Original Article

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Association of Lipid Accumulation Product with Insulin Resistance in Type 2 Diabetes Mellitus: A Cross-sectional Study

Biochemistry Section

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ABSTRACT

Introduction: The increased incidence of diabetes and Cardiovascular Disease (CVD) is attributed to the rising obesity rates, which is one of the major factors contributing to Insulin Resistance (IR). Although there is a close relationship between obesity and IR, not all cases of obesity lead to cardiometabolic complications. Visceral fat is considered to be the primary cause of IR. Lipid Accumulation Product (LAP) is postulated as a new continuous biomarker of visceral adiposity.

Aim: To determine the association between LAP and IR in T2DM.

Materials and Methods: This institution-based cross-sectional study was conducted over a period of three months at the Department of Biochemistry, Rajarajeswari Medical College and Hospital in Bengaluru, Karnataka, India. A total of 60 Type 2 diabetic patients (including newly diagnosed and known cases) were recruited as cases, along with 30 healthy controls. Height, weight, and Waist Circumference (WC) were measured. Fasting blood samples were collected for laboratory biochemical estimation of glucose, Total Cholesterol (TC), Triglycerides (TG), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), and fasting insulin. Statistical analysis for continuous variables was performed using unpaired Student's t-test, and Analysis of Variance (ANOVA) test was used for group comparisons.

Results: Fasting serum insulin (p-value=0.007), Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (p-value=0.001), and LAP index (p-value <0.001) were significantly higher in the case group. LAP index was divided into quartiles, Insulin and HOMA-IR showed statistical significance across the quartiles (p-value=0.005). The lipid profile analysis across LAP quartiles revealed a progressive increase in TG levels (p<0.001) and a decrease in HDL levels from Q1 to Q4 quartiles.

Conclusion: The study concludes that increased LAP levels are associated with IR in T2DM. LAP can serve as a useful marker for cardiometabolic risk in early-stage T2DM, enabling better disease stratification for improved prognosis.

Keywords: Dyslipidaemia, Insulin, Obesity, Triglyceride, Waist circumference

INTRODUCTION

Obesity is well known for its significant impact on health, and the increasing prevalence of obesity over the decades has led to an increased incidence of T2DM, CVD, and dyslipidaemia [1]. IR manifests as decreased glucose utilisation and plays a crucial role in the development of CVD [2,3]. The prevalence of diabetes and prediabetes in India is estimated to be 101 million and 136 million, respectively, in 2021 [4], and it is projected to reach atleast 124 million diabetics by 2045 [5]. The epidemic of IR is even increasing among younger individuals with lower body weights. While the primary role of adipose tissue is to release fatty acids, it also plays a significant role in releasing several proinflammatory cytokines, leading to increased IR and subsequent endothelial dysfunction. This raises a concerns as Indians are at a high-risk of developing T2DM [6].

There has been an overall increase in the prevalence of adult-onset diabetes across all strata due to economic development and nutritional transition, leading to a rise in overweight and obesity [5]. While there is a close relationship between obesity and IR, not all obese patients develop cardiometabolic complications [1]. Therefore, the major concern in the Indian scenario is the presence of high visceral fat, which represents underlying metabolic obesity. Visceral adipose tissue releases substances such as angiotensinogen, angiotensin-converting enzyme, proinflammatory cytokines, and cathepsins, which activate the renin-angiotensin system. This process underlies endothelial dysfunction and is considered a predominant cause of IR and CVD [2]. Studies comparing Indians with other populations have shown that Indians have lower beta cell reserves and poorer beta cell adaptation in T2DM [7-9].

