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MEDIDAS ULTRASSONOGRÁFICAS DE GORDURA ABDOMINAL E MEDIDAS ULTRASSONOGRÁFICAS AUTOMATIZADAS DA ESPESSURA MÉDIO-INTIMAL CAROTÍDEA EM ADOLESCENTES OBESOS

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Orientador:
Prof. Dr. Matteo Baldisserotto

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RESUMO

Importância: A obesidade tornou-se um importante problema de saúde pública devido à sua prevalência crescente nas últimas décadas e suas comorbidades. Muitos estudos têm relacionado gordura abdominal com anormalidades metabólicas e com aumento do risco de doenças cardiovasculares em adultos, mas poucos estudos examinaram essas questões em adolescentes. A doença aterosclerótica é a principal causa de morbidade e mortalidade em todo o mundo. A aterosclerose inicia-se na infância e a medida ultrassonográfica da espessura médio-intimal carotídea (EMIC) por ultrassonografia (US) pode ser usada para avaliar o risco cardiovascular nessa população. Ainda é uma questão de debate se a espessura da parede arterial aumenta com o índice de massa corporal (IMC).

Objetivo: O objetivo deste estudo foi avaliar a associação entre as medidas ultrassonográficas de gordura abdominal e as medidas ultrassonográficas automatizadas da EMIC, com dados antropométricos e laboratoriais em um grupo de adolescentes, a fim de identificar potenciais marcadores que possam ser usados para controlar o desenvolvimento de fatores de risco para doença cardiovascular.

Pacientes e métodos: Quarenta e cinco pacientes com idade entre 10 e 17 anos foram incluídos neste estudo de forma voluntária. Os indivíduos foram avaliados ambulatorialmente no Instituto da Criança da Universidade de São Paulo, em São Paulo, e no Hospital São Lucas, da Pontifícia Universidade Católica do Rio Grande do Sul, em Porto Alegre. Os adolescentes foram classificados como obesos ou eutróficos, de acordo com seu escore-z de IMC (adaptado para as crianças e adolescentes brasileiros). Determinou-se a circunferência abdominal (CA), a razão entre a circunferência abdominal e estatura (CA:A) e o índice de conicidade (IC) de todos os pacientes. Amostras de sangue foram obtidas de todos os indivíduos após 12 horas de jejum para medição da glicemia, triglicerídeos (TG), colesterol total (COL), HDL-colesterol (HDL), LDL-colesterol (LDL), insulina e apolipoproteína B (apoB). O índice HOMA-IR (Homeostasis Model Assessment), modelo matemático que quantifica a resistência à insulina por meio da fórmula: HOMA-IR = Insulina jejum (µUI/mL) x Glicose jejum (mmol/L) / 22,5, foi calculado, e todos os pacientes receberam uma

avaliação ultrassonográfica das gorduras (subcutânea, pré-peritoneal e intra-abdominal) e da EMIC.
Resultados: As medidas ultrassonográficas de gordura abdominal associaram-se com as medidas antropométricas, a glicose, a insulina e o HOMA-IR (exceto glicose e gordura pré-peritoneal máxima). Na análise multivariada, o escore-z do IMC, o IC e o HOMA-IR permaneceram associados de forma independente com o somatório de gordura dos pacientes. Apenas a gordura subcutânea mínima associou-se de forma independente com o HOMA-IR. Em relação à avaliação ultrassonográfica vascular, a EMIC não foi associada com o sexo ou com o escore-z do IMC. No entanto, EMIC de ambos os lados associou-se positivamente com a altura. Além disso, EMIC direita associou-se positivamente com CA e com o HOMA-IR e negativamente com os níveis de apoB. Na análise multivariada, apenas a altura permaneceu independentemente associada com EMIC (direita e esquerda).
Conclusões: A gordura subcutânea pode ser mais útil do que a gordura visceral como um marcador para a resistência à insulina em adolescentes. Na aferição ultrassonográfica da espessura médio-intimal carotídea, apenas a altura foi independentemente associada com esse método automatizado. Estudos adicionais devem ser conduzidos de forma prospectiva, a fim de identificar potenciais marcadores que possam ser utilizados para evitar o desenvolvimento e a progressão de patologias cardiovasculares em pacientes pediátricos.

Palavras-chave: Gordura abdominal. Gordura abdominal subcutânea. Gordura intra-abdominal. Obesidade. Ultrassonografia. Espessura médio-intimal carotídea. Adolescente. Técnicas de diagnóstico cardiovascular. Resistência à insulina.

ABSTRACT

Importance: Obesity has become a major public health problem due to its growing prevalence in recent decades and its comorbidities. Many studies have related abdominal fat to metabolic abnormalities and increased risk of cardiovascular diseases in adults, but there are few studies that have examined these questions in adolescents. Atherosclerotic disease is the major cause of morbidity and mortality around the world. Atherosclerosis has been demonstrated to begin in childhood and measurement of carotid artery intima-media thickness (cIMT) by ultrasonography (US) can be used to evaluate cardiovascular risk in this population. Whether the thickness of arterial wall increases with body mass index (BMI) is still a matter of debate.

Objective: The purpose of this study was to assess the association between ultrasound measurements of abdominal fat and automated US measurements of cIMT with anthropometric and laboratory data in a group of adolescents in order to identify potential markers that may be used to control the development of risk factors for cardiovascular disease in adolescents.

Patients and Methods: Forty-five patients aged 10 to 17 years were enrolled in this study voluntarily. The subjects were evaluated in a pediatric outpatient clinic at either the Instituto da Criança da Universidade de São Paulo in São Paulo or the Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul in Porto Alegre. Adolescents were classified as obese or eutrophic according to their body mass index z-score for Brazilian children and adolescents. We determined waist circumference, waist-to-height ratio and conicity index from all subjects. We obtained blood samples from all subjects after 12 hours of fasting to measure glycemia, triglyceride, total cholesterol, HDL-cholesterol, LDL-cholesterol, insulin, and apolipoprotein B levels. We calculated the patients' HOMA-IR index, a mathematical model that quantifies insulin resistance based on the formula: HOMA-IR = fasting Insulin (µUI/mL) x fasting glucose (mmol/L) / 22.5. All patients received an ultrasound assessment of subcutaneous tissue, pre-peritoneal fat, and intra-abdominal fat and all of them received an US assessment of the common carotid artery intima-media thickness.

Results: Ultrasonographic measures of abdominal fat were found to be associated with anthropometric measurements, glucose level, insulin level, and HOMA-IR (except glucose and maximal pre-peritoneal fat). In our multivariate analysis, body mass index z-score, conicity index, and HOMA-IR remained independently associated with the subjects' sum of fat. Only minimal subcutaneous fat associated independently with HOMA-IR. In relation to the vascular US evaluation, cIMT was not associated with sex or BMI z-score. However, cIMT on both the right and the left sides was found to associate positively with height. Additionally, cIMT on the right side was found to associate positively with waist circumference and HOMA-IR, and negatively with apolipoprotein B levels. In our multivariate analysis, only height remained independently associated with cIMT (right and left).

