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LIPID ACCUMULATION PRODUCT INDEX PREDICTOR TOOL INSULINIC RESISTANCE UNDIAGNOSED IN ADOLESCENTS GIRLS

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ABSTRACT

Objective: To evaluate the predictive capacity of the lipid accumulation product in the detection of insulin resistance in female adolescents. **Methods:** A cross-sectional study was carried out with 113 adolescents from public schools, aged 10 to 19 years. The anthropometric, sociodemographic, hemodynamic and biochemical variables were evaluated. The waist height ratio, waist hip ratio and lipid accumulation product were determined through protocols described in the literature. The presence of insulin resistance was determined through HOMA-RI, using a cut-off point =3.16. Data analysis was performed using the statistical program SPSS version 25. **Results:** The means of variables, body mass index, waist circumference, waist height ratio, hip waist ratio, triglycerides, HDL-C, LAP, insulin, glycemia and HOMA-RI, in addition to the prevalence of overweight and central adiposity were higher in the group with insulin resistance. The LAP presented a higher correlation (r = 0.44) with the HOMA-RI and the larger area under the ROC curve (0.75) than the anthropometric indicators evaluated. **Conclusion:** Given its low cost, reproducibility, and greater discriminatory power against anthropometric indicators, LAP can be used as a screening tool for adolescents with insulin resistance.

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INTRODUCTION

Insulin Resistance (IR) can be defined as the diminution in the capacity of insulin to stimulate glucose utilization, generating as a compensatory mechanism an increase in production and secretion of insulin (hyperinsulinemia) by pancreatic β-cells, while glucose tolerance remains unchanged (Gobato *et al.*, 2014).It is also recognized as a risk factor for the development of several metabolic disorders such as hypertension, type 2 diabetes *Mellitus,* hepatic steatosis, and in women may be associated with Polycystic Ovary Syndrome (PCOS) (Thota *et al.*, 2017).

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The gold standard for the evaluation of IR is the hyperinsulinemic-euglycemic clamping. But, despite its precision, this method is of hard application in clinical practice due to its high cost and long time duration (Abruzzese *et al.*, 2017). An alternative, simple and stable method already very utilized and widespread in literature for the evaluation of IR is the homeostasis model assessment (HOMA-IR) (Xia *et al.*, 2012). Nevertheless, the insulin hormone dosage is required to perform its calculations which causes increase in its cost. Thus, new indices arise as tools of great interest for the identification of IR, given they possess high efficiency and low cost (Abruzzese *et al.*, 2017). Following this line, the Després[5] group proposed thelipid accumulation product index (LAP) that combines an anthropometric measure (waist circumference) and a biochemical one (triglycerides).

This index is a reliable IR marker in postmenopausal women, in women with polycystic ovary syndrome (PCOS) and in non-diabetic individuals (Abruzzese *et al*., 2017; Kahn, 2005; Shabestari *et al*., 2016; Xia *et al*., 2012). It is also strongly linked to a cardiometabolic risk profile (Després, 2017; Shabestari *et al*., 2016). It still is very low the amount of scientific research that explain about LAP applicability in the prediction of IR in female adolescents, mainly in Northeastern states. Therefore, knowing the importance of IR tracing in this age range and its relation to the development of PCOS and other metabolic disorders the present study intends to evaluate LAP's predictive power in face of the anthropometric indicators in IR identification in teenagers.

METHODOLOGY

Sample and study model: The employed model is a cross-sectional study performed with 113 female adolescents whose ages range from 10 to 19 years. The sample comes from the school population of five public system schools from São Luís/MA, Northeastern Region of Brazil. The size of the sample was calculated by estimation of proportion having as a base the prevalence of weight excess in female adolescents of 4,0% (Ministério da Saúde, 2010),suggested prevalence for an outcome of 10%, error tolerance of 5% (type I error) and test power of 80% (type II error), with a 10% addition for possible losses or refusals. The mensuration of all the variables was performed by trained researchers using standardized techniques and calibrated equipment. The measurements were done in duplicate and the average was considered in data analysis. In order to prevent intra and inter observer bias the mensuration was made by a single investigator. This study was approved by the Ethics Committee of Research with Human Beings according to legal opinion 2.638.202. The study follows the norms of the Helsinki Declaration. The written consent of the parents or legal responsible of all the adolescents were obtained and participation was voluntary.

