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REVIEW ARTICLE

A Systematic Review on the Association between Lipid Accumulation Product Index and Type 2 Diabetes Mellitus*

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Abstract

Introduction. Excess fat accumulation contributes to the development of type 2 diabetes mellitus (T2DM). Lipid accumulation product (LAP) is an index computed from waist circumference and triglycerides, which represents increased lipotoxicity. We aim to study the relationship of LAP index and T2DM and its utility as a predictor for T2DM development.

Methodology. A literature search in PubMed and Cochrane database was performed to retrieve and review studies reporting the association between LAP and T2DM.

Results. Two cross-sectional studies from Japan and the United States, and one cohort study from Iran were obtained. A high LAP was associated with a higher risk of T2DM [odds ratio (OR) 19.1, 95% confidence interval (CI) (6.6-55.5) for women; and OR 7.4, 95% CI (5.1-10.8) for men].

Conclusion. LAP was strongly associated with T2DM. Its utility in predicting the development of T2DM needs to be confirmed.

Key words: lipid accumulation product, type 2 diabetes mellitus, insulin resistance, obesity

INTRODUCTION

The prevalence of obesity has escalated globally, invariably affecting low- to middle-income countries. The prevalence of global obesity has increased by about 8.1% in men and 8.2% in women from 1980 to 2013.[1] In a shorter period of time, the prevalence of obesity in adult Indonesians from 1993 to 2007 has also increased rapidly by 11% in men and 13 to 16% in women.[2] The most common etiology for this rapid increase in obesity in low- to middle-income countries is lifestyle change toward high calorie intake and sedentary behavior leading to positive energy balance.[3-5]

Positive energy balance eventually leads to hypertrophy of adipocytes and ectopic lipid accumulation in multiple organs in the body.[6,7] Lipids that overly accumulate outside the non-adipose tissues will be ineffectively oxidized.[8] These unoxidized excess fatty acids lead to abnormal lipid accumulation, which further results to pancreatic beta cell failure, fatty liver, reduced insulin-stimulated glucose uptake in muscle and myocardial insulin resistance.[9] In the end, excessive fat accumulation will contribute to the development of insulin resistance and type 2 diabetes mellitus.

Body mass index (BMI), a common marker of obesity that can be used in measuring lipid accumulation, might not completely represent abnormal adipose tissue deposition.[7,10] Lipid accumulation product (LAP) is an index of lipid accumulation that is computed from waist circumference and triglycerides (TG). LAP was found to have the ability to represent lipotoxicity.[11] Previous studies have reported the relationship between LAP index and the incidence of T2DM.[11-12] However, the cut-off point of LAP index which may contribute to the development of T2DM is still uncertain. Moreover, because the current LAP index formula was derived from a Caucasian population, its applicability in different ethnic groups needs to be further explored. We aim to evaluate the relationship of LAP index and T2DM and its potential as a predictor for T2DM development. In addition, the cut-off point of LAP index associated with T2DM was also evaluated.

METHODOLOGY

This systematic review followed recommendations from the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). Literature search was performed from September 10 to 11, 2018 in PubMed

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and Cochrane Central Trial Database - EMBASE. The formulated research question is: "Is LAP index associated with T2DM?" We used the terms: [[lipid accumulation product (Title/Abstract)] OR LAP (Title/Abstract)] AND diabetes (Title/Abstract) in PubMed. For the Cochrane Central Trial Database - EMBASE we used the terms: LAP in Title Abstract Keyword OR lipid accumulation product in Title Abstract Keyword AND diabetes in Title Abstract Keyword AND predictor in Title Abstract Keyword. We included studies that were published within the last 10 years, in English, conducted on humans, and among adult subjects. Grey literature, interventional studies and poor-quality studies were excluded in this review.

Retrieved articles were reviewed independently by two investigators (GA and DLT) in order to gain potentially relevant articles. All disagreements on inclusion/exclusion were discussed and resolved by consensus. Two reviewers (GA and DLT) independently extracted data from included studies. Information on study background (journal, title, year of publication), background characteristics (country, study design, sample, and duration of observation), cut-off point of LAP index, and odds ratio/hazard ratio of LAP index for incidence of T2DM were extracted. All relevant studies were assessed for risk of bias using the Newcastle Ottawa Scale (NOS) in order to be included in the review. Studies with NOS score above 7 were considered as high-quality; a score of 6 to 7 was considered as moderate; and a score less than 6 was considered as poor-quality.

