Universidade Federal do Rio Grande Do Sul
Faculdade de Medicina
Programa de Pós-Graduação em Ciências Médicas: Endocrinologia

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Associação entre Marcadores de Adiposidade Corporal e Resistência à Ação da Insulina em Pacientes com Diabetes Melito Tipo 1

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FORMATO DA DISSERTAÇÃO DE MESTRADO

Esta dissertação de mestrado segue o formato proposto pelo Programa de Pós-graduação em Ciências Médicas: Endocrinologia da Universidade Federal do Rio Grande do Sul, sendo apresentada em dois capítulos, um referencial teórico acerca do tema proposto e um artigo original a ser submetido para publicação em periódico de Qualis A Internacional na classificação da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

SUMÁRIO

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Capítulo I.

CC – Circunferência da Cintura

DCV – Doenças Cardiovasculares

DEXA – Absorciometria de Raios-X de Dupla Energia

DM – Diabetes Melito

EGDR – Taxa Estimada de Disponibilização de Glicose

HAS – Hipertensão Arterial Sistêmica

HDL – Lipoproteína de Alta Densidade

IAC – Índice de Adiposidade Corporal

IC– Índice de Conicidade

IMC – Índice de Massa Corporal

LAP – Produto de Acumulação Lipídica

RCE – Relação Cintura-Estatura

RCQ – Relação Cintura Quadril

RI – Resistência à Ação da Insulina

SM – Síndrome Metabólica

Capítulo II.

ADA – American Diabetes Association

AUC – Area Under the Curve

BAI – Body Adiposity Index

BMI – Body Mass Index

CI – Conicity Index

CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration

CVD – Cardiovascular Disease

DEXA - Dual Energy X-Ray Absorptiometry

EGDR – Estimated Glucose Disposal Rate

HbA1c – Glycated Hemoglobin

HC – Hip Circumference

HCPA – Hospital de Clínicas de Porto Alegre

HOMA-IR – Homeostatic Model Assessment Insulin Resistance

IR – Insulin Resistance

LAP – Lipid Accumulation Product

LDL – Low-Density Lipoprotein

MDRD – Modification of Diet in Renal Disease

ROC – Receiver Operating Characteristic

T1D – Type 1 Diabetes

T2D – Type 2 Diabetes

TG – Triglycerides

WC – Waist Circunference

WHR – Waist-Hit Ratio

WHtR – Waist-Height Ratio

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Capítulo I.

Referencial Teórico

Diabetes Melito, resistência à ação da insulina e medidas antropométricas

DIABETES MELITO, RESISTÊNCIA À AÇÃO DA INSULINA E MEDIDAS ANTROPOMÉTRICAS

O diabetes melito (DM) é uma doença caracterizada por hiperglicemia crônica de etiologia multifatorial, associada a alterações no metabolismo de carboidratos, proteínas e lipídeos, podendo ter como origem a deficiência absoluta de insulina associada ou não à presença de resistência a sua ação[1]. É uma condição que acomete aproximadamente 8% da população mundial, com incidência crescente. A estimativa é de que existam hoje 382 milhões de pessoas com DM, e para o ano de 2035 está previsto um incremento de 210 milhões de novos casos da doença[2]. Aproximadamente 90% dos casos de DM correspondem ao DM tipo 2, enquanto o DM tipo 1 representa em torno de 5-10% dos casos[2].

Um estudo realizado no Brasil mostrou que o excesso de peso é um fator importante para o desenvolvimento de DM tipo 2[3]. Entre as mulheres 49% e 58% do percentual de DM tipo 2 foram atribuíveis ao sobrepeso e à obesidade, respectivamente. Entre os homens, esses percentuais foram 40% e 45%, respectivamente[3]. A projeção para os próximos anos é de que a incidência de DM tipo 1 aumente ainda mais[2], e esteja associada ao excesso de peso em indivíduos insulino-dependentes[4]. Essa alteração no perfil de indivíduos com DM tipo 1 reforça a relevância de se estudar alterações metabólicas nesta população.

O DM possui elevada morbidade, alto custo para o sistema de saúde e associação com complicações vasculares crônicas como retinopatia, neuropatia, doença renal e também doenças cardiovasculares (DCV)[2], em função disso é uma condição de extrema importância dentro do sistema de saúde atual.

As DCV são as principais causas de mortalidade nos pacientes com DM[2], estudos mostram que a presença de resistência à ação da insulina (RI) é um importante fator de risco para o desenvolvimento de aterosclerose e de DCV, tanto em indivíduos com DM quanto naqueles sem a doença[5,6,7]. O acúmulo de gordura abdominal está associado a RI, e as duas condições clínicas podem estar relacionadas com a síndrome metabólica (SM)[7,8]. A presença de SM em DM tipo 1 pode contribuir para o aumento do risco de DCV e complicações crônicas[5,8]. Estima-se que cerca de um quarto da população adulta do mundo tenha SM[9], o que eleva em duas vezes a probabilidade de morte e em três vezes a probabilidade de ataque cardíaco ou acidente vascular cerebral nesses indivíduos em comparação com aqueles sem a síndrome[10]. Além disso, indivíduos com SM têm risco de cinco vezes de desenvolver DM tipo

2[11]. A RI e a SM afetam indivíduos com DM tipo 1 e apresentam impacto negativo sobre as complicações microvasculares[12].

Não há um consenso sobre a melhor definição de RI, alguns autores a definem como uma redução da capacidade da insulina em estimular à utilização ou aproveitamento da glicose[13]. A fisiopatogênese da RI pode estar relacionada com alterações na sinalização da insulina nos tecidos-alvos como fígado, músculo esquelético e tecido adiposo, tornando esses tecidos menos sensíveis à ação da insulina[2]. A redução da sensibilidade à ação da insulina leva à hiperinsulinemia compensatória, induzindo a alterações metabólicas como modificações na distribuição de gordura corporal, com especial acúmulo na região abdominal, elevação da pressão arterial e dos níveis séricos de triglicerídeos e redução dos valores de colesterol-HDL[14]. Com isso, a presença de RI aumenta o risco de desenvolver SM, DM tipo 2 e DCV[1,6]. A RI é uma característica mais prevalente em indivíduos com DM tipo 2, porém em indivíduos com DM tipo 1 também pode estar presente[6,14,15] e é uma possível preditora de complicações vasculares crônicas[13,20].

