LITERATURE SYSTEMATIC REVIEW ARTICLE

C-REACTIVE PROTEIN, METABOLIC SYNDROME AND CARDIOVASCULAR RISK FACTORS: A SYSTEMATIC REVIEW

PROTEÍNA C-REATIVA, SÍNDROME METABÓLICA E FATORES DE RISCO CARDIOVASCULARES: UMA REVISÃO SISTEMÁTICA

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ABSTRACT

Objective: to assess the association of C-reactive protein (CRP), metabolic syndrome (MS) and cardiovascular risk factors in overweight children and adolescents. Method: this is a systematic review, conducted in the Publisher Medline (PubMed) database, Virtual Health Library (VHL) through the Scientific Electronic Library Online (Scielo) and the very Scopus, through the descriptors: “C-reactive protein” and “metabolic syndrome x” and “cardiovascular diseases”, in journals published between January 2006 and June 2011. We evaluated the studies emphasized the association between CRP and metabolic syndrome with cardiovascular disease were excluded or revisions that addressed medication or had a different focus of the goal. Proceeded with a critical reading of the manuscripts found by peers for inclusion in the study. Results: the 11 selected studies evaluated individuals between 1 and 19 years, the most were conducted in Europe, the predominant design was cross. The most of the studies concerned to verify the relationship between inflammatory markers and development of MS or cardiovascular diseases, only one study looked if at whether the patterns of adiponectin are related to the phenotype of obesity. Conclusion: most studies evaluated suggested an influence of CRP in the onset of MS and cardiovascular diseases. Descriptors: c-reactive protein; metabolic syndrome x; cardiovascular diseases; obesity.

RESUMO

Objetivo: verificar a relação da proteína c-reativa (PCR), síndrome metabólica (SM) e fatores de risco cardiovascular em crianças e adolescentes obesas ou com sobrepeso. Método: estudo de revisão sistemática, realizada nas bases de dados Publisher Medline (PubMed), Scopus, na Biblioteca Virtual da Saúde (BVS) por meio da Scientific Electronic Library Online (Scielo) com emprego dos descritores: "C-reactive protein" e "metabolic syndrome x" e "cardiovascular diseases", em periódicos publicados entre janeiro de 2006 e junho de 2011, com vista a responder a seguinte questão de pesquisa: qual a relação da proteína c-reativa (PCR), síndrome metabólica (SM) e fatores de risco cardiovasculares em crianças e adolescentes obesas ou com sobrepeso? Foram avaliados os estudos que enfatizaram a associação entre a PCR e SM com o risco cardiovascular, sendo excluídos revisões ou os que trataram de medicamento ou tivessem um foco diferente do objetivo. Procedeu-se com a leitura crítica por pares dos manuscritos encontrados para inclusão no estudo. Resultados: os 11 estudos selecionados avaliaram indivíduos entre 1 e 19 anos, a maioria foi realizado na Europa, o delineamento predominante foi o transversal. A maioria dos estudos preocupou-se em verificar a relação entre os marcadores inflamatórios e o desenvolvimento da SM ou de doenças cardiovasculares, apenas um dos estudos observou se os padrões de adiponectina se relacionavam com o fenótipo de obesidade. Conclusões: a maioria dos estudos avaliados sugeriu haver influência da PCR no aparecimento de SM e doenças cardiovasculares. Descritores: proteína c-reativa; síndrome x metabólica; doenças cardiovasculares; obesidade.

