

## Risk Factors for the Development of Atherosclerosis in Childhood and Adolescence

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### Summary

Cardiovascular diseases (CVD) are a major cause of death in developed countries as well as in developing countries. In general, the clinical manifestations of CVD, such as myocardial infarction, stroke and peripheral vascular disease, are caused by an atherosclerotic process with onset as from the middle age. However, current studies indicate that the atherosclerotic process starts to develop in childhood. The pathogenesis of atherosclerosis has been studied as to its inflammatory aspect. Among the inflammatory markers, C-reactive protein (CRP) has been extensively studied in individuals with CVD, including those apparently healthy. High CRP levels have been related to risk factors for atherosclerosis: family history of coronary artery disease (CAD), dyslipidemia, hypertension, diabetes mellitus, obesity, smoking and sedentary lifestyle. A great part of these risk factors may be influenced by lifestyle modifications, such as changes in eating habits and engagement in physical activities. The effects of physical activity on CRP levels in adulthood are documented in the literature, however little is known on the influence of an active or sedentary lifestyle of children and adolescents on CRP levels. Thus, the objective of this study is to review the impact of physical activity of children and adolescents on CRP levels and the risk factors for the development of CVD.

### Introduction

Cardiovascular diseases (CVD) are a major cause of death in developed countries as well as in developing countries<sup>1</sup>. In general, the clinical manifestations of CVD start in the middle age. However, recent studies indicate that the atherosclerotic process starts to develop in childhood. Fatty streaks precursor of atherosclerotic plaques appear in the aortic intima at three years of age, and in the coronary arteries during adolescence<sup>2</sup>.

Thus, atherosclerosis gradually changed from a model of a chronic degenerative disease exclusively affecting patients with advanced age to a model of a subclinical chronic inflammatory disease already existing in childhood<sup>3</sup>.

The pathogenesis of atherosclerosis has been studied as

### Key words

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to its inflammatory aspect. Inflammatory markers such as C-reactive protein (CRP) have been studied in individuals with CVD, including those apparently healthy<sup>4</sup>.

CRP has been a widely used inflammatory marker for the detection of CVD because its plasma concentration is easy to determine and it has the best clinical and epidemiological correlation to date. High blood CRP levels have been found in inflamed tissues, atherosclerotic vessels and infarcted myocardium<sup>5</sup>.

Its utilization has been important for the possibility of identifying new pathways for the prevention and treatment of CVD and of risk factors for atherosclerosis<sup>4,6</sup>: family history of coronary artery disease (CAD), dyslipidemia, hypertension, diabetes mellitus, obesity, smoking and sedentary lifestyle<sup>4</sup>.

A great part of these factors may be influenced by lifestyle changes, thus reducing cardiovascular events and increasing the individuals' life expectancy. Modifications in eating habits and practice of physical activities are lifestyle changes that may significantly diminish risk factors for CVD and reduce CRP<sup>6</sup>.

The strategies for CRP reduction were initially based on pharmacological treatments<sup>4,7</sup>. Although these studies prove the positive effect of these therapies on CRP reduction in adults, little is known of the effect of physical activity on CRP in childhood and adolescence.

The demonstration that cardiovascular diseases may originate in childhood and adolescence leads to the need that these risk factors be extensively investigated in these phases, with the purpose of planning increasingly earlier and possibly finding more effective interventions on these factors, thus further reducing morbidity and mortality.

### Cardiovascular diseases

The pathophysiology of CVD, the major causes of morbidity and mortality worldwide, starts at an early age. CVD are part of the group of chronic non-communicable diseases that comprise the plurimetabolic syndrome (obesity, hypertension, diabetes mellitus and dyslipidemia) caused by risk factors resulting from changes in lifestyle habits<sup>8</sup>.

The likelihood of occurrence of CVD increases in the presence of multiple risk factors established for atherosclerosis. These may be modifiable or non-modifiable. The non-modifiable risk factors are age, gender and family history. The modifiable risk factors are dyslipidemia, hypertension, eating habits, smoking, diabetes mellitus, obesity and sedentary lifestyle<sup>9</sup>.