A presença de RI no DM tipo 1 é melhor identificada pela técnica do clampe euglicêmico hiperinsulinêmico[16], entretanto na prática clínica sua utilização torna-se impraticável em função de ser uma técnica invasiva e de alto custo. Contudo, Orchard e colaboradores desenvolveram uma fórmula baseada na técnica de clampe, sendo utilizada como alternativa para a avaliação da RI por possuir uma boa correlação com a técnica de referência[16]. A fórmula denominada taxa estimada de disponibilização de glicose (EGDR) mensura o grau de sensibilidade à insulina e possui uma relação inversa com a RI. A EGDR utiliza em sua fórmula a relação cintura-quadril (RCQ), a hemoglobina glicada (HbA1c) e presença de hipertensão arterial sistêmica (HAS=1, se presente e HAS=0, se ausente):

$$\text{EGDR } (mg.kg^{-1}.min^{-1}) = 24,3 - 12,2\ (RCQ) - 3,3\ (HAS) - 0,6\ (HbA1c)$$

Esta fórmula tem sido utilizada como uma estimativa aceita de RI em pacientes com DM tipo 1[5,12,15,17,18]. EGDR é uma fórmula fácil com base em parâmetros clínicos e laboratoriais e apresenta boa relação com a presença de SM, bem como com complicações crônicas do diabetes[5,12].

A relação entre RI e gordura corporal está associada em indivíduos com DM tipo 1[7,19] e sua presença pode ocasionar uma série de complicações metabólicas, com isso torna-se necessária a avaliação da composição corporal com o intuito de predizer RI e assim poder atuar com medidas preventivas.

Em relação à composição corporal, alguns métodos indiretos avaliam a distribuição de gordura, e entre eles estão os exames de imagem como a tomografia computadorizada e a ressonância magnética, que estimam mais precisamente a localização e a quantidade de tecido adiposo em várias regiões do corpo[21,22]. Esses métodos possuem boa precisão para determinar a quantidade de tecido adiposo visceral, porém a utilização em pesquisas clínicas é limitada devido ao alto custo, difícil operação, necessidade de preparo para realização e exposição do paciente à radiação[21]. Em comparação a estes métodos, a absortometria de raios-x em dupla energia (DEXA) é utilizada em pesquisas como método indireto de referência para avaliar a composição corporal. O DEXA é comumente utilizado para medir a densidade mineral óssea, porém o exame também resulta na avaliação da composição corporal, avaliando a quantidade de gordura e de massa magra[23]. É um exame rápido, fácil de executar e exige mínimo preparo para sua realização[24].

Por outro lado, as medidas antropométricas são facilmente obtidas, possuem baixo custo e boa acurácia e por meio delas é possível identificar fatores de risco para o desenvolvimento de complicações metabólicas[25]. A literatura evidencia que algumas dessas medidas antropométricas podem também ser utilizadas para avaliar indiretamente o acúmulo de gordura corporal[23,26,27]. Porém cada medida possui uma particularidade especial e pode predizer ou determinar melhor um desfecho específico em diferentes populações (Tabela 1).

Tabela 1 – Medidas antropométricas e suas fórmulas

MEDIDAS ANTROPOMÉTRICAS	FÓRMULAS	REFERÊNCIAS
Circunferência da Cintura (CC)	CC (cm)	28
Relação Cintura-Quadril (RCQ)	CC (cm) / CQ (cm)	28
Relação Cintura-Estatura (RCE)	CC (cm) / Estatura (cm)	29
Índice De Conicidade (IC)	$\frac{\text{CC (cm)}}{0.109 \sqrt{\text{Peso (kg) / Estatura (m)}}}$	30
Produto de Acumulação Lipídica (LAP)	[CC (cm) - 65] x TG (mmol/L), em homens [CC (cm) - 58] x TG (mmol/L), em mulheres	31
Índice de Massa Corporal (IMC)	Peso (kg) / Estatura $(m)^2$	32
Índice de Adiposidade Corporal (IAC)	$\frac{\text{CQ (cm)}}{\text{Estatura (m)} \sqrt{\text{Estatura (m)}}} - 18$	33

CQ = circunferência do quadril; TG = triglicerídeos

A medida mais comumente utilizada na população em geral é o índice de massa corporal (IMC), que estima o estado nutricional. Indivíduos com IMC abaixo de 18,5 kg/m^2

são considerados desnutridos e entre 18,5 e 24,9 kg/m^2 são considerados eutróficos[32]. A classificação de IMC que prediz maior risco de doenças crônicas não transmissíveis é de valores iguais ou acima de 25 kg/m^2, que indicam sobrepeso, e valores iguais ou acima de 30 kg/m^2, que indicam obesidade[32]. Indivíduos com excesso de peso apresentam um risco de complicações crônicas e também de mortalidade[21]. Uma desvantagem dessa medida é que o IMC avalia a massa corporal do indivíduo, porém não distingue a quantidade de tecido adiposo e tecido muscular[25], dificultando a avaliação quando mensurada individualmente.

