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REVIEW

Inflammatory Biomarkers and Components of Metabolic Syndrome in Adolescents: a Systematic Review

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Abstract— Metabolic syndrome (MetS) has been prevalent among adolescents. The association between the concentration of inflammatory markers and the individual components of the metabolic syndrome indicates that inflammation, when there is no recent or ongoing disease, mediated by an inflammatory process, is an event that may precede the development of metabolic disorders in teenagers. The objective of this study is to verify the association of inflammatory biomarkers with the components of metabolic syndrome in adolescents. From a search of 3 databases, 13 articles met the study inclusion criteria. Two investigators independently extracted data from included studies. The evaluated inflammatory biomarkers are related to the components of MetS (insulin resistance, central and visceral obesity, arterial hypertension, dyslipidemia), which may increase the risk of developing the syndrome in adolescents. The results of this review are of clinical relevance, since the evaluation of inflammatory biomarkers in the presence of metabolic alterations can help to identify the risk factors that lead to the progression of MetS in adolescents.

KEY WORDS: cytokines; inflammation; metabolic syndrome; adolescent

INTRODUCTION

Overweight in adolescents is associated with increased chances of becoming an obese adult, but also of developing, still in adolescence and maintaining in adulthood, metabolic complications. In this context, metabolic syndrome (MetS), a set of changes involving disorders in glucose metabolism, dyslipidemias, abdominal obesity, arterial hypertension, and systemic chronic inflammation, with pro-thrombotic and pro-inflammatory processes, has been prevalent among adolescents [1–6].

Due to the chronic inflammation process, individuals with metabolic syndrome have high levels of cytokines and other inflammatory markers, characterizing the condition of subclinical inflammation, with possible endothelial dysfunction and cardiovascular risk [7–11]. Some of the inflammatory biomarkers involved in the inflammation-obesity-insulin resistance triad are interleukins (IL-6, IL-10, and IL-18), C-reactive protein

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(CRP), leptin, adiponectin, tumor necrosis factor (TNF-α), and fibrinogen [12–15].

Such biomarkers are indicated in the measurement of inflammation; they are elevated when in the presence of metabolic changes and are associated with MetS in the presence or absence of obesity [16]. According to Cruz et al. [17], the association between the concentration of inflammatory markers and the individual components of the metabolic syndrome indicates that inflammation, when there is no recent or ongoing disease, mediated by an inflammatory process, is an event that may precede the development of metabolic disorders in teenagers.

Therefore, the objective of this review was to verify the association of inflammatory biomarkers with the components of metabolic syndrome in adolescents.

METHODOLOGY

The systematic review was conducted according to the recommendations of the *Preferred Reporting Items for Systematic Reviews* (PRISMA) Guideline [18] and based on the guiding question "How do inflammatory biomarkers relate to the components of metabolic syndrome in adolescents?". The research and selection of articles were carried out in January 2021 in the electronic databases: Latin American and Caribbean Literature in Health Sciences (LILACS), *Publisher Medline* (PUBMED), and *Scientific Electronic Library Online* (SciELO).

The search for articles was based on the combinations of the descriptors in the English language, namely: ["*Metabolic Syndrome*" AND "*Inflammation*" AND "*Adolescents*" AND "*Body Composition*" OR "*Nutritional Status*" AND "*Cytokines*" OR "*C-reactive Protein*" OR "*Leptin*" OR "*Interleukin*" OR "*Tumor Necrosis Factor-alpha*"], also ["*Metabolic Syndrome*" AND "*Adolescents*" AND "*Obesity*" AND "*Insulin Resistance*" AND "*Cytokines*"], and finally ["*Metabolic Syndrome*" AND "*Inflammation*" AND "*Body Composition*" AND "*Cytokines*"]. The age filter was used for the PUBMED search, in order to obtain only studies conducted with the adolescent population.

As inclusion criteria, original articles conducted with adolescents were considered. There was no distinction of language and, in order to preserve relevant information, the time of publication of the studies was not considered. Review articles, experimental studies, guidelines, theses, dissertations, and abstracts were excluded.

The steps for the search are presented in the translated flowchart (Fig. 1) proposed by PRISMA recommendations [18]. Two reviewers made the searches independently, following the proposed steps: research of articles carried out in the same databases cited, with conference of the total number of articles found; exclusion of duplicate articles; reading of the title for initial selection; subsequent selection for reading the abstracts; and finally, complete analysis in order to verify which studies met the proposed objective. The included and excluded studies were determined in a consensual manner among the reviewers.

Reverse search was performed, which consists in the analysis of the references of the selected articles to identify studies that by chance did not appear in the databases, which also went through the steps of analysis and inclusion/exclusion already mentioned.

The data of the selected studies were organized in a spreadsheet in *Microsoft Excel* so that they could be explored in the construction of this review. From this, a table was prepared with the presentation of the main points of these studies, namely: author, year of publication, title, sample size, objectives, main results, and conclusions. The outcome studied was the association of inflammatory biomarkers with metabolic syndrome.

The risk of bias of the selected articles was evaluated, using the tool recommended by The Joanna Briggs Institute (TJB). The evaluation was done independently, by two researchers, with the help of the checklist for cross-sectional analytical studies, which contains eight questions that can be answered as "yes," "no," "unclear," or "not applicable." "Yes" answers indicate a low risk of bias, and for "no" answers, a high risk of bias is expected.

This study was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) and registered under the number CRD42020198911.

RESULTS

The research identified 623 articles in the three databases used, which were selected following the proposed protocol, resulting in 09 articles. The reverse search allowed to include 04 articles, totaling 13 articles in this review (Fig. 1).