## Non-modifiable risk factors for cardiovascular diseases

The risks for CVD increase with age, and at every 10 years there is a possibility of mortality from these diseases increasing by 2.5 times. The magnitude of the risk factors and the occurrence of clinical manifestations emerge later in women than in men<sup>10</sup>.

As regards genetic inheritance, detailed history taking of family diseases reveals a genetic susceptibility for the development of CAD<sup>11</sup>. In Romaldini et al study<sup>12</sup>, of 109 children and adolescents with a premature CVD family history, 41.1% were observed to present one or more risk factors for atherosclerosis.

## Modifiable risk factors for cardiovascular diseases

Hypertension is a modifiable risk factor considered very important for CVD in both genders, irrespective of ethnical group or age bracket. However, children with higher blood pressure levels tend to progress over life, maintaining higher blood pressure levels than their peers and showing a greater probability of becoming hypertensive adults<sup>13</sup>.

According to Rabelo<sup>10</sup>, dyslipidemia – abnormal circulating lipid or lipoprotein levels, is caused by alterations in their production, catabolism or clearance as a consequence of genetic and/or environmental factors, inappropriate diet and/or sedentary lifestyle, and, according to the National Cholesterol Education Program<sup>14</sup>, high blood cholesterol, particularly increased LDL, is the main predictor of CVD. This occurs because LDL particles contain 70% of the blood cholesterol, and are thus the main target of medical intervention.

Increased serum HDL levels reduce the relative risk for CVD. The mechanism for this protective effect stems from the HDL ability to perform reverse cholesterol transport, that is, to remove it from the cells and transport it to the liver for further excretion. HDL also prevents oxidation and aggregation of LDL particles in the arterial wall, thus diminishing the atherogenic potential of this lipoprotein<sup>15</sup>.

Diabetes mellitus is one of the major public health problems worldwide, especially in developing countries<sup>15,16</sup>. Its risk factors are hyperglycemia, lipoprotein alterations and hypertriglyceridemia, which cause modifications in the vascular biology and accelerate molecular and cellular events which lead to atherosclerosis<sup>10</sup>.

Obesity is also an important predictor of CVD, and arterial wall lesions are already observed in obese children<sup>17</sup>. The prevalence of obesity in childhood and adolescence has short and long-term consequences because it is associated with an abnormal lipid profile, with increased concentrations of total cholesterol, triglycerides and LDL, and decreased HDL<sup>14</sup>. In addition to being a risk factor for low-birth weight, placental abruption and pulmonary diseases, smoking is also an important risk factor for CVD because it reduces blood HDL concentrations<sup>10</sup>.

McGille et al study<sup>18</sup> suggests that secondhand smoke is related to low plasma HDL levels, which is associated with

a significant endothelial dysfunction. In relation to the direct effects, evidences demonstrate that a mild airway obstruction and slowed growth of lung function in adolescents are associated with smoking<sup>19</sup>.

Another risk factor that has been pointed out as one of the factors responsible for the higher CVD prevalence is the change in eating habits, through a reduction in fruit and vegetable consumption and increase in the percentage of saturated and animal fat, thus leading to lower ingestion of antioxidant food micronutrients which are important for the control or reduction of the deleterious action of free radicals in the body; this delays or prevents their oxidation<sup>20</sup>.

Finally, a sedentary lifestyle has been pointed out as another risk factor for CVD, already existing in childhood and adolescence. It has been observed that children have reduced their level of physical activity for several reasons, among which we can mention the lower tendency to walk and/or ride a bicycle, and the increased use of cars for transportation. Also, children have been performing less recreational and sports activities in their free time, with increased sedentary activities such as watching television, playing videogames, and using the computer<sup>21</sup>.

The practice of physical exercises is known to have a positive effect on cardiovascular risks in adults, and, in children, it had first been related to a strategy for physical development<sup>22</sup>. However, some data show that lower levels of physical activity and sedentary lifestyle are associated with a higher prevalence of childhood obesity, pointing out to a sedentary lifestyle as a risk factor present in early age<sup>23</sup>.

The demonstration that CVD may originate in childhood and adolescence leads to the need that these risk factors be extensively investigated during this period, with the objective of planning increasingly earlier and, possibly, taking more effective interventions on these factors, thus reducing morbidity and mortality in the future.

