Revisión
Inflammatory markers in relation to body composition, physical activity and assessment of nutritional status of the adolescents

Valter Paulo Neves Miranda¹, Maria do Carmo Gouveia Peluzio², Eliane Rodrigues de Faria³, Sylvia do Carmo Castro Franceschini² and Silvia Eloiza Priore²

¹Doctoral student of the graduate program in Nutrition Science from the Federal University of Viçosa, Minas Gerais. ²Lecturer in the graduate program in Nutrition Science at the Federal University of Viçosa, Minas Gerais. ³Lecturer at the Federal University of Espírito Santo, Vitória, Espírito Santo, Brazil.

Abstract

Introduction: The evaluation of inflammatory markers during adolescence can monitor different stages and manifestation of chronic diseases in adulthood. The control of the subclinical inflammation process through changes in lifestyle, especially in the practice of physical activity and dietary education can mitigate the effects of risk factors that trigger the process of atherosclerosis.


Methods: A literature review was performed in the following electronic databases: PUBMED, SCIELO and CONCHRANE COLLECTION. The following associated terms were used "inflammation AND cardiovascular diseases AND nutritional status OR body composition OR physical activity". There were topics created for the discussion of subjects: obesity and risk factors for cardiovascular disease during adolescence; expression of inflammatory markers in adolescence; development of cardiovascular disease with inflammatory markers, and finally, inflammatory markers, physical activity and nutritional evaluation.

Results: It was observed that the inflammatory markers may manifest in adolescence and be related to risk factors for cardiovascular diseases. Physical activity and nutritional evaluation featured as non-pharmacological measures to control the incidence of inflammatory markers and cardiovascular risk factor.

Conclusions: Intervention studies may clarify how the adoption of a more proper lifestyle can influence the inflammatory process.

Correspondence: Valter Paulo Neves Miranda.
Graduate program in Nutrition Science,
Department of Nutrition and Health / CCBII.
Campus Universitário.
CEP: 36570-900. Viçosa – MG.
E-mail: vpmiranda@yahoo.com.br

MARCADORES INFLAMATORIOS EN RELACIÓN A COMPOSICIÓN CORPORAL, ACTIVIDAD FÍSICA Y EVALUACIÓN DEL ESTADO NUTRICIONAL DE ADOLESCENTES

Resumen

Introducción: La evaluación de los marcadores inflamatorios en la adolescencia puede monitorear diferentes etapas y manifestación de las enfermedades crónicas en la edad adulta. El control del proceso de inflamación subclínica mediante cambios en el estilo de vida, especialmente en la práctica de la actividad física y la educación dietética puede mitigar los efectos de los factores de riesgo que desencadenan el proceso de la aterosclerosis.

Objetivo: Hacer una revisión crítica sobre los marcadores inflamatorios como un factor de riesgo de enfermedad cardiovascular (ECV) en relación con la composición corporal, la actividad física y la evaluación del estado nutricional de los adolescentes.

Métodos: Una revisión de la literatura se realizó en las siguientes bases de datos electrónicas: PUBMED, SCIELO y COLECCIÓN CONCHRANE. Los siguientes términos asociados se utilizaron "composición de la inflamación y las enfermedades cardiovasculares y el estado nutricional, organismo o la actividad física". Había temas creados para la discusión de la materia: factores de obesidad y riesgo de enfermedad cardiovascular en la adolescencia; desarrollo de la enfermedad cardiovascular con marcadores inflamatorios y, por último, los marcadores de inflamación, la actividad física y la evaluación nutricional.

Resultados: Se observó que los marcadores inflamatorios pueden manifestarse en la adolescencia y se relacionan con factores de riesgo de enfermedades cardiovasculares. La actividad física y la evaluación nutricional ofrecida como medidas no farmacológicas para el control de la incidencia de los marcadores inflamatorios y factores de riesgo cardiovascular.

Conclusión: Los estudios de intervención pueden aclarar cómo la adopción de un estilo de vida más adecuado puede influir en el proceso inflamatorio.
Abbreviations

PAL: Physical activity Level.
BMI: Body mass index.
CAM: Cellular adhesion molecule.
CNCD: Chronic non-communicable diseases.
CRP: C-reactive protein.
CVD: Cardiovascular disease.
DEE: daily energy expenditure.
IL-1: Interleukin-1.
IL-6: Interleukin-6.
IL-8: Interleukin-8.
IL-10: Interleukin-10.
LDL: Low density lipoprotein.
LPL: Lipoprotein lipase enzyme.
Lp-PLA2: Lipoprotein associated to phospholipase A2.
MCP-1: Monocyte chemotact protein-1.
PAI-1: Plasminogen activator inhibitor-1 (PAI-1).
TNF-α: tumor necrosis factor α.