The selected articles (Table 1) were published between 2003 and 2019 and presented a minimum sample size of 72 adolescents [19] and maximum of 524 [17], considering adolescents aged 10 to 19 years old. Four studies used the NCEP III criteria for the definition of

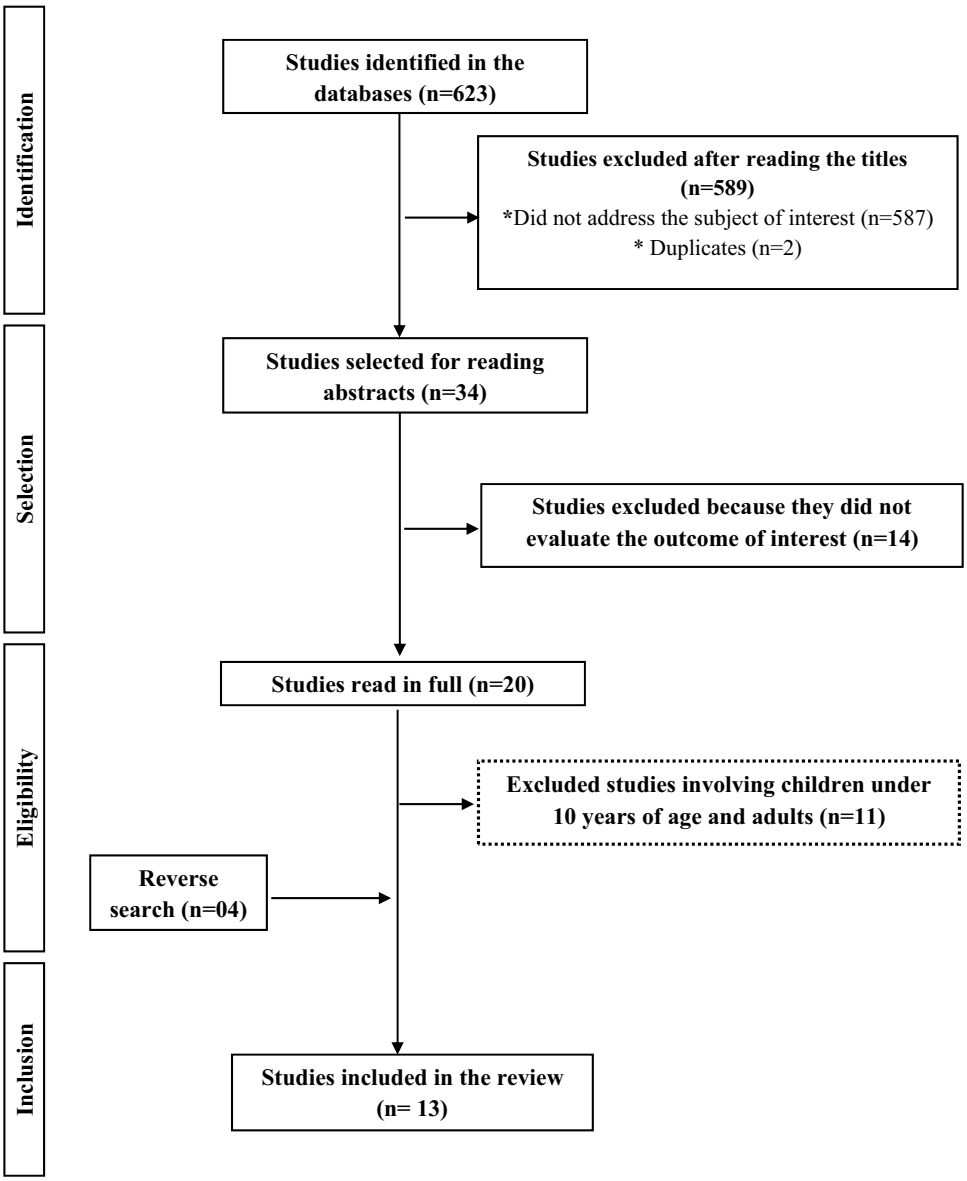

Fig. 1 Flowchart of identification and selection of the articles included in the systematic review.

metabolic syndrome [14, 19–21], and the definition of the IDF [22] was used in four studies [23–26].

Cruz et al. [17] considered four categories of components for the diagnosis of MetS: body composition, evaluated by BMI and waist circumference, according to WHO [27]; blood pressure, according to the 6th Brazilian Guideline on Hypertension [28]; glucose metabolism, evaluated by fasting glucose, fasting insulin, and HOMA-IR; and lipid metabolism, evaluated by total cholesterol, HDL, LDL, and triglycerides. The authors did not specify which definitions were used to evaluate glucose and lipids. Gilardini et al. [29] used the definition of WHO [30] in an adapted way to diagnose MetS, disregarding microalbuminuria, evaluating HDL and triglyceride separately, and replacing the evaluation of the waist hip/ratio with the waist circumference. Nishina et al. [31], Garanty-Bogack et al. [32], and Fujita et al. [33] did not specify which definition they used.

Studies showed that all biomarkers evaluated were significantly altered in adolescents with obesity; however, Carvalho et al. [19] observed that the biomarkers TNF-α, IL-6, and IL-10 were altered even in eutrophic adolescents, but who had excess body fat.

The markers most evaluated by the authors were CRP in seven studies and leptin in five. The study by Cardoso-Saldana et al. [21] presented the highest number of altered components (BMI, waist circumference, body fat percentage, LDL, HDL, triglycerides, total cholesterol, and insulin) associated with a single marker, CRP. The analysis of the 13 studies showed that the inflammatory biomarkers leptin, CRP, IL-6, IL-10, IL-18, fibrinogen, TNF-α, and adiponectin correlate with the components of MetS (obesity, dyslipidemia, insulin resistance, and arterial hypertension) and may increase the risk of developing the syndrome in adolescents.

Considering that the different types of inflammation (allergic, autoimmune, microbial, metabolic, physical, and constitutive)[34] can lead to an increase in inflammatory biomarkers and that the metabolic inflammation underlying MetS can be combined with some type of inflammation, we pay attention to analyze the presence of different types of inflammation in each of the studies included in this review. No patients with recent or ongoing diseases mediated by any type of inflammation were recorded in any of these studies, which allows us to associate high levels of inflammatory biomarkers with MetS.

The selected articles showed 80.7% of the responses as "yes" (Fig. 2) in the critical evaluation recommended by the TJB, as shown in Table 2, which indicates low risk of bias, according to Yao et al. [35].