Conclusions: Subcutaneous fat may be more useful than visceral fat as a marker for insulin resistance in adolescents. In the US measurements of both cIMT, only height was independently associated with this automated method. Further studies should be conducted on a prospective basis in order to identify potential markers that could be used to prevent the development and progression of cardiovascular pathology in pediatric patients.

Key-words: Abdominal Fat. Subcutaneous Fat, Abdominal. Intra-Abdominal Fat. Obesity. Ultrasonography. Carotid intima-media thickness. Adolescent. Diagnostic techniques, cardiovascular. Insulin resistance.

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LISTA DE ABREVIATURAS

ApoB: apolipoproteína B

CA: circunferência abdominal

CA:A: razão entre a circunferência abdominal e estatura

COL: colesterol total

EMIC: espessura médio-intimal carotídea

HDL: HDL-colesterol

HOMA-IR: Homeostasis Model Assessment of Insuline Resistance

IC: índice de conicidade

IMC: índice de massa corporal

LDL: LDL-colesterol

RM: ressonância magnética

TC: tomografia computadorizada

TG: triglicerídeos

US: ultrassonografia

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CAPÍTULO I

APRESENTAÇÃO
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1.1 APRESENTAÇÃO

A obesidade na infância é hoje considerada uma doença de proporções epidêmicas (1). A prevalência de obesidade, na Inglaterra, em crianças de dois a dez anos subiu de 9,9% para 13,4% entre 1995 e 2004 (2) e, nos Estados Unidos, aumentou de 10 a 13% entre 2000 e 2004 (3). Dados da Organização Mundial de Saúde mostram aumento da prevalência de obesidade no Brasil em crianças menores de cinco anos de 6,6%, em 1996, para 7,3%, em 2006 (4), sendo a região Sul com a maior prevalência nessa faixa etária – 8,8% (5).

As complicações do excesso de peso podem afetar crianças, mas a maior preocupação está focada em consequências em longo prazo (6). A obesidade tem se mostrado um importante preditor para distúrbios metabólicos, incluindo hiperinsulinemia, intolerância à glicose, dislipidemia, hipertensão e doença cardiovascular (7-10). A gordura visceral desempenha um papel crítico na patogênese da síndrome metabólica por meio do aumento da produção de ácidos graxos livres, citocinas e peptídeos vasoativos que exercem efeitos diretos na vasculatura, aumentando o risco cardiovascular (11).

Vários critérios têm sido adotados para definir obesidade na infância e na adolescência, existindo, ainda, divergências na literatura (12). Índice de massa corporal (IMC) é um indicador útil da adiposidade global (9). Há evidências crescentes de que não apenas o total de gordura, mas também a sua distribuição corporal, determina o risco para doenças metabólicas e cardiovasculares (10). A circunferência abdominal tem demonstrado ser um marcador altamente sensível e específico do acúmulo de gordura corporal superior em crianças (13). A razão da circunferência abdominal pela altura está sendo cada vez mais utilizada para acessar o risco de doenças relacionadas à obesidade central (13). Métodos de imagem têm sido usados para acessar a distribuição corporal de gordura. Tomografia Computadorizada (TC) e Ressonância Magnética (RM) são técnicas de imagem acuradas para acessar a distribuição de gordura corporal, mas suas desvantagens são o alto custo, a exposição à radiação (no caso da TC) e o uso limitado ao cenário de pesquisa. Ultrassonografia (US) tem sido proposta como uma técnica alternativa não invasiva para medir espessura da gordura subcutânea e visceral (14) mostrando-se como método confiável, reproduzível para diagnosticar obesidade intra-abdominal (15) e superior aos dados derivados de medidas antropométricas nas associações com fatores de risco cardiovascular (11, 16).

Em relação ao risco cardiovascular, sabe-se que a aterosclerose se inicia na infância (17) e se desenvolve silenciosamente por décadas antes que eventos clínicos, como infarto do miocárdio ou acidente vascular encefálico ocorram. (18). Novas tecnologias permitem identificar a progressão da doença da parede arterial (19) e a medida ultrassonográfica da espessura médio-intimal carotídea (EMIC) é um método factível, direto, não invasivo e com boa correlação histológica que permite avaliar e detectar lesões pré-clínicas da parede arterial (1, 17). Estudos na infância mostraram aumento significativo da EMIC em crianças com diabetes tipo 1, hipertensão e hipercolesterolemia familiar, enquanto dados discordantes no aumento de tal espessura são reportados em crianças obesas (1).

Poucos estudos avaliaram as associações das medidas ultrassonográficas de gordura e das medidas ultrassonográficas da EMIC com medidas antropométricas, e alterações metabólicas em crianças e adolescentes. Nesse estudo, nós avaliamos as associações entre as medidas ultrassonográficas de gordura (gorduras pré-peritoneal, subcutânea e intra-abdominal) e da espessura médio-intimal carotídea com as medidas antropométricas, e dados laboratoriais em um grupo de adolescentes com o objetivo de identificar potenciais marcadores que possam ser usados para ajudar a prevenir o desenvolvimento de fatores de risco para doença cardiovascular em crianças e adolescentes.

A dissertação compõe-se dos seguintes capítulos: introdução (apresentação, justificativa e objetivos), desenvolvimento (artigo original 1 e artigo original 2) e conclusão.

Os artigos originais recebem os seguintes títulos:

1-) Gordura subcutânea: um marcador melhor do que gordura visceral para resistência à insulina em adolescentes obesos;

2-) Avaliação ultrassonográfica automatizada da espessura médio-intimal carotídea em adolescentes obesos.

1.2 JUSTIFICATIVA

A obesidade tornou-se um importante problema de saúde pública devido à sua prevalência crescente nas últimas décadas e suas comorbidades (7). Dados de pesquisas nacionais brasileiras realizadas desde 1970 têm indicado um aumento na prevalência desta doença (20). A obesidade na infância é um importante fator de risco para o desenvolvimento de síndrome metabólica na idade adulta, incluindo diabete tipo 2 e doenças cardiovasculares (21). O padrão de distribuição de gordura corporal é de grande importância para a morbimortalidade cardiovascular (22). A gordura visceral tem um papel importante na patogênese de doenças metabólicas e cardiovasculares em adultos e crianças (3), enquanto a patogenia da gordura subcutânea parece ser diferente entre esses grupos etários (23).

A ecografia abdominal é um método confiável e reprodutível para acessar a quantidade de tecido adiposo intra-abdominal e para diagnosticar obesidade intra-abdominal (15), bem como para quantificar a gordura subcutânea (24). Em relação ao risco cardiovascular, a medida da espessura médio-intimal carotídea é atualmente recomendada pela American Heart Association para inclusão na avaliação do risco de desenvolvimento de doença cardiovascular em pacientes adultos de risco intermediário classificados pelo escore de Framingham (19) e, em pacientes pediátricos de alto risco, a avaliação ultrassonográfica carotídea pode ser utilizada para avaliar o risco coronariano (25).

1.3 OBJETIVOS

Objetivo geral

Verificar a associação entre medidas ultrassonográficas de gordura e da espessura médio-intimal carotídea com medidas antropométricas e dados laboratoriais em adolescentes.

