Atherosclerosis subclinical and inflammatory markers in obese and nonobese Children and adolescents

Aterosclerose subclínica e marcadores inflamatórios em crianças e adolescentes obesos e não obesos

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Abstract

We conducted a systematic review of intima-media thickness(IMT) and inflammatory markers, compared IMT and identified by meta-analysis related to EMI and inflammatory variables in obese and non-obese children and adolescents. We searched for articles in databases Pubmed, Bireme and Science Direct, during years 2000 and 2010, with the following key words in English: "obesity", "adolescents", "atherosclerosis" and "child ", They were used in two combinations: obesity + adolescents + atherosclerosis + child + obesity and atherosclerosis. We used meta-analysis to compare IMT between obese and non-obese patients. We carefully selected 16 articles for final analysis. There were differences in the thickness of IMT between obese and non-obese patients in 12 studies, confirmed by meta-analysis. Obese patients had concentrations of C-reactive protein higher in 13 articles analyzed ($p < 0.05$) and lower adiponectin levels in 4 ($p < 0.05$). In general, obese men had lower concentrations of adiponectin and higher values of IMT and C-reactive protein than non-obese men, showing the relationship between obesity and early inflammatory process. We concluded that there is a relationship of obesity with increased IMT and changes in concentrations of inflammatory markers in this phase.

Keywords: Atherosclerosis. Obesity. Ultrasonography. Child. C-reactive protein. Adiponectin. Meta-analysis.

Resumo

Objetivo: Realizou-se revisão sistemática sobre espessamento médio-intimal (EMI) e marcadores inflamatórios, comparou-se EMI por metanálise e analisou-se a correlação entre EMI e variáveis inflamatórias em crianças e adolescentes obesos e não obesos. **Fontes dos dados:** Buscaram-se artigos nas bases de dados Pubmed, Bireme e Science Direct, nos anos de 2000 e 2010, com as seguintes palavras-chave em ingles: "obesity", "adolescents", "atherosclerosis" e "child", sendo utilizados em duas combinações: obesity+adolescents+atheros clerosis e obesity+child+atherosclerosis. Utilizou-se meta-análise para comparar EMI entre obesos e não obesos. **Síntese dos dados:** Selecionou-se criteriosamente 16 artigos para análise final. Houve diferença da espessura de EMI entre obesos e não obesos em 12 estudos, confirmada pela meta-análise. Os obesos apresentaram concentrações de proteína C-reativa mais elevada em 13 artigos analisados ($p < 0,05$) e menores de adiponectina em 4 ($p < 0,05$). Em geral, os obesos apresentaram concentrações menores de adiponectina e maiores valores de EMI e Proteina c-reativa do que os não-obesos, evidenciando relação entre obesidade e início de7 processo inflamatório**. Conclusões:** Conclui-se que há relação da obesidade com aumento do EMI e alterações nas concentrações dos marcadores inflamatórios nesta fase.

Palavras-chave: Aterosclerose. Obesidade. Ultrassonografia. Crianças. Proteína c-reativa. Adiponectina. Metanálise.

Introduction

Cardiovascular diseases remain the leading cause of death in industrialized countries, in that coronary artery disease (CAD) is the most frequent[1]. The development of CAD is related to obesity, hypertension and dyslipidemia, which are problems strengthened by unsuitable eating habits and sedentarism[2]. With regard to obesity, its maintenance for a long period is associated with the emergence of inflammatory markers, changes in the metabolic profile and lack of physical activity[3], and it is a risk factor that has increased substantially among the general population. The concern with obesity in childhood and adolescence has been highlighted in many studies, showing that the development of coronary atherosclerosis in young adults[4] takes place early, and is accelerated by the presence of obesity in childhood[5-7].

The atherosclerotic process has several inflammatory markers in augmented concentrations, and it is more evident in obese and dyslipidemic individuals[8-10]. Although the relationship between fat mass and vascular function is still little understood[6], obesity, as an independent factor, shows decreased vasodilation response, even when there is need for increased blood flow[6]. What has been observed is that obese individuals have a higher frequency of systemic blood hypertension[6], metabolic syndrome[7], dyslipidemia[11] and other cardiovascular risk factors that contribute to alterations on the endothelial wall.