DISCUSSION

MetS is a condition characterized by the grouping of anthropometric, physiological, and biochemical changes that raise the risk of cardiovascular diseases being developed [36]. Although the prevalence of this condition varies among children and adolescents from several studies due to the use of different diagnostic criteria, it has been high in this public [37].

There is no consensus on the definition of MetS, which has been a challenge for clinical practice and for the creation of health policies. Some organizations have formulated new diagnostic criteria to be applied in practice, and other studies seek to adapt the proposals defined for adults, considering specific cut-off points for adolescents. In this sense, the criterion proposed by NCEP-ATPIII [38] has been the most used for this population, because it is easy to apply in clinical practice, important in adolescent health care [39, 40]. In the studies analyzed, the most used diagnostic criteria were those proposed by NCEP-ATPIII [38] and IDF [22], despite some authors [17, 29] use adaptations of the criteria.

The analyses performed by the studies showed the association of inflammatory markers with obesity, diabetes, dyslipidemia, and arterial hypertension, which are considered components of the metabolic syndrome.

The pathogenesis of MetS involves complex events, but two factors are essential for the genesis of this disorder: central obesity and insulin resistance, which are the major metabolic disorders in childhood and adolescence. Other factors such as dyslipidemia, hypertension, pro-inflammatory and pro-thrombotic status, physical

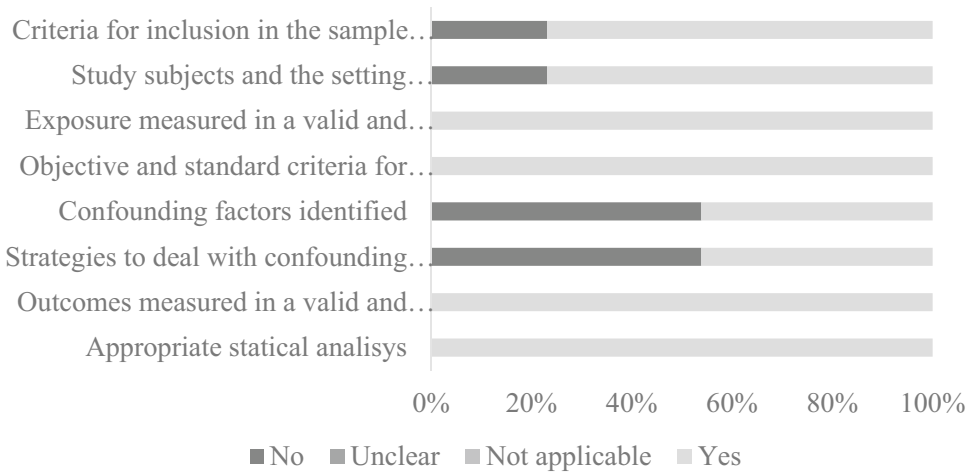

Fig. 2 Risk of bias of each item assessed and summary presented as percentages across all studies included in the systematic review.

Table 1 Summary of the Main Results of the Articles Selected for the Systematic Review

Author/year/location	Sample/avarage age (years old)	Objectives	Analyzed markers	Main results
Fujita et al. [33] Japan	400 adolescents (197 boys) 11.2 ± 0.3	Investigate the relationships between body fat and serum leptin levels and between serum leptin and AP levels using DXA in healthy school-age children	Leptin	Leptin strongly correlated with all body fat parameters in both sexes: Fat mass (M, $r = 0.86$, $p < 0.01$/F, $r = 0.86$, $p < 0.01$) Fat Mass Index (M, $r = 0.87$, $p < 0.01$/F, $r = 0.87$, $p < 0.01$); Body Fat Percentage (M, $r = 0.81$, $p < 0.01$/F, $r = 0.78$, $p < 0.01$) Leptin mediated the association between body fat percentage and systolic blood pressure in both sexes (M, 129.4%; $p < 0.01$/F, 83.9%; $p < 0.01$)
Madeira et al. [23] Brazil	275 adolescents (160 boys) -	To check, based on a sample of prepubescent children, which serum leptin value is most suitable for identifying the metabolic syndrome	Leptin	MetS (33), TG (102.96 ± 55.35 mg/dL), HOMA-IR (2.15 ± 1.83) and leptin (18.6 ± 14.47 ng/mL) were significantly ($p < 0.0000$) higher in the group of obese children The most appropriate leptin cutoff point was 13.4 ng/dL (sensitivity 67.6%; specificity 68.9%; accuracy 72.1%) In the multiple logistics model for predicting MetS, adjusted for sex and age, a leptin level above 13.4 ng/dL was significantly associated with MetS ($p = 0.002$) For each 1 ng/dL increase in leptin levels, the chances of MetS increase by 3% ($p = 0.002$; OR: 1.03; CI95% 1.01–1.05)
Can et al. [24] Turkey	86 adolescents (38 boys) 43 with MetS 14.70 ± 1.15 (MetS) 15.10 ± 1.12 (Control)	Investigate serum levels of C-reactive protein in a population of adolescents with MetS	CRP	WC, weight, SBP, DBP, BMI percentile, HOMA-IR, TG, CT were significantly higher in adolescents with MetS ($p < 0.001$) BMI ($p < 0.05$) and LDL ($p < 0.01$) were significantly higher in the MetS group HDL levels were lower in MetS ($p < 0.001$) CRP levels were significantly higher in the MetS group (4.69 ± 5.54 mg/L vs. 0.58 ± 0.78 mg/L; $p < 0.001$) AUC: 0.919 (cutoff point = 1.02 mg/L, sensitivity = 85% and specificity = 91%)

Table 1 (continued)