Objetivos específicos

1. Verificar a presença de associação entre as medidas ultrassonográficas de gordura (gordura subcutânea, pré-peritoneal, intra-abdominal e o somatório de gordura) com o sexo, a idade, a estatura, o índice de massa corporal, a circunferência abdominal, a razão entre a circunferência abdominal e a estatura, e o índice de conicidade em adolescentes;

2. Verificar a presença de associação entre as medidas ultrassonográficas de gordura (gordura subcutânea, pré-peritoneal, intra-abdominal e o somatório de gordura) com a apolipoproteína B, o perfil lipídico, a insulina, a glicose e o índice HOMA-IR em adolescentes;

3. Verificar a presença de associação entre a espessura médio-intimal carotídea direita e esquerda medidas por ultrassonografia com o sexo, a idade, a estatura, o índice de massa corporal e a circunferência abdominal em adolescentes;

4. Verificar a presença de associação entre a espessura médio-intimal carotídea direita e esquerda medidas por ultrassonografia com a apolipoproteína B, o perfil lipídico, a insulina, a glicose e o índice HOMA-IR em adolescentes.

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CAPÍTULO II

2.1 ARTIGO ORIGINAL I

GORDURA SUBCUTÂNEA: UM MARCADOR MELHOR DO QUE GORDURA VISCERAL PARA RESISTÊNCIA À INSULINA EM ADOLESCENTES OBESOS

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Abstract	Importance: Many studies have related abdominal fat to metabolic abnormalities and increased risk of cardiovascular diseases in adults, but there are few studies that have examined these questions in adolescents. Objective: The purpose of this study was to assess the association between ultrasound measurements of abdominal fat with anthropometric and laboratory data in adolescents in order to identify potential markers that may be used to control the development of risk factors for cardiovascular disease in adolescents. Design: Cross-sectional study. Setting: The subjects were evaluated in a pediatric outpatient clinic at either the Instituto da Criança da Universidade de São Paulo in São Paulo or the Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul in Porto Alegre. Participants: Forty-five patients aged 10 to 17 years were enrolled in this study voluntarily. Adolescents were classified as obese or eutrophic according to their body mass index z-score for Brazilian children and adolescents. We determined waist circumference, waist-to-height ratio, conicity index, and obtained blood samples from all subjects. All patients received an ultrasound assessment of subcutaneous tissue, pre-peritoneal fat, and intra-abdominal fat. Main Outcome Measures: Association among ultrasonographic measures of fat with anthropometric and laboratory measurements. Results: Ultrasonographic measures of abdominal fat were found to be associated with anthropometric measurements, glucose level, insulin level, and HOMA-IR (except glucose and maximal pre-peritoneal fat). In our multivariate analysis, body mass index z-score, conicity index, and HOMA-IR remained independently associated with the subjects' sum of fat. Only minimal subcutaneous fat associated independently with HOMA-IR. Conclusion and Relevance: Subcutaneous fat may be more useful than visceral fat as a marker for insulin resistance and, as a consequence, for cardiovascular risk in obese adolescents.
Associate Editor	Assigned
Subject Areas	Adolescent health, Adolescent medicine, Endocrinology, Metabolic disease
Potential Conflicts of Interest	No, the author(s) has no potential conflicts of interest to be disclosed.

May 14, 2013

Editorial Board

JAMA Pediatrics

Dear Editors,

I'm sending the study " **SUBCUTANEOUS FAT: A BETTER MARKER THAN VISCERAL FAT FOR INSULIN RESISTANCE IN OBESE ADOLESCENTS**" for your appreciation. Few studies have evaluated how well ultrasound measurements of fat associate with anthropomorphic measurements and laboratory data in juveniles. The significance of an accumulation of visceral versus subcutaneous fat in obese children has not yet been established and, therefore, this manuscript tries to contribute for this purpose.

We declare that:

1. There are no prior publications or submissions with any overlapping information, including studies and patients;
2. The current manuscript has not been and will not be submitted to any other journal while it is under consideration by *JAMA Pediatrics*;
3. There is no potential conflict of interest, real or perceived, for all named authors.
4. The authors declare that they didn't receive any form of payment, grant or honorarium to produce this manuscript.
5. We declare that each author listed on the manuscript has seen and approved the submission of this version of the manuscript to *JAMA Pediatrics* and takes full responsibility for the manuscript.

We thank you for your attention and we look forward to hearing from you at your earliest convenience.

Yours Sincerely,

Arthur Lazaretti, M.D., Pediatric Nephrologist

SUBCUTANEOUS FAT: A BETTER MARKER THAN VISCERAL FAT FOR INSULIN RESISTANCE IN OBESE ADOLESCENTS

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Introduction

Obesity has become a major public health problem due to its growing prevalence in recent decades and its comorbidities [1]. Indeed, the American Heart Association categorizes obesity as a major risk factor for coronary disease [2]. There is growing evidence that one's risk for metabolic and cardiovascular diseases is determined by not only total fat, but also one's fat distribution in the body [3].

Body mass index (BMI) is a useful indicator of global adiposity [4]. Being a simple and reasonably reliable, albeit crude, measure of obesity, it is now widely recommended for pediatric use [5]. However, obesity cannot be considered a homogenous condition. In fact, regional fat distribution in obese patients may be a more important determinant of cardiovascular and metabolic pathogenesis than global fat volume [6]. However, BMI may be a less reliable index of obesity in children than in adults.

Waist circumference (WC) has been shown to be a highly sensitive and specific marker of upper body fat accumulation in children [7]. Thus, WC measurement, either alone or in combination with stature—which influences WC—may offer a more sensitive means for identifying overweight and obese children at increased risk for developing metabolic complications than BMI [7]. The ratio of WC to height (WC:H) is increasingly being used to assess the risk for diseases related to central fatness [7]. The conicity index (CI), a parameter of waist circumference in relation to height and weight, appears to have a prognostic value in juveniles that is similar to that of waist to hip ratio in adults [8].

Imaging methods, such as computed tomography (CT) and magnetic resonance (MR), can reveal body fat distribution with good accuracy. However, these techniques have several disadvantages, such as high cost, radiation exposure (in the case of CT), and limited access by researchers. Recently, ultrasonography (US) has been proposed as an alternative, non-invasive technique for obtaining accurate measures of subcutaneous and visceral fat thickness [9]. Evaluations of intra-abdominal fat (IAF) using US, as proposed by Armellini et al. [10], have been shown to correlate strongly with visceral fat area measurements obtained by CT [11]. Abdominal echography, when applied using a strict protocol, is a reliable and reproducible method to quantify intra-abdominal adipose tissue and diagnose intra-abdominal obesity [12], especially when CT and MR are not available [13]. The advantages of US methods include speed, broad availability, and relatively low cost [14].

Visceral fat thickness, as measured by US examination, has correlated consistently with total visceral fat and with cardiovascular risk factors [9]. In multiple regression models, the addition of US measures significantly improved the estimates of visceral fat and subcutaneous fat in both men and women over and above the contribution of standard anthropometric variables [13]. Furthermore, US measurements associate better with cardiovascular risk factors than do values derived from anthropometric measures [15, 16].