A circunferência da cintura (CC) avalia o acúmulo centralizado de adiposidade abdominal e é utilizada como marcador de risco para DCV[25]. A classificação é realizada de acordo com o gênero e a etnia, valores de CC superiores a 80 cm em mulheres e 94 cm em homens identificam obesidade abdominal em indivíduos caucasianos[2] e segundo a Organização Mundial da Saúde os mesmos valores são capazes de predizer risco aumentado para DCV[28]. No estudo de Rodrigues e colaboradores, indivíduos com DM tipo 1 e obesidade visceral tiveram um risco adicional para a aterosclerose subclínica[34], enquanto que outro estudo com DM tipo 2, mostrou que a CC determinou risco cardiometabólico relacionado a obesidade abdominal[35]. Sujeitos com ou sem DM podem não apresentar obesidade pelo IMC, porém podem apresentar CC elevada, o que indica adiposidade abdominal. Entretanto a medida isolada da CC avalia adiposidade central, mas não avalia a distribuição de gordura corporal.

A relação cintura-quadril (RCQ) utiliza pontos de corte de acordo com o gênero, e medidas acima de 0,85 cm em mulheres e de 0,90 cm em homens estão relacionadas com risco aumentado de mortalidade por DCV[26,28]. A mensuração da RCQ em indivíduos deve ser associada a outras medidas antropométricas, visto que sujeitos eutróficos e obesos podem apresentar o mesmo resultado da RCQ devido às proporções corporais mensuradas.

A relação cintura-estatura (RCE) utiliza medidas de fácil aferição, por meio da RCE é possível avaliar obesidade abdominal, sendo utilizada como preditora de risco coronariano[27,33]. Autores sugerem que a medida RCE é mais precisa do que a CC na identificação de risco cardiovascular[33], e que um ponto de corte de 0,5 é capaz de predizer risco cardiometabólico[37], de DCV e de diabetes melito[36].

O Índice de conicidade (IC) é uma medida utilizada como preditora de DCV e alterações metabólicas[30,37], e também demonstra ter associação com risco de eventos coronarianos em pacientes com DM tipo 2[38]. O IC busca representar o corpo no formato de

um duplo cone com uma base comum, que tem por finalidade identificar o acúmulo de gordura na região abdominal[38]. O cálculo do IC considera medidas simples como CC, estatura e peso corporal, podendo ser facilmente utilizado na prática clínica, porém ainda não há pontos de corte definido para ser utilizado individualmente.

O produto de acumulação lipídica (LAP) relaciona em sua fórmula a CC e o nível sérico de triglicerídeos, avaliando diferentemente os gêneros. Essa medida tem sido relatada como preditora de diabetes, de SM e de DCV[32] e associada a RI em diferentes populações[39,40].

Índice de adiposidade corporal (IAC) relaciona medidas de fácil aplicação como a circunferência do quadril e a estatura, o IAC foi criado com o intuito de estimar o percentual de gordura corporal, porém também não possui um ponto de corte bem definido[33]. Autores sugerem uma correlação com risco cardiometabólico[41], entretanto por ser uma medida mais recentemente estudada, sua relação com complicações metabólicas ainda não está bem esclarecida.

Diante da ampla variedade de medidas antropométricas associadas à adiposidade corporal e da ausência de definição de qual o melhor método antropométrico que avalie a relação da distribuição de gordura corporal com a presença de RI em pacientes com DM tipo 1, torna-se relevante estudar fórmulas práticas que possam predizer risco de RI nesta população.

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Capítulo II.

Artigo Original

Adiposity markers and insulin resistance in type 1 diabetes patients

ADIPOSITY MARKERS AND INSULIN RESISTANCE IN TYPE 1 DIABETES PATIENTS

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ABSTRACT

Background: Obesity is associated with risk of clinical and metabolic complications such as dyslipidemia, hypertension and type 2 diabetes. Previous studies have demonstrated that visceral obesity is related to type 1 diabetes (T1D), cardiovascular disease and insulin resistance (IR). This study aims to evaluate the association among different body adiposity markers and IR in adults with T1D. **Methods:** Cross-sectional study in outpatient adults with T1D in a hospital in southern Brazil. Data were collected from 2008 to 2013, the anthropometric measurements were waist circumference (WC), waist-height ratio (WHtR), body mass index (BMI), conicity index (CI), lipid accumulation product (LAP) and body adiposity index (BAI). IR was measured using estimated glucose disposal rate (EGDR) equation, considering an inverse relationship between EGDR and IR, and it was analyzed in tertiles (tertile 1 ≤5.4; tertile 2 >5.4 and <8.4 and tertile 3 ≥8.4 $mg.kg^{-1}.min^{-1}$). Areas under the receiver operating characteristic curves (AUC) were calculated to measure the discriminating power among the different body adiposity markers and compares their predictive effect on insulin resistance. **Results:** A total of 128 subjects were enrolled (52% women) with mean age of 38.7 ± 11.3 years and median of EGDR 7.2 (4.4–8.7) $mg.kg^{-1}.min^{-1}$. Individuals classified in the first tertile of EGDR (higher IR) had higher values of WC, WHtR, CI, LAP and BMI when compared with individuals in the others tertiles. EGDR was negatively correlated with WC (r= -0.36, p< 0.01), WHtR (r= -0.39, p< 0.01), CI (r= -0.44, p< 0.01), LAP (r= -0.41, p< 0.01) and BMI (r= -0.24, p< 0.01). After gamma regression analyses, adjusted for age, gender, serum triglycerides and renal status, WC (β= -0.01; p<0.01), WHtR (β= -2.20; p<0.01), CI (β= -1.83; p<0.01), LAP (β= -0.007; p<0.01) and BMI (β= -0.02; p= 0.006) remained negatively associated with EGDR. AUC showed that CI had larger area in simple analysis, and compared by gender LAP was higher in men and WHtR in women. **Conclusions:** The studied adiposity markers were associated with IR, except for the BAI. Markers that include WC appear to be better predictor of IR than isolated WC measure. CI, and WHtR showed greater tendency to identify IR in adults with T1D. This study suggests that through anthropometric measurements is possible to predict IR in adults with T1D and these measurements must be used by health professionals, since they are easily used on clinical application.

Key words: Insulin Resistance. Body Adiposity Markers. Type 1 diabetes.