## Prevalence of risk factors for atherosclerosis in childhood and adolescence

Brazilian data on the risk factors for atherosclerosis in childhood and adolescence show that the prevalence of essential hypertension in these phases range from 0.8% to 8.2%<sup>24-25</sup>. A frequent association between hypertension and overweight or obesity is demonstrated.

In the past 30 years, a sharp decline in the prevalence of malnutrition among children and adolescents and a more rapid increase in the prevalence of overweight/obesity were observed. The analysis of data of children and adolescents between two and 17 years of age, from the Survey on Life Standard<sup>26</sup> (SLS) collected in Brazil in 1997 by the IBGE (Brazilian Institute of Geography and Statistics), demonstrated that the prevalence of obesity was 10.1%, and was higher in the Southeastern than in the Northeastern region (11.9% and 8.2%, respectively).

IBGE data<sup>27</sup> in 2003 point out to an increase by 8.5% in the prevalence of overweight in adolescents (10.4% in the Southeastern region and 6.6% in the Northeastern region) and a prevalence of obesity among adolescents of 3.0% (1.7% in the Northeastern region and 4.2% in the Southeastern region).

The prevalence of excess weight was higher among families with a higher income, except in the city of Porto Alegre, where girls from public schools had higher BMI than those from private schools.

As regards dyslipidemias, Moura et al<sup>28</sup> found a prevalence of high blood cholesterol of 35% among 1,600 school children aged between 7 and 14 years who were studied in the city of Campinas, State of SP, and identified mean serum levels of total cholesterol, triacylglycerols, LDL and HDL of 160, 79, 96, and 49mg/dl, respectively.

In a population sample from the city of Florianópolis, mean levels of total cholesterol, triacylglycerols, LDL and HDL of 162, 93, 92 and 53 mg/dl were found in 1,053 school children aged between 7 and 18 years. In that study, 10% of the individuals presented high blood cholesterol, 22% hypertriglyceridemia, 6% high LDL, and 5% low HDL<sup>29</sup>.

Another risk factor that is already present in childhood and adolescence is smoking. In Brazil, until the 1980's, smoking was present among elementary school and high school students in one to 34% of the young people interviewed. Researches conducted in 10 Brazilian capitals involving 24,000 elementary school and high school students in the years of 1987, 1989, 1993 and 1997 showed an increasing number of young people trying cigarettes in all capitals. Another important conclusion of the 1997 research is related to the tendency of a balance in the consumption among students of both genders, unlike what occurred in the year of 1987, when the male gender predominated<sup>30</sup>.

As regards sedentary lifestyle, few studies on its prevalence among Brazilian children and adolescents are available, ranging from 42 to 93.5%, depending on the criteria used<sup>31</sup>.

## Atherosclerosis

The pathogenesis most frequently found in CVD is atherosclerosis, which is a disease resulting from endothelial dysfunction and inflammation. The vascular endothelium regulates vascular homeostasis, leading to adaptive functional changes with the release of several substances with clotting and anti-clotting activities - able to promote molecule adhesion - and with vasoactive actions. Vascular homeostasis is the result of the dynamic regulation of these functions. Nitric oxide (NO) is the main antiatherogenic substance, that is, it has an endothelial protective action<sup>32</sup>.

The loss of the endothelial protective action may occur in the presence of inflammatory factors and cardiovascular risk factors, with increased propensity towards vasoconstriction, thrombosis, inflammation, and cell proliferation in the vessel wall. Thus, the loss of NO biological activity, known as endothelial dysfunction, may be the event triggering the atherosclerotic disease in humans, turning its assessment in an early marker of the risk for atherosclerosis<sup>33</sup>.

Therefore, in the last few years, the role of inflammation in the pathogenesis of atherosclerosis and the occurrence of atherothrombotic events as determinants of CVD has been evidenced<sup>4</sup>. It has also been verified that this process may begin early in life. Aortic fatty streaks develop in childhood and fibrous plaques may be observed before 20 years of age<sup>10</sup>.