Anthropometric Evaluation: Weight was measured using an electronic balance (Seca® 803, Hamburgo, Alemanha). Height was measured using a portable vertical stadiometer (Seca® 213, Hamburgo, Alemanha). Waist circumference (WC) and hip circumference (HC) were measured with an inextensible anthropometric measuring tape (Seca® 201, Hamburgo, Alemanha), according to the procedure described in the DiretrizesBrasileiras de Obesidade (ABESO, 2016). The BMI was calculated through the relation (Thota *et al*., 2017): weight/height(kg/m²), and the nutritional state of the adolescents was defined through the cut-off points proposed by the World Health Organization (ABESO, 2016). The waist-to-height ratio (WHtR) was calculated by the formula (Ashwell and Shiun, 2005): [WC (cm) / height (cm)]. The waist to hip ratio (WHR) was calculated through the division (ABESO, 2016) WC (cm) / HC(cm).

Arterial Pressure Measurement: The mensuration of systolic arterial pressure (SAP) and diastolic arterial pressure (DAP) was performed having as a base the protocol of the VII DiretrizesBrasileiras de Hipertensão Arterial (SBC, 2016).

Biochemical Analysis: Blood collection was done through the vacuum collection system, after fasting of 12-14 hours, and the samples were analyzed in the Clinical Analysis Laboratory of the University Hospital from the Maranhão Federal University. Insulin was evaluated by the immunotest of electrochemiluminescence (ECL), the lipid and glycemic profile by the colorimetric enzymatic method. IR was evaluated through HOMA-IR (SBD, 2014): [fasting insulin (U/mL) x fasting glycemya (mmol/L)/22,5]. The cut-off point to evaluate the presence of IR was of (HOMA-IR) < 3,16 (SBD, 2014), being utilized as a standard in the analysis of the ROC Curve. LAP was calculated, through the following formula (Kahn, 2005): [WC (cm) – 58] x [triglycerides (mmol/L)].

Statistical Analysis: Statistical analysis was done in SPSS software (version 25.0, Chicago, IL, EUA). Kolmogorov-Smirnov test was used to verify data normality. Groups were compared using the t-Student test for independent samples if data distribution turned out to be normal, otherwise the applied test was Mann-Whitney U. In the comparison of proportions the chi-squared test was used. The correlation coefficients were used to analyze the associations between HOMA-IR and the anthropometric indicators/LAP. The ROC curve analysis was utilized to evaluate the discriminatory power of IR in the evaluated indicators. The results were considered statistically significant if $p < 0,05$.

RESULTS

Table 1 shows the anthropometric, sociodemographic, hemodynamic and biochemical variables stratified through the presence of IR. It was observed a greater prevalence in weight excess and central adiposity, as well as bigger values of BMI, WC, WHR, WHtR, triglycerides (TG), HDL-C, insulin, glycemia, LAP and HOMA-IR in the group with IR ($p<0,05$) in comparison to the group without IR. Table 2 shows the correlation coefficients of IR indicators. HOMA-IR displayed a moderate correlation with LAP ($r=0,45$), and a weak correlation to the anthropometric indicators WC, WHR, WHtR. In the evaluation of the predictive power of IR indicators, the LAP index showed a bigger area over the ROC curve (0,75) than the anthropometric indicators, such as BMI (0,69), for example (Table 3). Although the anthropometric indicators, such as WC, BMI and WHtR, for example, present a series of advantages, such as low cost, reproducibility and innocuity, in the evaluation of metabolic disorders in adults and adolescents, several studies (Bozorgmanesh*et al*., 2010; Kahn, 2005; Nascimento-Ferreira *et al*., 2017; Ozler *et al*., 2016; Tingting *et al*., 2015)noted that alternative methods such as LAP tend to be more efficient. In a conducted study with adolescents with and without PCOS it was verified that LAP was an important index in the diagnosis of insulin resistance in overweight girls even among the ones without polycystic ovary syndrome (Ozler *et al*., 2016).