Thus, inflammation, obesity and insulin resistance will typically be expressed together and will contribute to the development of cardiovascular diseases. Studies in children and adolescents highlight the relationship between inflammatory markers and endothelial dysfunction[8,12-15]. Fat tissue releases pro-inflammatory substances, such as the tumor necrosis factor α(TNF-α), interleukin-6 (IL-6) and resistin, in addition to anti-inflammatory substances, such as adiponectin. While pro-inflammatory substances negatively affect endothelial

health, anti-inflammatory substances work inversely, with positive effects on the endothelium[16,17].

Some studies show that a low adiponectin concentration is associated with obesity[15,18-20], therefore compromising glucose and lipid metabolism. The adiponectin protein, when in suitable concentrations, inhibits monocyte adhesion to endothelial cells and the accumulation of lipids in macrophages, stimulating the production of endothelial nitric oxide[15]. High levels of C-reactive protein (CRP), in turn, are related to the emergence of cardiovascular diseases and diabetes[8]. Thus, augmented CRP levels in obese individuals are considered as a relevant indicator of the presence of inflammation. CRP is produced in response to stimulation from pro-inflammatory cytokines and is often used for the diagnosis of inflammatory and infectious conditions.

Non-invasive techniques have been used to assess early atherogenesis markers in adults with cardiovascular risk factors[21,22]. Studies highlight high-resolution arterial ultrasound[21,22], which enables us to assess the endothelium wall thickness and it is a non-invasive test. The evaluation consists of measuring, by means of the ultrasound image, the distance between the tunica intima and the tunica media[6,22], known as intima--media thickness (IMT). Increased thickness is considered a risk factor for coronary artery disease[20]. Some studies have shown that obese children have higher endothelium thickness than healthy children[5,7,22], thus becoming more susceptible to cardiovascular events in adult life. Therefore, diagnosis and prevention of cardiovascular risk factors among children and adolescents are crucial in prevention and public health measures.

However, few studies analyze IMT in children and adolescents[5,7,15,23] and, to the present, there is no systematic review relating obesity, inflammatory markers, IMT and factors associated with increased endothelium thickness in children and adolescents. Thus, this systematic review analyzed inflammatory variables in obese and non obese children and adolescents and compared their IMT, using meta-analysis to identify cardiovascular risk factors associated with obesity.

Methods

A systematic review and meta-analysis study was performed. To develop the study we conducted a reference search using Pubmed, Bireme and Science Direct databases. The selection of keywords was based on DECs (Bireme's Health Sciences Descriptors) and included the following descriptors in English and Portuguese: obesity (*obesidade*), adolescents (*adolescentes*), atherosclerosis (*aterosclerose*) and child (*criança*), used in two combinations: obesity + adolescents+ atherosclerosis and obesity + child + atherosclerosis. The search was conducted without field restriction (all fields). We used publications from 2000 to 2010, because adipocytokines were discovered at the end of the 1990's[24]. Two researchers duplicated the work, searching all databases and, after applying all inclusion and exclusion criteria, compared papers found. In cases of disagreement, papers were jointly reviewed by researchers.

The following inclusion criteria were adopted:

- only original papers;
- studies conducted with children and/or adolescents;
- studies that assessed endothelial function;
- studies that had abstracts;
- studies that assessed endothelial function based on intima-media thickness.

We then applied exclusion criteria:

- studies repeated in the databases and/or duplicated in the two searches (child and adolescents);
- studies that did not have an obese study group and non obese/control group;
- studies that had interventions and/or treatment; and
- studies that did not assess CRP and/or adiponectin.

The exclusion of studies that did not include both groups (obese and non obese) aimed at verifying the relation between obesity and augmented IMT, which would not be possible with one of the groups only. The option not to include studies with intervention aimed to diagnose the clinical condition without the effects of different treatments. The exclusion of studies that did not assess one of the inflammatory markers described (CRP and/or adiponectin) sought to ensure analysis of the relation between IMT and the referred inflammatory markers.

