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

Gratcia Ayundini,1 Cindy Astrella,2 Dicky Tahapary,2,3 Pradana Soewondo2,3

1Department of Internal Medicine, Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine, Universitas Indonesia
2Metabolic, Cardiovascular and Aging Cluster, The Indonesian Medical Education and Research Institute, Faculty of Medicine, Universitas Indonesia
3Division of Endocrinology and Metabolism, Department of Internal Medicine, Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine, Universitas Indonesia

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...
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 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.FI/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 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
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
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 characterize body fat distribution, a known determinant BMI has an inherent inability to distinguish weight associated with muscle or fat mass. Hence, the cut-off point of LAP index which may related of T2DM still cannot be confirmed, and may possibly vary according to the different populations.7,20-25 To this end, as the 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.

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 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 cut-off values for the LAP index. The available calculated cut-off points using AUC analysis was in the Japanese, while the other studies used quartiles as the cut-off points.\(^{11-12,14}\) Many studies have shown that different ethnic and age groups are correlated with different levels of insulin resistance and body fat composition.\(^{16-19}\) 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.\(^{20-25}\) 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.

Acknowledgments

The authors would like to convey their appreciation to Nida Amalina for her technical assistance during manuscript writing.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

The authors declared no conflict of interest.

Funding Source

This study was funded by PITTA grant fund number 2112/UN2. R3.1/HKP.05.00.00/2018.

References

1. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: A systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2014;384(9945):766-81. PMID: 24880830. PMCID: PMC4624264. https://doi.org/10.1016/S0140-6736(14)60460-8.  
2. Roemling C, Quim M. Obesity trends and determinants in Indonesia. Appetite. 2012;58(3):1005-13. PMID: 22402303. https://doi.org/10.1016/j. appet.2012.02.053.  
3. Zulkiewicz-Sobczak W, Wróblewska P, Zwoliński J, et al. Obesity and poverty paradox in developed countries. Ann Agric Environ Med. 2014;21(3):590-4. PMID: 25292135. https://doi.org/10.5064/21239966.1120008.  
4. Soewondo P, Ferrario A, Tahapary DL. Challenges in diabetes management in Indonesia: A literature review. Global Health, 2013;9:63. PMID: 24299164. PMCID: PMC3901560. https://doi.org/10.1186/1744-8603-9-63.  
5. Mihardja L, Soertisno U, Sorgendo S. Prevalence and clinical profile diabetes mellitus in productive aged urban Indonesians. J Diabetes Investig. 2014;5(5):507-12. PMID: 25411617. PMCID: PMC4188107. https://doi.org/10.1111/jdi.12177.  
6. Bays HE; Gonzalez-Campoy JM, Henry RR, et al. Is adiposopathy (sick fat) an endocrine disease? Int J Clin Pract. 2008;62(10):1474-83. PMID: 18681905. PMCID: PMC2658008. https://doi.org/10.1111/j.1742-4221.2008.01484.x.  
7. Hardy OT, Creech MP, Corvera S. What causes the insulin resistance underlying obesity. Curr Opin Endocrinol Diabetes Obes. 2012;19(2):81-7. PMID: 22327367. PMCID: PMC3408351. https://doi.org/10.1097/MED.0b013e32834a1e13.  
8. Matsuzura Y. Obesity and metabolic syndrome: The contribution of visceral fat and adiponectin. Diabetes Manag. 2014;4(4):391-401.  
9. Kusminski CM, Shetty S, Orii L, Unger RH, Scherer PE. Diabetes and apoptosis: Lipotoxicity. Apoptosis. 2009;14(12):1484-95. PMID: 19421860. https://doi.org/10.1007/s10495-009-0352-8.  
10. Dai D, Chang Y, Chen Y, 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):1231. PMID: 27983669. PMCID: PMC5201372. https://doi.org/10.3390/ijerph13121231.  
11. Kahn HS. The lipid accumulation product is better than BMI for identifying diabetes: A population-based comparison. Diabetes Care. 2006;29(1):151-3. PMID: 16379316.  
12. Wakahayashi 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. PMID: 24304961.
13. Bozorgmanesh M, Hadaegh F, Azizi F. Predictive performance of the visceral adiposity index for a visceral adiposity-related risk: Type 2 diabetes. Lipids Health Dis. 2011;10:88. PMID: 21619588. PMCID: PMC3126709. https://doi.org/10.1186/1476-511X-10-88.

14. Bozorgmanesh M, Hadaegh F, Azizi F. Diabetes prediction, lipid accumulation product, and adiposity measures; 6-year follow-up: Tehran lipid and glucose study. Lipids Health Dis. 2010;9:45. PMID: 20459710. PMCID: PMC2876156. https://doi.org/10.1186/1476-511X-9-45.

15. Bray GA, Heisel WE, Afshin A, et al. The science of obesity management: An Endocrine Society scientific statement. Endocr Rev. 2018;39(2):79-132. PMID: 29518206. PMCID: PMC5888222. https://doi.org/10.1210/er.2017-00253.

16. WHO Consultation on Obesity. Obesity: Preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:i-xii,1-253. PMID: 11234459.

17. Misra A, Vikram NK. Insulin resistance syndrome (metabolic syndrome) and obesity in Asian Indians: Evidence and implications. Nutrition. 2004;20(5):482-91. PMID: 15105039. https://doi.org/10.1016/j.nut.2004.01.020.

18. Araneta MR, Barrett-Connor E. Ethnic differences in visceral adipose tissue and type 2 diabetes: Filipino, African-American, and white women. Obes Res. 2005;13(8):1458-65. PMID: 16129729. https://doi.org/10.1038/oby.2005.176.

19. Dwimartutie N, Setiati S, Oemardi M. The correlation between body fat distribution and insulin resistance in elderly. Acta Med Indones. 2010;42(2):66-73. PMID: 20513929.

20. Wulan SN, Westerterp KR, Plasqui G. Ethnic differences in body composition and the associated metabolic profile: A comparative study between Asians and Caucasians. Maturitas. 2010;65(4):315-8. PMID: 20799586. https://doi.org/10.1016/j.maturitas.2009.12.012.

21. Nair KS, Bigelow ML, Asmann YW, et al. Asians Indians have enhanced skeletal muscle mitochondrial capacity to produce ATP in association with severe insulin resistance. Diabetes. 2008;57(5):1166-71. PMID: 18282554. https://doi.org/10.23736/s0012-5972.07-1556.

22. Rush EC, Goedecke JH, Jennings C, et al. BMI, fat and muscle differences in urban women of five ethnicities from two countries. Int J Obes. 2007;31(8):1232-9. PMID: 17342075. https://doi.org/10.1038/sj.ijo.0803576.

23. Gurrici S, Hartiyanti Y, Hautvast JG, Deurenberg P. Differences in the relationship between body fat and body mass index between two different Indonesian ethnic groups: The effect of body build. Eur J Nutr. 2004;43(4):213-21. https://doi.org/10.1007/s00394-004-0427-8.

24. Forouhi NG, Jenkinson G, Thomas EL, et al. Relation of triglyceride stores in skeletal muscle cells to central obesity and insulin sensitivity in European and South Asian men. Diabetologia. 1999;42(8):932-5. PMID: 10491752. https://doi.org/10.1007/s001250050125.

25. Ginsberg HN, Zhang YL, Hernandez-Ono A. Regulation of plasma triglycerides in insulin resistance and diabetes. Arch Med Res. 2005;36(3):232-40. PMID: 15925013. https://doi.org/10.1016/j.arcmed.2005.01.005.