INTRODUCTION

Obesity, especially abdominal adiposity, is related to clinical and metabolic complications such as dyslipidemia, hypertension, type 2 diabetes (T2D) and insulin resistance (IR)[1,2]. Individuals with IR have increased risk for developing T2D and cardiovascular disease (CVD), as well elevated risk of mortality[2]. CVD is the most common cause of death and disability among subjects with diabetes, especially in individuals with late diagnosis and poor control[3,4]. Recently, IR has been attributed also to type 1 diabetes (T1D)[5], and it increases the risk for micro and macrovascular complications[6]. Early identification of IR provides better control and disease prevention, reducing healthcare costs and improving life quality[7].

The IR evaluation in individuals with T1D is ideally performed by euglycemic-hyperinsulinemic clamp method, however this method is considered invasive and expensive[8]. Estimated glucose diposal rate (EGDR) is an equation developed to estimate the IR in T1D individuals, and it has been used as a good parameter in clinical studies[9-11].

The evaluation of body fat distribution is important due the association between abdominal obesity and IR[12]. Methods that assess body composition such as dual energy X-ray absorptiometry (DEXA) and computed tomography are more precise to identify abdominal obesity, but their use in clinical practice is limited due its high cost and complexity of operation[13].

Anthropometric measurements are non-invasive, easy to apply and have low cost. Measurements such as waist circumference (WC), waist-hip ratio (WHR), waist-height ratio (WHtR), body mass index (BMI), conicity index (CI), lipid accumulation product (LAP) and body adiposity index (BAI) can be considered body adiposity markers by evaluating of adipose tissue accumulation[14-18]. These measures have been studied in association with cardiometabolic risk in T2D patients and healthy individuals[14-18]; however the association with IR and T1D is still poorly studied.

The projection for the next years is increased diabetes incidence[19] associated with weight gain in individuals with T1D[20]. Therefore, it is necessary to understand and study practical measurements to assess the early IR.

In absence of definition about which are the best anthropometric measurements to assess IR in patients with T1D, this study aims to evaluate different body adiposity markers in adults with T1D and to evaluate the possible relation between these markers and IR.

METHODS

Study population

Cross-sectional study with outpatient T1D adults carried out in Endocrinology Division of Hospital de Clínicas de Porto Alegre (HCPA), Brazil. Data were collected by trained individuals, from 2008 to 2013. T1D was defined by onset before 40 years of age, presence of ketonuria or ketonemia at the time of diagnosis, and dependence on insulin therapy to sustain life. The inclusion criteria were: age between 18-59 years and diagnosis of T1D for more than 5 years. Exclusion criteria were hemodialysis and/or decompensated heart failure.

This study was conducted in accordance with Helsinki Declaration and was approved by HCPA Research Ethics Committee, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil. Written informed consent was obtained from all patients.

Clinical Evaluation

Blood pressure was measured with digital sphygmomanometer OMRON® model HEM 705 CP through two consecutive measurements with one minute interval, with the individual seated after five minutes rest. The use of antihypertensive drugs and blood pressure levels of systole equal or above 140 mmHg and diastolic equal or above 90 mmHg were considered diagnosis of hypertension, according to American Diabetes Association (ADA)[21].

Metabolic syndrome was defined according to the International Diabetes Federation classification[19] and diabetes kidney disease was defined according to ADA criteria[21]. Glomerular filtration rate (GFR) was calculated by the Modification of Diet in Renal Disease (MDRD)[22] equation and also by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)[23] equation, considering gender and race.

IR was measured by EGDR formula, which calculates insulin sensitivity degree, using WHR, HbA1c and hypertension presence[8]:

$$EGDR\ (mg.kg^{-1}.min^{-1}) = 24.3 - 12.2\ (WHR) - 3.3\ (Hypertension) - 0.6\ (HbA1c)$$

Antropometric Evaluation and Body Adiposity Markers

The weight and height measurements were obtained with digital anthropometric scale Marte® LS200A with maximum capacity of 201 kg, and sensitivity of 50 g, according to the technique described by Gordon et al[24]. BMI was calculated from these measurements, using the cutoff points for adults recommended by the World Health Organization[25]. WC was measured using metric tape made a non-elastic material in the standing position, midway between the lowest costal rib and the iliac crest and hip circumference was measured at the largest circumference between the iliac crest and the trochanter[26]. WHR was defined as the ratio between waist circumference and hip circumference.

The adiposity markers used were WC, WHtR, CI, LAP, BMI and BAI evaluated were calculated with equations according to Table 1:

Table 1 - Body adiposity markers and its equations

MARKERS	EQUATIONS	REFERENCES
WC	WC (cm)	26
WHtR	WC (cm)/ Height (cm)	28
CI	$\frac{\text{WC (cm)}}{0.109 \sqrt{\text{Body weight (kg) / Height(m)}}}$	29
LAP	[WC (cm) - 65] x TG (mmol/L) to men [WC (cm) - 58] x TG (mmol/L) to women	30
BMI	Body weight (kg)/ Height $(m)^2$	25
BAI	$\frac{\text{Hip Circunference (cm)} - 18}{\text{Height (m)} \sqrt{\text{Height (m)}}}$	31

WC = waist circumference; WHtR = waist-height ratio; CI = conicity index; LAP = lipid accumulation product; BMI = body mass index; BAI = body adiposity index; TG = triglycerides

Laboratory Evaluation

Blood exams were performed in twelve hour fasting. The evaluation of glucose fast was performed by enzymatic colorimetric glucose-peroxidase method (Biodiagnóstica®), glycated hemoglobin (HbA1c) by liquid chromatography high performance (Merck-Hitachi

9100; Merck®, Darmstadt, Germany), triglycerides and cholesterol levels using the enzymatic method (ADVIA® 1800 AutoAnalyzer, Germany) and LDL-cholesterol fraction was calculated according to Friedewald equation[27] when plasma triglyceride level was below 400 mg/dL.