Author/year/location	Sample/avarage age (years old)	Objectives	Analyzed markers	Main results
Gonzaga et al. [20] Brazil	200 obese children and adolescents (being 127 adolescents, 43 boys) 13.7 ± 2.3 (girls) 2.7 ± 1.9 (boys)	Check the association between leptin and cardiometabolic risk factors	Leptin	The leptin levels were higher in the groups: girls, adolescents, WC and high SBP ($p < 0.005$) Leptin levels were significantly higher in high TG (22.7 ± 10.1; $p < 0.005$), in the presence of MetS (25.2 ± 12.4; $p < 0.005$), in high insulin (30.7 ± 12; $p < 0.001$) and high IR (28.7 ± 11.3; $p < 0.001$) In the regression analysis, leptin showed significant negative correlation with HDL ($\beta = -0.16$; $p < 0.005$) and positive correlation with TG ($\beta = 1.78$), insulin ($\beta = 0.32$), HOMA-IR ($\beta = 0.07$), BMI ($\beta = 0.21$), WC ($\beta = 0.49$), all with $p < 0.001$, and SBP ($\beta = 0.22$, $p < 0.005$)
Cruz et al. [17] Brazil	524 adolescents (247 boys) 13 ± 1.29	To evaluate the associations between MetS components and CRP concentrations in Brazilian adolescents	CRP	Adolescents with higher BMI ($p = 0.001$) and also BF percentage ($p = 0.0026$) had significantly higher CRP concentrations (1.43 mg/dL and 1.37 mg/dL) than those with normal BMI and BF percentage CRP concentrations were positive and significantly correlated with BMI ($r = 0.17$; $p = 0.0001$), WC ($r = 0.015$; $p = 0.0005$), HDL-c ($r = 0.13$; $p = 0.003$), FI ($r = 0.12$; $p = 0.003$) and SBP ($r = 0.11$; $p = 0.01$) A negative and significant correlation was observed between the concentrations of CRP and FG ($p = 0.05$), total cholesterol ($p = 0.05$) and LDL ($p = 0.0007$) A multiple linear regression analysis was performed to evaluate the predictability of CRP concentrations by MetS components. The best model explained 7% of the variation in CRP concentrations
González et al. [14] Spain	362 adolescents (143 boys) 14.8 ± 1.4	Evaluate the levels of inflammatory markers and their association with MetS in adolescents	Adiponectin Leptin	Adiponectin levels decreased and leptin levels increased, according to BMI ($p < 0.001$ and $p < 0.001$) and the presence of MetS ($p < 0.05$ and $p < 0.01$), in girls and boys Adiponectin (OR:0.88; CI95% 0.79–0.98; $p = 0.023$) and leptin (OR: 1.03; CI95% 1.01–1.06; $p = 0.014$) were significantly correlated with MetS

Table 1 (continued)

Author/year/location	Sample/avarage age (years old)	Objectives	Analyzed markers	Main results
Litwin et al. [25] Poland	74 adolescents (49 boys) 30 Control and 44 with Hypertension Control: 12.7 ± 3.3 Hypertension: 13.7 ± 2.7	Evaluate the profile of inflammatory mediators in children and adolescents with and without hypertension	CRP Adiponectin	Hypertensive group presented, in relation to the control: Significantly higher BMI (25.5 ± 4.9; $p = 0.03$) Significantly higher CRP level (1.2 ± 1.1; $p < 0.0001$) Lower serum adiponectin concentration (6.5 ± 1.5 pg/ml) Children with metabolic syndrome ($n = 9$) had higher CRP (1.9 ± 1.6 mg/L) compared to children without MetS ($n = 35$) ($p = 0.007$) CRP levels significantly correlated with the number of MetS criteria ($p = 0.0001$; $r = 0.479$)
Mauras et al. [26] United States	203 adolescents, being 115 obese (106 boys, being 59 obese) Pre-pubertal: 9.6 ± 0.2 (obese and lean) Pubertal: 14.0 ± 0.2 (obese) and 15.0 ± 0.3 (lean)	Investigate whether markers of inflammation and prothrombosis are abnormal in obese children without established comorbidities of MetS during puberty, compared to lean and age-matched controls	CRP Fibrinogen IL-6	CRP and fibrinogen showed significantly higher levels in the obese group, compared to lean controls, in pre and in puberty IL-6 presented significantly lower mean in the lean group, both in the pre-pubertal (0.4–1.0; $p < 0.001$) and in the pubertal (0.5–1.4; $p = 0.01$) The CRP showed positive correlation with body and visceral adiposity measurements ($r = 0.76$, $p < 0.0001$ for BF percentage and $r = 0.73$, $p < 0.0001$ for WC) Fibrinogen also showed this correlation ($r = 0.47$, $p < 0.0001$ for BF percentage and $r = 0.40$, $p < 0.0001$ for WC)
Carvalho et al. [19] Brazil	72 female adolescents 15 (14–17)	Evaluate the peripheral expression of inflammatory markers in adolescents with different nutritional States and their correlation with metabolic syndrome parameters	TNF-α IL-6 IL-10	There was no significant difference in peripheral expression of inflammatory cytokines between groups of different nutritional status In the eutrophic group with high BF percentage, it was observed positive correlation between TNF-α and IL-6 ($r = 0.0463$, $p < 0.05$), TNF-α and IL-10 ($r = 0.675$, $p < 0.01$), IL-6 and IL-10 ($r = 0.584$, $p < 0.01$), and IL-6 and glycemia ($r = 0.503$; $p < 0.05$) In the overweight group, a positive correlation was found between IL-6 and triglycerides ($r = 0.463$, $p < 0.05$)

Table 1 (continued)

