Atherosclerotic risk factors in adolescence

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Abstract

Objective: to assess the impact of atherosclerotic risk factors on adolescence.

Methods: nonsystematic literature review.

Results: the progression and severity of atherosclerosis are related to the presence (number), magnitude and duration of some risk factors.

Conclusions: preventive health measures should be early implemented in order to ensure a healthy childhood and adolescence, and avoid future cardiovascular disease.

Introduction

Currently, the atherosclerotic disease (AD) is one of the main causes of morbidity and mortality worldwide. Based on the available data, the World Health Organization (WHO) estimates that out of the 50 million deaths that occurred in 1997, 29% were caused by cardiovascular diseases such as coronary artery disease (CAD) and cerebrovascular disease. While in developed countries, from 1985 to 1997, the mortality secondary to cardiovascular diseases decreased from 51% to 46%, in developing countries it increased from 16% to 24%. Moreover, in developing countries, cardiovascular diseases affect younger subjects more often than in developed countries.

Traditionally, AD is considered a typical middle-age disease. CAD, the most frequent and lethal form of AD, reaches a significant incidence rate starting at age 45 years in men and 55 years in women. The atherosclerotic process, however, starts decades before the appearance of clinical symptoms (myocardial infarction, cerebral vascular accident, peripheral vascular disease).

The progression and severity of the atherosclerotic process are related to the presence (number), magnitude, and duration of a series of risk factors. The fact that most risk factors for AD start or are acquired during childhood, with a tendency to persist during adult life, renders the understanding of these factors for this age group extremely important.

The objective of this review is to discuss the relevance of atherosclerotic risk factors in childhood and adolescence, in addition to discussing data from epidemiological studies carried out in Brazil on the matter.

Natural history of the atherosclerotic disease

Over 40 years ago, Enos, Holmes, and Beyer showed the presence of signs of coronary atherosclerosis among United States soldiers killed in action in the Korean war and whose age average was 22 years. Out of 300 necropsies, there was
macroscopic evidence of arteriosclerosis in three fourths of cases; also, in 3% of cases there was total occlusion in branches of the coronary artery tree. Owing to these results, many studies were carried out with the objectives of elucidating the natural history of the atherosclerotic process.3

The Pathobiological Determinants of Atherosclerosis in Youth (PDAY)4 and the Bogalusa Heart Study5 were decisive for the understanding of the genesis and progression of atherosclerosis. In addition to confirming development of atherosclerotic lesions in youth, these studies also showed the importance of risk factors in this process. As a whole, these studies emphasize the notion that atherosclerosis is a pediatric problem, considering that lipid lesions (fatty streaks) in the aortas develop extensively during childhood; that fatty streaks in the coronary arteries start developing during adolescence; and that fibrous plaques can be observed before the age of 20 years, presenting significant progression during the third decade of life.

According to the study by Stary on presence of atherosclerotic lesions of coronary arteries in the first forty years of life, early lesions, or lesions type I and II, can be found in individuals aged less than one year. After puberty, approximately 61% of individuals presented some type of atherosclerotic lesions in the coronary arteries; out of which around 15% were type III and IV lesions, in other words, intermediate and raised lesions. After forty years of life, approximately 95% of the population presents some type of atherosclerotic lesion.6

Data from the PDAY study indicate that this process starts during the second decade of life, and is aggravated at approximately age 25 years. After the age of thirty years, the formation of lesions directly related to occlusion of the coronary arteries is already in process.4

Risk factors for atherosclerotic disease

Risk factors can be defined as those being associated to an increase in the probability that a disease will develop. In this sense, however, it should be clear that no factor in itself is strictly essential or sufficient to cause AD. As we have mentioned earlier, in general, the greater the number and magnitude of risk factors for AD, the greater the risk for early morbidity and mortality. Furthermore, the risk factors for AD present a synergistic relationship instead of simply a cumulative relationship.

The risk for cardiovascular events increases with the presence of multiple risk factors for AD. Just recently, Berenson et al.7 observed that as the number of cardiovascular risk factors increases, so does the severity of asymptomatic coronary and aortic atherosclerosis in young people. The authors carried out autopsies in young subjects aged 2 to 39 years and showed that subjects with 0, 1, 2, and 3 or 4 risk factors had, respectively, 0.6 percent, 0.7 percent, 2.4 percent, and 7.2 percent of the coronary arteries covered with collagenous fibrous plaques.