The studies selected were also analyzed with regard to quality of methods, following an assessment protocol developed for this study. The assessment included six criteria:

- Component 1 (random selection) took into consideration the papers that selected subjects randomly;
- Component 2 (execution of sampling calculation) analyzed the studies that informed calculation of a representative or minimum sample to detect the differences analyzed;
- Component 3 (*n* higher than 50 subjects) weighted the minimum number of 50 individuals in each group;
- Component 4 (maturation stage) considered maturation assessment and control in statistical analyses;
- Component 5 (detailed carotid ultrasound method) analyzed the detailed explanation of at least three of the four items considered relevant for the study (positioning of individual, measurement site, number of measurements, how maximum IMT was calculated); and
- Component 6 (inter-observer and intra-observer coefficient) considered the papers that measured inter-observer and intra-observer coefficients, regardless of the values presented.

Scoring of the quality of the article was performed independently, by two investigators. Any questions were analyzed jointly by researchers. The methodological quality of the papers reviewed can be seen in Table 1. The higher the score, the better the quality of the article.

After this stage, we analyzed the correlations found between IMT values and cardiovascular risk factors, taking into consideration blood pressure (BP), body mass index (BMI), inflammatory markers, lipid profile, maturation, body composition and concentrations of resistin, leptin, alanine aminotranspherase, insulin, immunoglobulin G, insulin and the homeostatic model assessment (HOMA-IR).

We then conducted data meta-analysis in Minitab software, version 15. We used the Shapiro-Wilk test to verify normality, and afterwards the Levene test to verify homogeneity between groups. We calculated effect of size of the paper (ES)[25] and used one way ANOVA test to identify significant differences between the groups. The significance level adopted was $p < 0.05$.

Results

In the electronic search performed, 3,211 studies were found, in that 1,949 corresponded to the descriptor *child* and 1,262 to *adolescents*. After applying the inclusion criteria, we selected 69 papers in the search for *child* and 95 in the search for *adolescents*, totaling 164 papers. After exclusion criteria, we were left with 16 studies, which were analyzed in the present study (Figure1).

Of the 16 papers reviewed, fifteen were published from 2005 to 2009, eleven in high strata journals with (ranked A2 and A1), as per the ranking of the Coordination for the Improvement of Higher Level Personnel (CAPES 2009). Sample participants varied in age and nationality. Two papers included young adults, one study was conducted with Brazilian adolescents and children, and 12 papers were conducted with European populations. All papers included individuals of both genders. Key information about the 16 studies reviewed can be found in Table 2.

Obese individuals showed higher values of IMT than those in control groups. In the 12 studies reviewed, this difference was significant. In obese groups, IMT levels ranged

Table 1 - Methodological quality of studies reviewed.
Tabela 1 *- Qualidade metodológica dos estudos analisados.*

Reference	1	2	3	4	5	6	Total
Mangee *et al.* 2004	-	-	+	-	-	-	**1**
Pilz *et al.* 2005	-	-	+	-	+	-	**2**
Kapiotis *et al.* 2006	-	+	+	-	+	-	**3**
Meyer *et al.* 2006	-	-	-	+	+	+	**3**
Beauloye *et al.* 2007	-	-	+	+	-	+	**3**
Arnaíz *et al.* 2007	+	+	-	+	+	+	**5**
Roh *et al.* 2007	-	-	-	-	-	-	**0**
Giannini *et al.* 2008	-	-	-	+	+	-	**2**
Pacífico *et al.* 2008	-	-	+	+	+	+	**4**
Mangee *et al.* 2008.	-	-	+	-	+	-	**2**
Wilders-Truschnig *et al.* 2008	-	-	-	+	+	+	**3**
Arnaíz *et al.* 2008	+	+	-	+	-	+	**4**
Giannini *et al.* 2009	-	-	-	+	+	+	**3**
Mangee *et al.* 2009,	-	-	+	-	+	-	**2**
Kelishadi *et al.* 2009	+	+	-	+	-	-	**3**
Vercoza *et al.* 2009	-	-	+	-	+	+	**3**

1 - random selection or random, 2 - sample calculation performed, 3 - N greater than50; 4 - Assessment maturational stage, 5 - detailed methodology carotid ultrasound; 6- coefficient interobserver or intraobserver agreement
1 - random selection or random, 2 - sample calculation performed, 3 - N greater than50; 4 - Assessment maturational stage, 5 - detailed methodology carotid ultrasound; 6- coefficient interobserver or intraobserver agreement

from 0.37 mm to 0.74 mm; in non-obese it ranged from 0.29 mm to 0.57 mm (Table 3).