Bozorgmanesh *et al.,* (2010) verified that even for individuals of both sexes who are less than 20-49 years old, LAP was a strong predictor of altered fasting glycemia in comparison to BMI, waist to hip ratio and waist to stature ratio. These results corroborate to the present study where LAP presented a bigger correlation with HOMA-IR and a bigger area over ROC curve when compared to the anthropometric indices. A possible explanation for the better results of LAP when compared to anthropometric measurements is the combination of information referring to visceral fat (Nascimento-Ferreira *et al*., 2017) (TG and WC), given that the determinant of IR is not merely the obesity degree, but the body fat distribution (Carpio *et al*., 2017).

Table 1. General characteristics of the sample stratified through the presence of insulin resistance

Variables	Total	Without IR	With IR	P-value
n	113	59	54	
Age (years)[#]	14,42±2,01	14,66±1,93	14,15±2,07	0,176
Bodymass (kg)[#]	58,00±10,77	55,19±9,83	61,07±11,00	0,003
Stature (m)[§]	1,57±0,07	1,57 (1,52-1,62)	1,57 (1,54-1,61)	0,954
BMI (kg/m²)[#]	23,38±3,60	22,29±3,48	24,56±3,38	0,001
Eutrophic[*]	46	71,74 (33)	28,26 (13)	<0,001
Weightexcess[*]	67	38,80 (26)	61,2 (41)	
WC (cm)[#]	74,98±9,46	72,70±9,43	77,47±8,93	0,007
HC (cm)[#]	93,63±8,52	92,31±9,30	95,08±7,38	0,085
WHR[#]	0,80±0,06	0,79±0,07	0,81±0,06	0,029
WHtR[#]	0,48±0,06	0,46±0,06	0,49±0,06	0,013
Normal[*]	72	59,72 (43)	40,28 (29)	0,027
Altered[*]	41	39,02 (16)	60,98 (25)	
SAP (mmHg)[§]	106,47±11,50	107 (100-110)	110 (100-120)	0,486
DAP (mmHg)[§]	67,18±9,60	66 (60-75)	62 (60-71,25)	0,556
AP				
Normal[*]	95	52,63 (50)	47,37 (45)	0,52
Elevated[*]	18	50 (9)	50 (9)	
Total cholesterol (mg/dL)[#]	161,19±31,02	159,80±28,24	162,72±34,01	0,619
Triglycerides (mg/dL)[§]	94,17±41,66	73 (60-90)	112 (65-151,50)	<0,001
HDL-C (mg/dL)[§]	41,57±12,80	45,0 (34-52)	35,5 (30-42)	0,001
LAP[§]	18,90±15,48	9,88 (7,2-16,5)	18,96 (12,8-40,8)	<0,001
Glycemia (mg/dL)[§]	83,54±6,51	81 (77-86)	87 (82,7-9)	<0,001
HOMA-IR[§]	3,47±1,89	2,31 (1,8-2,7)	4,41(3,7-5,4)	<0,001
Insulin (uUI/mL)[§]	16,72±8,95	10,95(9,3-13,4)	20,31(17,4-24,9)	<0,001

Abbreviations: BMI – body mass index; WC – waist circumference; HC – hip circumference; WHR – waist to hip ratio; WHtR- waist-to-height ratio; SAP- systolic arterial pressure; DAP – diastolic arterial pressure; AP – arterial pressure; LAP- lipid accumulation product; Weight excess: >percentile 85; altered: >0,05; Elevated Arterial Pressure: ≥ p 90 < p 95 e ≥120/80 mmHg e < p 95 (10-17 years old), 18-19 years old: SAP 121-139 mmHg/DAP 81-88 mmHg; [*] Chi-squared test values are presented as percentage (frequency) ; [#]t-Student test values are presented as average ± standard deviation; [§]Mann-Whitney U test values are presented as median (interquartile range 25-75%).

Table 2.Correlation matrix between anthropometric indicators, LAP, triglycerides e HOMA-IR

	BMI	WC	WHR	WHtR	LAP	HOMA-IR
HOMA-RI	0,32[**]	0,25[**]	0,21[*]	0,23[*]	0,44[**]	1
Triglycerides	0,18	0,18[*]	0,14	0,13	0,70[**]	0,40[**]

Abbreviations: BMI – body mass index; WC- waist circumference; WHR – waist hip ratio; WHtR- waist to height ratio; LAP – lipid accumulation product; [**] Correlation is significant at level 0,01; [*] Correlation is significant at level 0,05.