Visceral obesity, measured as Waist Circumference (WC), has a stronger correlation with IR than the conventional Body Mass Index (BMI), as it does not indicate the ideal body fat index [2,10]. WC serves as a simple marker for visceral obesity in metabolic syndrome, but it does not reflect excess body fat in circulation [10]. Furthermore, it cannot completely differentiate between visceral adiposity and subcutaneous abdominal adiposity. Elevated TG levels have been considered a marker of visceral adiposity [11] and a vascular risk factor, as it is associated with the risk of CVD regardless of low LDL levels. Lowering TG levels, along with LDL, has shown more benefits than reducing LDL alone [12].

The LAP index is postulated as a new continuous biomarker of visceral adiposity since it incorporates both major risk factors, such as TG and WC [12]. The LAP index provides a better assessment of lipotoxicity compared to other conventional parameters, such as WC alone, as it overcomes the limitations of using WC as a sole marker [12]. Thus, LAP has been suggested to have a stronger correlation with visceral adipose tissue and serves as an independent risk indicator for IR, diabetes, and CVD [13,14]. IR is evaluated using the HOMA-IR method, which is a reliable surrogate measure for insulin sensitivity based on fasting insulin and glucose parameters. A value of ≥2.5 is considered indicative of IR [15].

There is a scarcity of LAP research conducted on the Indian population. Therefore, the present study was undertaken to estimate the LAP index in the Indian scenario and analyse its relationship with IR in patients with T2DM.

MATERIALS AND METHODS

This cross-sectional study was conducted over a three-month period from July 2015 to September 2015 at Department of Biochemistry, Rajarajeswari Medical College and Hospital, Bengaluru, Karnataka, India. Institutional Ethical Committee clearance (RRMCH-IEC/06/2015)

was obtained for the study. Samples were collected from patients attending the Outpatient Department (OPD) in the Department of Medicine using convenient sampling.

Inclusion criteria: The study included patients aged 35-60 years. A total of 60 Type 2 diabetes patients, including newly diagnosed and known cases, were included as cases. Thirty healthy individuals who visited for general health check-ups were selected as controls.

Exclusion criteria: Patients with thyroid disorders, renal disease, known CVD, those on hypolipidaemic drugs, and pregnant individuals were excluded from the study.

Written informed consent was obtained from the study participants, and a detailed history and clinical examination were conducted. Anthropometric measurements, such as height and weight for calculating BMI, were recorded. WC was measured in the horizontal plane at the level of the umbilicus during minimal respiration.

Sample collection: Fasting blood samples were collected using proper aseptic precautions from the antecubital vein. A fluoride tube was used for glucose estimation, and a clot activator tube was used for lipid profile and insulin. Samples were kept at room temperature for 30 minutes to allow clotting, followed by centrifugation at 2000 rpm for 10 minutes to obtain sera/plasma. The samples were stored at -20°C until a convenient batch was available for analysis. All samples were analysed using a fully automated analyser (Erba EM360). Glucose estimation was performed using the glucose oxidase and peroxidase method [16]. Total Cholesterol (TC) was estimated using the cholesterol esterase and peroxidase method (CHOD-POD) based on the modifications by Allain CC et al., and Roeschlau P et al., [17,18]. TG levels were estimated using the TG-GPO Trinder method [19], while HDL was estimated using the Trinder reaction [20]. LDL analysis was based on a modified Polyvinyl Sulfonic Acid (PVS) method and quantified using the Trinder reaction according to the kit insert instructions. Serum insulin was analysed using the Maglumi 800 Chemiluminescence (CLIA) method as mentioned in the kit insert instructions. IR was calculated using the HOMA-IR formula: HOMA-IR=(fasting insulin×fasting glucose)/405 [21]. The LAP (LAP) was calculated as follows: for men, {WC (cm)-65}×{TG concentration (mmol/L)}, and for women, {WC (cm)-58}×{TG concentration (mmol/L)} [22].