It is also important to note that the IMT measurement site varied among studies. Five studies measured two or more segments of the carotid artery and calculated the mean[7,13,27,28,30]. Eight studies only measured the common carotid artery[12,15,26,29,31-34] and three did not specify where measurements where taken[15,35,36]. In addition, the number of measurements performed was different, ranging from 3 to 16. However, despite differences in methodology, all studies showed higher IMT values among the obese. These results were significant in 15 studies, suggesting a close relation between obesity and endothelial dysfunction.

For the meta-analysis between IMT means of obese and control groups, we first calculated variance, that showed that the groups came from the same population ($p = 0.66$). As studies analyzed showed a homogeneous effect size (mean ES = 0.24; $p = 0.53$), we used ANOVA to compare groups. The means presented by obese groups were higher than those from non-obese groups (0.52 and 0.43, respectively; $p < 0.05$).

As for the assessment of inflammatory markers, ten papers only assessed CRP, one paper only assessed adiponectin and five included both analyses. For adiponectin, four papers found a significant difference, among the six that used this assessment. In these studies, adiponectin concentrations ranged from 5.5 µg/ml to 16.08 µg/ml in obese groups and from 6.0 µg/ml to 17.72 µg/ml in control groups. Among the 15 studies that assessed CRP, thirteen found significant differences, in that the values regarding this variable were higher in obese groups. CRP levels ranged from 0.9 mg/L to 3.9 mg/L among the obese and from 0.2 mg/L to 1.2 mg/L among the non-obese.

Of the 16 studies, fifteen checked correlations among the previously mentioned variables. Of these, two found a significant correlation between IMT and CRP, and five found an inverse correlation between IMT