Thus, atherosclerosis gradually changed from a model of a non-communicable chronic degenerative disease exclusively affecting patients with advanced age to a model of a subclinical chronic inflammatory disease already existing in childhood<sup>3</sup>.

The factors contributing to the development of atherosclerosis are hyperlipoproteinemia, increased platelet aggregation, decreased vascular endothelial cells, and increased smooth cell proliferation. Leukocytes, monocytes and macrophages are present in the atherosclerotic lesion, thus suggesting a developing inflammatory reaction<sup>34</sup>.

Another inflammatory mechanism is the relationship between high CRP levels and increased rate of adiposity, triglycerides, and a low HDL/total cholesterol ratio<sup>35</sup>.

In the presence of oxidized LDL, of infectious agents in the vascular wall or of tissue lesion (necrosis or ischemia), leukocytes are activated. Once activated, they start to produce different cytokines, interleukins, tumor necrosis factor alpha, and gamma interferon. Especially, interleukin-6 (IL-6) stimulates the hepatocytes to produce RNAm for the production of acute phase proteins such as fibrinogen, CRP and serum amyloid A protein<sup>35</sup>.

It has been demonstrated that atherosclerosis is not simply a lipid storage disease, and that inflammation has a key role in the initiation, progression and destabilization of atheroma<sup>36</sup>. A marker of the inflammatory activity is the increased circulation of acute phase proteins produced in the liver, such as CRP and fibrinogen. CRP is one of the most sensitive acute phase proteins, and its concentration significantly increases during acute inflammation<sup>37-38</sup>.

## Acute phase reaction of inflammation

Living beings survive thanks to the maintenance of a dynamic and complex balance, which is often jeopardized by inner and outer forces. The maintenance of this balance is ensured by some physiological mechanisms, so that any factor disturbing the organism's integrity (such as trauma or tissue infection) is able to trigger a series of metabolic and systemic changes that aim to reestablish the homeostasis. These changes comprise the inflammation process and the group of humoral and cell reactions initiated soon after the damage, and are collectively called acute phase reaction<sup>39</sup>.

The acute phase reaction enables survival during the immediate post-tissue lesion period by triggering the synthesis and secretion of several cell mediators in the site of the damage, which mobilize the metabolic response of the entire organism. The purpose of all these changes is to halt or destroy infectious agents, to prevent the maintenance of tissue damage, and to activate the repair mechanisms required for the organism to resume its normal functioning. Thus, the acute phase reaction is a homeostatic, dynamic and protective response that hosts make use of against the different aggressions they are subjected to<sup>40</sup>.

Mostly, inflammatory mediators act locally to limit the consequences and extent of tissue damage. Under conditions in which this local homeostatic capacity is exceeded, whether by the magnitude of the aggression or by failure of

the regulating mechanisms, the inflammatory response goes beyond the limits of its microenvironment and may express itself systemically<sup>41</sup>.

### Molecular mechanisms of the acute phase reaction

Irrespective of the nature of the triggering stimulus, the activated cells of the mononuclear phagocytic system (blood monocytes and tissue macrophages) initiate a cascade of events of the acute phase response by secreting cytokines of the interleukin-1 (IL-1) family and tumor necrosis factor (TNF) in an initial stage. These molecules act both locally and systemically<sup>42</sup>.

Locally, they act mainly on fibroblasts and endothelial cells, causing the release of a second set of cytokines that include IL-6, IL-8, and the inflammatory and chemotactic macrophage proteins, in addition to IL-1 and TNF themselves. The inflammatory and chemotactic macrophage proteins along with IL-1 and IL-8 attract monocytes and neutrophils to the inflammation site; monocytes and neutrophils, in turn, secrete a third set of cytokines including TNF and other chemotactic factors that exert a feedback on the inflammatory process<sup>43</sup>.

The vascular endothelium plays a central role in the communication between the inflammatory site and blood leukocytes, both via the expression of adhesion molecules that facilitate tissue migration of monocytes and neutrophils, and via the modification of the vascular tonus mediated by metabolites of the arachidonic acid (prostaglandins, thromboxane and leukotrienes), by nitric oxide, and by kinins, thus causing vasodilation, increased vascular permeability and arterial hypotension<sup>44-46</sup>.