Ethics approval and consent to participate

This study was approved by the ethics committee of the Faculty of Medicine Universitas Indonesia (No 1293/UN2. F1/ETIK/2018).

RESULTS

Our comprehensive search identified 83 publications. After removing duplicates and screening by title and abstract, a total of 7 studies matched the research question. After retrieving the full manuscripts, 3 studies were excluded. These were due to interventional design or diagnostic nature. One study recruited subjects with metabolic syndrome. A total of 2 cross-sectional studies and one prospective cohort study were included in the synthesis, which were performed in Japan, the United States and Iran, respectively (Table 1).[11,12,14] The search and selection process based on the PRISMA flow diagram is outlined in Figure 1. The largest population included 10,170 patients, while the longest duration of follow-up was 6 years.

LAP index cut-off point

All of the included studies performed the analysis separately according to gender. The study by Wakabayashi et al., analyzed the LAP index cut-off point using receiver operating characteristic (ROC) curve analysis.[12] The area under the curve (AUC) values for LAP index with diabetes were 0.763 (0.709-0.816) for women and 0.764 (0.742-0.787) for men, with cut-off points of 21.1 for women and 37.2 for men.[12] The other two studies by Bozorgmanesh et al., and Kahn et al., used quartiles as reference, and considered LAP index values in the 4th quartile as high.[11,14] In the study by Kahn et al., a LAP index of 66.1 for the

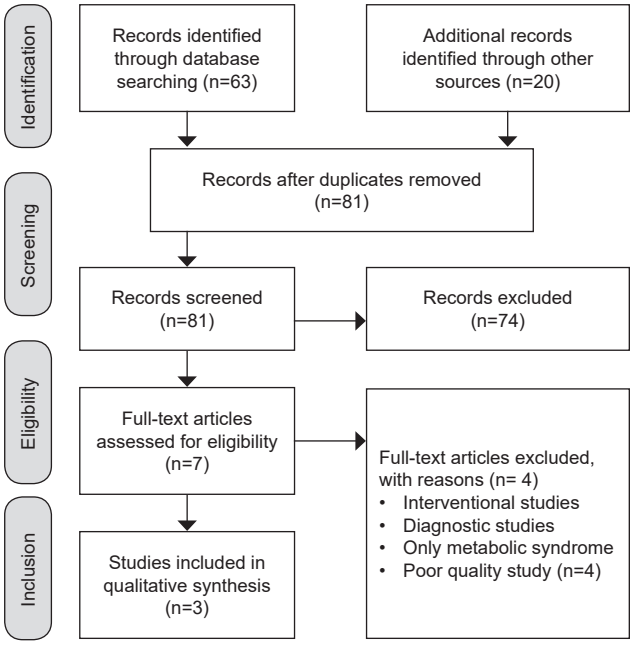

Figure 1. Preferred reporting items for systematic review and meta-analyses flow diagram.

4th quartile was considered high.[11] There is no data on the quartile values in the study by Bozorgmanesh et al (Table 1).[14]

Odds ratios for T2DM

Wakabayashi et al., demonstrated a strong association between LAP index and T2DM in the Japanese population.[12] Using the cut-off values for LAP index of 21.1 and 37.2 for women and men respectively, the OR for T2DM in subjects with high LAP index was 19.09, 95% CI (6.57-55.50) for women; and 7.40, 95% CI (5.10-10.75) in men (Table 1 and Figure 2).

The study by Kahn et al., compared LAP index and BMI for identifying T2DM. The LAP, BMI and homeostatic model of insulin resistance (HOMA-IR) variables that were skewed were logarithmically (ln) transformed. They found that the standardized T2DM OR for (ln)LAP was larger compared to (ln)BMI in each age and sex group. The greatest difference in standardized OR between LAP index and BMI was observed in younger women [5.55, 95% CI (3.48-8.84) versus 2.35 (1.82-3.04)], while the smallest difference was seen in older men [2.33, 95% CI (1.89-2.86) versus 1.95 (1.49-2.54)]. In addition, the upper quartiles of the LAP index (cut-off points of >66.1 for men and >60.4 for women) was found to be associated with more than twice the likelihood of 4th quartiles of BMI for having diabetes (Table 1, Figure 2).[11]

The study by Bozorgmanesh et al., consisted of both cross-sectional and longitudinal analyses. Based on their cross-sectional analysis, LAP index is a strong predictor of diabetes in young individuals, especially among women. LAP had almost consistently stronger association (higher coefficient of determination, R^2) with baseline fasting plasma glucose (FPG) and 2-hour post-challenge plasma glucose (2h-PCPG) than BMI, especially in women (10.2 versus 6.9 and 17.3 versus 9.8, respectively). In younger

