Lipid accumulation product (LAP) as a potential index to predict risk of insulin resistance in young, non-obese Asian Indian males from Southern India: observations from hyperinsulinemic-euglycemic clamp studies

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ABSTRACT

Introduction We aimed to compare the predictive accuracy of surrogate indices namely the lipid accumulation product (LAP) index, homeostatic model of assessment of insulin resistance (HOMA-IR), fasting glucose-insulin ratio (FG-IR) and the quantitative-insulin sensitivity check index (QUICKI), against the *M* value of hyperinsulinemic-euglycemic clamp (HEC), and to determine a cut-off value for the LAP index to predict risk of insulin resistance in non-obese (body mass index <21 kg/m^2), normoglycemic, Asian Indian males from Southern India.

Research design and methods Data of HEC studies performed in 108 non-obese, normoglycemic, Asian Indian males was obtained retrospectively and the *M* value (a measure of whole-body insulin sensitivity) was calculated. The *M* value is the rate of whole-body glucose metabolism at the hyperinsulinemic plateau (a measure of insulin sensitivity) and is calculated between 60 and 120 min after the start of the insulin infusion in the HEC procedure. The LAP index, the HOMA-IR, FG-IR and QUICKI were calculated. Spearman's correlation and logistic regression analysis were performed. Cut-off value for the LAP index was obtained using receiver operating characteristics with area under curve (AUC) analysis at 95% CI. P value <0.05 was considered to be statistically significant.

Results Significant negative correlation was observed for the *M* value with LAP index (r=−0.39, p<0.001) while significant positive correlation was noted with FG-IR (r=0.25; p<0.01) and QUICKI (r=0.22; p<0.01). The LAP index cut-off value ≥33.4 showed 75% sensitivity and 75% specificity with AUC (0.72) to predict risk of insulin resistance in this cohort.

Conclusion The LAP index showed higher predictive accuracy for the risk of insulin resistance as compared with HOMA-IR, QUICKI and FG-IR in non-obese, normoglycemic Asian Indian males from Southern India.

INTRODUCTION

The global burden of non-communicable diseases is driven majorly by type 2 diabetes

Significance of this study

What is already known about this subject?

► Surrogate indices of fasting insulin resistance such as homeostatic model of assessment of insulin resistance (HOMA-IR), fasting glucose-insulin ratio (FG-IR) and the quantitative-insulin sensitivity check index (QUICKI) have been validated against the *M* value of hyperinsulinemic-euglycemic clamp (HEC) studies in various ethnic groups; however, triglyceride-based surrogate indices have been scarely validated against the HEC studies, especially in Asian Indians.

What are the new findings?

► In this study, we have demonstrated the lipid accumulation product (LAP) index to have superior value to predict the future risk of insulin resistance in non-obese, normoglycemic (BMI <21 kg/m^2) Asian Indian men.

► The cost of screening the LAP index is less when compared with HOMA-IR, QUICKI and FG-IR, as the LAP index relies on waist circumference and serum triglyceride values.

How might these results change the focus of research or clinical practice?

► The LAP index can be used as a cost-effective surrogate index to screen for insulin resistance in clinical settings and epidemiological settings.

mellitus (T2DM), cardiovascular diseases, cancers, stroke, chronic respiratory diseases.[1] South Asians, especially Asian Indians feature a unique phenotype characterized by increased body fat, less muscle mass and increased abdominal fat,[2] even at low body mass index (BMI).[3] This phenotype predisposes to insulin resistance, T2DM and cardiovascular diseases.