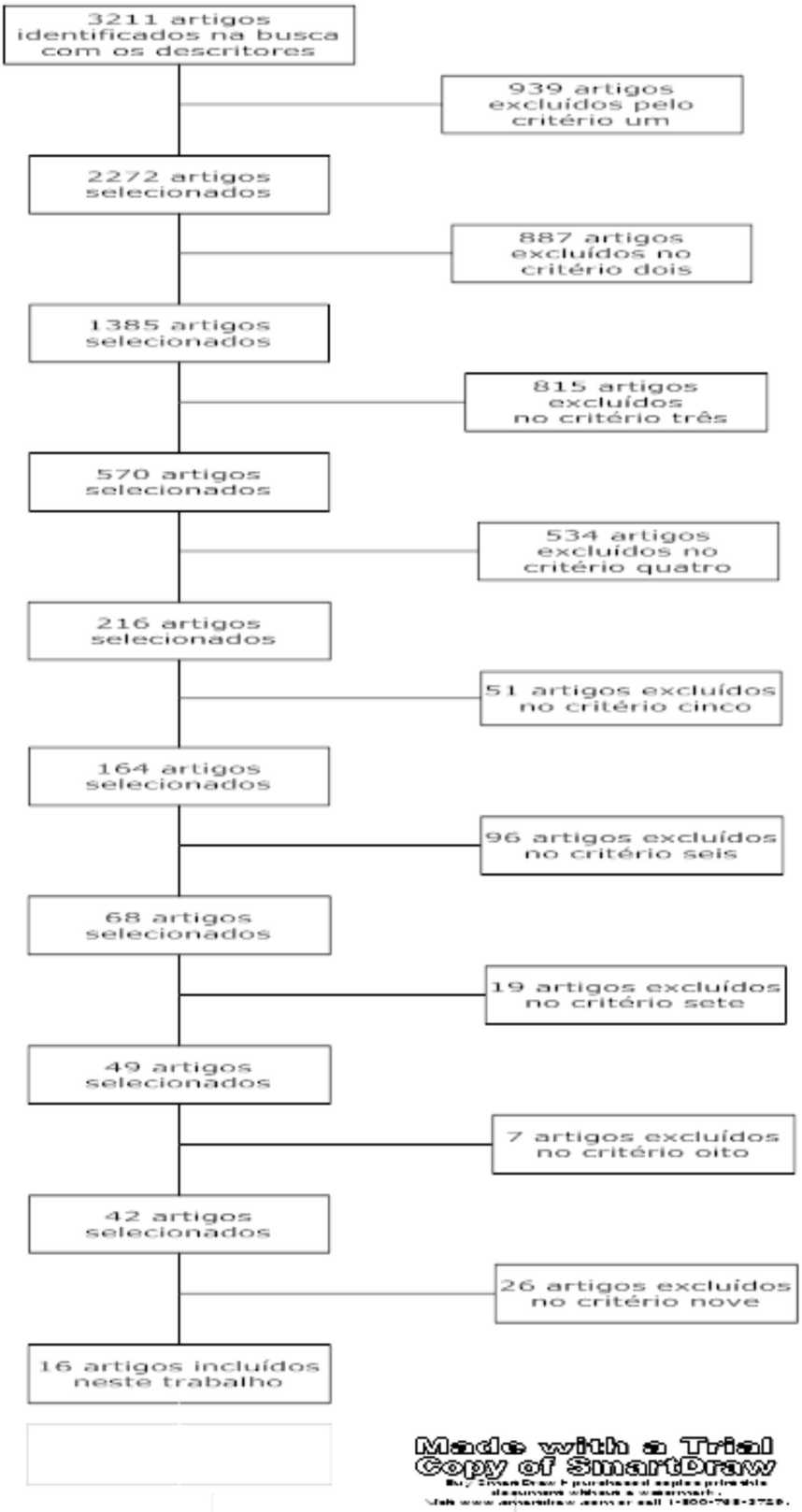

Figure 1 - Number of articles selected in each study phase.
Figura 1 *- Número de artigos selecionados em cada etapa do estudo.*

Table 2 - *Articles included in the review.*
Tabela 2 *- Artigos incluídos na revisão.*

Author/Year and place	Journal	Sample	Age (years)
Mangee *et al.* 2004, Graz, Austria	Experimental and Clinical Endocrinology & Diabetes	96 children and adolescents, including 52 controls, 10 diabetic and 34 obese patients.	8-20
Pilz *et al.* 2005, Graz-Austria	Atherosclerosis	240 children and adolescents, 140 obese and 100 paired controls	9-17
Kapiotis *et al.* 2006, Vienna, Austria	Journal of American Heart Association	59 children and adolescents, including 50 obese and 9 eutrophic patients.	8-16
Meyer *et al.* 2006, Rostock, Alemanha	Journal of the American College of Cardiology	52 adolescents, including 32 obese and 20 controls.	12–16
Beauloye *et al.* 2007, Bruxelas, Bélgica.	The Journal of Clinical Endocrinology & Metabolism	197 adolescents, including 104 obese and 93 controls	12-13
Arnaíz *et al.* 2007, Santiago, Chile	Revista Chilena de Pediatría	83 children, including 26 obese and 57 eutrophic	8-11
Roh *et al.* 2007, Daejeon, Korea	Journal of Korean Medical Science	83 adolescents, including 38 obese and 45 controls	14-16
Giannini *et al.* 2008,	Atherosclerosis	94 crianças, sendo 53 obesos e 41 não-obesos,.	5-10
Chieti, Italia	Atherosclerosis	94 children, including 53 obese and 41 non-obese,.	5-10
Pacífico *et al.* 2008 Roma, Itália	Pediatric Research	92 children including 62 obese and 30 controls	8-12
Mangee *et al.* 2008, Graz, Austria.	Obesity	125 children and adolescents, including 70 obese and 55 controls	9-16
Wilders-Truschnig *et al.* 2008, Graz, Austria	Experimental and Clinical Endocrinology and Diabetes	103 crianças e adolescentes, sendo 35 obesos e 68 controles	10-14
60 children and adolescents, 30 obese and 30 with suitable weight	10-16	120 crianças sendo, 80 crianças pré-púberes obesas e magras, e 40 controles pareados	7-10
Arnaíz *et al.* 2008, Santiago, Chile	International Journal of Cardiology	103 children and adolescents, including 35 obese and 68 controls	10-14
	Atherosclerosis	100 adolescentes, divididos em 4 grupos, obeso e não obeso, com e sem sindrome metabólica. Sendo 50 obesos e 50 controles	12-18
Giannini *et al.* 2009, Chieti, Itália	European Journal of Endocrinology	120 children including 80 pre-pubertal obese and thin children, and 40 paired controls	7-10
Mangee *et al.* 2009, Graz, Austria	Atherosclerosis	146 children and adolescents, including 71 obese and 75 controls with normal weight.	9-16
Kelishadi *et al.* 2009, Isfahan, Iran	Atherosclerosis	100 adolescents, divided into 4 groups, obese and non obese, with and without metabolic syndrome. Including 50 obese and 50 controls	12-18
Vercoza *et al.* 2009, Porto Alegre, Brasil	Pediatric Cardiology	93 children and adolescents, including 41 obese and 52 controls	4-14