Table 1. Summary of included studies

Author	Year	Population	Design	LAP[a] index cut-off point	Result
Kahn et al[11]	2006	9,180 (4,733 women and 4,447 men) US[b] civilians age ≥18 years	Cross-sectional	4th Quartile 4 1st Quartile 4th Quartile of LAP index ≥66.1	LAP[a] index is superior to BMI[c] for identifying adults with diabetes. The greatest difference in standardized OR[d] was seen in younger women [5.55, 95% CI[e] (3.48-8.84) versus 2.35 (1.82-3.04)]. The smallest difference was among older men [2.33 (1.89 -2.86) versus 1.95 (1.49-2.54)].
Wakabayashi et al[13]	2014	10,170 (3,267 women and 6,903 men) Japanese age 35 to 40 years	Cross-sectional	ROC[i] curve analysis: AUC[j] for women: 0.763 (0.709-0.816) AUC[j] for men: 0.764 (0.742-0.787) Cut –off points: 21.1 for women 37.2 for men	The prevalence of a high LAP index was calculated to be 23.7% in women and 28.8% in men. The OR[d] for diabetes in subjects with high LAP[a] index was 19.09, 95% CI[e] (6.57-55.5) in women and 7.40, 95% CI[e] (5.10-10.75) in men after adjusting for age, smoking, alcohol consumption and regular exercise.
Bozorgmanesh et al[15]	2010	8,671 (4,989 women and 3,682 men) age ≥20 years in Tehran, Iran	Cross-sectional and longitudinal cohort	Quartile 4 versus quartile 1 (no data given for quartile values)	Cross-sectional analysis: LAP[a] index is a strong predictor of diabetes and in young individuals, especially among women. The OR[d] of LAP[a] with the prevalence of T2DM[f] was 2.1 (1.8-2.5), p<0.001 for age 20-49 years old and 1.5 (1.3-1.8) for age ≥50 years old. Longitudinal analysis: LAP[a] index was better in predicting T2DM[f] compared to BMI[c] but relatively similar to WHpR[g] and WHtR[h]. OR[d] for prediction of T2DM[f] prevalent in young women (age 20-49) was higher in LAP[a] than BMI[c] [2.1, 95% CI[e] (1.8-2.5) versus 1.6,(1.5-1.9), p<0.001.

[a] LAP, lipid accumulation product
[b] US, United States
[c] BMI, body mass index
[d] OR, odds ratio
[e] CI, confidence interval
[f] T2DM, type 2 diabetes mellitus
[g] WHpR, waist-hip ratio
[h] WHtR, waist-height ratio
[i] ROC, receiver operating characteristic
[j] AUC, area under the curve

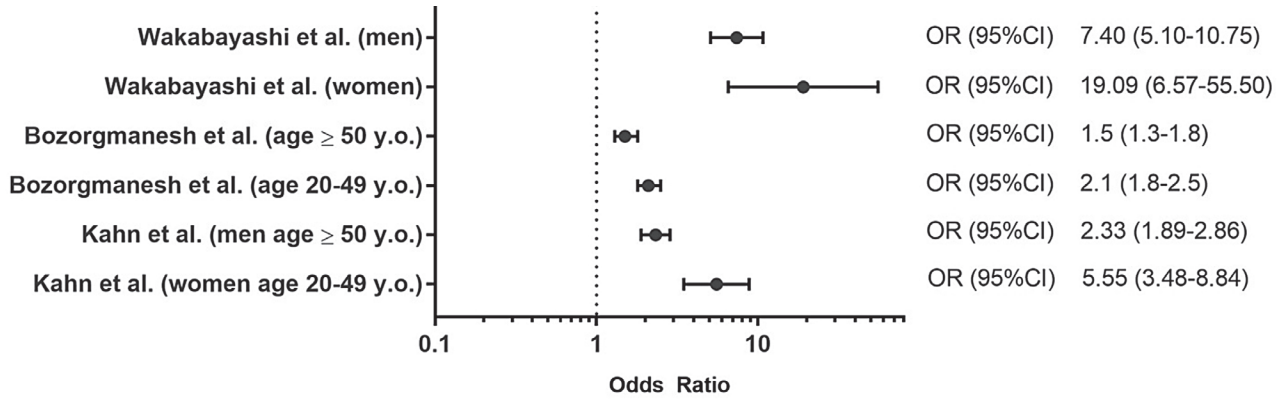

Figure 2. The odds ratio of LAP index and T2DM among the included cross-sectional studies.