Table 3. Area under ROC Curve of the insulin resistance indicators

Variables	ROC Curve (CI 95%)	Error	P-Value
LAP	0,75 (0,66-0,84)[*]	0,046	<0,001
BMI (kg/m²)	0,69 (0,59-0,79)[*]	0,051	<0,001
WC (cm)	0,66 (0,55-0,76)[*]	0,052	0,004
WHtR	0,65 (0,54-0,75)[*]	0,053	0,008
WHR	0,61(0,50-0,72)[*]	0,056	0,041

Abbreviations: CI 95% - confidence interval; LAP- lipid accumulation product; BMI – body mass index; WC – waist circumference; WHtR- waist to height ratio; WHR – waist to hip ratio. [*]: Area under ROC curve demonstrating its discriminatory power for insulin resistance in female adolescents (inferior limit CI 95% >0,50).

In different studies it is verified the interaction between the fat accumulation pattern and metabolic risk, being demonstrated that metabolic risk is lower in women with a smaller waist circumference, and that hypertriglyceridemia is a strong cardiovascular risk factor for women in comparison to men (Han *et al*., 1995; Hokanson and Austin, 1996; Ioachimescu *et al*., 2010; Kahn and Cheng, 2008). Moreover, it is known that individuals with an increase of abdominal fat are more prone to metabolic disorders, that develop during childhood and adolescence. And that this excessive accumulation of body fat, mainly the one located in the central or visceral region favors the elevation of free fatty acids in blood circulation, which can impact negatively the signaling of insulin, lower the receptors sensibility in cellular membranes and create the insulin resistance condition (Andrade *et al*., 2016). Another advantage of LAP utilization is its low cost in comparison to other used methods such as the gold standard euglycemic clamp, which despite its recommendation by the guidelines of theAmerican Diabetes Association, is not a commonly used method due to its high cost and because it is an invasive and complex method (Thota *et al*., 2017),as well as the insulin and C-peptide(Thota *et al*., 2017)dosage that are of high cost when compared to the TG serum dosage and mensuration of WC. Our study also noted that the prevalence of weight excess and central adiposity was bigger in the group with IR. Furthermore, girls with IR had a bigger mean/median in the variables BMI, WC, WHR, WHtR, triglycerides, HDL-C, LAP, glycemia, insulin and HOMA-IR. Corroborating with our results, Alvim *et al.,* (2018)in evaluating 296 children and adolescents of Vitória/Brasil also found a high prevalence of overweight and bigger values of BMI, WC, WHtR, triglycerides, insulin, glucose and HOMA-IR in the group with elevated IR. However, in the present study the indicator that presented a bigger correlation with HOMA-IR was LAP.

On the other hand, Alvim *et al*.(2018), observed a bigger correlation between HOMA-IR and WHtR. Nevertheless, the presence of IR among the population of adolescents is worrisome once it is a risk factor for the development of type 2 Diabetes and cardiovascular disorders in this population (Alvim *et al*., 2018; Kahn, 2005). Therefore, the LAP index shows promising results for the prediction of cardiovascular and metabolic events in studies with healthy women or with polycystic ovary syndrome (Amato *et al*., 2013; Mostajeran and Shashavari, 2014; Wiltgen and Benedetto, 2009), as well as expressing physiological alterations related to lipid accumulation such as insulin resistance (Kahn, 2005; Mostajeran, 2014) with a performance better than other anthropometric indicators.

Limitations: Among the limitations of the study we can highlight the lack of tracing and/or diagnosis of adolescents that could be polycystic ovary syndrome bearers, besides the absence of an inflammatory marker to correlate with IR.

Conclusion

The present study showed that LAP is an easy access, low cost and reproducible tool that can be utilized in female adolescents screening, with insulin resistance. However, prospective studies are necessary for additional validation.

Declarations

Ethics approval and consent to participate: This study was approved by the Human Research Ethics Committee of the Federal University of Maranhão, protocol number 2.638.202.

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List of abbreviations

IR- Insulin Resistance
HOMA-IR - homeostasis model assessment
LAP - lipid accumulation product index
PCOS - polycystic ovary syndrome
WC- Waist circumference
HC- hip circumference
WHtR- waist-to-height ratio
SAP - systolic arterial pressure
DAP - diastolic arterial pressure
BMI - body mass index

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