Currently, the established risk factors for AD are age and sex (men aged > 45 years and postmenopausal women), family history of atherosclerotic disease, dyslipidemia, arterial hypertension, smoking, diabetes mellitus, obesity, and sedentariness.8 Other factors such as stress, increase in homocystein levels, fibrinogen, and lipoprotein Lp(a) are still not widely recognized due to the lack of established epidemiological relevance and uniformly accepted laboratory facilities and/or standardization.8

The risk factors may be classified into changeable and unchangeable according to the possibility of intervention on the factors.8

Changeable risk factors

This group includes dyslipidemia, smoking, sedentariness, diabetes mellitus, obesity, and arterial hypertension.

Dyslipidemia

Dyslipidemia can be defined as a condition in which there are abnormal circulating levels of lipids and lipoproteins due to alterations in production, catabolism, or clearance in the circulation as a consequence of genetic and/or environmental factors. Among the environmental factors that exert an influence on determining the lipidic profile of patients, diet is one of the most important ones.

With the exception of age of individuals, dyslipidemia is the most important predictive factor for CAD. The importance of the risk for AD, which can be verified by high levels of total cholesterol (TC) (more specifically, LDL cholesterol) and low levels of HDL cholesterol (HDL-C), is well-known. The atherogenicity of triglyceride-rich particles, however, is controversial.

The serum levels of lipids and lipoproteins can vary markedly during the first two years of life, and during sexual maturation. At age 2 years, individuals achieve the cholesterol levels that should be maintained throughout the first ten years of life, independently of sex or race. During adolescence and sexual maturation, however, these changes are sex- and race-dependent. Despite the fact that HDL-C levels present a tendency to decrease during adolescence in both sexes and in different races, this trend is more striking in Caucasian boys. The levels of LDL-C, in turn, present a mild decrease during adolescence but tend to increase, independently of sex and race, during the sexual maturation stage. The levels of triglycerides and VLDL-C increase in all individuals during puberty, but, after sexual maturation, the increase is more significant in Caucasian males. Thus, the lipid levels for the adult life are established after the sexual maturation stage.

Total cholesterol (TC) and LDL cholesterol (LDL-C): during the past 40 years, there is significant epidemiological evidence showing, conclusively, that hypercholesterolemia,
especially the increase in LDL-C serum levels, is a direct predictor of AD. LDL-C particles contain approximately 70% of the cholesterol in blood and constitute the main target of intervention according to the guidelines of the National Cholesterol Education Program (NCEP).9,10

The positive, independent, continuous and gradual association between serum LDL-C levels and risk for AD has been reported in both sexes and in all age groups. In general, a 1% increase in LDL-C levels can increase in 2 to 3% the risk for CAD.

The increase in LDL-C levels, especially in LDL-C modified by oxidation or glycosylation (diabetics), represents one of the main causes of endothelial damage/dysfunction, an initial event of the atherogenic process. In addition to the levels of LDL-C, the composition of these particles also exerts an influence on the risk for atherosclerosis. The subclass phenotype B LDL particles, which are smaller and more dense (rich in cholesterol), present a greater atherogenic potential. Several studies have shown that the decrease in LDL-C levels is highly effective in the reduction of the risk for CAD in both primary and secondary prevention measures.11,12

The earlier publications of the PDAY13 already indicated that increased LDL-C levels were possibly related to the extension of all types of atherosclerotic lesion in coronary arteries. Others have shown a significant (P=0.009) positive association between presence of raised atherosclerotic lesions in subjects aged 30 to 34 years; this finding was similar for both sexes.4