Statistical Analysis

Data were described as mean and standard deviation (mean ± SD), median and interquartile range [median (IQR)] for continuous variables and absolute number and percentage [N (%)] for categorical variables. Spearman correlation coefficient and Kruskal-Wallis test were used for nonparametric variables. Tukey test was used for post-hoc analysis. The chi-square test was performed when appropriate, for categorical variables. Gamma regression models were constructed and used to evaluate possible association among body adiposity markers and IR risk, and the independent variables were chosen according to univariate analysis.

The EGDR was analyzed in tertiles (tertile 1 ≤5.4; tertile 2 >5.4 and <8.4 and tertile 3 ≥ 8.4 $mg.kg^{-1}.min^{-1}$), considering an inverse relationship between EGDR and IR.

Areas under the receiver operating characteristic curves (AUC) were calculated to measure ability of adiposity markers to discriminate IR. The confidence interval (95%) of sensibility and specificity were analyzed in WinPepi Program version 11.47.

All data were analyzed using Statistical Package for Social Sciences Software, version 18.0 (SPSS Inc., Chicago, IL, USA), considering statistical significance $p< 0.05$.

RESULTS

A total of 128 subjects were included (52% women) with mean age of 38.7 ± 11.3 years and median of EGDR 7.2 (4.4–8.7) $mg.kg^{-1}.min^{-1}$. The subjects were classified according to the IR (stratified in EGDR tertiles) in relation to clinical and laboratory characteristics (Table 2). According to EGDR tertiles, individuals with increased IR (lowest values EGDR) showed higher values of HbA1c, triglycerides, higher blood pressure levels, lower glomerular filtration rate and also presented higher prevalence of metabolic syndrome and diabetic kidney disease than individuals of the others groups.

These individuals in the first EGDR tertile (lowest levels) also displayed higher values of WC, CI, WHtR and LAP when compared with individuals of the others tertiles (Table 3). BMI was borderline (p= 0.052) and there was no difference for BAI (p= 0.975).

Table 4 shows the correlation analysis between the adiposity markers and EGDR, in which negative correlations among all analyzed variables was observed. After gamma regression analysis in individual models of body adiposity markers adjusted for age, gender, triglyceride and renal status (glomerular filtration rate or diabetic kidney disease), WC, WHtR, CI, LAP and BMI remained associated with RI, as described at Table 5.

Receiver operating characteristic (ROC) curves were constructed with WC, WHtR, CI, LAP and BMI to compare and evaluate the best predictor of IR presence (lower tertile) (Figure 1). The AUC of CI had the highest absolute value between areas (Table 6). Table 7 lists AUC values by gender showing that the highest result was WHtR in women and LAP in men.

DISCUSSION

In the present study most of the evaluated adiposity markers were associated with IR, except for the BAI. After regression analysis, adjusted for confusion factors, all markers analyzed remained associated with IR at all models; however WHtR and CI showed greater influence on EGDR variation.

A previous study that evaluated visceral obesity markers in healthy subjects, demonstrated that CI was more accurate in men and WHtR was a better predictor only in older women[32]. Similar results were observed in our study, which showed that the CI adiposity markers were increased in adults with T1D, especially in men, and only the WHtR was significant in women.

Ashwell et al.[33] showed that a boundary value of 0.5 for WHtR indicates increased morbidity and mortality risk for men and women in different ethnic groups and has proven to be more sensitive than BMI. Similar results were found when evaluate WHtR cutoff, analyzed sensibility and specificity. The WHtR showed better tendency to identify IR compared to BMI.

The ROC curve analysis showed that some markers, when stratified by gender, seem to be better IR discriminate in men than women. Only WHtR was able to predict IR among women, while in men all the markers except BMI were able to predict IR, being the LAP its greater predictor IR.

Another study[34] found that IR was significantly associated with body weight, BMI, WC, WHR and WHtR in both gender ($p< 0.001$) and these obesity indexes were positively associated with IR in healthy adolescents. WHtR proved to be an independent metabolic syndrome predictor in T1D adolescents[14]. However in T1D adults the best AUC to predict IR was CI, after LAP and then WHtR.

In a cross-sectional study[35] that evaluated 21.038 men and 15.604 women, AUC of WHtR was significantly greater than BMI and WC to predict diabetes, hypertension, high total cholesterol, high triglycerides and low HDL-cholesterol ($p< 0.05$ for all) in both genders. The WHtR to predict metabolic syndrome was also higher in women ($p< 0.05$) and was associated with cardiometabolic risk, even among individuals considered healthy according to BMI and WC classification[35].

Regarding CI, a Brazilian study[32] proved that it was more accurate to assess visceral obesity in healthy men [AUC 0.97 (95% confidence interval: 0.918-1.017)]. In the present study, the CI AUC was 0.76 (95% confidence interval: 0.61–0.86) in men and when compared with others markers in the entire population AUC of CI was the largest area: 0.72 (95% confidence interval: 0.62–0.81). This is an important finding since CI evaluates abdominal obesity and is associated with IR, CI can detect changes in body fat distribution, allowing comparisons among individuals with different measurements of body weight and height.

According to a case-control study with 300 individuals[36], WC had the highest predictive accuracy (AUC= 0.77 in men and 0.74 in women) in T2D. WC was the best predictor of T2D risk compared with WHtR, CI, BMI and abdominal volume index and was also strongly correlated with biochemical markers of diabetes such as serum glucose and lipid profile[36].

WC is a simple, non-invasive and accurate predictor of diabetes risk[36] that can be applied in various formulas to predict IR risk. However in T1D male adults the WC showed only to be better than BMI.

The LAP demonstrated to be one of the most accurate in the discrimination of IR in men, but different results were described in the literature. In study with 768 non-diabetic Spanish adults, that studied the ability of LAP compared with traditional measures of IR, found that in men and women the LAP showed a slightly better performance to detect IR evaluated with Homeostatic Model Assessment Insulin Resistance (HOMA-IR)[37]. A case-control study with 32 participants showed that LAP measurement could identify insulin sensitivity in T2D overweight subject[38].