Table 3 - *Averages for IMT group and standard deviation used in the meta-analysis.*
Tabela 3 - *Médias de EMI por grupo, desvio padrão e dados utilizados na metanálise sobre os mesmos.*

Reference	Obese			Controls			DPe	DPc
	N	IMT means	SD	N	IMT means	SD		
Mangee et al. 2004	34	0.60 (0.50-070)**	0.10	52	0.47 (0.40-0.54)	0.07	0.00	0.01
Pilz et al. 2005	104	0.68 (0.67-0.69)**	0.01	100	0.53 (0.52-0.54)	0.01	0.00	0.00
Kapiotis et al. 2006	50	0.37 (0.33-0.41)*	0.04	9	0.34 (031-0.37)	0.03	0.00	0.00
Meyer et al. 2006	32	0.49 (0.41-0.57)**	0.08	20	0.39 (0.34-0.44)	0.05	0.00	0.01
Beauloye et al. 2007	104	0.47 (0.39-0.56)**	0.06	93	0.44 (0.35-0.53)	0.09	0.01	0.00
Arnaíz et al. 2007	26	0.50 (0.47-0.53)	0.03	57	0.49 (0.46-0.52)	0.03	0.00	0.00
Roh et al. 2007	38	0.52 (0.43-0.61)**	0.09	45	0.41 (0.34-0.48)	0.07	0.00	0.01
Gianinni et al. 2008	53	0.43 (0.37-0.49)**	0.06	41	0.32 (0.25-0.39)	0.07	0.00	0.00
Pacífico et al. 2008	62	0.49 (0.46–0.52)**	0.03	30	0.39 (0.35- 0.43)	0.04	0.00	0.00
Mangee et al. 2008	70	0.74 (0.66-0.82)**	0.08	55	0.57 (0.48-0.66)	0.09	0.01	0.01
Wilders-Truschnig et al. 2008	30	0.61 (0.52-0.70)**	0.09	30	0.49 (0.41-0.57)	0.08	0.01	0.01
Arnaíz et al. 2008	35	0.50 (0.47-0.53)	0.03	45	0.49 (0.46- 0.52)	0.03	0.00	0.00
Giannini et al. 2009	40	0.40 (0.34-0.46)**	0.06	40	0.31 (0.25-0.37)	0.06	0.00	0.00
Mangee et al. 2009	71	0.74 (0.66-0.82)**	0.08	75	0.57 (0.48-0.66)	0.09	0.01	0.01
Kelishadi et al. 2009	24	0.37 (033-0.41)*	0.04	32	0.29 (0.27-0.31)	0.02	0.00	0.00
Vercoza et al. 2009	41	0.46 (0.38-0.54)*	0.08	52	0.43 (0.37-0.49)	0.06	0.00	0.01

NOTA: Comparação entre média dos grupos obeso e não obeso dos artigos originais: *p < 0,05; **p > 0,01; N - número de indivíduos; DP - desvio padrão; DPe - variância do grupo experimental; DPc - variância do grupo controle.
*NOTE: Comparison of average obese and non-obese group of original articles: *p < 0.05; **p > 0.01; N - number of individuals; DP - standard deviation; Dpe - variance of experimental group; DPc - variance control group.*

and adiponectin. In addition, the variables that showed a significant correlation with IMT in more than one study were BMI, systolic pressure, HOMA-IR and insulin. In addition, CRP correlated to BMI. Adiponectin showed an inverse correlation with HOMA-IR, BMI, waist circumference (WC) and systolic pressure, but a positive correlation with HDL-C and apolipoprotein A.

