

Both LAP index and VAI index was calculated from waist circumference in its formula as well as triglycerides value and additional HDL cholesterol level for VAI. BMI alone might not completely represent abnormal tissue deposition [25,26]. Hence, adding other factors such contributing to lipid deposition and metabolic syndrome in the formula might be potentially strengthen the dyglycemia prediction ability, particularly in LAP index in which both triglyceride and HDL cholesterol were calculated.

Our study confirmed previous studies which reported that VAI can be used as T2DM predictor among several Asian population, conducted in Tehran [42], Saudia Arabia [43] and China [31,33,44–46]. In our study, VAI was positively associated with the risk of diabetes in women, possibly attributed to behaviour, environmental and genetic influences-that were differ from previous study. All of the analysis in this study was performed separately in each gender since healthy women have more adipose mass, more circulating free fatty acid (FFA), higher intramyocellular lipid content, and only two thirds the skeletal muscles mass of men [47,48]. These factors can promote insulin resistance in women. However, another study reported that women are resistant to FFA induced insulin resistance, possibly only in premenopausal population [49].

The present study was the first study to evaluate association between LAP index, VAI and dysglycemia status, and their role as the predictor of the current dysglycemia status as well as predicting future dysglycemia status. The use of community based settings as the population sample, direct measurements of the anthropometric indices rather than self-reported data, and regular follow-up of all study population become the strengths of this study. However, several limitations were found in this study. First, this study was conducted using secondary data with short period of cohort in a limited area in Bogor (West Java). This may not represent Indonesia as a multi-ethnicity country. Second, there was no data on HbA1c. Third, we did not compare the result of LAP index with actual physical measurements of visceral adiposity by DEXA, MRI or CT scan. Lastly, there was no data regarding major adverse cardiovascular events (MACE) since VAI has been linked as surrogate marker for cardio metabolic disease. Hence, future studies which exclude subjects with MACE with ethnic specific LAP index and VAI formula should be conducted in order to investigate the true power of LAP index and VAI for diagnosing or predicting diabetes status.

5. Conclusion

In summary, worsening dysglycemia status was associated with increased LAP index and VAI in both sexes. In men, higher VAI but not LAP index was associated with higher risk of having prediabetes and T2DM. Higher VAI was superior than general obesity measurements (BMI and waist circumference) for the diagnosis of prediabetes but not for diagnosing T2DM. In women, higher VAI and LAP index was associated with higher chance of having prediabetes and T2DM. However, both indices were not superior compared to the general obesity measurements. In terms of predicting prediabetes and T2DM, in men, neither higher VAI nor higher LAP was associated with higher risk to develop prediabetes and T2DM in the future. In women, higher VAI was associated with higher risk to develop T2DM but not prediabetes in the future. If anything, this was superior to other general obesity measurements. Further large multicenter studies that included diverse ethnicities and longer follow-up will be needed to verify the performance of LAP index and VAI in predicting T2DM.

Consent for publication

All authors consent to publish this study. The authors guarantee that any data of this study has not been published anywhere else as a whole or in part. All authors have declare to approve the publication of this study and any person named as co-author is aware and agreed of the publication and the order authors naming.

Availability of data and material

The authors confirm that the data supporting the results of this study are available within the article and or supplementary material.

Author contributions

Idea and study design: DLT, RN, GA, PS; Data collection and analysis: RN, DLT, M, MK, WR, CA, NA; Article draft writing: RN, GA, CA; Draft revision: DLT, PS, M, MK, WR, NA, CA; Writing supervision: DLT, PS. RN and GA have contributed equally

in writing this article, while DLT and PS have contributed equally in supervising the writing of this article.

Acknowledgements

This study is funded by PITTA grant fund number 2112/UN2.R3.1/HKP.05.00/2018. The authors convey appreciation to the National Institute of Health Research and Development, Ministry of Health Republic of Indonesia for giving the data access of the Bogor Cohort Study for this article.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107798.