Introduction

The changes that happen with adolescents can influence their behavior in various physical, cognitive and social aspects, including the adoption of a less active lifestyle, with inadequate food habits. Miranda et al. verified that the stature, body mass index (BMI) and percentage of fat were different between the stages of classification of somatic maturation of female adolescents.

The adoption of a sedentary lifestyle, with low physical activity level (PAL) and consumption of hyper caloric diets with low fiber intake are factors for the increased prevalence of overweight, obesity and consequently metabolic changes in the body during adolescence. These changes can happen in a sex-specific manner, therefore, an accurate estimate of body composition is important in assessing and monitoring the nutritional status of adolescents.

The increased prevalence of cardiovascular diseases (CVD) and their association with risk factors have contributed to the increase in morbidity and mortality in several countries, including in Brazil. The accumulation of body fat is one of the main risk factors for developing cardiometabolic diseases. The obesity has been regarded as a chronic systemic inflammatory disease. This inflammatory profile together insulin resistance can cause metabolic syndrome, diabetes and other risk factors cardiometabolics.

Adipose tissue does not have only the function of energy reserve, but are also biologically active cells that operate in the subclinical inflammation mechanism and that interfere with the neuroendocrine signaling that regulates insulin. Failure of the metabolic action of insulin changes the metabolism of carbohydrates and lipids, which can trigger the subclinical inflammatory process. There is evidence that the inflammatory process leads to instability of the plaque within the artery wall. Thus, there is a need to check the development of the inflammation process from adolescence, to avoid the worsening of CVD over the age.

Alves et al. presented data that showed the ability to decrease levels of inflammatory cytokines and/or anti-inflammatory cytokines increase that physical activity can result in adolescents. Other scientific papers evaluated changes in lifestyle, especially in the practice of PA and dietary education, which are factors that may exert anti-inflammatory functions.

From the information gathered on the relationship of the procedure of subclinical inflammation, cardiovascular diseases and the protective effect of physical activity and diet, the objective of this study was to review inflammatory markers as a risk factor of cardiovascular disease in relation to body composition, physical activity and assessment of nutritional status of adolescents.

Methods

A literature review was performed in the following electronic databases: PUBMED, SCIELO and CONCHRANE COLLECTION. The following associated terms were used \textit{“inflammation AND cardiovascular diseases AND nutritional status OR body composition OR physical activity.”}

All terms are indexed in the system of Health Science Descriptors (DeCs/MeSH). The period for the search has not been established, therefore, it is proposed to investigate the scientific articles regarding inflammatory markers associated with nutritional status, body composition and physical activity in adolescents.

Results

There were not analyzed works with investigations that do not address clinical inflammation in humans, theses, book chapters, books, medical guides, reviews and governmental bulletins.
Obesity and risk factors for cardiometabolic disease during adolescence.

Obesity is a chronic disease characterized by excessive accumulation of body fat as a result of a chronic positive energy balance, its etiology is associated with reduced levels of physical activity and food intake of high energy density. It is taken as a global epidemic and its prevalence is growing in developed and in-development countries. Approximately 43 million children and adolescents are overweight or in obese conditions in the world, representing an estimate of 6.7%. In 2020 this figure can reach almost 60 million, 9.1% children and adolescents. In Brazil, the prevalence of obesity among adolescents in Brazil reached around 5.9% boys and 4.0% girls.

The accumulation of body fat is one of the main risk factors for developing cardiometabolic diseases (CD). According to the Brazilian Society of Cardiology the CD will continue to be the leading cause of death in the world, approximately 7.3 million/year, and such number should overcome 23.6 million by 2030. In Brazil, CVDs are a health problem of great magnitude, corresponding to 31.3% of the causes of death.

According to Despres et al. the increase in consumption of densely energetic food is associated, along with sedentarism, to visceral obesity, which increases overall cardiovascular risk. Caloric insufficiency in the diet, low consumption of fruits, vegetables and the habit of skipping breakfast. This eating pattern is worrisome, since it can lead to overweight and higher probability of chronic non-communicable diseases (CNCDs) such as diabetes, hypertension and dyslipidemias in adult life.