The hyperinsulinemic-euglycemic glucose clamp (HEC) procedure is universally accepted as the 'gold standard' reference method to measure insulin sensitivity as it measures whole body glucose disposal at a given level of insulinemia under steady-state conditions.[4] However, the HEC procedure is expensive, requires trained scientific manpower and vigilant medical supervision, thus making it impractical for use in large epidemiological and clinical studies. Surrogate indices of fasting insulin resistance such as the quantitative-insulin sensitivity check index (QUICKI), homeostasis model assessment of insulin resistance (HOMA-IR), fasting glucose-insulin ratio (FG-IR) have been applied in population-based studies across different ethnic groups.[5] We have previously shown HOMA-IR is less reliable when validated against M value of HEC procedure in non-obese (BMI <23 kg/m^2) Asian Indian males, thereby emphasizing the need for a better surrogate index of insulin resistance in non-obese Asian Indians.[6] Surrogate indices such as HOMA-IR, QUICKI and FG-IR are based on fasting insulin levels. The cost for an insulin assay is expensive, thereby making insulin-based surrogate indices less feasible in resource-limited clinical settings and epidemiological studies with large sample sizes. Alternatively, lipid-based surrogate indices of fasting insulin resistance have garnered much interest. One such index is the lipid accumulation product (LAP), which is an ordinal index of insulin resistance derived from one anthropometric variable, that is, waist circumference and one biochemical variable namely serum triglycerides. It was first applied in the National Health and Nutrition Examination Survey sample database as a superior measure of cardiovascular risk in comparison to BMI, in a cohort of non-Hispanic blacks and Mexican Americans.[7]

A recent HEC-based study on Italian subjects with varying degrees of insulin resistance had demonstrated that the LAP index had higher predictive accuracy for individuals with increased vascular stiffness, when compared with triglyceride (TG)/high-density lipoprotein ratio, TG-glucose index and visceral adiposity index (VAI).[8] Another HEC-based study in Chinese women compared the LAP index, VAI, waist circumference, BMI, HOMA-IR and the Chinese VAI. The study reported that in Chinese women, the Chinese VAI was strongly associated with the M value of HEC procedure and also outperformed the VAI, HOMA-IR, waist circumference and BMI.[9]

A few studies on the LAP index in Asian Indians have shown higher predictive accuracy of the LAP index for insulin resistance.[10–12] However, such observations have not been correlated with the HEC procedure, which is the gold standard method to determine hepatic and peripheral insulin resistance in Asian Indians. While glucose-based and insulin-based surrogate indices have been validated against the HEC procedure, such an attempt has not been made for the LAP index in any study from India. We hypothesized that the LAP index may be useful to predict future risk of insulin resistance in normoglycemic Asian Indians. Therefore, the primary objective of this study was to correlate the LAP index and other surrogate indices namely HOMA-IR, QUICKI and FG-IR with the M value derived from HEC clamp studies. The secondary objective was to derive significant determinants of the LAP index and to determine a cut-off value for the LAP index to predict insulin resistance in a cohort of non-obese, normoglycemic Asian Indian males from Southern India.

METHODOLOGY

The study was approved after review by the institutional research Board and human ethics committee of Christian Medical College, Vellore, India (Research Committee Minute Number: 13348/RETRO/28/08/2020 of Christian Medical College, Vellore, India). Data for this study were obtained retrospectively from the primary study based on HEC procedures in normoglycemic, Asian Indian males from Southern India.[13] The sample size was calculated using the formula:

$$n = \frac{Z^2_{1-\alpha/2}\,p\,(1-p)}{d^2}$$

Wherein n denotes number of participants, p denotes expected proportion, d denotes absolute precision and $1-\alpha/2$ denotes desired level of CI. The sample size for the study objective was calculated as 113 subjects with absolute precision of 90% with an expected proportion of 0.75% at 95% CI. This study is exclusively based on male subjects who were recruited from the birth registry at the Community Health and Development (CHAD) program, Christian Medical College (CMC), Vellore, India. The participants were identified from 23 randomly selected villages from Vellore district, Tamil Nadu, South India. The contact details of the subjects born in this area were obtained from the birth registry of the CHAD program at CMC, Vellore, which has a prospective surveillance system of population-based data. Male individuals aged between 18 and 22 years were shortlisted from the database and invited for participation. The objectives of the study were explained to the participants and a cohort of 108 men without obesity were recruited with informed written consent. Individuals unwilling to participate in the study (n=5; 4.27%) were excluded. As the primary study was exclusively on male subjects, female subjects were not recruited as per the study design. Furthermore, individuals with prediabetes, impaired fasting glucose and dyslipidemia were excluded from participation.