REFERENCES

[1] International Diabetes Federation. IDF diabetes atlas eighth edition 2017. International diabetes federation; 2017. 150 p.
[2] World Health Organization. Global report on diabetes [Internet]; 2016. <http://www.who.int/about/licensing/%5Cnhttp://apps.who.int/iris/bitstream/10665/204871/1/9789241565257_eng.pdf>.
[3] Defronzo RA. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58(4):773–95.
[4] Schwartz SS, Epstein S, Corkey BE, Grant SFA, Gavin JR, Aguilar RB. The time is right for a new classification system for diabetes: rationale and implications of the β-cell-centric classification schema. Diabetes Care 2016;39(2):179–86.
[5] Guebre-Egziabher Fitsum, Alix Pascaline M, Koppe Laetitia, Pelletier Caroline C, Kalbacher Emilie, Fouque Denis, et al. Ectopic lipid accumulation: a potential cause for metabolic disturbances and a contributor to the alteration of kidney function. Biochimie 2013;95(11):1971–9.
[6] Rader DJ. Effect of insulin resistance, dyslipidemia, and intra-abdominal adiposity on the development of cardiovascular disease and diabetes mellitus. Am J Med. 2007;120(3 SUPPL. 1):12–8.
[7] Ravussin E, Smith SR. Role of the adipocyte in metabolism and endocrine function, 7th ed. Endocrinology: Adult and Pediatric. Elsevier; 2016. p. 627–47.e9 p.
[8] Després J-P, Prud'homme D, Pouliot MC, Tremblay A, Bouchard C. Estimation of deep abdominal adipose-tissue accumulation from simple anthropometric measurements in men. Am J Clin Nutr 1991;54(3):471–7.
[9] Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al. Visceral adiposity index: a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care 2010;33(4):920–2.
[10] Lee JJ, Beretvas SN, Freeland-Graves JH. Abdominal adiposity distribution in diabetic/prediabetic and nondiabetic populations: a meta-analysis. J Obes 2014;2014.
[11] Bjorntorp P, Bray GA, Carroll KK, Chuchalin A, Dietz WH, Ehrlich GE, et al. Preventing and managing the global epidemic. WHO Tech Rep Ser 2000;253.
[12] Bray GA, Heisel WE, Afshin A, Jensen MD, Dietz WH, Long M, et al. The science of obesity management: an endocrine society scientific statement. Endocr Rev 2018;39(2):79–132.
[13] Shuster A, Patlas M, Pinthus JH, Mourtzakis M. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. Br J Radiol 2012;85(1009):1–10.
[14] Fujita M, Sato Y, Nagashima K, Takahashi S, Hata A. Predictive power of a body shape index for development of diabetes, hypertension, and dyslipidemia in Japanese adults: a retrospective cohort study. PLoS ONE 2015;10(6):1–19.
[15] Neeland IJ, Turer AT, Ayers CR, Powell-Wiley TM, Vega GL, Farzaneh-Far R, et al. Dysfunctional adiposity and the risk of prediabetes and type 2 diabetes in obese adults. JAMA – J Am Med Assoc 2012;308(11):1150–9.
[16] Amato MC, Giordano C. Visceral adiposity index: an indicator of adipose tissue dysfunction. Int J Endocrinol, 2014, 2014.
[17] Amato MC, Giordano C, Galia M, Riscimanna AC, Vitabile S, Midiri M, et al. Visceral adiposity index. Diabetes Care 2010;33(4):920–2.
[18] Badan Penelitian dan Pengembangan Kesehatan. Studi Kohort Penyakit Tidak Menular (PTM); 2011.
[19] Riddle MC. American diabetes association standards of medical care in diabetes-2018. Diabetes Care 2018;41.
[20] Whelton PK, Carey RM, Aronow WS, Casey DE, Collins KJ, Himmelfarb CD, et al. Clinical practice guideline 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults a report of the american college of cardiology; 2018.
[21] Ministry of Health Republic of Indonesia. Profil Kesehatan Indonesia tahun 2019. Jakarta; 2010.
[22] The Kahn HS. Lipid accumulation product is better than than BMI for identifying diabetes. Cardiovasc Metab Risk 2006;29(1).
[23] PERKENI. Konsensus Pengendalian dan Pencegahan Diabetes Melitus Tipe 2 di Indonesia 2015. Perkeni; 2015. 78 p.
[24] Pingali P. Westernization of Asian diets and the transformation of food systems: implications for research and policy. Food Policy 2007;32(3):281–98.
[25] Hardy OT, Czech MP, Corvera S. What causes the insulin resistance underlying obesity? Curr Opin Endocrinol Diabetes Obes 2012;19(2):81–7.
[26] Dai D, Chang Y, Chen Y, Chen S, Yu S, Guo X, et al. Visceral adiposity index and lipid accumulation product index: two alternate body indices to identify chronic kidney disease among the rural population in Northeast China. Int J Environ Res Public Health 2016;13(12):1–11.
[27] Amato MC, Giordano C, Pitrone M, Galluzzo A. Cut-off points of the visceral adiposity index (VAI) identifying a visceral adipose dysfunction associated with cardiometabolic risk in a Caucasian Sicilian population. Lipids Health Dis [Internet] 2011;10(1):183.
[28] Vieira BA, Sauer P, Marcadenti A, Piovesan CH. Asociación entre el índice de pal (el producto de acumulación lipídica) y el perfil metabólico en pacientes hospitalizados. Nutr Hosp. 2015;31(6):2771–4.
[29] Bozorgmanesh M, Hadaegh F, Azizi F. Diabetes prediction, lipid accumulation product, and adiposity measures; 6-year follow-up: Tehran lipid and glucose study 2010;1–9.
[30] Wakabayashi I, Daimon T. A strong association between lipid accumulation product and diabetes mellitus in Japanese women and men. J Atheroscler Thromb 2014;21(3):282–8.
[31] Zhang M, Zheng L, Li P, Zhu Y, Chang H, Wang X, et al. 4-Year trajectory of visceral adiposity index in the development of type 2 diabetes: a prospective cohort study. Ann Nutr Metab 2016;69(2):142–9.