Author/year/location	Sample/avarage age (years old)	Objectives	Analyzed markers	Main results
Cardoso-Saldaña et al. [21] Mexico	325 adolescents (143 boys) 13.4 ± 0.9	Investigate CRP levels in a pediatric population and evaluate their relationship with traditional coronary risk factors, and examine the association between CRP levels and metabolic syndrome components	CRP	Participants with some component of MetS had the highest prevalence of CRP, but the statistical difference was observed mainly for WC > 90lh percentile (OR: 4.1; CI95% 2.4–6.9), TG > 110 mg/dl (OR:2.0; CI95% 1.2–3.3), and HDL < 40 (OR: 2.8; CI95% 1.6–4.7) mg/dl, or having three or four MetS components (OR:3.4; CI95% 1.7–6.6) ($p < 0.007$) CRP levels were significantly correlated ($p < 0.01$) with WC ($r = 0.341$), TG ($r = 0.244$), HDL ($r = -0.315$) and insulin ($r = 0.298$), and ($p < 0.05$) with TC ($r = 0.024$) and LDL ($r = 0.111$) In the regression analysis, CRP was significantly associated with MetS ($\beta = 0.155$; $R^2 = 2.4\%$); WC ($\beta = 0.304$; $R^2 = 9.3\%$); low HDL ($\beta = 0.168$; $R^2 = 3.5\%$); High TG ($\beta = 0.148$; $R^2 = 2.2\%$)
Gilardini et al. [29] Italy	162 adolescents (66 boys) 14 (9–18)	Compare the use of various biomarkers as differential correlates in obese children and adolescents with and without MetS to identify those who may have an associated increased risk	Adiponectin Uric Acid IL-18 Fibrinogen CRP	Adiponectin correlated ($p < 0.0001$) mainly with obesity ($r = -0.315$), HOMA ($r = -0.274$), TG ($r = -0.254$) and HDL ($r = 0.342$) CRP correlated with obesity ($r = 0.244$, $p < 0.01$) and HOMA-IR ($r = 0.182$, $p < 0.05$) Uric acid correlated ($p < 0.0001$) with obesity ($r = 0.500$), HOMA-IR ($r = 0.264$), TG ($r = 0.290$) Subjects with MetS presented higher IL-18 value ($p < 0.001$), however, such cytokine was not correlated with the risk of increased MetS (OR: 2.71; $p = 0.123$) Individuals with a value of adiponectin ≤ the mean value had a significantly higher chance ratio for MetS (OR: 10.71; $p < 0.0001$) Higher levels of CRP (OR:1.82; $p = 0.131$) and fibrinogen (OR:1.12; $p = 0.823$) were not associated with increased risk of MetS

Table 1 (continued)

Author/year/location	Sample/avarage age (years old)	Objectives	Analyzed markers	Main results
Garanty-Bogack et al. [32] Poland	211 obese adolescents (122 boys) Male: 12.22 ± 2.6 Female: 13.6 ± 2.3	Explore the relationship between insulin resistance and markers of acute phase reaction and endothelial activation in obese children and adolescents	CRP IL-6 IL-1 Fibrinogen	In children without carbohydrate metabolism disorders, HbA1c significantly correlated with markers of inflammation, except for IL-1 After adjustment by sex, age, BMI and FM, HbA1c maintained a significant correlation with CRP ($r=0.18$, $p<0.01$), Fibrinogen ($r=0.15$, $p<0.05$) and IL-6 ($r=0.28$, $p<0.001$) Most markers of inflammation were significantly correlated with HOMA IR After adjustment by sex, age, BMI and FM, IR remained significantly correlated with CRP ($r=0.17$, $p=0.017$)
Nishina et al. [31] Japan	192 obese adolescents (137 boys) Male: 9.6 ± 2.0 (FHHBP) 10.0 ± 1.8 (NFHHBP) Female: 10.4 ± 2.1 (FHHBP) 10.1 ± 2.4 (NFHHBP)	Investigate the relationship between SBP, serum insulin and leptin levels, visceral fat accumulation and family history of hypertension	Leptin	In the regression analysis, in both sexes, the level of leptin correlated significantly and positively with blood pressure M, $r=0.296$, $p<0.01$ (FHHBP) F, $r=0.393$, $p<0.05$ (FHHBP) and $r=0.577$, $p<0.01$ (NFHHBP) In the regression analysis, in both sexes, the level of leptin correlated significantly and positively with insulin: M, $r=0.334$, $p<0.01$ (FHHBP) F, $r=0.417$, $p<0.05$ (FHHBP) and $r=0.589$, $p<0.01$ (NFHHBP)

Legend: *AP*, arterial pressure; *AUC*, area under the ROC curve; *BF*, body fat; *BMI*, body mass index; *CI*, confidence interval; *CRP*, C-reactive protein; *DBP*, diastolic blood pressure; *DXA*, dual-energy X-ray absorptiometry; *F*, female; *FG*, fasting glucose; *FHHBP*, family history of high blood pressure; *FI*, fasting insulin; *FM*, fat mass; *HbA1c*, glycated hemoglobin; *HDL*, high density lipoprotein; *HOMA-IR*, index of resistance to insulin; *IL-6*, interleukin-6; *IL-18*, interleukin 18; *IR*, insulin resistance; *LDL*, low density lipoprotein; *M*, male; *MetS*, metabolic syndrome; *NFHHBP*, no family history of high blood pressure; *OR*, odds ratio; *SBP*, systolic blood pressure; *TC*, total cholesterol; *TG*, triglycerides; *WC*, waist circumference. β, linear regression coeficiente; r = Pearson's correlation coefficient; R^2, determination coefficient

Table 2 Risk of Bias for Each Individual Study Assessed by Joanna Briggs Institute Critical Assessment Checklist for Prevalence Studies

Studies	Criteria							
	1*	**2***	**3***	**4***	**5***	**6***	**7***	**8***
Fujita et al., 2019[33]	N	N	Y	Y	N	N	Y	Y
Madeira et al., 2017[23]	Y	Y	Y	Y	Y	Y	Y	Y
Can et al., 2016[24]	N	Y	Y	Y	N	N	Y	Y
Gonzaga et al., 2014[20]	Y	Y	Y	Y	Y	Y	Y	Y
Cruz et al., 2013[17]	Y	Y	Y	Y	Y	Y	Y	Y
Gonzáles et al., 2012[14]	N	N	Y	Y	Y	Y	Y	Y
Carvalho et al., 2010[19]	Y	Y	Y	Y	N	N	Y	Y
Mauras et al., 2010[26]	Y	Y	Y	Y	N	N	Y	Y
Litwin et al., 2010[25]	Y	Y	Y	Y	N	N	Y	Y
Gilardini et al., 2006[29]	Y	Y	Y	Y	Y	Y	Y	Y
Cardoso-Saldaña, 2007[21]	Y	Y	Y	Y	Y	Y	Y	Y
Garanty-Bogacka et al., 2005[32]	Y	N	Y	Y	N	N	Y	Y
Nishina et al., 2003[31]	Y	Y	Y	Y	N	N	Y	Y