All eligible participants underwent baseline medical assessment and anthropometry namely BMI and waist circumference. BMI was calculated using the formula weight (kg) divided by height (m^2). Waist circumference was measured using a non-elastic measuring tape with the participant in standing position and in relaxed breathing state. The maximum circumference of the waist measured midway between iliac crest and lower most margin of the ribs was noted, and the hip circumference was measured at the maximum circumference of

gluteus maximus muscle. Waist circumference ≥90 cm in males as per the Asian Indian cut-off values.[14]

Eligible participants were instructed to report to the study centre at 07:00 hours after an overnight fasting lasting 8 hours after supper and to avoid consuming any form of beverages in the morning. A physician examined the vital physiological parameters, prior to the start of the procedure. The participants underwent a non-tracer-based 120 min HEC procedure for assessment of whole-body insulin sensitivity. In the HEC procedure, two indwelling intravenous catheters were inserted contralaterally in the veins of the antecubital fossa. In one catheter, a continuous insulin infusion was initiated and the flow rate was maintained at 40 mU/kg/min using an automated infusion pump during the entire duration of the 2 hours clamp. To maintain euglycemia, 25% dextrose solution was infused and plasma glucose levels were measured by drawing blood samples from another antecubital vein, every 5 min using a bedside glucose analyzer (Analox GM-9D). The dextrose infusion rate was adjusted to maintain a stable plasma glucose concentration of 90 mg/dL (5 mmol/L) throughout the clamp procedure. Blood samples for biochemical estimation of insulin, C-peptide and plasma glucose were drawn at baseline and at the end of the steady state phase (ie, last 30 min of the basal phase and the last 30 min of the clamp period).[15] Plasma glucose levels were measured by glucose-oxidase method. Serum insulin and C-peptide levels were measured by the chemiluminescence method using diagnostic kits supplied by Siemens, on the Immulite 2000 system (Siemens Healthcare Diagnostic Products, Llanberis, Gwynedd, UK). Chemistry and Immunoassay controls supplied by Bio-Rad were used as internal precision controls (coefficient of variation (CV) 10.2% for insulin and 3.7% for C-peptide).[13] Serum lipid profile including TGs was measured using an enzyme-based colorimetric method in an automated analyzer (COBAS-B, 101 system, Roche Diagnostics).

The *M* value is a measure of whole-body insulin sensitivity derived during a steady state wherein euglycemia (90 mg/dL of plasma glucose) is achieved by infusing high levels of insulin in a HEC procedure. It is calculated between 60 and 120 min after the start of the insulin infusion, based on the formula of DeFronzo *et al.*[4] In this study, we applied the *M* value cut-off value ≤4.7 mg/kg/min to define insulin resistance using HEC procedures. This value has been validated earlier using the results of 18 independent HEC procedures at a constant insulin infusion rate of 40 mU/m² in different ethnic groups.[16] Therefore, the *M* value cut-off ≤4.7 mg/kg/min is applicable for the current study. The following surrogate indices of insulin resistance were calculated by using specific formulae viz, LAP index: waist circumference (cm)−65 (in male subjects)×TGs (mmol/L),[17] QUICKI: 1/[log fasting insulin (mU/L)+log fasting glucose (mg/dL)],[18] HOMA-IR: fasting glucose (mmol/L)×fasting insulin (mU/L)/22.5,[19] FG-IR: fasting glucose (mg/dL)/fasting insulin (mU/L).[20]

Table 1 Baseline characteristics of the study cohort	
Variables (n=108)	**Mean±SD/Median**
Age (years)	19.7±1
Body masss index (kg/m²)	19.1±2.5
Waist circumference (cm)	70.6±5.7
Waist-to-hip ratio	0.82±0.04
Waist-to-height ratio	0.40±0.03
Systolic blood pressure (mm Hg)	118±8.5
Diastolic blood pressure (mm Hg)	76.8±6
Fasting glucose (mg/dL)	87.6±6.5
Postprandial blood glucose (mg/dL)	100.5±21.2
Fasting insulin (pmol/L)	5.2±3.6*
Postprandial insulin (pmol/L)	37±29*
Fasting C-peptide (ng/mL)	1.8±1.2*
Postprandial C-peptide (ng/mL)	5.5±3
Total cholesterol (mg/dL)	130.7±27.6
Low-density lipoprotein cholesterol (mg/dL)	80±22.6
High-density lipoprotein cholesterol (mg/dL)	31.4±7.0
Serum triglycerides (mg/dL)	78.5±31.1

Values are presented as mean±SD or median (median shown with asterisk (*)).