In the present study, BMI did not show to be the best predictor of IR in T1D, probably because it evaluates the ratio of body weight and height, but it does not consider body muscle composition and amount of abdominal fat tissue. These results indicate that not only the degree of obesity, but also the distribution of body fat is a factor risk for IR. BMI anthropometric measurement is often used in clinical practice, and possibly if used in combination with other measures such as CI, WHtR and LAP, can be a good parameter to evaluate adults individuals with T1D.

BAI was not associated with IR in T1D, and a similar result was found in a study[17] which BAI had the weakest correlation with fasting glucose, 2-hour glucose, blood pressure levels, as compared with other indices such as WC, WHtR, WHR and BMI. Other study[16] indicated that BAI can be considered a global adiposity measure, but not proved to be better than BMI, suggesting that BMI and WHtR to identifying adults with cardiovascular risk.

The limitations of this study were inherent to a cross-sectional design. Thus, it was not possible to determine cause-and-effect relation, but only to report associations. Also, it is important to recognize that these adiposity markers are indicators of risk and not diagnostic for IR.

In summary, our results showed that all adiposity markers were associated with IR, except for BAI. Markers that include WC appear to be a better predictor of IR than isolated WC measure. The WC is the most commonly measure used in clinical practice, but it is not the best parameter to evaluate IR in T1D, especially in women. The comparison among all adiposity markers demonstrated that CI and WHtR was better to identify IR in T1D adults. This study suggests that through the associated anthropometric measurements is possible to predict IR in adults with T1D and these measurements must be used by health professionals, since they are easily employed on clinical application.

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Disclosure

All authors have no conflict of interest to declare.

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Table 2 - Clinical and laboratory characteristics according of EGDR tertiles in subjects with type 1 diabetes

Characteristics	Total	1º tertile EGDR (≤ 5.4)	2º tertile EGDR (>5.4 <8.4)	3º tertile EGDR (≥ 8.4)	p-valor
n	128	42	43	43	-
Caucasian N (%)	112.0 (87%)	32.0 (76%)	39.0 (91%)	41.0 (95%)	0.077
Age (years)	39.0 (30–49)	39.5 (28.7–52)	40.0 (30.5–50.0)	40.0 (30–46)	0.429
Women N (%)	66.0 (52%)	20.0 (30%)	22.0 (33%)	24.0 (37%)	0.750
Diabetes time (years)	17.7 ± 8.9	19.8 ± 8.5	15.6 ± 8.6	17.6 ± 9.4	0.64
Weight (kg)	69.7 ± 12.2	72.7 ± 12.0	68.8 ± 12.3	67.6 ± 11.9	0.139
Glucose (mg/dL)	167.0 (122–286)	166.0 (32–513)	167.0 (42–699)	174 (38–442)	0.867
HbA1c (%)	8.7 (7.9–10.3)	10.3 (7.0–19.3)[b]	9.3 (6.1–12.2)[c]	8.0 (5.8–10.0)	< 0.001
Total cholesterol (mg/dL)	190.5 ± 37.5	198.6 ± 40.8	192.4 ± 35.0	180.9 ± 35.2	0.090
LDL- cholesterol (mg/dL)	108.2 (88.0–132.4)	109.7 (101.4–148.2)	101.8 (78.1–129.8)	101.8 (85.4–126.0)	0.114
HDL- cholesterol (mg/dL)	59.5 ± 17.4	37.3 ± 16.0	61.6 ± 19.9	59.7 ± 16.2	0.532
Triglycerides (mg/dL)	85.0 (60–118)	106.5 (27–218)[b]	84.0 (34–273)	78.0 (40–223)	0.040
Glomerular filtration rate MDRD (mL/min/1.73m^2)	95.5 ± 27.7	84.8 ± 32.4[a,b]	100.5 ± 27.7	101.1 ± 18.8	0.008
Glomerular filtration rate CKD-EPI (mL/min/1.73m^2)	97.6 ± 24.9	86.4 ± 29.7[a,b]	101.4 ± 24.0	104.9 ± 15.7	0.001
C-reactive protein (mg/dL)	1.6 (0.6-4.9)	2.0 (0.8-4.6)	2.0 (0.6-7.1)	1.0 (0.4-2.8)	0.057
Systolic blood pressure (mmHg)	124.8 ± 19.4	113.5 ± 20.8[a,b]	122.5 ± 20.3	120.5 ± 12.3	0.033
Diastolic blood pressure (mmHg)	74.6 ± 12.1	77.4 ± 9.7*	74.6 ± 14.7	71.5 ± 7.0	0.001
Presence of hypertension N (%)	51.0 (39.9%)	40.0 (31.3%)	11.0 (8.6%)	0.0 (0%)	0.064
Presence of diabetic kidney disease N (%)	29.0 (22.7%)	21.0 (16.4%)[a,b]	6.0 (4.7%)	2.0 (1.6%)	< 0.001
Presence of metabolic syndrome N (%)	41.0 (32.0%)	28.0 (21.9%)[a,b]	9.0 (7%)	4.0 (3.1%)	< 0.001

Data expressed in mean ± SD, median (interquartile range) and individuals number (N) and percentage (%). MDRD = Modification of Diet in Renal Disease Study; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration. [a] Difference between tertile 1 and tertile 2, [b]Difference between tertile 1 and tertile 3, [c]Difference between tertile 2 and tertile 3, *Post hoc tests are not performed for diastolic blood pressure because at least one group has fewer than two cases.