Discussion

The present review showed that obesity is associated with cardiovascular risk factors, since IMT and CRP concentrations

Table 4 - IMT related variables, statistical tests and the objective analysis.
Tabela 4 - *Variáveis relacionadas com o EMI, teste estatístico utilizado e objetivo da análise.*

Reference	Objective	Statistical test	Variables associated or correlated to IMT
Mangee et al. 2004	Check association between variables	Regression analysis	IMC (r=0.68 p < 0.01)
Pilz et al. 2005	Check association between adiponectin and other parameters	Simple linear regression analysis	Inversely with adiponectin (r=-0.34 p<0.01)
Kapiotis et al. 2006	Correlate IMT. Flow-mediated diameter. CRP with other metabolic variables	Spearman rank correlation	Age (r= 0.33 p<0.05) and FMD (r= 0.40 p<0.05)
Meyer et al. 2006	-----	------	No correlation was analyzed
Beauloye et al. 2007	Check correlation between IMT mean EMI biomarkers of cardiovascular risk in the obese group	Univariate correlation analysis	IMC (r= 0.32 p<0.01), level of systolic hypertension (r= 0.23 p<0.01), resistin (r= 0.22 p<0.03), insulin (r= 0.22 p<0.03) and HOMA-IR (r= 0.21 p<0.04)
Arnaíz et al. 2007	Correlate IMT and other variables	Linear regression analysis	LDL (r2=0.41 p<0.03),
Roh et al. 2007	Correlate IMT with o BMI, lipid profile and blood pressure	Multivariate and univariate regression analysis	IMC (r= 0.61 p<0.01), systolic (r= 0.51 p<0.01 and diastolic pressure (r=-0.30 p<0.01), and inversely with HDL (r=-0.22 p<0.05)
Gianinni et al. 2008	Check the effect of insulin resistance and other inflammatory parameters in IMT increase	Multiple linear regression analysis	No variable showed substantial correlation
Pacífico et al. 2008	Check association between IMT logarithm and other variables	Univariate linear regression analysis	Age (b=0.02. p<0.01), Tanner (b=0.056p< 0.01), IMC (b=0.020 p<0.01), fat mass (b=0.009 p<0.01), systolic pressure (b=0.009 p<0.01), alanine aminotranspherase (b=0.022 p<0.0019),. Hepatic steatosis (b=0.081 p<0.01), insulin (b=0.004 p<0.01), HOMA-IR (b=0.020 p<0.01), leptin (b=0.003 p<0.02), and inversely with adiponectin ((b=-0.009 p<0.02),
Mangee et al. 2008	Check correlation in adiponectin levels with other parameters	ANOVA correlation analysis	Inverse adiponectin (r=-0.28 p<0.01)
Wilders-Truschnig et al. 2008	Assess relation between Immunoglobulin G with CRP and EMI	Multiple linear regression analysis	Immunoglobulin G (r= 0.51 p< 0.01), CRP.
Arnaíz et al. 2008	Check association between adiponectin and other variables	Pearson correlation and multiple linear regression analysis	No variable showed substantial correlation
Giannini et al. 2009	Investigate the independent effect of insulin resistance and IMT oxidative stress	Multiple linear regression analysis	HOMA-IR (β=0.307 p<0.01)
Mangee et al. 2009	Check correlation between ratio LMW/ total adiponectin and other metabolic and cardiovascular risk parameters	ANOVA univariate correlation analysis	Total /LMW adiponectin ratio
Kelishadi et al. 2009	Investigate relation of HOMA-IR with other variables	Pearson Correlation .	No variable correlated significantly
Vercoza et al. 2009	Assess association between two variables	Pearson and Spearman correlation	BMI score z (r=0.259 p<0.01); systolic pressure (r= 0.26 p<0.01), excess weight/ obesity (r=0.23 p<0.02)

EMI - espessamento médio intimal; FMD - diâmetro de fluxo mediado; LMW - baixo peso molecular; IMC - índice de massa corporal; HOMA-IR - modelo de avaliação homeostático de resistência a insulina; PCR - proteína c-reativa; LDL - lipoproteína de baixa densidade; HDL - lipoproteína de alta densidade.
EMI - intimal medial thickening; FMD - diameter flow-mediated; LMW - low molecular weight; IMC - body mass index; HOMA-IR - homeostatic model assessment of insulin resistance; PCR - c-reative protein; LDL - low density lipoprotein; HDL - high density lipoprotein.

were higher in obese children and adolescents and adiponectin showed lower levels in this population. Analysis of the 16 papers selected showed IMT differences in obese and non-obese children and adolescents, as well as in plasmatic concentrations of adiponectin and CRP