Statistical analysis

Continuous variables were summarised as mean±SD/median (minimum and maximum) values as appropriate. Spearman's correlation analysis was applied to test for significance in correlation between variables. Multivariate logistic regression analysis was applied to derive significant determinants of the LAP index. Receiver operating characteristics (ROC) analysis with area under the curve (AUC) was applied to determine the sensitivity and specificity of the cut-off value determined for LAP index. The value with optimal sensitivity and specificity was determined as cut-off value for each index. The p value <0.05 was considered to be statistically significant. STATA software (V.14.2) was used for statistical analysis.

RESULTS

The baseline characteristics of the study cohort is presented in table 1 and the *M* value and surrogate indices of insulin sensitivity/resistance are presented in table 2.

Considering the *M* value of the HEC procedure as the gold standard measure of insulin sensitivity, significant negative correlation was observed with the LAP index while significant positive correlation was observed with FG-IR and QUICKI (table 3).

We performed logistic regression analysis and derived BMI, low-density lipoprotein-cholesterol (LDL-C) and

Indices of insulin sensitivity/resistance in the study cohort (n=108)

Indices of insulin sensitivity/resistance	Mean±SD/ Median
M value (on HEC procedure)	10.3±3.8
Lipid accumulation product index	25.4±13.8*
HOMA-IR	0.9±0.8*
QUICKI (measure of insulin sensitivity)	0.4±0.06
Fasting glucose-insulin ratio	34.6±23.4*

Values are presented as mean±SD/median (median shown with asterisk (*)).
HEC, hyperinsulinemic-euglycemic glucose clamp; HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative-insulin sensitivity check index.

serum TGs as significant determinants of the LAP index in this cohort. Accordingly, a decrease of 0.80 units of BMI (in kg/m^2), 0.40 units of TGs (in mmol/L), 0.30 (mg/dL) of LDL-C can lead to one unit decrease in the LAP index for non-obese, normoglycemic males from Southern India as shown in table 4.

ROC analysis for the LAP index derived a cut-off value ≥33.4 with 75% sensitivity and 75% specificity with 10.3% and 98.7% as positive predictive value and negative predictive values, respectively for the Younden's index of 0.51. Using the LAP index cut-off value ≥33.4, we classified subjects as at risk of insulin resistance and insulin sensitive. Accordingly, the mean value of LAP index in insulin-sensitive individuals (LAP index value: 10.5, n=79) was significantly higher (p<0.001) than the mean LAP index value (LAP index value: 67.1, n=29), in individuals classified to be at risk of developing insulin resistance in future. To compare the sensitivity and specificity of all surrogate indices, we applied a pooled ROC analysis with LAP index, FG-IR, HOMA-IR and QUICKI and plotted the AUC at 95% CI (figure 1). The AUC was significantly higher for the LAP index when compared with HOMA-IR, QUICKI and FG-IR at 95% CI (table 5).

DISCUSSION

This is the largest Indian study of HEC procedures done in non-obese, normoglycemic males from Southern

Spearman's correlation of *M* value with surrogate indices of insulin resistance/sensitivity

Measures of insulin sensitivity/ resistance	*rho*	*P* value
Lipid accumulation product index	−0.39	<0.001
Fasting glucose-insulin ratio	0.25	<0.01
QUICKI	0.22	<0.01
HOMA-IR	0.06	0.52

P<0.05: statistically significant.
HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative-insulin sensitivity check index.