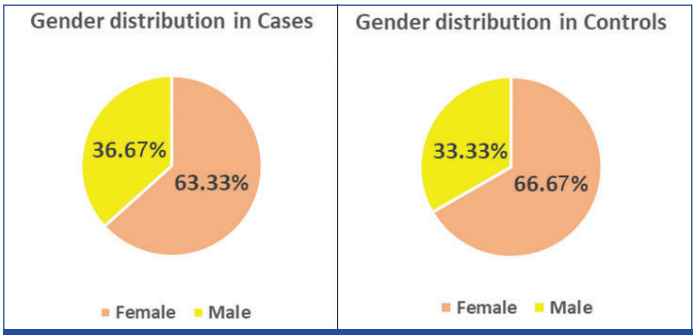
STATISTICAL ANALYSIS

The data was analysed using descriptive statistical analysis, and the results were expressed as mean±SD. Categorical variables such as gender, HOMA-IR, WC, and BMI were presented as percentages. For continuous variables, statistical analysis was performed using unpaired Student's t-test with a 95% confidence interval. The cases were divided into quartiles based on the median LAP index [19]. Analysis of Variance (ANOVA) was used to test the significance between LAP quartiles and variables such as insulin, Fasting Blood Glucose (FBG), HOMA-IR, and lipid profile in the cases. A p-value <0.05 was considered statistically significant.

RESULTS

Gender distribution is shown in [Table/Fig-1]. The proportion of women was over 60% in both groups, but the gender distribution was matched (p-value=0.06).

The mean age for cases was 53±9.3 years, and for controls, it was 50±6.7 years, with no statistically significant difference. There was also no statistical significance observed in the anthropometric variables such as BMI (p-value=0.16) and WC (p-value=0.19) between the groups. However, FBG levels were significantly higher in cases (153±62.4 mg/dL) compared to controls (86.9±9.5 mg/dL) (p-value <0.001). Cases also had significantly higher fasting insulin levels (p-value=0.007), HOMA-IR (7.12±7.73) (p-value=0.001), and LAP index (p-value <0.001) compared to controls. TC, TG, and LDL were higher in cases, but only TG showed statistical significance, with levels of 196.53±111.5 mg/dL in cases and 149.73±59.71 mg/dL in controls (p-value=0.01) [Table/Fig-2].



[Table/Fig-1]: Gender distribution between controls and cases.

Parameters	Cases (n=60)	Controls (n=30)	95% CI	p-value
Age (years)	53±9.3	50±6.7		0.06
BMI (kg/m^2)	28.1±3.7	27.2±4.5	27.2-29	0.16
WC (cm)	93±8.6	91±10.5	90.7-95	0.19
FBG (mg/dL)	153±62.4	86.9±9.5	137-168.7	<0.001*
Insulin (mU/L)	17.8±14.5	10.32±4.52	14.1-21.5	0.007*
HOMA-IR	7.12±7.73	2.24±1	5.2-9	0.001*
LAP	72.8±44.5	49.9±21.8	61.5-84	<0.001*
Total cholesterol (mg/dL)	183.20±40.54	182.77±44.90	172.9-193.4	0.48
Triglyceride (TG) (mg/dL)	196.53±111.55	149.73±59.71	168.2-224.7	0.01*
HDL (mg/dL)	40.36±9.89	42.06±9.55	37.7-42.8	0.22
LDL (mg/dL)	121.20±33.70	124.80±31.26	112.6-129.7	0.31

[Table/Fig-2]: Demographic, anthropometric and biochemical variables expressed as Mean±SD.
*p-value <0.05 considered statistically significant. HDL: High density lipoprotein; LDL: Low density lipoprotein; BMI: Body mass index; WC: Waist circumference; FBG: Fasting blood glucose; HOMA-IR: Homeostatic model assessment of insulin resistance; LAP: Lipid accumulation product

A total of 81.34% of cases had HOMA-IR ≥2.5, compared to only 23.31% of controls. BMI ≥25 [23] was found in 79.68% of cases and 63.27% of controls. HOMA-IR ≥2.5 was considered in this study due to the high proportion of females in both study groups [Table/Fig-3].