RESUMEN

Objetivo: investigar la relación entre la proteína c-reactiva (PCR), el síndrome metabólico (SM) y factores de riesgo cardiovascular en niños y adolescentes obesos o con sobrepeso. Método: se trata de una revisión sistemática, realizada en las bases de datos Publisher Medline (PubMed), Biblioteca Virtual en Salud, través de la base Scientific Electronic Library Online (Scielo) y la muy Scielo y Scopus, a través de los descriptores: "la proteína C reactiva" y "síndrome metabólico x" y "las enfermedades cardiovasculares en revistas publicadas entre enero de 2006 y junio de 2011. Se evaluaron los estudios que buscaron la relación entre la PCR y el síndrome metabólico con la enfermedad cardiovascular, fueron excluidas revisiones que abordaron la medición o tiene un enfoque diferente de la meta. Procedió a una lectura crítica de los manuscritos encontrados por sus compañeros para su inclusión en el estudio. Resultados: los 11 estudios seleccionados evaluaron a individuos de 1 y 19 años, la mayoría se llevaron a cabo en Europa, el diseño predominante fue cruzado. La mayoría de los estudios correspondientes para verificar la relación entre los marcadores inflamatorios y el desarrollo de SM o enfermedad cardiovascular, sólo un estudio analizó si los patrones de adiponectina estaban relacionados con el fenotipo de la obesidad. Conclusión: la mayoría de los estudios consideró que hay una influencia de la PCR en la aparición de la esclerosis múltiple y la enfermedad cardiovascular. Descriptores: proteína c-reactiva; síndrome x metabólico; enfermedades cardiovasculares; obesidad.

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INTRODUCTION

It is considered metabolic syndrome (MS) a set of cardiovascular risk factors, such as central adiposity, dyslipidemia, insulin resistance (IR) and hypertension. The development of cardiovascular disease (CVD) currently represents a major cause of morbidity and mortality worldwide. A recent systematic review examined the worldwide prevalence of MS and found values between 0.1% and 49.7%, mainly concentrated in individuals with excess fat.

In addition to the components of MS, the pathogenesis of atherosclerosis, inflammatory factors are also involved and its complications have drawn the attention of researchers and health authorities. Accordingly, it has been sought to answer a few questions not yet completely understood, inflammation is the result of some or all of the components associated with the SM? The inflammation is a consequence or cause of MS? It has been suggested that the increase of inflammatory cytokines derived from adipocytes may be partially responsible for the metabolic changes seen in obese patients.

The first study linking obesity and C-reactive protein (CRP) was published in 1999. From this publication several other studies have been performed to elucidate the relationship between increased CRP levels in response to increased secretion of cytokines of adipose origin, found in obese individuals. Other studies have found elevated levels of CRP in obese children and adolescents, indicating that in the early stages, there is already a degree of inflammation in relation to non-obese population. However, no reports are available and sufficiently condensed to ensure its usefulness as a marker of cardiovascular risk and diabetes in childhood.

The inflammation plays a role in atherogenesis by expression of human adipocytes and release of proinflammatory cytokines such as interleukin 6 (IL-6), which are responsible for producing a state of low-grade inflammation. IL-6 stimulates the production of the liver PCR, which is an acute phase protein and a sensitive marker of systemic inflammation. Study of children and adolescents Americans showed that fibrinogen and CRP are associated with increased risk for coronary artery disease.

The role of CRP in cardiovascular risk prediction in adults is already well established in the literature, but there is still no consensus on its use in the stratification of cardiovascular risk in childhood. Thus, in order to answer the research question: what is the relationship of C-reactive protein (CRP), metabolic syndrome (MS) and cardiovascular risk factors in children and adolescents are obese or overweight? Was developed the following objective:

- Check the ratio of C-reactive protein (CRP), metabolic syndrome (MS) and cardiovascular risk factors in children and adolescents are obese or overweight.

METHOD

A systematic review of the literature, national and international, carried out between the months of May and June 2011. The data presented are from papers published from January 2006 to June 2011.

A search of scientific literature was conducted in the Publisher databases Medline (Pubmed), Scopus, the Virtual Health Library (VHL) through the base Scientific Electronic Library Online (Scielo) and Scielo own. Were established to research and used for crossing the following descriptors in the Medical Subject Headings, "C-reactive protein" and "metabolic syndrome x" and "cardiovascular diseases".