IMT values showed a major variation only among the obese (difference of up to 0.37mm), which possibly occurred because of the age group studied and individuals' time of obesity. Studies that included adolescents in the final phase of puberty in the sample [28,31-34,39] showed higher IMT variation, which can be particularly observed in the study of Mangge et al[31]. In addition, inconsistent results may be justified by the different sited used to measure IMT, as well as by the different methods used to calculate mean IMT values. Other factors to influence IMT variation can include examiners' technical knowledge and experience, considering that this measurement tends to be lower among children and adolescents, thus leading to measurement errors. To minimize these factors, we recommend the calculation of intra-observer and inter-observer variation coefficients. However, only six studies showed these results[15,26-30].

The meta-analysis procedures conducted in the present study strengthened the results of the studies reviewed, showing that obesity is associated with endothelial alterations in childhood and adolescence, enabling us to state that the presence of obesity is a predisposing factor for higher IMT levels.

In relation to adiponectin, studies showed similar results. In the six studies that included the assessment, the obese showed lower levels than the non-obese. In four studies, differences between the two groups were significant[12,13,32,33], confirming that obesity reduces adiponectin concentrations, which contributed to the development of arteriosclerotic disease. Adiponectin function as an anti-inflammatory marker is to inhibit monocyte adhesion to endothelial cells and lipid accumulation in the macrophages, in addition to stimulating the production of nitric oxide[15].

Adiponectin concentration showed significant inverse correlations with other risk factors, like BP, WC, BMI and insulin resistance. In the studies reviewed, this marker correlated positively to HDL-c and apolipoprotein A, showing that adiponectin has antiatherogenic effects. As well established, high density lipoprotein exerts a protective effect on the endothelium, due to its capacity of mediating reverse cholesterol transport[37]. In the elderly, studies show that low HDL-c levels are more specific predictors for risk of death by CAD than increased total cholesterol[38]. In the studies reviewed, we can identify that this relation is also found in children, however without severe complications in this age group.

CRP is an acute phase plasma protein mainly produced by hepatocytes, and is augmented in response to an inflammatory process. In all the studies analyzed, the obese showed higher CRP concentrations than the non-obese. This difference was significant in 14 papers[5,7,12,13,,27-36,39]. A strong relation between CRP and obesity was confirmed by the correlation between CRP and BMI, found in four studies[13,26,36,39], which suggests a possible inflammatory effect in obesity. It is important to note that the studies reviewed showed differences with regard to CRP measurement units. Most adopted mg/L, in one study values were transformed into logarithms and another used ng/ml. However, results and correlations were similar.

One limitation of this study was that, in the selection of articles, we only identified the presence of obese and non-obese groups, regardless of BMI cutoff points and obesity criteria identified by the authors. Another possible limitation was the lack of a clear age delimitation for selection of the studies reviewed, resulting in a large age range and absence of control over maturational influence over variables. Despite all that, according to the survey conducted, we observed that the scientific community lacks studies that can investigate relations

between the variables studied in the Brazilian population, especially in the age group approached in the present review. Only one study involved Brazilian adolescents. Such studies are important due to the relationship detected between obesity and increased intima-media thickness. The prevalence of child-adolescent excess weight has grown worldwide and, in Brazil, the prevalence of excess weight has reached up to 25.5%[40].

In summary, the articles reviewed confirm that obese adolescents have a higher risk of presenting early signs of atherosclerosis, and therefore are more susceptible to the development of cardiovascular diseases in adult life.

Conclusion

We concluded that, despite differences in methods, the few studies that assessed intima-media thickness in obese and non-obese adolescents showed a relationship between obesity and IMT, which was statistically confirmed by the meta-analysis conducted in the present review. With regard to CRP, we observed the same association, that is, most studies did find higher CRP levels among the obese, indicating the beginning of an inflammatory process. On the other hand, the obese showed lower levels of adiponectin, which suggests decreased antiatherogenic function, effect for which the substance is responsible.

We highlight there is a need for studies to be conducted with Brazilian children and adolescents on IMT and its associations with known risk factors, because little is known about these processes in childhood. It is also important to have an early diagnosis of atherosclerosis, since complications among children and adolescents are not frequent. IMT, as a method for diagnosis, may provide good understanding and be used as the base for planning treatment and interventions, so as to prevent complications from the disease in adult life.

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