Few studies have evaluated how well US measurements correlate with anthropomorphic measurements and laboratory data in juveniles. The significance of an accumulation of visceral versus subcutaneous fat in obese children [14] and young adults [17] has not yet been established and remains controversial. In this study, we examined how closely pre-peritoneal, subcutaneous, and intra-abdominal fat measures associate with anthropometric and laboratory data in a group of adolescents with the aim of identifying potential markers that could be used to help prevent the development of risk factors for cardiovascular disease in children and adolescents.

Methods

Subjects

Two groups of subjects, 10–17 years of age, were enrolled in this study: an obese group meeting the criterion for obesity according to BMI z-score for Brazilian children and adolescents [18], and a eutrophic group consisting of subjects with BMIs not meeting that obesity criterion. The exclusion criteria were hepatorenal disease, use of drugs that are potentially hepatotoxic or nephrotoxic, and diagnoses with a chronic disease, such as hypertension or diabetes mellitus. The subjects were evaluated in a pediatric outpatient clinic at either the Instituto da Criança da Universidade de São Paulo in São Paulo or the Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul in Porto Alegre. This research project was approved by the Research Ethics Committee of both institutions. Parents or legal guardians read and signed an informed consent approved for this study by the University's Review Board.

Measurements

The individuals were weighed and measured according to standardized procedures[19][32], while barefoot and wearing only light clothing. For body weight determination, we used a mechanical Filizola® brand scale with a coupled stadiometer that was calibrated by the National Institute of Metrology, Standardization and Industrial Quality of Rio Grande do Sul (INMETRO-RS). The BMI for each subject was calculated as follows: BMI = body weight (kg) / height^2 (m)]. Each subject's waist circumference was measured twice with an anthropometric fiberglass tape at the midpoint between the last rib and the iliac crest, and we recorded the average of two measures. The waist-to-height ratio was determined by dividing waist circumference (cm) by height (cm), and CI was calculated from weight, height, and WC using the following mathematical equation:

$$\text{C Index} = \frac{\text{Waist Circumference (m)}}{0.109\sqrt{\dfrac{\text{Body Weight (Kg)}}{\text{Height (m)}}}}$$

Blood pressure was measured with an aneroid sphygmomanometer in accordance with the criteria recommended by the National High Blood Pressure Education Program Working Group on Children and Adolescents[20][33]. We obtained blood samples from all subjects after 12 hours of fasting to measure glycemia, triglyceride (TG), total cholesterol (TC), HDL-cholesterol (HDL), LDL-cholesterol (LDL), insulin, and apolipoprotein B (apoB) levels. TC, HDL, and TG levels were measured enzymatically, and LDL levels were calculated using the Friedewald formula. The TC, LDL, HDL and TG values were stratified by percentile according to age and sex [21]. Insulin and apoB levels were determined with chemiluminescence and automated immunonephelometry, respectively.

We calculated the patients' HOMA-IR index, a mathematical model that quantifies insulin resistance based on the formula: HOMA-IR = fasting Insulin (µUI/mL) x fasting glucose (mmol/L) / 22.5. All patients received an US assessment of subcutaneous tissue, pre-peritoneal fat, and intra-abdominal fat and each patient's sum of fat was calculated according to this formula: Smax + Smin + Pmax + Pmin + IAF.

US of subcutaneous tissue, pre-peritoneal fat, and intra-abdominal fat

We performed US examinations using an HD11 Philips machine (Philips Medical Systems, Bothell, WA). The transducer was placed on the skin gently to avoid compressing the fat beds. US measurements of the subcutaneous, pre-peritoneal, and visceral abdominal fat were performed with patients lying in a supine position. A 7.5–10 MHz linear transducer was maintained perpendicular to the skin in the upper middle abdominal region as we performed each exam longitudinally from the xiphoid process to the umbilical region across the length of the linea alba, taking care that the surface of the liver was nearly parallel to the skin.

Maximum subcutaneous fat thickness (Smax) was measured 5 cm from the umbilicus on the umbilical line, while minimum subcutaneous fat thickness (Smin) was measured immediately below the xiphoid process. We performed the measurements directly from the screen, using an electronic caliper on the skin-fat interface (excluding the skin) and on the muscle-fat interface, and then measured the average thickness. Measurements of the maximum and minimum beds of pre-peritoneal fat (Pmax and Pmin, respectively) were performed in the region where the fat was most easily visualized, immediately below the xiphoid process, between the internal side of the linea alba and the surface of the liver.

Finally, we used a 3.5–5.0-MHz curvilinear transducer to measure the thickness of the visceral fat bed, commonly referred to as IAF, between the internal side of the abdominal muscle and the anterior wall of the aorta.

Statistical analysis

Demographic data are reported as means ± standard deviation (SD), for parametric variables, or medians with interquartile ranges, for non-normally distributed variables. Generalized Linear Models were used to analyze the relationships between the main outcomes (sum of fat) and the predictor variables (sex, age, height, weight, z-score BMI, WC, WC:H, CI, and HOMA-IR index). In another multivariate analysis model, US fat measurements were taken as predictor variables and HOMA-IR was taken as the outcome variable. Initially, all covariates that presented with $p < 0.15$ and with clinical relevance were included in the multivariate model. Covariates for which critical (i.e. not significant) *p* values were obtained were then excluded individually. This exclusion step was repeated until all variables remaining in the model presented had *p* values <0.05. All analyses were performed with SPSS v.18 software (SPSS Inc, Chicago, IL).

Results

The characteristics of the enrolled subjects are summarized in Table 1. The cohort was majority female (53.3%) and majority obese (55.5%), with a mean BMI of 27.23 ± 8.46 kg/m^2 and a mean age of 13.06 ± 2.34 years. The average anthropometric values and US measurements of abdominal fat are reported in Table 1. About two-thirds of the subjects in the study cohort had TC (64.4%) and LDL (68.8%) levels below the 75^{th} percentile (considered acceptable for their age). However, nearly half (46.5%) of the subjects had HDL levels above the 50th percentile for their sex and age, and nearly a third (32.5%) had TG levels above the 75^{th} percentile.

Univariate analysis (Tables 2 and 3) indicated that our US measurements of abdominal fat (Pmax, Smax, Pmin, Smin, IAF, and the sum of these variables) were directly associated with the following anthropometric measurements: BMI z-score, WC, WC:H, and CI. Additionally, blood glucose level, blood insulin level, and HOMA-IR associated directly with measures of abdominal fat (except blood glucose was not associated with Pmax). None of the fat measures had associations with gender or height. Age was found to be associated with all of the US fat measures except Pmax and Pmin.

In multivariable model using sum of fat as the outcome variable and BMI z-score, CI, and HOMA-IR as predictor variables (Table 4), sum of fat was found to associate positively with the aforementioned predictor variables. In another multivariate analysis model, in which US fat measurements were taken as predictor variables and HOMA-IR was taken as the outcome variable, only minimal subcutaneous fat was found to associate independently with HOMA-IR (β = 2.166; 95% CI, 1633–2699; $p < 0.001$).