These cardiovascular events tend to occur more intensively among adults and elderly, however, researchers have reported that the origin of these cardiovascular diseases occur in childhood and adolescence. Obese teenagers have increased risk for developing chronic non-degenerative diseases, besides psychosocial damage caused by the stigma of obesity.

It is already well established in the literature the relationship of low density lipoprotein (LDL) with atherosclerotic diseases and the mechanisms by which this lipoprotein participates in the atherogenic process. The permanence of LDL in the subendothelial space increases the possibility of it suffering modifications on lipid and protein composition, because once modified, especially oxidized, the LDL is not recognized by the scanning receptors present on endothelial cells, such as macrophages that attempt to eliminate them, initiating the inflammatory process.

The behavior of peripheral blood cells involved in inflammation can be a predictor of ischemic cerebrovascular diseases and peripheral arterial diseases. Understanding the distribution and implications of such risk factors among adolescents is of interest for the prevention of future diseases.

Manifestation of inflammatory markers in adolescence.

Endothelial cells have physiological functions in maintaining the integrity of the arterial wall and constitute the permeable barrier where occur diffusions and exchanges and/or active transport of various substances. The cytotoxic effect of oxidized LDL causes endothelial dysfunction, proliferation and reorganization of the extracellular matrix, as well as stimulate the endothelium for the production and release of chemotactics and adhesion molecule for leukocytes on the endothelial surface.

The secretion of adhesion molecules is regulated by cytokines synthesized in small concentrations by the arterial endothelium, and in the presence of endothelial dysfunction the concentration of such cytokines rise, stimulating the production of adhesion molecules, which favors recruitment and adhesion of monocytes in the endothelial surface.

Adhesion molecules can promote endothelial injury by decreasing the distance between monocytes and endothelial cells, besides facilitating the attack of active oxygen species such as superoxide anion, hydrogen peroxide and hydroxyl radicals generated by active monocytes. The inflammatory and monocyte chemotact protein-1 (MCP-1) along with interleukin-1 (IL-1) and interleukin (IL-8), draws the inflammatory focus to monocytes and neutrophils, which secrete other cytokines, including the tumor necrosis factor (TNF-α) and other chemotactic factors, which provide feedback the inflammatory process.

After the aggression on the endothelial wall, blood flow increases, as well as vascular permeability, greatest recruitment of macrophages to the focus of the aggression and, consequently, release of inflammatory markers as response of acute phase and aggression to the endothelium. On systemic level, the liver is the primary target of the inflammatory markers, supplying the essential metabolites to the stress response and the components required for the first-line defense on inflammation site. The hepatocyte responds to four types of mediators of the inflammatory responses: cytokines, interleukin-1 (IL-1) and TNF-α (stimulate liver production of C-reactive protein) and C3 component of the complement and serum amyloid protein A.

The C-reactive protein (CRP) is considered the main acute phase protein. One of its most important functions is its ability to bind to components of the cell membrane, forming complexes that activate release of opsonins and eventual phagocytosis and removal of these circulation structures. Children and adolescents with higher values of waist circumference had higher levels of CRP, plas-
minogen activator inhibitor-1 (PAI-1) and hepatocyte growth factor. The obesity can be associated with an increase of subclinical inflammation indicated by higher values of CRP.

Table I presents characteristics of inflammatory markers according to their categories, according to Volp et al, with additional information and other markers.

**Development of cardiovascular diseases with inflammatory markers**

The secretion of adhesion molecules is regulated by cytokines synthesized in small concentrations by the arterial endothelium, and in the presence of endothelial dysfunction these cytokines concentrations rise, stimulating the production of adhesion molecules, favoring thus the recruitment and adherence of monocytes to the endothelial surface. Adhesion molecules can promote endothelial injury by decreasing the distance between monocytes and endothelial cells and facilitate the attack of active oxygen species such as superoxide anion, hydrogen peroxide and hydroxyl radicals generated by active monocytes.