India. HEC procedures are considered the gold standard procedure to measure peripheral and hepatic insulin sensitivity. Mostly, HEC procedure-based studies done so far are on small sample sizes as it is labour intensive, technically demanding and highly expensive.[21] In this study, we have shown significant correlation of the *M* value of HEC procedure with LAP index and shown that the diagnostic accuracy of the LAP index was higher than HOMA-IR, FG-IR and QUICKI as shown by ROC AUC. This proves that the LAP index is a better predictor for risk of insulin resistance in this cohort of non-obese, normoglycemic males from Southern India. Recently, a case-control study in middle-aged, overweight Asian Indians from India by Ray *et al* has shown that LAP index is a better predictor of metabolic syndrome when compared with BMI and waist circumference.[11] We compared the observations of Ray *et al*[11] and the current study. The former study derived a LAP index cut-off value of ≥38.05 with 76.4% and 91.1% specificity in a cohort of subjects with obesity[11] whereas in the current study, we derived a lower cut-off value ≥33.4 with 75% sensitivity and 75% specificity. It may be noted that the case control study by Ray *et al* included subjects with obesity with metabolic syndrome,[11] in contrast to our study exclusively on non-obese, normoglycemic males. Specifically, the mean waist circumference and serum TG levels in the current study were significantly lower than that of Ray *et al*,[11] thus leading to difference in cut-off values of the LAP index between two studies. In the current study, BMI, LDL and TGs were derived as significant determinants of the LAP index. However, the study by Ray *et al* in Indians did not include biochemical variables and therefore derived BMI and waist circumference as independent determinants of LAP index. Furthermore, it did not correlate the LAP index with other surrogate indices of fasting insulin resistance or the *M* value of HEC procedure, whereas the current study has accomplished this lacuna.

Another Indian study has shown significantly higher value (p<0.001) of the LAP index in patients with psoriasis when compared with normal subjects. The LAP index was significantly higher (p<0.05) in the moderate-to-severe psoriasis group as compared with the mild psoriasis group.[22] In a population-based study from Gujarat, it has been shown that the LAP index showed superior diagnostic accuracy for metabolic syndrome in asymptomatic subjects with normoglycemia aged between 18 and 79 years. The ROC AUC for the LAP index was 0.82 for a cut-off value 34.7.[10] In comparison to the same, the LAP index cut-off value derived in our study (≥33.4) is nearly similar with an ROC AUC of 0.71. However, the study by Joshi *et al*[10] was not based on HEC procedures unlike the current study.

Internationally, the LAP index has been studied in other ethnic groups. An earlier study in 768 elderly Caucasians with normoglycemia had shown the LAP index as a superior predictor of metabolic syndrome. Specifically, the cut-off value (≥51.82) for LAP index showed higher sensitivity (0.85) and specificity (0.85).[23]

Table 4 Logistic regression analysis for significant determinants of the lipid accumulation product index

Predictors	Beta-coefficient	OR	SE	95% CI	*P* value
Body mass index (kg/m^2)	−0.80	0.45	0.17	0.32 to 0.63	<0.001
Serum triglycerides (mg/dL)	−0.40	1.0	0.01	0.93 to 0.98	<0.001
Low-density lipoprotein-cholesterol (mg/dL)	−0.30	1.0	0.01	0.95 to 0.99	<0.01

P<0.05: statistically significant.
CI, confidence Interval; OR, odds ratio; SE, standard error.

The LAP index has also been applied as a surrogate measure of metabolic syndrome in a Chinese cohort by Li *et al*. On comparing the LAP index cut-off values of Li *et al*[17] and Teverna *et al*,[23] we report a significantly lower cut-off value ≥33.4 with 75% sensitivity and 75% specificity for the Indian population. The differences can be evidently attributed to ethnic variations and differences in age groups between the studies.

The LAP index has been validated recently in a larger cohort of Chinese subjects (n=711) with type 2 diabetes mellitus in comparison to VAI and waist circumference-TG index. Among these indices, the highest AUC was observed for the LAP index cut-off value ≥44.0 in both male and female subjects. Furthermore, LAP index was found to be a simple and superior indicator of metabolic syndrome in the study cohort.[24] In comparison to the study by Ma *et al*[24] the LAP index cut-off value to detect risk of insulin resistance in the current study is significantly lower, which could be attributed to the differences in ethnicity, age, gender and physiological status of the cohorts between the two studies. Wiltgen *et al*, derived a LAP index cut-off value of ≥34.5 (sensitivity 84%; specificity 79%) in a cohort of Brazilian women (n=95) with metabolic syndrome and observed significant

Figure 1 Receiver operating characteristic area under curve with sensitivity, in % (on Y-axis) and 1–specificity in % (on X-axis) at 95% CI for the LAP index, FG-IR, QUICKI and HOMA-IR. FG-IR, fasting glucose-insulin ratio; HOMA-IR, homeostatic model of assessment of insulin resistance; LAP index, lipid accumulation product index; QUICKI, quantitative-insulin sensitivity check index.

positive correlation of the LAP index with HOMA-IR and waist circumference.[25] However, the authors suggested that the LAP index should be validated against the glucose clamp procedure in Asian Indians. The current study has accomplished this milestone and has shown significant correlation of the LAP index with QUICKI in a cohort of non-obese, normoglycemic Asian Indian males.