	Cut-off level	Cases (n=60)	Controls (n=30)
HOMA-IR	<2.5	11 (18.33%)	23 (76.59%)
	≥2.5	49 (81.34%)	7 (23.31%)
WC (cm)	≥85 (female)	50 (83%)	23 (76.59%)
	≥90 (male)		
	<85 (female)	10 (16.6%)	7 (23.31%)
	<90 (male)		
BMI (kg/m^2)	≥25	48 (79.68%)	19 (63.27%)
	<25	12 (19.92%)	11 (36.63%)

[Table/Fig-3]: Percentage of HOMA IR cut-off [15] and percentage of anthropometric measurement-Waist Circumference (WC) cut-off [23] and Body Mass Index (BMI) [23] distribution between controls and cases.

The LAP index was categorised into quartiles in cases based on the median value [22]: Q1 <41.64 (n=16), Q2 41.64-60.55 (n=14), Q3 60.56-104.44 (n=14), and Q4 >104.44 (n=16) as shown in [Table/Fig-4]. HOMA-IR and insulin levels showed a statistically significant increase from Q1 to Q4 (p-value=0.005) [Table/Fig-4].

Lipid profile variables were analysed across the LAP quartiles in cases, as shown in [Table/Fig-5]. TG levels progressively increased across the LAP quartiles (p-value=0.001). Although TC and LDL did not show statistical significance, their values increased across the quartiles.

Variables	LAP Index				p-value
	Q1 n=16 (<41.64)	Q2 n=14 (<41.64-60.55)	Q3 n=14 (60.56-104.44)	Q4 n=16 (>104.44)	
HOMA-IR	3.5±2	5.9±5.9	6.2±3.8	12.7±12	0.005*
Insulin (mU/L)	10.5±4	15.6±11.9	16.8±8.1	28.3±22	0.005*
FBG (mg/dL)	132.8±67	145.3±58	146±45.5	187.8±68.2	0.08

[Table/Fig-4]: Variables across LAP quartiles in cases; Results expressed as Mean±SD.
*p-value <0.05 considered statistically significant. FBG: Fasting blood glucose

Variables	LAP Index				p-value
	Q1 (<41.64)	Q2 (41.64-60.55)	Q3 (60.56-104.44)	Q4 (>104.44)	
TG (mmol/L)	1.2±0.2	1.6±0.3	2.2±0.5	3.7±1.4	0.001*
TC (mg/dL)	174.5±42.5	177.6±35	188.2±36.4	192.3±48.2	0.5
HDL (mg/dL)	42.2±9.8	41.8±9.3	40.6±11.9	36.8±8.2	0.4
LDL (mg/dL)	118.2±38.6	120.5±34.3	127.2±32.4	128.7±31.6	0.8

[Table/Fig-5]: Lipid profile variables across LAP quartiles; Results expressed as Mean±SD.
*p-value <0.05 considered statistically significant

DISCUSSION

In the present study, it was found that the LAP index was increased in type 2 diabetic cases compared to healthy controls. There was a significant increase in HOMA-IR with increasing quartiles of the LAP index in cases, indicating a predictive relationship between IR and LAP. These findings were consistent with a study by Mirmiran P et al., who concluded that increased central lipid accumulation was associated with higher IR, oxidative stress, and systemic inflammation in diabetic patients [22]. Although the present study excluded cases with CVD, Ioachimescu et al., reported that LAP was a predictor of mortality in non diabetic individuals with CVD [1].

The study by Wakabayashi I and Daimon T also demonstrated strong associations between LAP and hyperglycaemia and diabetes [12]. Based on these findings, the present study aimed to analyse the role of the LAP index in relation to IR in diabetic patients and found that LAP was significantly higher in diabetics. Insulin has specific actions in adipose tissue, including increasing glucose uptake, TG synthesis, and suppressing TG hydrolysis, thereby reducing the release of Free Fatty Acids (FFAs) into the bloodstream [24]. However, when there is excess accumulation of lipids in non adipose tissues, it can lead to lipotoxicity. This can be physiologically dangerous as it is associated with high levels of FFAs derived from adipocytes, which promotes TG accumulation [25,26]. Excess FFAs can dysregulate cell signaling, cellular function, and sometimes lead to apoptosis.