Table 2. Critical appraisal and bias risk analysis of the selected articles using the Newcastle Ottawa Scale Study

	Selection	Comparability	Outcome	Total
Kahn et al.[11]	****	**	***	9
Wakabayashi et al.[13]	****	**	**	8
Bozorgmanesh et a.l[15]	****	**	***	9

women (ages 20 to 49 years) and older men (age 50 years and above), the LAP explained greater variability than waist-to-height ratio (WHtR) and waist-to-hip-ratio (WHpR) in the baseline levels of FPG (7.2, 3.6 and 4.6 in women; 5.6, 3.2 and 3.6 in older men; respectively) and 2h-PCPG (8.5, 5.1 and 4.9 in women; 8.8, 6.3 and 6.5 in older men) (Table 1 and Figure 2). In the longitudinal analysis, LAP index performed similarly with BMI, WHtR and WHpR in both sexes and across age groups to predict the incidence of T2DM. The LAP index was only superior compared to BMI in younger men (ages 20 to 49 years).[14]

Study quality

The critical review and bias risk analyses were conducted by using the Newcastle Ottawa Scale (Table 2). All of the included studies were identified as good quality as they reached a score of more than 7.[11-12,14] One study did not report funding sources which may contribute to the risk of bias.[11]

DISCUSSION

Studies have shown that excessive fat accumulation could lead to adipocyte dysfunction and an increase in the risk of T2DM, as well as other cardiovascular risks.[15] This study is the first systematic review to provide evidence on the association of LAP index, a practical equation for estimating body fat accumulation, with T2DM.[11-12,14]

In most population-based studies, BMI, waist circumference, WHpR and WHtR are the most common measures of obesity. Although studies have demonstrated the utility of BMI in assessing population-based mortality and disease-specific morbidity, there are some limitations in using BMI alone to diagnose obesity. First, BMI has an inherent inability to distinguish weight associated with muscle or fat mass. Second, BMI does not characterize body fat distribution, a known determinant of metabolic risk.[15-16] In this aspect, WHpR and WHtR might better represent central obesity, particularly visceral fat, which has been reported to be strongly associated with T2DM. In this study, we observed that LAP index had stronger relationship with T2DM in comparison to BMI, but not to WHpR and WHtR.[14] However, the evidence on the predictive power of LAP on T2DM is still limited and insufficient.

The available studies on LAP and T2DM used different approaches in determining the LAP index value that may contribute to the incidence or development of T2DM. In addition, the studies included different ethnic backgrounds, particularly Asian and Caucasian.[11-12,14] Ethnicity may influence body fat composition as Asians tend to have higher abdominal adiposity.[17] Hence, the cut-off point of LAP index which may related of T2DM still cannot be confirmed, and may possibly vary according to each population.

The stronger relationship of T2DM and LAP index compared to BMI but not WHpR and WHtR can be explained in several possible ways. First, simple measurement of central obesity might be sufficient to identify T2DM. This measurement mostly measures visceral fat, which plays an important role in the development of chronic low-grade inflammation and insulin resistance, and eventually to the development of T2DM. Second, because the formula for LAP index also includes waist circumference, it already includes a measurement of central obesity. We may then speculate that the lipolysis process, represented by TG levels, may also be related to central obesity. Thus, the addition of TG levels in the formula does not add precision in identifying or predicting T2DM.

It is important to note that in the 3 different populations included in our analysis, we observed different of cut-off values for the LAP index. The available calculated cut-off point using AUC analysis was in the Japanese, while the other studies used quartiles as the cut-off point.[11-12,14] Many studies have shown that different ethnic and age groups are correlated with different levels of insulin resistance and body fat composition.[18-19] For the same BMI as Caucasians, the body fat percentage in Asians would be 5 to 7% higher in Indian men; 8% in Indian women; 1 to 4% in Japanese women; 5% and 7% for Indonesian men and women from Malay ancestry, respectively; and 1.3% and 1.7% for Indonesian Chinese men and women, respectively.[7,20-25] To this end, as the LAP index was developed using Caucasian populations, further studies are needed to determine a specific LAP index formula for Asians.

Conclusions

The LAP index was superior to BMI in identifying T2DM risk, but not to WHpR and WHtR. However, the current available studies were not sufficient to establish the role of LAP index in predicting T2DM. Since the current LAP index was developed from studies on Caucasian populations, further research is needed to evaluate the cut-off values for that could be used effectively in identifying or predicting T2DM in other populations.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

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