South Asians feature higher prevalence of lipoprotein abnormalities and have a twofold to threefold higher risk of developing cardiovascular disease[26] and T2DM[27] as compared with white Caucasians.[28] It is important to note the presence of insulin resistance even in non-obese, normoglycemic Asian Indians,[29] due to atherogenic dyslipidemia, specifically chronic hypertriglyceridemia.[26] Hypertriglyceridemia results from increased fatty acid synthesis and decreased fatty acid oxidation, which in turn leads to increased hepatic secretion of very low-density lipoprotein cholesterol.[30] As an effect, there is an increased hepatic influx of non-esterified, free fatty acids (FFA), mediated by lipoprotein lipase enzyme,[31] resulting in the onset of peripheral and hepatic insulin resistance.[32] In the pancreas, the influx of FFAs leads to decreased beta cell function and insulin resistance, irrespective of body weight.[33] At the adipose tissue, the influx of FFAs and insulin resistance results in decreased glucose metabolism and impaired glycerol synthesis, irrespective of body weight and age.[34] In such a scenario, it is imperative to screen Asian Indians of representative sample sizes for metabolic syndrome, using novel surrogate indices based on TGs. The results of this HEC-based study evidenced superior performance of the LAP index which is cost-effective as compared with HOMA-IR and QUICKI which rely on plasma insulin levels thus proving its utility in low-cost clinical settings. The LAP index has high feasibility value, as it does not necessarily require an overnight fasting state making it an ideal index for use in epidemiological studies.
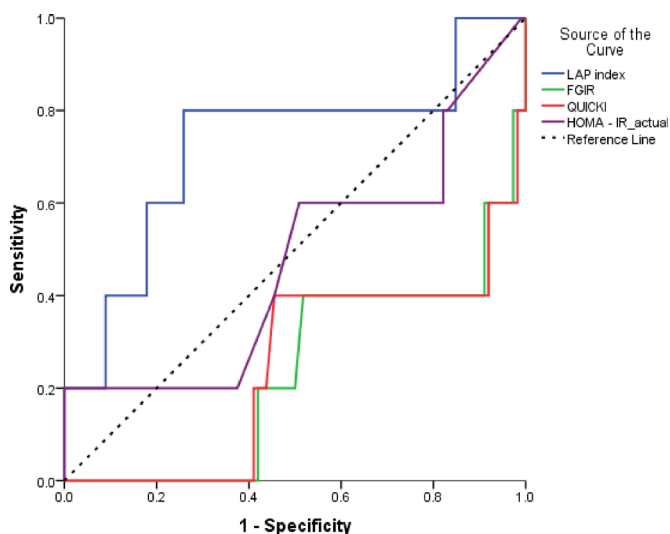
Limitations of the study

This study is cross-sectional in an exclusive cohort of non-obese, normoglycemic males from Southern India, which limits the applicability of the study observations to the cohort. Thus, the need to test this index in females becomes imperative. In addition, gender-specific studies on LAP index, across age and BMI groups need to be done. Furthermore, as this study is on normoglycemic subjects, specific cut-off values for LAP index in patients with T2DM are required. Nevertheless, the study observations

Table 5 Receiver operating characteristic area under curve (AUC) for surrogate indices

Indices of insulin sensitivity/resistance	AUC	Cut-off value	Sensitivity (%)	Specificity (%)	95% CI	SE
Lipid accumulation product index	0.72	≥33.4	75	75	0.50 to 0.94	0.14
HOMA-IR	0.55	≥0.75	75	46	0.26 to 0.85	0.15
QUICKI	0.31	≥0.40	50	50	0 .04 to 0.57	0.13
Fasting glucose-insulin ratio.	0.29	≥23.4	50	48	0.04 to 0.53	0.12

CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; QUICKI, quantitative-insulin sensitivity check index; SE, standard error.

based on HEC procedure in non-obese normoglycemic, Asian Indian males are important and can be validated in clinical settings and through population-based studies from different parts of India.

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