With the recruitment of leukocytes in the focus of the injury and release of inflammatory markers, blood flow and vascular permeability may be increased, which occurs soon after the aggression. Although it may succeed the acute inflammation, chronic inflammation often begins insidious, latent and, in most cases is asymptomatic.

| Table I |
|-----------------|---------------------------------|-----------------|
| **Description of markers associated with inflammation, adapted from Volp et al. (2008)** | | |
| **Markers associated with inflammation** | **Description** | **References** |
| Interleukin-6 (IL-6) | Pro-inflammatory cytokine, involved in the development of hyperinsulinemia and metabolic syndrome, as it plays important role in the metabolism of carbohydrates and lipids to increase lipolysis, with inhibition of lipase (LPL). | Petersen e Pedersen, Gomes et al. |
| Tumor necrosis factor-α (TNF-α) | Cytokine with autocrine, paracrine, and endocrine action. It acts in the adipocyte, playing a regulatory role in the accumulation of body fat. | Poldene et al. |
| Interleukin 10 (IL-10) | Pleiotropic cytokine produced by helper T cells, T lymphocytes, B lymphocytes, monocytes and macrophages. It has anti-inflammatory properties, whose main function is the regulation of the immune system. | Puglizi e Fernandez |
| Monocyte chemoattractant protein 1 (MCP1) | Controls the function of monocytes through its receptor, is involved in inflammatory changes in the arterial wall, damaging the endothelium-dependent vasodilation. | DOD et al. |
| C-reactive protein (CRP) | Acute phase protein, synthesized by the liver and regulated by cytokines, predominantly IL-6, TNF-α and IL-1. Modest elevations of CRP levels are also present in chronic inflammatory conditions, such as atherosclerosis, and its levels roughly triplicate in the presence of risk of peripheral vascular diseases. | Alisson et al., Santos et al. |
| Lipoprotein associated to phospholipase A2 (Lp-PLA2) | Monomeric enzyme, which hydrolyze oxidized surface of LDL phospholipids, generating bioactive products, which leverage the inflammatory process. | Volp et al. |
| Plasminogen activator inhibitor 1 (PAI-1) | Physiological inhibitor of fibrinolysis which increases the risk of thrombosis. | Alisson et al., Santos et al. |
| Leptine | Key molecule in the regulation of body weight and energy balance, since it regulates appetite and energy expenditure via central nervous system. | Carvalho, Colaço e Fortes |
| Cellular adhesion molecule (CAM) | Cell adhesion molecules (CAM) are glycoproteins expressed on the cell surface, where they mediate contact between two cells or between cells and the extracellular matrix. | Gomes et al. |
At systemic level, the liver is the primary target of the inflammatory markers, supplying the essential metabolites to the stress response and the components required for the first-line defense on inflammation site\textsuperscript{36}. The hepatocyte responds to four types of mediators of the inflammatory responses: cytokines IL-1 and TNF-\(\alpha\) which stimulate hepatic production of C-reactive protein (CRP), C3 complement C3 component and serum amyloid protein A; cytokines type IL-6 and IL-11 that stimulate most acute phase proteins of type 1; and glucocorticoids that act synergistically with cytokines IL-1 and IL-6, stimulating the production of some proteins of acute phase, mainly CRP\textsuperscript{11,30,36}.

Inflammatory proteins and macrophage chemotactics, along with IL-1 and IL-8, draws the focus to inflammatory monocytes and neutrophils, which in turn, secrete a third set of cytokines, including TNF-\(\alpha\) and other chemotactic factors, which provide feedback to the inflammatory process\textsuperscript{28,31}. C-reactive protein (CRP) is considered the main acute phase protein. One of its most important functions is its ability to bind to components of the cell membrane, forming complexes that activate the classical pathway, with release of opsonins and eventual removal of these structures and phagocytosis of circulation\textsuperscript{32,37}.

The vascular endothelium plays important role in the communication between the site where the inflammatory process is occurring and the circulating leukocytes\textsuperscript{11,32}. The loss of the protective action of the endothelium can occur in the presence of inflammatory and cardiovascular risk factors with increasing propensity to vasoconstriction, thrombosis, inflammation and cellular proliferation in the vessel wall\textsuperscript{38}.

Gottlieb, Bonardi and Moriguchi\textsuperscript{39} point out that obesity-related metabolic multi-factors are the main causes for the mechanism of inflammatory response, endothelial injury and deformation of the atherosclerotic plaque. Onat\textsuperscript{40} reported that populations prone to glucose intolerance and insulin resistance indicate pro-inflammatory state and oxidative stress, directly involved to factors of metabolic syndrome. De León \textit{et al.}\textsuperscript{41} demonstrated direct relationship between hypertension, insulin resistance and inflammatory markers. Serum levels of biomarkers provide important information on inflammation and its processes, such as vascular cell activation, oxidative stress and recruitment of leukocytes and macrophages\textsuperscript{42}. Guebre-Egziabher, Kalbacher, Fouque\textsuperscript{43} verified in patients with chronic kidney disease abnormal values of cytokines and adipokines. Yet these researchers have highlighted that the set of metabolic abnormalities relate to other metabolic diseases by adipose tissue dysfunction, which consequently induces inflammation and insulin resistance.