There are few national studies on the prevalence of risk factors for atherosclerosis including children and/or adolescents. In the existing studies, the averages for TC vary according to region, positive family history of AD, and age. Gerber and Zielinsky,14 while assessing students aged six to 16 incomplete years from the public and private schools of the city of Bento Gonçalves, state of Rio Grande do Sul, Brazil, obtained an average (± SD) TC of 167.22 ± 30.57. Rabelo et al.,15 in a study of students aged 17 to 19 years from a private university in São Paulo, obtained a similar average (167.67 ± 29.87). An average TC below 160 mg/dl was described in São Paulo by Bertolami et al.,16 an average (± SD) for both sexes.4  Findings from the Bogalusa Heart Study necropsies indicated significant differences in antemortem data in relation to presence of atherosclerotic lesions in coronary arteries. One of the differences found was that HDL-C levels were lower in individuals who presented fibrous plaques in comparison to those who did not present this type of lesion.5

The beneficial effects of HDL-C particles were demonstrated in the PDAY studies. Elevated plasma levels of this lipoprotein were negatively associated to the extension of all types of atherosclerotic lesion in coronary arteries. This negative association was found significant (P=0.03) in relation to the presence of raised atherosclerotic lesions in the age group of 25 to 34 years; it was also similar in both sexes.4 Findings from the Bogalusa Heart Study necropsies indicated significant differences in antemortem data in relation to presence of atherosclerotic lesions in coronary arteries. One of the differences found was that HDL-C levels were lower in individuals who presented fibrous plaques in comparison to those who did not present this type of lesion.5

The results from national studies demonstrate average levels of HDL-C higher than 45 mg/dl in subjects aged less than 20 years, and higher than 40 mg/dl in subjects aged older than 20 years. The differences in averages of HDL-C according to sex are reported in both the national and international literature; these differences indicated higher HDL-C levels in women independently of age.

Triglycerides (TG): for several years, isolated hypertriglyceridemia was not considered a risk factor for...
AD. However, the hypothesis that some lipoproteins rich in TG exert an independent contribution to the atherosclerotic process has received some scientific support from both animal and human studies. In a metaanalysis of 17 prospective studies, which included 57,277 subjects, the authors showed that high levels of TG were related to an approximately 30% increased risk in men and a 75% increase in women. The risk of cardiovascular disease following increase in TG levels remained significant despite the adjustment for other risk factors, such as decreased HDL-C levels.20

Hypertriglyceridemia can promote atherogenesis due to its metabolic consequences. The presence of high levels of triglycerides can cause the formation of small and dense LDL-C particles and/or the decrease in HDL-C levels; hypertriglyceridemia can also induce a pro-coagulant state.

Despite the limited data, the literature suggests that a decrease in TG levels can reduce atherosclerotic events.21

In the PDAY study, the elevated plasma levels of VLDL and LDL-C were positively associated to both the presence and extension of all types of atherosclerotic lesions in coronary arteries.4 The findings of the Bogalusa Heart Study showed that increased levels of VLDL and TG were associated to atherosclerotic lesions in the coronary arteries (fatty streaks and fibrous plaques).5

Most national studies with children and/or adolescents reported average TG levels lower than desirable, according to the recommendations by the Second Brazilian Consensus on Dyslipidemias (< 130 mg/dl).8 Also, the prevalence of subjects with above the desirable levels was small.

**Diet:** since the 1993 publication of the first experimental study relating cholesterol intake with premature atherosclerosis, the study of fat and cholesterol intake has caught the attention of researchers. In the Seven Countries Study, published practically three decades ago, Keys et al.22 showed that the intake of saturated fat was the better predictor of mortality by cardiovascular disease.

The necessity to maintain a restriction of the intake of fat, cholesterol and total calories in order to attain normal cholesterol levels is well-established. Both the National Cholesterol and Education Program (NCEP)10 and the Second Brazilian Consensus on Dyslipidemias8 recommend a total intake of fat of less than 30% of the total calories; and the intake of saturated fat should not exceed 10% of this percentage. The cholesterol intake should be less than 300 mg/day.

Clinical studies were carried out with the objective of assessing impact of nutritional changes on lipidic profiles. A decrease of 35% and 40% to 15% and 20% on fat content in diet is associated to a decrease of approximately 10% to 20% in serum levels of TC and LDL-C.

Based on the concept that primary prevention should start during childhood, European and North-American groups have recommended populational strategies for children and adolescents with the objective of decreasing the risk for clinical symptoms of AD at a more advanced age. One of the main objectives of these recommendations is the adoption of a healthier diet including the limitation of fat and cholesterol intake.