Y, yes; *N*, no; *U*, unclear; *NA*, not applicable

1* Criteria for inclusion in the sample clearly defined

2* Study subjects and the setting described in detail

3* Exposure measured in a valid and reliable way

4* Objective and standard criteria for measurement

5* Confounding factors identified

6* Strategies to deal with confounding factors

7* Outcomes measured in a valid and reliable way

8* Appropriate statical analysis

inactivity, inadequate diet, genetic predisposition, and hormonal changes are also considered important in the development of MetS [41, 42].

Obesity is one of the main factors involved in the development of MetS, having seen its prevalence in this population [40, 43]. It is related to several components of MetS because it promotes chronic inflammation that triggers metabolic changes such as insulin resistance (IR), dyslipidemia, hypertension, and diabetes. The distribution of body fat also has a great influence on metabolic changes, so that visceral obesity further increases the risk of MetS [44, 45].

Visceral obesity is related to metabolic problems as follows: increased hypersensitivity of adipose tissue to glucocorticoids, increasing the capacity for arterial vasoconstriction, causing arterial hypertension; increased plasma glucose levels, which induce hyperinsulinemia and in the long term causes IR and type 2 diabetes mellitus (DM2); increased secretion of angiotensin, which promotes a greater risk of hypertension; increased secretion of inflammatory cytokines, such as IL-6 and TNF-α, which promote subclinical inflammation and lead to MetS and CVD; and an increase in circulating TG and a reduction in HDL levels, which alters blood viscosity, favors platelet aggregation, and increases cardiovascular risk [46]

In addition to obesity, another factor involved in the development of MetS is IR, a metabolic alteration in which defective insulin action in peripheral tissues results in compensatory hyperinsulinemia, so that blood glucose is maintained at normal levels. When the capacity of pancreatic beta cells reaches the maximum limit of insulin secretion, they fail and the body develops DM2; however, long before that, microvascular lesions already occur. IR is associated with the presence of body fat increasing cardiovascular risk; in addition, inflammatory cytokines such as TNF-α and IL-6 influence the metabolism of carbohydrates, reducing the phosphorylation of substrates-1 of the insulin receptor (IRS) and the synthesis and translocation of GLUT-4 to the cell membrane, causing impaired insulin signaling. The increase in free fatty acids in the

tissue also promotes inhibition of the phosphorylation of the IRS, which triggers IR. Thus, IR has increased the risk of MetS, DM2, and CVD among adolescents, especially in those with excess weight [37, 47, 48].

Hypertension is also an important factor in the development of MetS, because, in addition to vasoconstriction, hyperinsulin, especially in obese individuals, increases the renal reabsorption of sodium to water, activates the sympathetic nervous system, reduces the activity of the enzyme Na+-K+-ATPase, and elevates cellular calcium, thus promoting an increase in blood pressure [28, 49].

Another important factor is dyslipidemia, since changes in the lipid profile may already be present at this stage of life, characterized by increased levels of triglycerides, total and LDL cholesterol, and with low levels of HDL, which increases the risk of developing MetS in these individuals. It is important to consider that, on average, 40 to 50% of adolescents with dyslipidemia will have hyperlipidemia as adults, thus increasing the chances of developing DM2 and CVD [50–52].

It is important to consider that, although adipose tissue secretes inflammatory mediators causing inflammation to occur in the presence of obesity, MetS can be associated with inflammation independently of obesity. This is because the action of IR in the inflammatory process can occur in a similar way between obese and non-obese individuals, showing that inflammation and MetS are not restricted to excess weight [53–55].

Metabolic syndrome is accompanied by an inflammatory state that does not appear to result from tissue damage, nor does it present with infection or a sign of autoimmunity, and is called "low-grade" chronic inflammation [46]. This study showed the association of inflammatory markers (IL-6, IL-10, IL-18, TNF-α, leptin, CRP, adiponectin, and fibrinogen) with the components of MetS. Interleukin IL-6 is a pleiotropic cytokine that acts in an immune, cellular, and humoral way in the process of inflammation and tissue injury. It is a cytokine that has a cellular source, as it is produced and secreted by endothelial cells, smooth muscle cells, monocytes, and macrophages. Adipocytes, especially from visceral adipose tissue, are the main secretors of IL-6. It is a central mediator of the acute-phase response and determines the plasma production of fibrinogen, serum amyloid protein A (SAA), and C-reactive protein, being, therefore, the main procoagulant cytokine. Furthermore, the combined action of IL-1B and TNF-α stimulates smooth muscle cells to produce IL-6, which significantly increases the expression of growth factors (from fibroblasts and platelet derivatives) associated with the progression of atherosclerosis [56, 57].

In the context of MetS, it is involved in the processes of carbohydrate and lipid metabolism, leading to hyperinsulinemia by altering the expression of insulin receptors, and increased levels of fatty acids and glycerol, by inhibiting lipoprotein lipase and increasing lipolysis. In addition, it is strongly linked to the development of atherosclerosis, due to its negative correlation with HDL [57–59].

The plasma concentration of IL-6 is positively correlated with the increase in body mass, and insulin and catecholamines stimulate their secretion by adipocytes. This correlation also occurs with other cytokines and inflammatory mediators, so that one of its most discussed functions is the stimulation of CRP production, the main mediator of the inflammatory response, by hepatocytes [60, 61].