Discussion

A direct association between anthropometric measurements and US measurements of fat was observed in the present study of adolescents. Screening for adiposity in childhood is somewhat controversial at present because there is limited research in the literature that has related body composition in childhood directly to adult health outcomes [8]**.** To date, few studies have associated anthropometric measurements (BMI, WC, WC:H, and CI) with US measures of abdominal fat in pediatric patients and adolescents. However, Stolk et al. found that abdominal US examination was a reliable and reproducible method for quantitation of IAF and diagnosis intra-abdominal obesity in a group of moderately overweight Dutch adults [12]. Additionally, Gradmark et al. reported that BMI, WC:H and WC correlated with US measurements of superficial subcutaneous adipose tissue in a population-based cohort of Swedish adults and concluded that simple anthropometric measures of abdominal obesity provided reasonably valid estimates of abdominal adiposity in this population [22]. Meanwhile, robust statistical evidence from studies involving more than 300,000 adults in several ethnic groups demonstrates the superiority of WC:H over WC and BMI for detecting cardiometabolic risk factors in both sexes, indicating that waist-to-height ratio should be considered as a screening tool, at least in adults [23]. Notably, Taylor et al. demonstrated that, relative to CI, WC was a superior anthropometric indicator of regional fat distribution in children [8]. In our study, all anthropometric measures were found to be predictive of US measurements of abdominal fat, whereas CI emerged as an independent variable for prediction of sum of fat from US measurements.

Although sex differences are known to influence systemic body fatness as well as the pattern of fat distribution in both adults and children [14], we did not observe any associations of gender with particular fat measures in our study. However, we did find that age associated with subcutaneous fat measures, IAF and sum of fat. Our findings complement Meriño-Ibarra et al.'s study reporting that US measurements correlate with age as well as anthropometric and biochemical variables [24].

In our study, we found that blood glucose and insulin levels and HOMA-IR generally associated with measures of abdominal fat. However, we didn´t observe a significant association between maximum preperitoneal fat and glucose levels, constrasting with the findings of Tamura et al., who found that that Pmax was a better predictor of insulin levels in 9–15-year-olds than any other indices related to obesity [14].

Visceral fat's pathogenic role in children appears to be similar to that in adults. However, the role of subcutaneous fat in obesity in children appears to be different than that in adults [14]. Although visceral fat is generally considered to be more strongly associated with metabolic risk factors than subcutaneous fat, it is possible that subcutaneous fat may nevertheless contribute to greater absolute risk due to its greater volume [4]. Findings by Tershakovec et al. suggest that subcutaneous fat quantity may be associated with insulin resistance [25]. In our study, only Smin associated independently with HOMA-IR, corroborating the hypothesis that, in adolescents, subcutaneous fat may associate more closely with insulin resistance than visceral fat.

Our study have certain limitations. The sample size limits the power of some analyses, as the possible associations among laboratory data and the ultrasonographic measures of fat. Furthermore, no functional measure of insulin resistance was available in the study. Insulin resistance can be quantified directly by two general methods: glucose clamp technique or measurement of insulin-mediated changes in glucose disappearance rates after intravenous glucose challenge (minimal model approach). These methods provide precise quantitative measures of insulin resistance but they are costly, challenging to perform, moderately invasive and they are best suited for studies involving tens to hundreds of individuals, being impractical for routine clinical use [26]. Finally, we had only ultrassonographic measures of fat, not other techniques such as CT or MRI, but these other techniques's measures were not the purpose of the study and have several disadvantages, such as high cost, radiation exposure (in the case of CT), and limited access by researchers.

Based on this study's findings, we can conclude that BMI and anthropometric measurements are associated with US fat measurements, as well as with certain metabolic changes known to be associated with obesity-related morbidity. Our findings that subcutaneous fat measures associated robustly with HOMA-IR values in obese adolescents suggest that subcutaneous fat may be a more useful marker than visceral fat for development of insulin resistance and, as a consequence, for cardiovascular risk in obese adolescents.

Table 1. Characteristics of the patient cohort (N = 45).

Characteristic	Value[a]
Sex (No. females)	24
Nutritional status (No. Obese)	25
Age (y)	13.06 $\pm$ 2.34
BMI (kg/m^2)	27.23 $\pm$ 8.46
Median z-score BMI (25th–75th interquartile range)	2.69 (-0.15–3.26)
WC (cm)	90 $\pm$ 20
WC:H	0.56 $\pm$ 0.13
CI	1.26 $\pm$ 0.11
Pmax (cm)	1.03 $\pm$0.36
Smin (cm)	1.5 $\pm$ 0.92
Pmin (cm)	0.46 $\pm$ 0.27
Smax (cm)	1.88 $\pm$ 1.12
IAF (cm)	2.55 $\pm$ 1.21
Sum of fat (cm)	7.35 $\pm$ 3.39
ApoB (g/L)	0.63 $\pm$ 0.15
TC, No. (%) patients below 75th percentile[b]	29 (64.4%)
HDL, No. (%) patients above 50th percentile	20 (46.5%)
LDL , No. (%) patients below 75th percentile[b]	31 (68.8%)
TG, No. (%) patients above 75th percentile	14 (32.5%)
Insulin (pmol/L)	13.3 $\pm$ 9.98
Glucose (mmol/L)	4.73 $\pm$ 0.4
HOMA-IR	2.96 $\pm$ 2.57

[a]Unless otherwise indicated, values are means ± SDs.
[b]considered accetpable for age.
Abbreviations: BMI, body mass index; WC, waist circumference; WC:H, ratio between WC and height; CI, conicity index; Pmax, maximum pre-peritoneal fat; Smin, minimum subcutaneous fat thickness; Pmin, minimum pre-peritoneal fat; Smax, maximum subcutaneous fat thickness; IAF, intra-abdominal fat; ApoB, apolipoprotein B; TC, total cholesterol; HDL, HDL-cholesterol; LDL, LDL-cholesterol; TG, triglycerides; HOMA-IR, homeostasis model assessment.

Table 2. Univariate analysis between subcutaneous and preperitoneal fat measured by US, anthropometric data, and HOMA-IR index.

Variable	Pmax β (95% CI)	*p*	Smax β (95% CI)	*p*	Pmin β (95% CI)	*p*	Smin β (95% CI)	*p*
Obese nutritional status	0.247 (0.050–0.445)	.01	2.044 (1.775–2.313)	<.001	0.361 (0.242–0.481)	<.001	1.632 (1.385–1.879)	<.001
BMI Z-score	0.068 (0.020–0.115)	.005	0.505 (0.442–0.568)	<.001	0.096 (0.068–0.123)	<.001	0.400 (0.340–0.460)	<.001
WC	0.702 (0.212–1.192)	.005	5.174 (4.541–5.808)	<.001	1.018 (0.750–1.286)	<.001	4.028 (3.401–4.654)	<.001
WC:H	1.089 (0.325–1.852)	.005	8.180 (7.286–9.075)	<.001	1.541 (1.110–1.972)	<.001	6.428 (5.545–7.310)	<.001
CI	0.952 (0.078–1.827)	.03	7.192 (5.282–9.102)	<.001	1.235 (0.644–1.827)	<.001	5.576 (3.940–7.212)	<.001
HOMA-IR	0.045 (0.002–0.089)	.04	0.347 (0.258–0.435)	<.001	0.068 (0.042–0.094)	<.001	0.289 (0.218–0.360)	<.001

Abbreviations: US, ultrasonograhy; BMI, Body Mass Index; WC, waist circumference; WC:H, the ratio between WC and height; CI, conicity index; HOMA-IR, homeostasis model assessment of insulin resistance; Pmax, maximum pre-peritoneal fat; Smax, maximum subcutaneous fat thickness; Pmin, minimum pre-peritoneal fat; Smin, minimum subcutaneous fat thickness; IAF, intra-abdominal fat.