Systemically, the liver is the main target of inflammatory mediators, supplying the essential metabolites for the stress response and the components required for the first-line defense in the inflammation site<sup>47</sup>.

Using their specific receptors, the liver cells respond to four types of inflammatory response mediators. These mediators are the IL-1-type cytokines (IL-1 and TNF) which stimulate liver production of CRP, of the C3 component of complement, and serum amyloid A protein (SAA), which comprise the type-1 acute phase proteins; type IL-6 cytokines (IL-6 and IL-11) which stimulate most of the type-1 acute phase proteins; glucocorticoids that act synergistically with type IL-1; and IL-6 cytokines stimulating the production of some acute phase proteins. However, the most important action of glucocorticoids in the acute phase response is the inhibition of cytokine production by macrophages and endothelial cells, thus preventing its continued activation from having harmful consequences to the tissues; and, finally, growth factors which, along with glucocorticoids, modulate the liver response to cytokines<sup>47,48</sup>.

These acute phase proteins play an important role in host defense, such as direct neutralization of inflammatory agents, reduction of the extent of local tissue damage, and participation in tissue repair and regeneration. In addition, activation of complement proteins results in migration of neutrophils, macrophages and plasma proteins that participate in the destruction of infectious agents, clearance of cell debris from both the microorganisms and from the host themselves<sup>47,49</sup>.

CRP is considered the main acute phase protein. Among the several functions attributed to CRP, maybe the most important is its ability to bind to cell membrane components, thus forming complexes that activate the classical complement pathway, with opsonin release and occasional phagocytosis, as well as removal of these structures from circulation<sup>42</sup>.

Also, CRP binds to cell membranes only after membrane rupture. This property suggests an important role of CRP in the unspecific host defense due to removal of cell debris derived from necrotic cells or cells damaged during the inflammatory process, thus allowing tissue repair. Other functions attributed to CRP are growth inhibition of tumor cells, modulation of polymorphonuclear (PMN) and monocyte function, platelet aggregation and secretion<sup>42,50</sup>.

The speed and magnitude of the increase in CRP concentration depend on the type of inflammatory stimulus. This is probably related to the amount of protein that is required to effectively participate in the acute phase reaction. After an acute phase stimulus, CRP concentrations usually increase rapidly after tissue damage, reaching a peak within 24 to 72 hours, and then decrease steeply after resolution of the inflammatory process. The intensity of the CRP response is more closely correlated with the extent of tissue damage<sup>51</sup>.

Thus, we can observe that the magnitude and speed of CRP response could reflect the extent of tissue damage more precisely and earlier in time. CRP low baseline levels, rapid increase and short half-life are arguments in favor of its use in the assessment of disease activity<sup>52</sup>.

Although the acute phase response is not specific, it can be used in the clinical practice as part of the diagnosis, both to assess the intensity of inflammatory activity and to discriminate inflammatory from non-inflammatory diseases. However, inflammatory markers, especially CRP, have been intensively studied in individuals with CVD and even in those apparently healthy with the help of technological advances obtained in the determination of serum levels of these parameters<sup>53</sup>.

CRP stands out for its short plasma half-life (approximately 19 h) and its plasma concentration, exclusively related to the synthesis in this period. Also, the interest in the study of this protein has increased in the past years, since small increments in its production are associated with increased risk for CVD in patients with angina pectoris and also in healthy individuals<sup>52</sup>.

### CRP and cardiovascular diseases

Immunohistochemical studies have demonstrated the presence of CRP in inflamed tissues, in atherosclerotic vessels and in the infarcted myocardium. It has also been demonstrated that CRP enhances the expression of the tissue factor (clotting effect) of adhesion molecules, binds to plasma lipoproteins and activates the complement system *in vitro* and *in vivo*, which is present in the majority of foam cells of atherosclerotic plaques<sup>53</sup>.

Stefanadis et al<sup>54</sup> demonstrated a direct correlation between increased plaque temperature and higher levels of CRP and serum amyloid protein in patients with acute coronary syndromes. Patients with acute myocardial infarction also have

higher CRP levels correlated with a greater extent of the area of myocardial necrosis.