Table 3 - Distribution of adiposity markers by EGDR tertiles in subjects with type 1 diabetes

Marker	Total	1º tertile EGDR (≤ 5.4)	2º tertile EGDR (>5.4 <8.4)	3º tertile EGDR (≥ 8.4)	p-valor
n	128	42	43	43	-
WC	82.8 ± 9.5	86.9 ± 9.0[a,b]	82.2 ± 9.5	79.5 ± 8.6	0.001
WHtR	0.49 ± 0.05	0.51 ± 0.47[a,b]	0.49 ± 0.54	0.47 ± 0.52	< 0.001
CI	1.18 ± 0.07	1.21 ± 0.08[b]	1.17 ± 0.06	1.15 ± 0.06	0.001
LAP	19.5(11.9–30.2)	25.7 (18.1–38.3)[a,b]	15.3(10.4–30.9)[c]	15.9 (8.8–20.8)	0.005
BMI	24.6 ± 3.8	25.7 ± 4.2	24.5 ± 3.5	23.7 ± 3.6	0.052
BAI	58.3 ± 6.3	58.5 ± 5.2	58.3 ± 7.4	58.2 ± 6.2	0.975

WC = waist circumference; WHtR = waist-to-height ratio; CI = conicity index; LAP = lipid accumulation product; BMI = body mass index; BAI = body adiposity index. [a]Difference between tertile 1 and tertile 2, [b]Difference between tertile 1 and tertile 3, [c]Difference between tertile 2 and tertile 3.

Table 4 - Correlation between adiposity markers and insulin resistance measured by EGDR in individuals with type 1 diabetes

Markers	r	p-valor
WC	- 0.36	< 0.01
WHtR	- 0.39	< 0.01
CI	- 0.44	< 0.01
LAP	- 0.41	< 0.01
BMI	- 0.24	< 0.01
BAI	- 0.08	0.36

WC = waist circumference; CI = conicity index; LAP = lipid accumulation product; WHtR = waist-height ratio; BMI = body mass index; BAI = body adiposity index.

Table 5 - Gamma regression of body adiposity markers using as dependent variable EGDR

Variables	β	CI (95%)	p-valor
MODEL 1			
WC	- 0.014	- 0.021; -0.007	<0.001
WHtR	- 2.431	- 3.627; -1.235	<0.001
CI	- 2.027	- 2.981; -1.072	<0.001
LAP	-0.008	- 0.011; -0.004	<0.001
BMI	-0.021	-0.038; -0.004	0.017
MODEL 2			
WC	- 0.014	- 0.021; -0.007	<0.001
WHtR	- 2.322	- 3.508; -1.136	<0.001
CI	- 1.975	- 2.909; -1.041	<0.001
LAP	- 0.007	- 0.011; -0.004	<0.001
BMI	- 0.020	- 0.037; -0.003	0.023

Continue

Table 5 - Gamma regression of body adiposity markers using as dependent variable EGDR

Variables	β	CI (95%)	p-valor
MODEL 3			
WC	- 0.014	- 0.021; -0.007	<0.001
WHtR	- 2.208	- 3.573; -1.124	<0.001
CI	- 1.831	- 2.779; -0.883	<0.001
LAP	- 0.007	- 0.010; -0.004	<0.001
BMI	- 0.024	- 0.040; -0.007	0.006

WC = waist circumference; CI = conicity index; LAP = lipid accumulation product; WHtR = waist-height ratio; BMI = body mass index; CI = confidence interval. Model 1: Age, gender, triglyceride and glomerular filtration rate (MDRD). Model 2: Age, gender, triglyceride and glomerular filtration rate (CKD-EPI). Model 3: Age, gender, triglyceride and diabetes kidney disease. The lipid accumulation product was not adjusted for triglyceride since is contained in its equation.

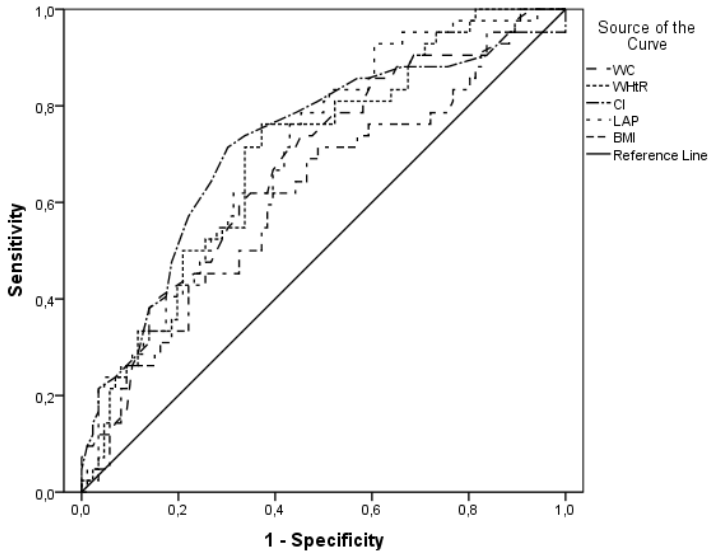

Figure 1 - ROC curve with Areas Under the Curve (AUC) of the waist circumference (WC), waist-height ratio (WHtR), conicity index (CI), lipid accumulation product (LAP) and body mass index (BMI) according to the most insulin resistant individuals.

Table 6. Description of adiposity markers to evaluate insulin resistance risk

Markers	AUC ± EP (CI 95%)	Cutoff	Sensibility% (CI 95%)	Specificity% (CI 95%)	p-valor
WC	0.678 ± 0.050 (0.580–0.776)	80.500	78.0 (61.8–80.5)	52.3 (35.5–64.4)	0.001
WHtR	0.697 ± 0.048 (0.603–0.791)	0.4969	76.2 (61.5–86.5)	62.8 (52.2–72.2)	< 0.001
CI	0.720 ± 0.050 (0.622–0.818)	1.1950	71.4 (58.9–84.7)	69.8 (55.8–75.4)	< 0.001
LAP	0.704 ± 0.047 (0.611–0.796)	13.8205	85.7 (72.1–93.3)	40.7 (30.9–51.2)	0.003
BMI	0.617 ± 0.053 (0.513–0.721)	24.9	59.5 (44.5–72.9)	60.5 (49.9–70.1)	0.032

WC = waist circumference; WHtR = waist-height ratio; CI = conicity index; LAP = lipid accumulation product; BMI = body mass index; AUC = area under the curve; SE = standard error; CI = confidence interval.