Studies with children with genetic hyperlipoproteinemia carried out in the early 1990s showed that the proposed diet changes (low-saturated fat, low-cholesterol diet) are feasible, effective and safe measures for the decrease in LDL-C levels. More recently, Lägstrom et al.23 demonstrated that these measures can be carried out early in life in a safe manner and independently of previous screening of the lipidic profile.

National studies on fat and cholesterol intake are even more scarce than those investigating other risk factors. These studies have indicated, nevertheless, that most children and adolescents exceed the recommendations of total fat, saturated fat, and cholesterol intake. In the study by Rabelo et al.,15 73.6% of the population sample from São Paulo presented a total fat intake corresponding to more than 30% of the total calorie intake. A cholesterol intake greater than or equal to 300 mg/day was observed in 32.7% of subjects aged 17 to 19 years. In the study by Fonseca et al.,24 carried out in the city of Rio de Janeiro, the authors observed significant differences in dietary habits according to age and sex. Young subjects presented a more unhealthy diet in comparison to older subjects. The difference between dietary habits of male and female individuals was also considerable and more marked between young individuals. The intake of food rich in saturated fat and cholesterol was significantly greater among male subjects.

**Smoking**

Smoking (defined as use of tobacco and acute or chronic intoxication as a result of this habit) is associated to a series of diseases, out of which the most important are the cardiovascular and neoplastic diseases. As to what concerns the cardiovascular diseases, smoking is among the most important risk factors for development of AD. Depending on the age group, the proportional mortality of smokers is approximately 1.36 to 2.76 times higher than that of nonsmokers.

The greater the number of cigarettes smoked and the longer the duration of the habit of smoking, the greater the exposure to risk. In addition to the duration of the smoking habit, premature smoking habits during childhood and adolescence are also related to an increase in morbidity and mortality.

In Brazil, it is estimated that smoking is a habit present in approximately 40% of adult males and 25% of adult
females. Smoking also represents an important public healthcare concern in relation to children and adolescents due to the high prevalence in these age groups and to the harmful effects of smoking at an early age. In a study including several Brazilian capitals, Cartini et al. observed that smoking starts at a very early age among public school students. In that sense, the authors observed that, on average, 11.6% of children aged 10 to 12 years had already at least experimented smoking cigarettes. The deleterious effects of smoking are time- and dose-dependent.

Smoking represents an important risk factor during the initial stages of development of AD in adolescents and young adults. Serum concentrations of thiocyanate in blood, a marker of smoking, are strongly associated to prevalence of raised atherosclerotic lesions, especially in the abdominal aorta of necropsied young subjects. The effects of smoking can be observed in adolescents up to the age of 15 years. In the PDAY study, the more marked effects were observed in the age group of 25 to 34 years.4

Passive smoking is also considered an important risk factor for CAD by the American Heart Association for both adults and children. Risks owing to passive smoking have been demonstrated in several studies. A review of the literature indicated that nonsmokers with daily exposure to smoking were at greater risk for fatal and nonfatal cardiac events. The authors wrote that smoke-exposed children presented higher whole blood 2,3-diphosphoglycerate, which is an enzyme that increases the oxygen-hemoglobin dissociation in an attempt to compensate for chronic oxygen deprivation.26

In addition to its direct action, smoking can enhance the effects of other risk factors, such as dyslipidemia, hypertension, and diabetes.

The behavioral model of parents and friends plays an important role in influencing the acquisition of the smoking habit in youths. Consequently, anti-smoking campaigns should include an emphasis on the role of the family.

Regardless of the difficulties involved in quitting the habit of smoking, the interruption of this habit reduces the risk of cardiovascular events. Quitting smoking can bring benefits to the health of smokers independently of duration of the habit and age.

**Sedentariness**

Physical activity less than that necessary for maintaining good health is called sedentariness. Regular physical activity can play an important role in both prevention and treatment of a series of diseases, including the atherosclerotic disease.

As to the cardiovascular diseases, sedentariness represents an important independent risk factor in relation to development and progression of the diseases. The Center for Disease Control and Prevention in the United States attributes a relative risk of 1.9 to sedentariness in relationship to the development of cardiovascular disease.