In the absence of myocardial necrosis, higher CRP levels are correlated with a greater extent of atherosclerotic disease, even after correction for other risk factors. Apparently, healthy individuals with higher CRP levels, even those considered high normal levels, have a higher risk of developing peripheral arterial disease<sup>4</sup>.

In studies conducted with children and adolescents, an accumulation of abdominal fat and hyperinsulinemia associated with a thrombogenic and inflammatory profile have been observed. Increased concentrations of fibrinogen and plasminogen activator inhibitor 1 (PAI-1) have been reported in individuals with visceral obesity, thus increasing the risk of thrombosis in these individuals. High levels of certain inflammatory markers such as IL-6, TNF and CRP are also associated with abdominal obesity<sup>55</sup>.

Sudi et al<sup>56</sup> evaluated 20 obese boys and 40 obese girls and verified that after a weight-loss program (three weeks with a low-calorie diet and physical activity), a significant reduction in adiposity, in abdominal fat accumulation and in the fibrinolytic parameters occurred. The authors concluded that excess weight, body fat and abdominal obesity are predictive factors for alterations in the fibrinolytic system in younger individuals.

Because its serum levels are easy to determine and have the best clinical and epidemiological correlation to date, CRP is an inflammatory marker of special interest, given the possibility of elucidating new ways for the prevention and treatment of diseases with high prevalence, morbidity and mortality<sup>52</sup>.

## Effects of physical activity on cardiovascular diseases and CRP

From the point of view of prevention of atherosclerotic diseases, studies on physical activity in young people investigated their level of physical activity, the result of the interventions at school and in the community regarding health education, the strategies to increase the levels of physical activity, and the outcomes of physical activity in the prevention or in the control of cardiovascular risk factors<sup>57</sup>.

Although some studies demonstrate that adolescents who practice more physical activities tend to remain more active when they become young adults, others demonstrated that physical activity during childhood does not provide cardiovascular protection if not associated with a sustained active lifestyle in adulthood<sup>58</sup>.

The American Heart Association (AHA) establishes that the adoption of an active lifestyle should be encouraged from two years of age and maintained throughout adolescence until adulthood. As a general advice, healthy children should be encouraged to practice pleasant physical activities during leisure time or as organized physical exercises or sporting activities at least 30 minutes a day, three to four times a week, to become physically fit<sup>57,59</sup>. Since sedentary lifestyle is an important risk factor for atherosclerosis, regular physical exercises are very important in the prevention and control of CVD, by influencing almost

all its risk factors such as obesity, dyslipidemias, diabetes mellitus and hypertension<sup>19</sup>.

The benefits associated with an active lifestyle in children include, therefore, body weight control, lower blood pressure, and predisposition to maintain physical activity in adulthood. An active lifestyle is also associated with increased life expectancy and lower risk of developing CVD. Also among the effects of physical activity, individuals who practice it have lower triacylglycerol levels and higher HDL levels than sedentary individuals. High HDL levels act on LDL oxidation, thus leading to decreased formation of new atherosclerotic plaques, as well as helping stabilize those already existing<sup>59</sup>.

Williams et al<sup>59</sup> showed that cholesterol levels increase over time, pointing out that children with high LDL levels are more susceptible to maintain these high levels when they become adults.

In Prado and Dantas review<sup>60</sup>, most of the studies were observed to have demonstrated beneficial changes in HDL and LDL levels after an aerobic exercise program with different intensities, durations and frequencies, performed by individuals of varying age brackets and cardiorespiratory abilities.

Corroborating these findings, Matsudo et al review<sup>61</sup> showed that the regular practice of physical activity increases HDL, reduces triacylglycerol and LDL and also increases insulin sensitivity. Favorable effects of aerobic training have also been demonstrated on the activity of lipoprotein lipase, which would explain a better return of trygliceride-rich lipoprotein.

Francischi et al<sup>62</sup> evaluated the two main strategies of non-pharmacological treatment of overweight and obesity – the use of calorie restriction and physical exercises, and concluded that low-calorie diets are effective to reduce weight and fat, but can cause a loss of lean mass and, consequently, a reduction in metabolic rates. Physical training alone, without eating control, results in a modest weight loss. However, in association with diets, it facilitates compliance to eating control and ensures greater success in the maintenance of lean mass and reduction in fat mass.