Mauras et al. [26] showed that adolescents with obesity presented high concentrations of IL-6, which was a reflection of a pro-inflammatory and pro-thrombotic state in pre and in puberty ($p < 0.001$), even before MetS comorbidities set in. Garanty-Bogack et al. [32] also showed that IL-6 correlated with IR ($p < 0.001$) in obese adolescents. Carvalho et al. [19] also showed that IL-6 presented a positive correlation with TNF-α ($p < 0.05$), and with IL-10 ($p < 0.01$) in eutrophic adolescents with excess body fat, and that among those with excess weight, this cytokine correlated positively with triglycerides ($p < 0.05$). These studies show that IL-6 is an important inflammatory marker associated with the components of the metabolic syndrome (insulin resistance, obesity, and hypertriglyceridemia).

Interleukin 18 is a pro-inflammatory cytokine of the interleukin-1 (IL-1) family, expressed by macrophages by induction of other cytokines, such as IL-6 and TNF-α, which has pleiotropic function and relates the innate and acquired immune response. It has an important role in the development of atherosclerosis since it promotes chemotaxis of human T cells into the plaque, in addition to stimulating the expression of metalloproteinases that act making the atherosclerotic plaque more fragile, and therefore more vulnerable [62, 63].

Elevated levels of this cytokine have already been linked to obesity, type 2 diabetes, insulin resistance, atherosclerosis, and metabolic syndrome. Its plasma concentration has been associated with individual MetS components and its levels increase progressively in parallel with the greater number of MetS components [63].

In the study of Gilardini et al. [29], obese adolescents with MetS also had a higher IL-18 value ($p < 0.001$); however, this cytokine did not correlate with the increased risk of MetS (OR: 2.71; $p = 0.123$). Carraro et al. [64] observed that it was not shown as a good biomarker of MetS components in healthy young people, having not been able to detect early changes in metabolic characteristics. According to the authors, these findings can be justified by the small sample of the study.

Despite this, many studies have already shown that IL-18 levels are increased in patients with MetS and tend to increase the more components of the syndrome that are present. Some authors have shown that polymorphisms in the genes rs2115763 and rs1834481 are associated with high levels of this cytokine, so that only one polymorphism in these genes is sufficient to increase the level of IL-18, which lead to changes in insulin sensitivity and increase the risk of MetS, suggesting that this cytokine is involved in the pathogenesis of the syndrome [63, 65, 66].

TNF-α is a cytokine that, like IL-6, is also a mediator of the acute phase response, has cellular origin, and is produced by adipose tissue, with autocrine, paracrine, and endocrine action, regulating the accumulation of fat in adipocytes by inhibiting lipase and stimulating lipolysis. It has an inverse correlation with glucose metabolism and interferes with insulin signaling and expression of the GLUT-4 transporter, leading to hyperinsulinemia. Thus, TNF-α is associated with obesity and MetS because it is involved in lipid and glucose metabolism disorders [57, 67, 68].

The secretion of TNF-α is higher in obese individuals, so that its expression by adipocytes is presented as one of the causes of obesity linked to IR [69]. In the study by Carvalho et al. [19], there was no significant difference in the peripheral expression of this cytokine between groups of different nutritional states, since adolescents with normal weight but excess body fat had similar levels of TNF-α.

This cytokine acts in the inflammatory process as a mediator of the acute phase response, having an important role in the cascade and synthesis of other cytokines [57]. According to Carvalho et al. [19], TNF-α correlated positively with other cytokines: IL-6 ($r = 0.0463$, $p < 0.05$) and IL-10 ($r = 0.675$, $p < 0.01$) in obese adolescents and in those eutrophic but with excess body fat. Positive correlation between TNF-α and MetS components is also reported, which can predict, for example, the risk of cardiovascular diseases and be shown as a marker for myocardial infarction [68]. Elevated levels of this cytokine are thus related to metabolic abnormalities, being characteristic in adolescents with obesity.

IL-10 is a pleiotropic cytokine produced by macrophages, monocytes, and T and B lymphocytes, which has an anti-inflammatory function acting on the regulation of the immune system by inhibiting in a potent and continuous way the production of pro-inflammatory cytokines IL-2, IL-12, TNF-β, and INF-y, through negative feedback. Its anti-inflammatory and antithrombotic property shows its important role in the development of cardiovascular diseases. In addition, it is responsible for inhibiting the activity of T cells and macrophages and protecting against atherogenesis [70, 71].

IL-10 has been related to MetS for its regulatory effect on the immune system. In the study by Carvalho et al. [19], IL-10 levels did not show significant differences among adolescents of different nutritional states, but in the group of eutrophic adolescents with excess body fat, IL-10 was correlated with TNF-α, IL-6, and glucose, suggesting risk of development of metabolic diseases, regardless of obesity.

Leptin is a hormone produced by adipose tissue considered one of the most important adipocytocines that has neuroendocrine function and that signals the reduction of food intake, because in the long term, it induces satiety, besides also increasing energy expenditure. It acts on muscle, non-adipose tissue, and liver by peripheral actions, promoting fatty acid oxidation, preventing lipotoxicity, and inhibiting triglyceride accumulation, respectively [71].

It acts in the pathophysiology of obesity, contributes to IR, modulates vascular function, and stimulates vasoconstriction, processes that have strong influences on the development of MetS. It is high in obese adults and children, being associated with the degree of adiposity, promoting resistance to leptin [72–74].

Nishina et al. [31] showed that hyperleptinemia is significantly and positively correlated with hyperinsulinemia and elevated blood pressure in obese adolescents, regardless of family history. Similarly, Fujita et al. [33] showed that leptin showed a strong correlation with all body fat parameters and that it mediates the relationship between body adiposity and elevated blood pressure in adolescents of both sexes.

According to Leyva et al. [75], there is a strong relationship between leptin, IR, hyperinsulinemia, and other components of MetS, so changes in plasma concentration of leptin can be considered as additional components of MetS and high cardiovascular risk. In the study

of Madeira et al. [23], leptin level above 13.4 ng/dL was significantly associated with MetS, being a useful biomarker in metabolic and cardiovascular risk.