Table 3. Univariate analysis between intra-abdominal fat and the sum of fat measured by US, anthropometric data, and HOMA-IR index

Variable	IAF β (95% CI)	*p*	Sum of fat β (95% CI)	*p*
Obese nutritional status	1.865 (1.414 to 2.317)	<.001	6.082 (5.224–6.939)	<.001
BMI Z-score	0.466 (0.358–0.574)	<.001	1.520 (1.326–1.714)	<.001
WC	4.753 (3.689–5.818)	<.001	15.535 (13.751–17.319)	<.001
WC:H	7.677 (6.131–9.223)	<.001	24.682 (22.300–27.064)	<.001
CI	7.089 (4.879–9.298)	<.001	22.318 (16.927–27.709)	<.001
HOMA-IR	0.288 (0.162–0.413)	<.001	1.021 (0.746–1.297)	<.001

BMI, body mass lidex; WC, waist circumference; WC:H, the ratio between WC and height; CI, conicity index; HOMA-IR, homeostasis model assessment of insulin resistance; IAF, intra-abdominal fat.

Table 4. Multivariable analysis between the sum of fat, anthropometric data, and HOMA-IR index

Variables	Sum of fat β (95% CI)	*p*
BMI (Z-score)	0.979 (0.719–1.240)	<.001
CI	6.736 (2.518–10.954)	.002
HOMA-IR	0.296 (0.103–0.489)	.003

BMI,body mass index; CI, conicity index; HOMA-IR, homeostasis model assessment of insulin resistance.

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CAPÍTULO III

3.1 – ARTIGO ORIGINAL II

AVALIAÇÃO ULTRASSONOGRÁFICA AUTOMATIZADA DA ESPESSURA MÉDIO-INTIMAL CAROTÍDEA EM ADOLESCENTES OBESOS

European Journal of Pediatrics

Automated ultrasound evaluation of carotid intima-media thickness in obese adolescents

--Manuscript Draft--

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Abstract:	Atherosclerotic disease is the major cause of morbidity and mortality around the world. Atherosclerosis has been demonstrated to begin in childhood and measurement of carotid artery intima-media thickness (cIMT) by ultrasonography (US) can be used to evaluate cardiovascular risk in this population. Whether the thickness of arterial wall increases with body mass index (BMI) is still a matter of debate. The purpose of this study was to assess the association with automated US measurements of cIMT with anthropometric and laboratory data in a group of adolescents in order to identify potential markers that could be used to prevent the development and progression of cardiovascular pathology in pediatric patients. Forty-five patients aged 10 to 17 years were enrolled in this study voluntarily. Adolescents were classified as obese or eutrophic according to their BMI z-score for Brazilian children and adolescents. We determined waist circumference (WC) and obtained blood samples from all subjects. All patients received an US assessment of the common carotid artery intima-media thickness. The cohort was majority female and majority obese. cIMT was not associated with sex or BMI z-score. However, cIMT on both the right and the left sides was found to associate positively with height. Additionally, cIMT on the right side was found to associate positively with WC and HOMA-IR, and negatively with

	apolipoprotein B levels. In our multivariate analysis, only height remained independently associated with cIMT (right and left). Conclusion: Only height was independently associated with automated ultrasound measurements of both carotid intima-media thickness.
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Editorial Board

European Journal of Pediatrics

Dear Editors,

I'm sending the study "***Automated ultrasound evaluation of carotid intima-media thickness in obese adolescents***" for your appreciation. Few studies have evaluated how well automated ultrasound measurements of carotid intima-media thickness associate with anthropomorphic measurements and laboratory data in juveniles.

We declare that:

1. There are no prior publications or submissions with any overlapping information, including studies and patients;
2. The current manuscript has not been and will not be submitted to any other journal while it is under consideration by *European Journal of Pediatrics*;
3. This study had been approved by the ethics committee and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.
4. There is no potential conflict of interest, real or perceived, for all named authors.
5. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript to *European Journal of Pediatrics* and takes full responsibility for the manuscript.

We thank you for your attention and we look forward to hearing from you at your earliest convenience.

Yours Sincerely,

Arthur Lazaretti, M.D., Pediatric Nephrologist

Automated ultrasound evaluation of carotid intima-media thickness in obese adolescents

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Automated ultrasound evaluation of carotid intima-media thickness in obese adolescents

Introduction

Atherosclerotic disease is a major cause of morbidity and mortality worldwide [1]. Atherosclerosis has been demonstrated to begin in childhood [2] and it can develop silently for decades before the occurrence of clinical events [3]. From its earliest phases, atherosclerosis is related to the presence and intensity of known cardiovascular risk factors [4]. Recent attention has been focused on applying prevention measures for atherosclerosis beginning in childhood to reduce the risk of heart disease, stroke, and peripheral vascular disease later in life [5]

New technologies have enabled us to monitor progression of arterial wall disease [1]. Measurement of carotid artery intima-media thickness (cIMT) by ultrasonography is a feasible approach that is direct, non-invasive, and has good correlation with histology in the assessment and detection of preclinical lesions of the arterial wall [2; 6]. Thickening of the intima and media layers of the carotid artery provides predictive information in addition to traditional cardiovascular risk factor assessment. As a clinical and research instrument, cIMT measurement can be used to evaluate cardiovascular risk and to access the intervention effects on subclinical atherosclerosis grade [7].

Atherogenesis can be attributed to a generalized disturbance of endothelial function, and cIMT provides an index of coronary disease [8]. Although studies have shown significantly increased cIMT in children with type 1 diabetes, hypertension, and/or familial hypercholesterolemia, the cIMT data in obese children are less clear [6]. The American Heart Association recommends cIMT measurement for evaluation of risk for development of cardiovascular disease in intermediate-risk adult patients (according to Framingham risk score) [1] and in high-risk pediatric patients [8].

Obesity in childhood has reached epidemic proportions. Obesity is associated with hypertension, glucose intolerance, and inflammation markers in chronic adults and children. Furthermore, these clinical findings appear to be causally related to the initiation and progression of pro-atherogenic vascular changes, even in juveniles. Morphological and functional changes of the vascular wall are accepted universally as early and essential steps in the development of atherosclerosis, and detection of increased cIMT may reflect such structural changes [6]. Whether the thickness of arterial wall increases with body mass index (BMI) is still a matter of debate [9].