These authors also pointed out that regular aerobic training intensifies fat loss, however without preventing lean mass loss, whereas resisted training seems to minimize the latter. The combination of aerobic work with resisted training thus seems to ensure fat loss while preserving the lean mass.

Also in relation to overweight and obesity, Watts et al<sup>63</sup> observed that eight-year-old obese children presented decreased blood flow mediated by brachial artery dilatation, thus characterizing an endothelial alteration of this vessel. They also verified that physical exercises increased the arterial blood flow in this group, thus corroborating the importance of a physical exercise program as a form of treatment for obese children in the primary prevention for atherosclerosis.

The effects of physical exercises on systemic hypertension result from cardiovascular and respiratory adaptations that the human body suffers during exercise periods in order to supply the increased demands of the active muscles. As these adaptations are repeated, changes occur in these muscles, thus allowing the body to improve its performance. Physiologic and metabolic processes take place, thus optimizing oxygen

distribution to the tissues in activity. Therefore the pressure drop after physical training is related to hemodynamic, humoral and neural factors<sup>64</sup>.

As regards the effects of physical activity on the prevention and treatment of diabetes mellitus, a review between 1966 and 2000 showed that prospective studies indicate that higher levels of physical activity are clearly associated with a lower frequency of type-2 diabetes mellitus. However, it is not yet possible to clarify the dose-response effect of physical exercise on the treatment or prevention of this disease<sup>65</sup>.

The strategies for CRP reduction were initially based on pharmacological treatments<sup>47</sup>. However, these studies proved the positive effect of these pharmacological treatments on CRP reduction in adults. Recently, the effects of physical activity on CRP levels of children and adolescents have also become known.

It was only in 1999, that Smith et al<sup>66</sup> demonstrated, in a study with 43 adults, that long-term physical exercises are able to significantly reduce inflammatory cytokines and CRP levels.

More recently, the positive impact of the level of physical fitness on high-sensitivity CRP levels in 55-year-old women was reported, and lower plasma concentrations (0.43, 0.25, 0.23 mg/dl) were observed as the level of physical fitness improved (7.2, 9.1 and 10 METs), thus suggesting the participation of an antiinflammatory effect to explain the benefits of exercise on the prevention of CVD. However, it is worth pointing out that a great majority or almost all of these positive effects are reverted if the individual interrupts the practice of physical activity<sup>67</sup>.

Pate et al<sup>68</sup> had already demonstrated, in 1995, that detraining leads to decreased HDL and increased fat mass, BMI, leptin, LDL and triglycerides. Thus, the chance of success in the treatment or preventive management of CVD depends a great deal on the ability to develop strategies that ensure the engagement of people or patients in patterns of an active style for their whole life cycle.

In the study conducted by Okita et al<sup>69</sup> supervised aerobic training for two months was observed to significantly reduce

body weight and CRP levels in women, without association between decreased CRP and weight loss.

Smith et al<sup>66</sup> demonstrated that long-term physical exercises are able to significantly reduce inflammatory cytokines and CRP levels, and suggested the participation of an antiinflammatory effect to explain the benefits of exercises on the prevention of CVD.

Knowing that the atherosclerotic process precedes the clinical manifestations of CVD in years, even decades, and that the regular practice of physical activities reduces the incidence of morbidity and mortality from CVD, it seems prudent to minimize or reduce the known risk factors for CVD in the adult starting from childhood and adolescence, since physical activity seems to be an important protective factor for the prevention and control of CVD, since it influences almost all its risk factors<sup>59</sup>.

Recently, the literature has demonstrated the sedentary lifestyle as a risk factor for CVD and not only the practice of physical activities as a preventive and therapeutic mechanism for these diseases. However, the effects of physical activity on CRP levels as a risk factor for atherosclerosis have been more deeply investigated in adulthood, and little is known of these effects on children and adolescents. Therefore, further investigation on the effect of physical activity on CRP levels during childhood is necessary.

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No potential conflict of interest relevant to this article was reported.

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