The prevalence of sedentary individuals is elevated in both developed and developing countries. Technological development has contributed to a decrease in energy expenditure at work and during leisure activities. The decrease in the practice of physical activities, observed over the past two decades, is especially worrisome in the case of young adults due to both the high prevalence and the consequences of this decrease. Studies have reported that children and adolescents are heavier and tend to be more overweight and sedentary than earlier. The decrease in practice of physical activities in this age group has been attributed to the television, computers, and video-games being used as a form of leisure; to the concerns of parents in relation to safety of children (‘playing outside’); and to the lack of interest of the schools in promoting physical activity.27

Regular physical activity provides substantial benefits. Epidemiological studies have shown that practicing regular aerobic exercises reduces morbidity and mortality from cardiovascular diseases in both the general population and in individuals with CAD. Regular physical activity contributes to the prevention and reduction of the atherosclerotic process by means of several direct and indirect mechanisms that act on other risk factors. In addition to improving the myocardial oxygen supply and demand ratio, exercise is also associated to achieving and maintaining ideal weight; to increase in glucose tolerance and insulin sensitivity; to a decrease in pressure levels; to an increase in serum levels of HDL-C; to a decrease in TG levels; and to a decrease in plaque aggregation.

The relationship between regular physical activity and risk factors is similar for both children and adults. Data from the Bogalusa Heart Study associate an unsatisfactory physical conditioning during childhood to obesity and unfavorable blood pressure and lipidic levels. Moreover, sedentariness is among the main risk factors that, when present during adolescence, tend to remain during adult life.

Intervention studies with regular practicing of physical activities have shown encouraging results. A group from the University of North Carolina reported a decrease in cholesterol levels (approximately 10.1 mg/dl) in hypercholesterolemic children submitted, during eight weeks, to a 20-minute aerobic exercise program three times weekly, which also included talks on healthy diets, harmful effects of sedentariness, and smoking.28

Based on this information, the Healthy People 2000, which aims at promoting improvement of health of the population, included certain strategies aimed at young individuals. These strategies comprehend increasing the percentage of individuals aged 6 years or older who practice mild and moderate physical activity at least 30 minutes a day, and increasing the proportion of children and...
adolescents who participate in daily physical activity programs at school and in physical education classes and leisure activities (dancing, biking, swimming, and so on).

**Diabetes mellitus**

The diabetes mellitus (DM) can be defined as a group of metabolic disorders characterized by a state of hyperglycemia resulting from deficient secretion and/or action of insulin. Chronic hyperglycemia of diabetes is associated to long-term damage, dysfunction, and failure of several organs, especially the eyes, kidneys, heart, blood vessels, and nerves.

Currently, DM is one of the most important public healthcare problems in the world. It is of special concern in developing countries, where the prevalence and incidence rates are the highest. In Brazil, according to data from the National Diabetes Census, published in the epidemiological release of the Brazilian Public Healthcare System (SUS) from August 1992, the prevalence of DM in the population aged 30 to 69 years is 7.6%. It is estimated that the incidence of type 1 DM, which is observed in 10 to 20% of cases of DM, is 7.8 per 100,000 cases of patients aged less than 20 years.

Cardiovascular diseases lead the ranking of causes of death and represent the main cause of morbidity and professional disability in diabetic patients. Epidemiological studies have shown that the risk for CAD in these patients is approximately two to three-fold higher than that of the general population. Moreover, the atherosclerotic process is more severe in diabetic patients.

The reasons for diabetic patients being more subject to AD have been the focus of many research studies. The understanding is that the greatest risk has a multi-factor origin, such as: greater impact of AD risk factors; tendency to clustering of risk factors; presence of specific and additional risk factors following hyperglycemia and/or insulin resistance.

Out of the risk factors related to diabetes, the most important are hyperglycemia and lipoprotein alterations. Hyperglycemia plays an important role in the pathogenesis of CAD by causing structural and functional alterations in lipoproteins, changes in vascular biology, and accelerating molecular and cellular events that lead to atherosclerosis.