In practice, cIMT is most commonly measured manually in an ultrasound (US) examination. However, this method is time consuming and the results may be affected by the operator's experience or subjective judgment. Relative to manual measurement, automated measurement is faster and associated with less variability for all carotid segments, though both methods are reliable for measurement of carotid thickness [1]. Few studies have evaluated how well automated US measurements of cIMT associate with anthropomorphic measurements and laboratory data in juveniles.

In this study, we examined how closely automated US measurements of cIMT associate with anthropometric and laboratory data in a group of adolescents. Our aim was to identify potential markers that could be used to indicate intervention to prevent the development and progression of cardiovascular pathology in pediatric patients.

Materials and methods

Subjects

Forty-five adolescents, 10–17 years of age, were enrolled in this study. The subjects were classified according to their BMI z-score (for Brazilian children and adolescents) [10]. The exclusion criteria were hepatorenal disease, use of drugs that are potentially hepatotoxic or nephrotoxic, and diagnoses with a chronic disease, such as hypertension or diabetes mellitus. The subjects were evaluated in a pediatric outpatient clinic at either the Instituto da Criança da Universidade de São Paulo in São Paulo or the Hospital São Lucas da Pontifícia Universidade Católica do Rio Grande do Sul in Porto Alegre. This research project was approved by the Research Ethics Committee of both institutions. Parents or legal guardians read and signed an informed consent approved for this study by the University's Review Board.

Measurements

The individuals were weighed and measured according to standardized procedures [11], while barefoot and wearing only light clothing. For body weight determination, we used a mechanical Filizola® brand scale with a coupled stadiometer that was calibrated by the National Institute of Metrology, Standardization, and Industrial Quality of Rio Grande do Sul (INMETRO-RS). The BMI of each subject was calculated as follows: BMI = body weight (kg) / height^2 (m). Each subject's waist circumference (WC) was measured twice with an anthropometric fiberglass tape at the midpoint between the last rib and the iliac crest, and we recorded the average of two measures.

Blood pressure was measured with an aneroid sphygmomanometer in accordance with the criteria recommended by the National High Blood Pressure Education Program Working Group on Children and Adolescents [12]. We obtained blood samples from all subjects after 12 hours of fasting to measure glycemia, triglyceride (TG), total cholesterol (TC), HDL-cholesterol (HDL), LDL-cholesterol (LDL), insulin, and apolipoprotein B (apoB) levels. TC, HDL, and TG levels were measured enzymatically, and LDL levels were calculated using the Friedewald formula. The TC, LDL, HDL, and TG values were stratified by percentile according to age and sex [13]. Insulin and apoB levels were determined with chemiluminescence and automated immunonephelometry, respectively.

We calculated the patients' HOMA-IR index, a mathematical model that quantifies insulin resistance based on the formula: HOMA-IR = fasting Insulin (µUI/mL) x fasting glucose (mmol/L) / 22.5. All patients received an US assessment of the common carotid artery intima-media thickness.

Ultrasonographic measurement of cIMT

In this study, cIMT was measured digitally over a 1-cm segment of the artery located below the carotid artery bulb with a specially designed computer program (Philips Qlab 6.0). The automated tool measured multiple cIMT data points within several seconds, and yielded the following results for each measurement: mean, maximum, minimum, standard deviation (SD), number of acquired data points, and distance. The commercial software algorithm is based on a comprehensive analysis of the two-dimensional vessel structure represented in an ultrasound image, rather than on simple detection of grayscale gradients. This technique detects interfaces accurately with negligible influences by random image irregularities. The operator sets the starting and ending point of the measurement area manually and then the two lines along the boundaries of the cIMT are drawn automatically [14].

Statistical analysis

Demographic data are reported as means ± SDs for parametric variables, or as medians with interquartile ranges for non-normally distributed variables. Generalized Linear Models were used to analyze the relationships between the main outcome (cIMT) and the predictor variables (sex, age, height, weight, BMI z-score, WC, and HOMA-IR index). Initially, all covariates that presented with $p < 0.15$ and with clinical relevance were included in the multivariate model. Covariates for which critical (i.e. not significant) p values were obtained were then excluded individually. This exclusion step was repeated until all variables remaining in the model presented had p values <0.05. All analyses were performed with SPSS v.18 software (SPSS Inc, Chicago, IL).

Results

The demographic and clinical characteristics of the enrolled subjects, including anthropometric and cIMT values, are summarized in Table 1. The cohort was majority female and majority obese. About two-thirds of the subjects in the study cohort had TC and LDL levels below the 75th percentile (considered acceptable for their age). However, nearly half of the subjects had HDL levels above the 50th percentile for their sex and age, and nearly a third had TG levels above the 75th percentile.

According our univariate analysis, cIMT was not associated with sex or BMI z-score. However, cIMT on both the right and the left sides was found to associate positively with height. Additionally, cIMT on the right side was found to associate positively with WC and

HOMA-IR, and negatively with apoB levels (Table 2). In our multivariate analysis, only height remained independently associated with cIMT (right and left).

Discussion

In this study, we found that cIMT associated positively with height; none of the other demographic variables or laboratory findings associated significantly with cIMT in our multivariate analysis. The lack of association between BMI and cIMT is consistent with several studies. For example, Tounian et al. did not find a significant difference in cIMT size between 48 severely obese French children and 27 healthy controls [15]. In a cross-sectional study of 5–16-year-old Canadian children, no measure of adiposity was found to be predictive of cIMT [16]. Similar findings have been reported by other researchers, including Aggoun et al. [17], Di Salvo et al. [9], Núñez et al. [18], and Whincup et al. [19]. Nevertheless, in a systematic review of 26 observational studies, 22 of the reviewed studies reported a significantly increased cIMT in obese children and adolescents compared to a control group [2]. In some of these studies, a strong association between cIMT and blood pressure was reported, and some of these studies included obese children with hypertension, or with blood pressure values significantly higher than their referents [9].

Previous studies have demonstrated cIMT in adults to be highly dependent on age and sex [20-22]. However, we did not find an association of cIMT with sex or age in our juvenile subjects. Our negative findings in this regard are consistent with a prior study examining a large cohort of normal children and young adults in which cIMT was found not to be affected by age or sex until 18 years of age [23]. McCarthy and Ashwell found WC to be a highly sensitive and specific marker of upper body fat accumulation in children [24], and several other studies have shown WC to be associated with carotid artery dimensions [25-30]. In a study of Turkish children employing linear logistic regression, Hacihamdioğlu et al. found that WC was the only parameter that was associated with increased cIMT [28]. They concluded that children with abdominal obesity are at increased risk for atherosclerosis, and that WC can be used to screen for atherosclerosis risk in obese children [28]. In our study, WC was associated with cIMT on the right side in our univariate analyses, but did not remain significant after adjustment for other variables.

Our univariate analysis revealed that cIMT on the right side associated positively with HOMA-IR and negatively with apoB levels. Suzuki et al. found that insulin resistance was the most significant risk factor for cIMT in a study of 72 adult patients [31]. Additionally, in a study examining overweight Turkish children, Yilmazer et al. found that hyperinsulinemia correlated with increased cIMT [25]. Similar findings have been obtained in other studies [6; 26-29; 32], although some studies found no association between cIMT and HOMA-IR [19; 33]. The inverse association between cIMT and apoB in our data is consistent with a prior study of Japanese adults [31]. This finding is particularly important since among the many risk factors identified by epidemiological studies, only elevated levels of apoB-containing lipoproteins is known to drive the development of atherosclerosis in humans and experimental animals even in the absence of other risk factors [34].