102 articles were screened, and then proceeded to read the titles, abstracts and selected those that met the limits thus defined: articles on human subjects, in English, Spanish or Portuguese, available online complete and to investigate individuals aged less than 19 years. Later we proceeded to read the full articles, to analyze whether they addressed the relationship of CRP with metabolic syndrome and cardiovascular factors in children and adolescents. At the end of the selection were selected: an article in VHL, five in Pubmed, Scopus and a 10 in the Scielo. The article found in the VHL, Scielo and published in five Pubmed were also present in Scopus, so we selected 11 articles of interest to the study. The process of selection of studies is presented in Figure 1.

To analyze the collected data, two reviewers read critically, independently, to choose the articles that related concomitant PCR, MS and cardiovascular disease. The disagreement with the items to participate in the analysis were resolved by consensus among the authors, considering studies that evaluated concurrently SM, and not just its components, cardiovascular risk factors and CRP. These units were standardized and grouped according to the correlation of the core ideas presented: characteristics of the
After reading the titles and abstracts, 112 abstracts were selected in the VHL databases, Pubmed, Scielo and Scopus. We excluded 85 studies, of these, 60 had a different focus of the objective sought, 11 articles were not available, complete and online, 12 were literature review and two did not report the age group studied (>19 years). Of the 18 articles eligible for the study, seven were excluded because they were present in two databases, we selected the final 11 articles for analysis.

Figure 1 shows the main features of the articles on the influence of CRP in the development of MS and CVD in children and adolescents are obese or overweight. Four of the 11 selected studies were conducted in Europe. Publications in journals focused on pediatrics, diabetes and endocrinology. The design was the predominant cross, although it was found three case-control.

Regarding the inclusion criteria of participants, five participants selected studies grouped in obese and normal weight, three involved the general population, in one study participants were overweight and a rated Indian children. The age of children and adolescents ranged between 1 and 19 years.

Most of the studies concerned to verify the relationship between the markers and the development of MS inflammatory or cardiovascular diseases, only one of the studies showed that the patterns adiponectinas relate to the phenotype of obesity.

The main objective and the results are depicted in Figure 2. The most used criteria for diagnosing MS were obtained based on the classification proposed by NCEP-ATP III for adults, but the cutoffs are tailored to children and adolescents.
<table>
<thead>
<tr>
<th>References</th>
<th>Location</th>
<th>Subject (n)</th>
<th>Age (Years)</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Daghri et al., 2011</td>
<td>Saudi Arabia</td>
<td>General</td>
<td>1-80</td>
<td>Anthropometry, PA and exams (insulin, leptin, adiponectin, resistin, PCR and PAI-1)</td>
</tr>
<tr>
<td>Silva et al., 2010</td>
<td>Brazil</td>
<td>Teens (84)</td>
<td>10-15</td>
<td>Anthropometry, CA, CB, examinations (CT, HDL, LDL, Triglycerides, Anti-LDL, and PCR)</td>
</tr>
<tr>
<td>Mauras et al., 2010</td>
<td>USA</td>
<td>Obese and Eutrophic (623)</td>
<td>7-18</td>
<td>Case-control PA, CA and exams (glucose, lipids, CRP, Fibrinogen, adiponectin, insulin, testosterone, IGF-1, liver transaminases, DEXA)</td>
</tr>
<tr>
<td>Huang et al., 2009</td>
<td>Australia</td>
<td>General (1377)</td>
<td>14</td>
<td>Anthropometry, PA, examinations (insulin, glucose, triglycerides, HDL, LDL, PCR and uric acid)</td>
</tr>
<tr>
<td>Sorrano-Guillen et al., 2008</td>
<td>Spain</td>
<td>Obese (115)</td>
<td>6-18</td>
<td>Anthropometry, PA, exams (PCR, lipid profile, liver function, glucose, basal insulin)</td>
</tr>
<tr>
<td>Kosmna et al., 2008</td>
<td>Japan</td>
<td>Obese (321)</td>
<td>6-12</td>
<td>Anthropometry, PA and exams (adiponectin, leptin, resistin and PCR)</td>
</tr>
<tr>
<td>Lin et al., 2008</td>
<td>Taiwan</td>
<td>General (993)</td>
<td>12-19</td>
<td>Anthropometry, PA, and exams (lipids, insulin, PCR and aminotransferase)</td>
</tr>
<tr>
<td>Oliveira et al., 2008</td>
<td>Brazil</td>
<td>Obese and Eutrophic (407)</td>
<td>4-18</td>
<td>Anthropometry, PA, and exams (lipids, insulin, PCR and aminotransferase)</td>
</tr>
<tr>
<td>Gilardini et al., 2006</td>
<td>Italy</td>
<td>Obeseos (162)</td>
<td>9-15</td>
<td>Anthropometry, PA and exams (adiponectin, PAI-1, IL-18, CRP, Fibrinogen, uric acid, lipids, and insulin) and diagnosis of SM</td>
</tr>
<tr>
<td>Retnakaran et al., 2006</td>
<td>Canada</td>
<td>Indigenous (236)</td>
<td>10-19</td>
<td>Anthropometry, CA, body fat, exams (insulin, CRP, IL-6, adiponectin, leptin, CT, triglycerides, HDL, LDL, apoB and apoA1)</td>
</tr>
<tr>
<td>Martos et al., 2006</td>
<td>Spain</td>
<td>Obese and Eutrophic (43)</td>
<td>6-9</td>
<td>Exams: CRP, IL-6, total, vitamin B12, leptin, insulin, lipids, LDL, HDL, triglycerides, glucose, glycated hemoglobin, and Fibrinogen</td>
</tr>
<tr>
<td>Invitti et al., 2006</td>
<td>Italy</td>
<td>Obese and Eutrophic (588)</td>
<td>6-16</td>
<td>Family history, Anthropometry, PA and exams (glucose, lipids, uric acid, albumin, Fibrinogen, PAI-1, CRP, IL-6)</td>
</tr>
</tbody>
</table>