[32] Ayundini G, Astrella C, Tahapary D, Soewondo P. Review article a systematic review on the association between lipid accumulation product index and type 2 diabetes mellitus*. JAFES 2019;34(1):16–20.
[33] Liu PJ, Ma F, Lou HP, Chen Y. Visceral adiposity index is associated with pre-diabetes and type 2 diabetes mellitus in Chinese adults aged 20–50. Ann Nutr Metab 2016;68(4):235–43.
[34] Nusrianto R, Tahapary DL, Soewondo P. Visceral adiposity index as a predictor for type 2 diabetes mellitus in Asian population: a systematic review. Diabetes Metab Syndr Clin Res Rev [Internet] 2019;13(2):1231–5.
[35] Wu J, Gong L, Li Q, Hu J, Zha S, Wang Y, et al. A novel visceral adiposity index for prediction of type 2 diabetes and pre-diabetes in chinese adults: a 5-year prospective study. Sci Rep 2017;7:1–9.
[36] Carr MC. The emergence of the metabolic syndrome with menopause. J Clin Endocrinol Metab 2003;88(6):2404–11.
[37] Boulet MJ, Oddens BJ, Lehertb P, Vemer HM, Visserd A. Climacteric and menopause in seven south-east Asian countries. Maturitas 1994;19(157–176).
[38] Samil RS, Wishnuwardhani SD. Health of Indonesian women city-dwellers of perimenopausal age. Maturitas 1994;19:191–7.
[39] Hogervorst E, Kusdhany LS, Ismail RI, Auerkari EI, Bandelow S, Talbot C, et al. Age at natural menopause and memory function: modification by education endocrinology & metabolic syndrome age at natural menopause and memory function: modification by education and genotype. Endocrinol Metab Synd 2011;S7.
[40] Lee CG, Carr MC, Murdoch SJ, Mitchell E, Woods NF, Wener MH, et al. Adipokines, inflammation, and visceral adiposity across the menopausal transition: a prospective study. J Clin Endocrinol Metab 2009;94(4):1104–10.
[41] Shabestari AN, Asadi M, Jouyandeh Z, Qorbani M, Kelishadi R. Association of lipid accumulation product with cardio-metabolic risk factors in postmenopausal women. Acta Med Iran 2016;54(6):371–5.
[42] Janghorbani M, Amini M. The visceral adiposity index in comparison with easily measurable anthropometric markers did not improve prediction of diabetes. Can J Diabetes 2016;40 (5):393–8.
[43] Bozorgmanesh M, Hadaegh F, Azizi F, Harati H, Hadaegh F, Saadat N, et al. Predictive performance of the visceral adiposity index for a visceral adiposity-related risk: type 2 diabetes. Lipids Health Dis 2011;10(1):88.
[44] Du T, Sun X, Huo R, Yu X. Visceral adiposity index, hypertriglyceridemic waist and risk of diabetes: The China Health and Nutrition Survey 2009. Int J Obes 2014;38(6):840–7.
[45] Chen C, Xu Y, Guo ZR, Yang J, Wu M, Hu XS. The application of visceral adiposity index in identifying type 2 diabetes risks based on a prospective cohort in China. Lipids Health Dis 2014;13(1):1–8.
[46] Gu D, Ding Y, Zhao Y, Qu Q, Clin E, Diabetes E. Visceral adiposity index was a useful predictor of prediabetes. Exp Clin Endocrinol Diabetes 2017.
[47] Mauvais-Jarvis F. Sex differences in metabolic homeostasis, diabetes, and obesity. Biol Sex Differ 2015;6(1):1–9.
[48] Fuente-Martín E, Argente-Arizón P, Ros P, Argente J, Chowen JA. Sex differences in adipose tissue. Adipocyte 2013;2 (3):128–34.
[49] Frias JP, Macaraeg GB, Ofrecio J, Yu JG, Olefsky JM, Kruszynska YT. Decreased susceptibility to fatty acid-induced peripheral tissue insulin resistance in women. Diabetes 2001;50 (6):1344–50.