Various studies have demonstrated discrepancies between the intima-media thicknesses measured for the left and right common carotid arteries [35] and emphasized the importance of measuring and reporting values from both sides when conducting cIMT studies [36]. Atherosclerotic lesions may develop earlier on the left side than the right side due to the anatomical configuration of the left carotid artery, which originates directly from the aortic arch and therefore may be exposed to greater shear stress than the right carotid artery. Indeed, shear stress has been shown to influence the localization and rate of development of atherosclerotic lesions [36]. Interestingly, Luo and colleagues demonstrated that right cIMT correlates primarily with hemodynamic parameters, whereas left cIMT correlates better with biochemical indices (such as TC, LDL-C, and blood glucose level) [37].

However, in our univariate analysis, apoB level and HOMA-IR index (which is calculated from serum glucose and insulin values) were associated with cIMT on the right side only, which points to a relationship between right cIMT and biochemical parameters.

The present study is different from most prior work in that we measured cIMT with an automated US tool; most prior studies of cIMT in obese subjects were conducted with a manual measurement method. Manual cIMT measurement (point-to-point measurement of B-mode images) is also the most common technique used in clinical practice, even though it is time-consuming and the results may be compromised by lack of expertise or the subjective judgment of the observer [1], resulting in clinically important inter- and intra-observer variabilities [14]. The development of automated methods for measuring cIMT in standard US equipment can reduce US examination duration and lead to better reproducibility of results across observers. The automated method also enables new data to be compared to previously published data for different populations according to percentile [1]. Furthermore, the new system should prevent the problem of measurement drift over time [38]. Differences between our findings and prior findings may be due, at least in part, to the use of automated versus manual measurement techniques.

Our study has some limitations. Firstly, our sample size limits the power of some of the analyses. Secondly, no functional measure of insulin resistance was available in our study. Functional methods provide precise quantitative measures of insulin resistance, but they are costly, challenging to perform, moderately invasive, and are best suited for studies involving tens to hundreds of individuals; thus they are still impractical for routine clinical use [39]. Conversely, the main limitation of prior studies of cIMT in juveniles has been the heterogeneity of the US measurement protocols; indeed this heterogeneity may explain the wide ranges of cIMT values observed [40]. We used an automated protocol for measuring cIMT with the intention of contributing to future homogenization of these data.

Based on the present findings, we can conclude that height is associated with automated ultrasound measurements of both carotid intima-media thickness. Carotid intima-media thickness was not associated with any other demographic variables nor with laboratory findings when assessed with our automated US method. Nevertheless, this method may be useful for evaluation of the inflammatory process in association with childhood obesity. Further studies should be conducted on a prospective basis to evaluate the potential clinical value of this measure.

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Table 1. Patient characteristics (N = 45).

Characteristic	**Value**
Sex (females), n (%)	53.3 (%)
Nutritional status (Obese), n (%)	55.5 (%)
Age (years), mean $\pm$ SD	13.06 $\pm$ 2.34
BMI (kg/m^2) , mean $\pm$ SD	27.23 $\pm$ 8.46
BMI (z-score), median (interquartile range)	2.69 (-0.15 to 3.26)
WC (cm) , mean $\pm$ SD	90 $\pm$ 20
ApoB (g/L) , mean $\pm$ SD	0.63 $\pm$ 0.15
TC (patients below 75th percentile[a]), n (%)	29 (64.4%)
HDL (patients above 50th percentile), n (%)	20 (46.5%)
LDL (patients below 75th percentile[a]), n (%)	31 (68.8%)
TG (patients above 75th percentile), n (%)	14 (32.5%)
Insulin (pmol/L), mean $\pm$ SD	13.3 $\pm$ 9.98
Glucose (mmol/L), mean $\pm$ SD	4.73 $\pm$ 0.4
HOMA-IR, mean $\pm$ SD	2.96 $\pm$ 2.57
Right cIMT (mm), mean $\pm$ SD	0.457 $\pm$ 0.04
Left cIMT (mm), mean $\pm$ SD	0.445 $\pm$ 0.04

[a]considered acceptable for age.

Abbreviations: SD: standard deviation; BMI: body mass index; WC: waist circumference; ApoB: apolipoprotein B; TC: total cholesterol; HDL: HDL-cholesterol; LDL: LDL-cholesterol; TG: triglycerides; HOMA-IR: homeostasis model assessment of insulin resistance; cIMT: carotid intima-media thickness.

Table 2. Univariate analysis results for association of right and left cIMT measured by US with anthropometric and laboratory data.

Variables	**Right cIMT β (95% CI)**	***p***	**Left cIMT β (95% CI)**	***p***
Sex (male)	-0.001 (-0.025 to 0.023)	.920	0.013 (-0.010 to 0.037)	.250
BMI (z-score)	0.003 (-0.003 to 0.009)	.290	0.000 (-0.006 to 0.005)	.800
Height (cm)	0.002 (0.001 to 0.003)	.003*	0.002 (0.001 to 0.003)	<.001**
WC	0.001 (0.000 to 0.001)	.040*	0.000 (0.000 to 0.001)	.580
ApoB	-0.074 (-0.148 to -0.001)	.040*	-0.068 (-0.151 to 0.014)	.100
HOMA-IR	0.007 (0.002 to 0.012)	.004*	0.003 (-0.003 to 0.008)	.310

*p < 0.05

**p < 0.001

Abbreviations: US, ultrasonograhy; BMI, Body Mass Index; WC, waist circumference; apoB, apolipoprotein B; HOMA-IR, homeostasis model assessment of insulin resistance.

CAPÍTULO IV

CONCLUSÕES

4.1 CONCLUSÕES

Baseado nos achados de nosso estudo, podemos concluir que as medidas ultrassonográficas de gordura abdominal associaram-se com as medidas antropométricas (escore-z do índice de massa corporal, circunferência abdominal, razão entre circunferência abdominal e estatura, e índice de conicidade), a glicose, a insulina e o HOMA-IR (exceto glicose e gordura pré-peritoneal máxima). A idade não se associou apenas com a gordura pré-peritoneal. Na análise multivariada, o escore-z do índice de massa corporal, o índice de conicidade e o HOMA-IR permaneceram associados de forma independente com o somatório de gordura dos pacientes. Apenas a gordura subcutânea mínima associou-se de forma independente com o HOMA-IR.

Em relação à avaliação ultrassonográfica vascular, a espessura médio-intimal carotídea não foi associada com o sexo ou com o escore-z do índice de massa corporal. No entanto, a espessura médio-intimal carotídea de ambos os lados associou-se positivamente com a altura. Além disso, a espessura médio-intimal carotídea direita associou-se positivamente com a circunferência abdominal e com o HOMA-IR, e negativamente com os níveis de apolipoproteína B. Na análise multivariada, apenas a altura permaneceu independentemente associada com as espessuras médio-intimais carotídeas direita e esquerda.