Figure 2. Characteristics of studies on association between CRP and cardiovascular risk factors, 2006/2011. *Legend: blood pressure (BP), waist circumference (WC), arm circumference (AC), plasminogen activator inhibitor 1 (PAI-1), high density lipoprotein (HDL), low density lipoprotein (LDL), Insulin-like growth factor 1 (IGF-1), absorptiometry by dual energy x-ray absorptiometry (DEXA), total cholesterol (TC), C-reactive protein (CRP), interleukin 18 (IL-18), interleukin 6 (IL-6), apolipoprotein B (apoB), apolipoprotein A1 (apoA1).
DISCUSSION

As in other areas of research, we observed concentration of studies in Europe and two in Brazil, although there has also been an increased prevalence of obesity and its comorbidities among Brazilian children and adolescents. Research on the variation of PCR infantojuvenile in the Brazilian population are still limited and not conducive to monitoring of this inflammatory marker and cardiovascular risk, especially in overweight and obesity. As in adults, there is no consensus whether the increase is the result of PCR or are directly involved in the pathophysiology of chronic diseases.

Most of this systematic review showed an association of PCR values in the onset of MS and cardiovascular risk factors, however it was observed that in three manuscripts of the increase in PCR did not match the appearance of metabolic alterations, except those with a greater degree of obesity. Similarly, the study concluded that CRP may not have a role as to predict cardiovascular disease.

Case-control study with children and teenagers in Florida, United States, found that obese individuals with IR but without MS is 10 times higher concentrations of CRP than those without IR. Therefore, biomarkers such as CRP are associated with cardiovascular risk from childhood, independent of the presence
of MS. On the other hand, other studies reported that higher levels of CRP are found in obese individuals with MS.

Another survey, conducted in Italian obese children and adolescents, investigated the relationship between adiposity and metabolic syndrome. Their results demonstrated that they are synergistic in the inflammatory process. Through the association between MetS and biomarkers, including adiponectin, interleukin-18, PAI-1, CRP, fibrinogen and uric acid. These authors stated that a lower level of adiponectin was independently associated with the presence of MS in white children and adolescents with a mean age of 14 years.