In a study conducted by Kahn HS in US adults, it was shown that an elevated BMI value is less specific because it can represent increased lean tissue or protective subcutaneous fat, as opposed to an increased LAP [27]. The study concluded that LAP, is a continuous and reproducible marker that is better than BMI for identifying cardiovascular risk. In a cross-sectional study by Xia C et al., it was demonstrated that LAP had a greater impact on IR compared to BMI and WC [28]. This was in line with the present study, where WC and BMI did not show statistical significance (p-value=0.16 and p-value=0.19, respectively) between the groups. BMI, a popular marker of body fat, only modestly predicts medical risk. It is well-established that high relative weight associated with adipose tissue is not always detrimental, as the specific region of adipose tissue plays a beneficial role in storing and buffering circulating lipid fuels [27].

Contrary to the present study, Nusrianto R et al., concluded that a high LAP index was not a predictor of the development of T2DM, and even when an association between high LAP and T2DM was found, it was only observed in women [29]. Xiang S et al., demonstrated that LAP could be used to predict the risk of metabolic syndrome. In accordance with this study, it was found that HDL levels, which are part of metabolic syndrome, decreased across LAP quartiles; however, this difference was statistically insignificant (p-value=0.4) [30]. Hypertriglyceridaemia is commonly associated with low HDL-C levels, which is also a notable feature of the lipid abnormalities observed in diabetes [31].

LAP is a safe and cost-effective tool that includes WC for assessing intra-abdominal lipid deposition and fasting TG that release FFA into circulation. One possible explanation for this is that LAP, which comprises two components, exhibits stronger physiological correlations with lipid and lipoprotein metabolism, as well as the particle size of lipoproteins [22]. IR typically precedes the development of diabetes by an average of 10 to 15 years [32], and this provides a potential mechanism for the association between LAP and T2DM [11]. In IR, there is a decreased sensitivity to insulin in target tissues such as the liver, adipose tissue, and skeletal muscle [26]. This leads to a myriad of consequences as each tissue has different insulin sensitivity, and disruption of these molecular pathways results in a wide range of manifestations [33,34].

In the present study, lipid parameters did not show statistical significance between cases and controls, except for TG. This can be explained by the conversion of larger LDL particles to smaller dense particles (sdLDL). This phenomenon of qualitative change cannot be ruled out, as it makes the particles more susceptible to oxidative damage [27]. Yang SH et al., and Yu J et al., found a longitudinal association between the LAP index and the incidence of T2DM in non obese adults [23,35]. The studies concluded that the LAP index can be a useful additional indicator for identifying new-onset T2DM in non obese adults.

This highlights the need for a more comprehensive indicator to predict and manage risk factors for T2DM in seemingly healthy individuals and emphasises the importance of preventive measures in the early stages of dyslipidaemia. Therefore, early identification and stratification of prediabetes, diabetes, or the risk of CVD can be achieved using a comprehensive and practical tool like the LAP index. LAP can be considered a useful practical tool in day-to-day practice to enhance the risk stratification for unfavourable outcomes related to obesity.

Limitation(s)

The relatively small sample size and the lesser number of control subjects compared to the cases could compromise the statistical power. A larger prospective study could strengthen the role of LAP in assessing cardiovascular risk in diabetics and prediabetes. Additionally, a glucose tolerance test could have helped in prediabetes risk stratification.

CONCLUSION(S)

LAP shows a strong association with glucose haemostatic parameters and lipid levels in individuals with T2DM. This simple clinical tool can be more relevant in a primary care setting to identify patients who require further biochemical evaluation.

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