Both fasting and postprandial hypertriglyceridemia represent the lipidic alteration that is more characteristic of DM. The increase in serum levels of triglycerides occurs due to both an increased production and deficient catabolism. Insulin resistance is apparently at the basis of both mechanisms. Hypertriglyceridemia changes the composition of lipoproteins and is associated to a decrease in HDL-C serum levels and to the formation of small and dense LDL-C particles, which, in turn, have a greater atherogenic potential. When hyperglycemia becomes manifest, the LDL particles become even more atherogenic due to glycosylation.

The impact of glycemia on the risk for cardiovascular disease has also been assessed in nondiabetic individuals. Data from several studies corroborate the presence of a gradual relationship between glycemia and cardiovascular events, thus characterizing the earlier as a continuous cardiovascular risk factor, as is the case of serum cholesterol and arterial blood pressure.

While describing the metabolic alterations in adolescents and young adults born to diabetic parents, Berenson et al. showed that these individuals present fasting glycemia, glucagon, and triglycerides higher than those in the same age group. In approximately half the subjects, the glycemia levels observed 30 minutes into the glucose tolerance test were higher than 161 mg/dl. In addition, there was a significant prevalence of obesity and increase in arterial pressure in subjects born to diabetic parents. These findings suggest that anomalies of DM can be found in adolescents and young adults long before the clinical symptoms of the disease appear.

In the PDAY study, the authors observed a highly significant association between high glucose in plasma (measured by levels of postmortem glycosilated hemoglobin) and the extension of the atheromatous process. The authors verified that individuals aged 30 to 34 years with glycosilated hemoglobin levels greater than or equal to 8% presented, in their coronary arteries, an extension of fatty streaks three-fold greater, and of raised lesions eight-fold greater, than those of individuals in the same age group and with glycosilated hemoglobin levels less than 8%. In individuals aged 15 to 24 years, the extension of raised lesions in the coronary arteries was two-fold greater in the group of glycosilated hemoglobin levels greater than 8%.

**Obesity**

In short, obesity can be defined as a disease in which there is an excessive or abnormal accumulation of fat in adipose tissue with harmful effects on health. The energy imbalance found in obesity has genetic and environmental causes. A diet with high fat intake, a sedentary lifestyle, a low baseline metabolism, an elevated fasting respiratory quotient (tendency to greater oxidation of carbohydrates than lipids in standard conditions), and a high sensitivity to insulin are some of the factors at the basis of a positive energy balance.

Obesity is currently one of the most severe problems of public healthcare both in relation to adult, and children and adolescent groups. Due to the marked increase in obesity during the past few decades, which is also observed in developing countries, it is understood that there is a global epidemic of obesity. In Brazil, from 1975 to 1989, there was an increase in prevalence of obesity for both men (3.1% to 5.9%) and women (8.2% to 13.3%) aged 25 to 64 years.

Overweight can result in several harmful effects to health. Obesity results in an increased risk for the development of a series of diseases, which can be divided
into six comprehensive groups: cardiovascular diseases, including hypertension, CAD, and cerebral vascular accident; metabolic disorders, such as dyslipidemia and diabetes mellitus; respiratory diseases, more specifically sleep apnea; cancer; biliary calculus (gallstones); and osteoarticular diseases. The psychosocial problems caused by obesity contribute to a decrease in the quality of life of obese individuals.

The Framingham Heart Study considered obesity as the third most important predictive factor of CAD. In addition to being an independent risk factor for AD, obesity is associated to several other risk factors for AD, such as hypertension, DM type 2, and dyslipidemia.

Loss of weight, even if it is just moderate (over 10% of bodyweight) is related to an improvement in glycemic control, to a decrease in blood pressure levels, and to favorable changes in lipidic levels. The greater the loss of weight, the greater the benefits.

The magnitude, duration, and distribution of body fat are directly related to the severity of metabolic changes caused by excess weight, and to the resulting morbidity and mortality. However, in order to evaluate the impact of obesity on health, it is necessary to consider the body fat distribution. The abdominal (android) fat distribution presents a stronger association with morbidity and mortality in comparison to peripheral (gynecoid) obesity.

The examination of body fat distribution is important in both adults and children and adolescents. In a study with 2,996 children and adolescents aged five to 17 years, Freedman et al. observed that central or abdominal distribution of body fat was related to adverse concentrations of triacylglycerol, LDL-C, HDL-C, and insulin; these associations were independent of race, sex, age, weight, and height.