Gonzaga et al. [20] also evaluated leptin in obese adolescents and found that in females, there is a higher number of significant correlations between leptin and cardiometabolic risk factors. In the regression analysis, leptin showed negative correlation with HDL and positive with TG, insulin, HOMA-IR, BMI, WC, and with SBP, so the authors consider leptin as a useful marker of MetS and IR in obese adolescents. González et al. [14] also showed that leptin showed significant correlation with MetS, concluding that leptin can be used as a biomarker in the prediction of MetS in adolescents.

Another adipocytocin also synthesized by adipose tissue is adiponectin, which has an anti-inflammatory role in tissues, promoting reduction of IR, fibrosis in the liver, and, consequently, inflammation [76]. In addition to having influence on the mechanisms of hunger and energy expenditure, adiponectin regulates carbohydrate and lipid metabolism. Adiponectinemia has an inverse relationship with IR, obesity, cardiovascular diseases, and MetS [77–79], so that it has been considered as an additional indirect biomarker for the diagnosis of MetS [80].

According to Mohan et al. [81], reduced levels of adiponectin are associated with MetS and the components of MetS, especially with diabetes, IR, and dyslipidemia. Gilardini et al. [29] also found that adiponectin in adolescents correlated with obesity, HOMA, TG, and HDL, concluding that among other markers evaluated (IL-18, fibrinogen, and CRP), adiponectin was shown to be the best indicator of MetS in adolescents. Similarly, the study by González et al. [14] showed that adiponectin correlated significantly with MetS in adolescents, showing that such cytokine can be used as a biomarker in the prediction of MetS in adolescents.

CRP is one of the most used inflammatory markers in clinical practice, which has high sensitivity, stability, and accuracy. It is an acute phase protein synthesized mainly by hepatocytes, but it is also produced by other tissues, such as adipose, renal, vascular, and arterial, as well as macrophages. It has a role in the activation of the complement system and in the recruitment of phagocytic cells, besides being regulated by cytokines IL-6, IL-1, and TNF-α [82, 83].

In the presence of acute inflammation, CRP levels increase significantly, and in chronic processes, the increase is discrete, but similarly significant [84] being associated with IR, MetS, and the components of the syndrome. In the study of Garanty-Bogack et al. [32], CRP showed a significant positive correlation with HbA1c and IR in obese adolescents, because, according to the authors, inflammation is underlying IR.

According to Mauras et al. [26], adolescents with obesity have significantly higher values of CRP, compared to eutrophic adolescents; in addition, CRP showed positive correlation with measures of body and visceral adiposity. According to the authors, the increase in concentrations of this marker reflects a pro-inflammatory and prothrombotic state in adolescents, even before MetS comorbidities were present. In the study of Litwin et al. [25], the CRP level was significantly higher among adolescents with hypertension and in adolescents with MetS and significantly correlated with the number of MetS criteria.

Cardoso-Saldaña et al. [21] also showed that the levels of this marker were higher in adolescents who presented some component of MetS, especially when having three or four components. Still, Cruz et al. [17] found significant correlation with BMI, fasting glucose, and HDL, showing that the association found between individual components of MetS and CRP concentrations suggests that inflammation may be an early event in the development of metabolic disorders in adolescents.

Similarly, in the study by Can et al. [24], CRP levels were significantly higher in the group of adolescents with MetS. For the authors, this increase may be a result of the inflammatory state of MetS and may be a prominent indicator in the diagnosis of MetS in adolescents, who are generally neglected in terms of inevitable future complications.

Fibrinogen is a glycoprotein synthesized primarily by the liver that acts as a coagulation factor and as an acute phase reagent. It has an important role in the formation and growth of atheroma plaques, as well as in thrombus formation because it is involved in platelet aggregation and endothelial cell injury. Mediated by IL-6, its synthesis is significantly increased during inflammation [85, 86].

By increasing endothelial cells and proliferation of vascular smooth muscles, fibrinogen causes atherosclerosis, and by increasing fibrin, platelet aggregation, and higher plasma viscosity, it promotes arterial and venous thrombosis. High levels of fibrinogen in association with risk factors such as dyslipidemia, IR, sedentary lifestyle, arterial hypertension, and smoking increase the risk of thrombus formation [87, 88].

According to Garanty-Bogack et al. [32], fibrinogen was significantly correlated with HbA1c and HOMA-IR

in obese adolescents. In the study of Mauras et al. [26], fibrinogen was positively correlated with the measures of body and visceral adiposity also in a sample of adolescents, and in those with obesity, fibrinogen presented significantly higher levels, indicating a pro-inflammatory and pro-thrombotic state even before the MetS comorbidities were present. These findings indicate that fibrinogen may be a marker of MetS.

The analyzed markers act in a distinct and complex way in the metabolic pathway, so that more studies are needed to better understand the behavior of these in front of MetS. This study presented limitations such as the transversal nature of the studies, which does not allow to verify causal relationships and does not consider changes in the concentration of markers by numerous factors over time, which implies the need for longitudinal studies, and also, the absence of a specific cutoff point for inflammatory markers in this population.

As strengths, it is believed that this is the first study to present a review on the topic specifically for adolescents. The PRISMA Guideline was strictly followed to conduct this study and the TJB evaluation tool confirmed the low risk of bias of the studies selected to compose the review.

CONCLUSION

The analyzed studies showed that the inflammatory biomarkers IL-6, IL-10, IL-18, leptin, adiponectin, TNF-α, CRP, and fibrinogen are associated with the components of MetS and are useful in predicting MetS in adolescents with or without excess weight. The results of this review are of clinical relevance, since the evaluation of inflammatory biomarkers in the presence of metabolic alterations can help to identify the risk factors that lead to the progression of MetS in adolescents.

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AUTHOR CONTRIBUTION

ARFR and NSM participated in the research, selection, and evaluation process of the included articles; wrote the paper; analyzed data; and were ultimately responsible for the content. SCCF and SEP participated in the critical review of the paper. All authors have read and approved the final manuscript.

AVAILABILITY OF DATA AND MATERIAL

None.

CODE AVAILABILITY

None.

DECLARATIONS

Ethics Approval None.

Conflict of Interest The authors declare no competing interests.

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