In obese populations and between individuals with the highest number of MS components, high concentrations of CRP have been associated with intracellular inflammatory processes, culminating in the development of atherosclerosis and type 2 diabetes (DOWD 2010). Among the studies evaluated the majority grouped the participants in obese and normal weight, to better compare the variables, finding in all cases that the group of obese subjects had higher CRP concentrations. Because of concern for public health, since the studies analyzed the participants were children or adolescents. Another study evaluated adolescents with overweight and found that these subjects had inflammatory characteristics similar to obese adults.

In Brazil, a study with adolescents in São Paulo, found that CRP levels varied across the three groups (normal weight, overweight and obese) and the values observed in the obese group were higher than the reference values described in the literature for adults. Their results indicated that although there is no single cut off value for CRP, the participants had a subclinical inflammatory process associated with obesity, regardless of the cutoff point adopted.

A study conducted in Saudi Arabia sought to determine whether there were patterns of inheritance adiponectinas and their relationship with obesity-related phenotypes. The finding that BMI was influenced by five hormones (leptin, insulin, adiponectin, CRP and PAI-1), with the variables showing significant family inheritance, except for PCR. Thus, CRP is a sensitive marker of metabolic risk, in subjects with excess weight, yet its high level was not related to maternal or paternal inheritance. The other manuscript

C-reactive protein, metabolic syndrome and... has not evaluated the heritability of phenotypes related to obesity, though five of them also found the influence of hormone changes in BMI.

Elevated levels of CRP were also associated with abdominal circumference (AC) and increased levels of liver enzyme. Corroborating data from another study that described the association between high levels of CA in adolescents and elevated CRP levels.

It is understood that high levels of PCR are associated with the accumulation of visceral adipose tissue and the components of the MS. So it has been suggested that there is a possible role of visceral adipose tissue in the pathogenesis of atherosclerosis. Therefore, obesity, metabolic syndrome and atherosclerosis are closely related and may be determinants of an increased response of vascular inflammation.

Accordingly, other studies in children and adolescents found that the accumulation of abdominal fat and hyperinsulinemia are associated with a thrombogenic and inflammatory profile. Increased concentrations of fibrinogen and plasminogen activator inhibitor 1 (PAI-1) have been reported in individuals with visceral obesity, increasing the risk of thrombosis. Furthermore, high levels of certain inflammatory markers such as IL-6, TNF and PCR are also associated with abdominal obesity.

It is noteworthy that hypertriglyceridemia, change in CRP levels, the pre-diabetic and hepatic steatosis may play a role in the development of metabolic syndrome and type 2 diabetes. This relationship may involve increased levels of liver enzymes such as ALT. Bahia in the Brazilian study, found that the relationship between high levels of CRP and ALT are associated with uric acid, metabolic syndrome and subclinical coronary atherosclerosis. What underscores the potential use of these markers combined as a screening method to identify children at risk for cardiovascular disease.

The almost exclusive use of the cross-sectional design brought some limitations. The anthropometric and metabolic changes that make up the SM is changing, especially during puberty, there may be changes in the classification of the same individual in a short time.

The demonstration that CVD may originate in childhood and adolescence leads to the need for these risk factors are widely investigated during this period, in order to
plan interventions ever earlier and possibly more effective on these factors, reducing in future morbidity and mortality.

**CONCLUSION**

Most studies reviewed suggested a relationship between CRP, the metabolic syndrome and cardiovascular risk factors. However, it was noted that some studies have reported that elevated CRP levels did not correspond to the onset of metabolic alterations, except those with a greater degree of obesity. Thus, excess weight, MS and atherosclerosis appears to be linked to increased vascular inflammatory response.

Considering these findings and the demonstration that CVD may originate in childhood and adolescence, it is necessary that these risk factors are investigated in this period in order to contribute to increase early intervention and possibly more effective on these factors, reducing in future morbidity and mortality. Furthermore they are required to elucidate these issues further studies, especially in the pediatric population, the object of research of the authors of this article.

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