According to Paoletti \textit{et al.}\textsuperscript{26} the inflammatory component of atherogenesis has been increasingly recognized over the last decade. These authors point out that the process of inflammation participates in all stages of atherosclerosis, not only during the initiation and evolution of the lesions, but also with the precipitation of acute thrombotic complications. It is noted that the evaluation of inflammatory markers during adolescence can monitor different stages and manifestation of chronic diseases in adulthood. The control of the subclinical inflammation process can mitigate the effects of risk factors that trigger the process of atherosclerosis.

**Inflammatory markers, physical activity and nutritional evaluation.**

According to Pate \textit{et al.}\textsuperscript{44} physical activity can be understood with every action of free movement in space without systematization. The exercise is a systemized practice-oriented movement, showing the intensity control, dosage (amount) and frequency.

The daily energy expenditure (DEE) is a result of the sum of all types/purposes of physical activities carried out during the day, being the subcategory ‘intensity’ related to the amount of energy consumed by each activity\textsuperscript{44,45}. Researchers advise some recommendations that guide the practice of physical activity for children and teens: acting in accordance with international recommendations of activities that postulate accumulation of 60 minutes/day, preferably all days of the week, with a minimum duration of 15 minutes or more per session\textsuperscript{46}. According to the Global Recommendations on Physical Activity for Health\textsuperscript{47} children and adolescents (5 to 17 years old) should accumulate at least 60 minutes of moderate to vigorous physical activity daily. The bigger such accumulation of physical activity, the bigger will be the benefits to health. The activities should be primarily of aerobic character, with resistance training or similar being incorporated at least 3 times a week.

Changes in lifestyle, especially in the practice of physical activity and dietary education are factors that may exert anti-inflammatory functions\textsuperscript{47}. According to Martinez-Gomez \textit{et al.}\textsuperscript{48} activity and physical fitness can be important protection factors for subclinical inflammation among teenagers with cardiovascular and metabolic risk factors.

Researchers describe mechanisms that may explain the effect of physical exercise on the subclinical inflammation process. Shortly after the exercise there is an increase in the circulating levels of IL-6 derived from the muscle that induces an increase in the production of IL-1 and IL-10, which are anti-inflammatory cytokines, and it can be induced by IL-6 as well, inhibiting the production of cytokine TNF-\(\alpha\)\textsuperscript{2}. These miosins may be involved in mediating the beneficial effects of exercise health and play important roles in protection against diseases associated with low-grade inflammation.

Physical training is the stimulator of increased glucose uptake and insulin sensitivity in muscle\textsuperscript{2}. It is known that adipocytes in excess in the blood flow, in addition to being related to the metabolic syndrome factors, produce cytokines TNF-\(\alpha\) and interleukin-6
Inflammatory markers in adolescents

Inflammatory markers can manifest in adolescence and are related to risk factors for cardiovascular diseases. Body composition, physical activity and nutritional evaluation have presented themselves as non-pharmacological measures in controlling the incidence of inflammatory markers, due to the effect in the control of obesity, dyslipidemias, insulin resistance, diabetes and hypertension. However, much still needs to be done to clarify the correct prescription form of PAL taking into consideration the intensity, type, duration and frequency of exercise. Longitudinal design and intervention studies may clarify how adopting a lifestyle can influence the control of inflammatory markers and other related factors associated with cardiovascular diseases in adolescents.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Support: FAPEMIG - Foundation Support Research of Minas Gerais Research and CNPq - National Council for Scientific and Technological Development.

Author’s contribution

VPN Miranda and SE Priore were responsible for the development of the manuscript and general coordination of the study and the development of selection criteria Articles and writing the article. Employees MCG Peluzio, ER Faria, and SCC Franceschini were responsible for helping in the discussion, interpretation of prepared topics and critical review of the manuscript as a whole. Finally, SE Priore contributed to critical revision for text content, as well as review the final version of the article.

References