Table 7. Adiposity markers performance to evaluate insulin resistance risk by gender

Markers	AUC ± EP (CI 95%)	Cutoff	Sensibility% (CI 95%)	Specificity% (CI 95%)	p-valor
WC					
Women	0.623 ± 0.075 (0.476–0.770)	79.7	65.0 (38.6–78.1)	56.4 (44.3–71.7)	0.115
Men	0.763 ± 0.064 (0.611–0.860)	93.5	40.9 (23.2–61.3)	87.5 (73.9–94.5)	0.002
WHtR					
Women	0.664 ± 0.071 (0.524–0.803)	0.5	70.0 (53.1–88.8)	67.4 (48.6–75.5)	0.036
Men	0.737 ± 0.065 (0.610–0.865)	0.5	72.7 (56.5–89.8)	65.0 (47.0–75.8)	0.002
CI					
Women	0.641 ± 0.083 (0.477–0.804)	1.19	60.0 (38.6–78.1)	73.9 (55.2–80.9)	0.071
Men	0.791 ± 0.056 (0.681–0.900)	1.19	81.8 (66.6–95.2)	65.0 (47.0–75.8)	< 0.001
LAP					
Women	0.624 ± 0.075 (0.477–0.771)	13.8	80.0 (58.4–91.9)	30.4 (19.8–41.8)	0.112
Men	0.801 ± 0.054 (0.695–0.908)	13.8	90.9 (72.2–97.4)	50.0 (37.5–67.0)	< 0.001
BMI					
Women	0.583 ± 0.078 (0.429–0.736)	24.9	50.0 (29.9–70.0)	60.9 (48.6–75.5)	0.289
Men	0.646 ± 0.073 (0.502–0.790)	24.9	68.2 (47.3–86.3)	60.0 (44.6–76.6)	0.059

WC = waist circumference; CI = conicity index; LAP = lipid accumulation product; WHtR = waist-height ratio; BMI = body mass index; AUC = area under the curve; SE = standard error; CI = confidence interval

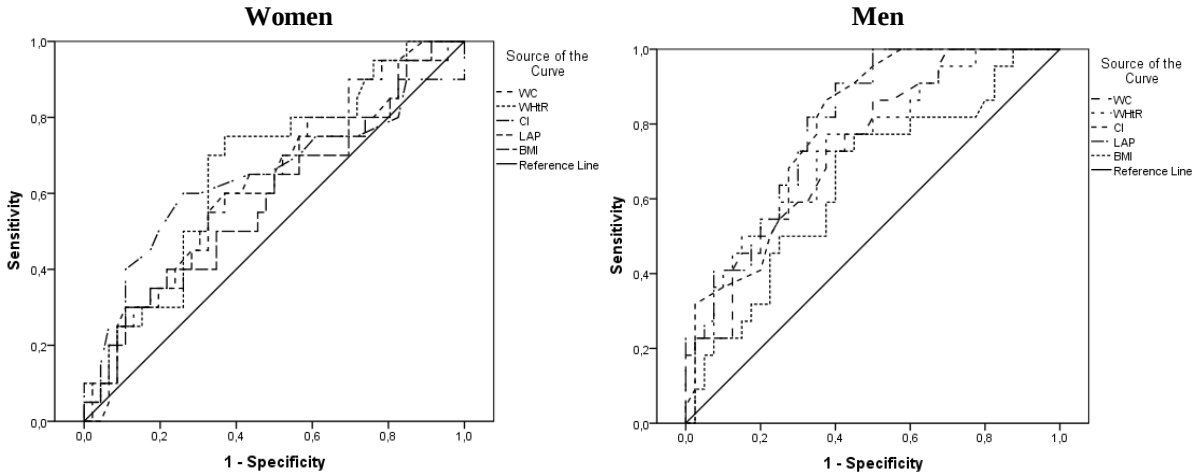

Figure 2 - ROC curve with Areas Under the Curve (AUC) of the waist circumference (WC), waist-height ratio (WHtR), conicity index (CI), lipid accumulation product (LAP) and body mass index (BMI) according to the most insulin resistant individuals by gender.

CONSIDERAÇÕES FINAIS

Os resultados do estudo sugerem que o índice de conicidade possui maior habilidade em predizer RI em adultos com diabetes tipo 1. Através de medidas antropométricas simples como circunferência da cintura, peso e estatura é possível identificar risco de RI, possibilitando que profissionais de saúde atuem com condutas preventivas.

Aferições isoladas de circunferência da cintura e de índice de massa corporal não foram os melhores preditores do desfecho estudado. Essas medidas antropométricas são frequentemente utilizadas na prática clínica, porém sugere-se a utilização dessas medidas associadas com o índice de conicidade para avaliar uma melhor relação com a RI em indivíduos adultos com diabetes tipo 1.

A partir desta dissertação, novos trabalhos e pesquisas poderão ser desenvolvidos em assuntos relacionados aos marcadores de adiposidade corporal, sendo possível a inclusão de outras medidas antropométricas como o diâmetro abdominal sagital, bem como utilizar um método de referência para avaliação da composição corporal considerado padrão ouro como o DEXA.

Sugere-se a realização de estudos prospectivos com avaliação da RI a partir do método de clampe em comparação com a fórmula EGDR e a verificação do desempenho de marcadores de adiposidade corporal comparados com o método de referência para avaliação da composição corporal. Além disso, abranger um maior número de indivíduos com diabetes tipo 1 e avaliar um ponto de corte definido para cada marcador estudado.