The elevated prevalence of obesity in childhood and adolescence is extremely concerning due to the long- and short-term consequences. Excess weight in these two age groups is associated to adverse blood pressure levels and unfavorable alterations in lipid and insulin levels. High blood pressure levels are associated to obesity especially during or after sexual maturation. Likewise, obesity is also strongly associated to an adverse lipidic profile; this relationship is more marked in boys than in girls. In the group of lipidic alterations associated to overweight, the increase in very low density lipoprotein (VLDL) is the most significant alteration. As in the case of adults, childhood obesity, especially that related to abdominal fat distribution, is associated to hyperinsulinemia and to clustering of other risk factors that are part of the plurimetabolic syndrome. This syndrome can be clearly identified in childhood; however, extremely high triglyceride levels become manifest only after thirty years of life.

Also, in the Muscatine Heart Study, obesity in adolescence was associated to presence of fatty streaks, elevated lesions, and coronary artery and aorta calcifications. Loss of weight, in turn, can be advantageous. Rocchini et al. showed that loss of weight (5 kg on average) presented a linear relationship with a fall in blood pressure levels of obese adolescents.

In relation to the long-term consequences, there is a lot of evidence that obese children and adolescents present a tendency to remain above their ideal weight in adult life. The probability of obesity persisting in adult life increases in cases in which it is present during adolescence. Parental obesity also affects the chances of a child’s becoming an obese adult. Whitaker et al. reported that parental obesity increases two-fold the risk of adult obesity among both obese and nonobese children under 10 years of age. This influence is probably due to both genetic and environmental factors.

Studies have shown that childhood obesity is related to an increased risk for several chronic diseases later in life. According to the Harvard Growth Study, whose results owe to a 55-year long follow-up, overweight in adolescence predicted a greater risk for AD in both male and female subjects independently of adult weight.

Considering that overweight is associated to several risk factors for AD, including the case of overweight children aged less than 10 years, we may posit that prevention and treatment of childhood and adolescent obesity can reduce the incidence of cardiovascular diseases in adult life.

Arterial hypertension

Arterial hypertension (AH), a multi-factor clinical entity, is understood as a syndrome characterized by presence of high tension levels associated to metabolic and hormonal alterations, and to trophic phenomena (cardiac and vascular hypertrophy).

AH is one of the most important risk factors for AD in both sexes and independently of ethnic or age group. The presence of AH is related to a high social cost, considering that it is responsible for approximately 40% of cases of early retirement and of absenteeism at work in Brazil. According to the Third Brazilian Consensus on Arterial Hypertension, the prevalence of AH is elevated, with estimates indicating that approximately 15 to 20% of the adult Brazilian population can be labeled hypertensive. Despite the fact that AH affects predominantly adults, its prevalence in children and adolescents cannot be ignored, with numbers varying from 2 to 13%. Brazilian epidemiological studies have shown that the prevalence of AH in this age group ranges from 6 to 8%.

In general, AH tends to increase progressively with age. In young adults, both the diastolic and systolic pressures tend to be higher in male individuals; among elderly
Data from several studies indicate a directly proportional relation between systolic and diastolic arterial pressures and the risk for AD. In this sense, anti-hypertensive treatment can decrease both occurrence of coronary events and the resulting mortality. A review of 17 prospective, randomized studies showed that small reductions of 5 to 6 mmHg in diastolic pressure and of 10 to 12 mmHg in systolic pressure were associated to a 38% decrease in risk for cerebral vascular accident, and 16% in risk for coronary disease.

Among the hypertension mechanisms that predispose individuals to occurrence of coronary events there can be cases of direct damage to the vascular system, including endothelial dysfunction and structural and hemodynamic cardiovascular disorders. Hypertension also allows for proinflammatory activity, increasing the formation of hydrogen peroxide and free radicals in plasma, which, in turn, decrease the formation of nitric oxide by the endothelium increasing leukocyte adhesion and peripheral resistance.

Left ventricular hypertrophy is one of the most important structural and hemodynamic cardiovascular alterations (sequelae). The prognostic value of left ventricular hypertrophy in hypertensive patients is associated to high mortality rates due to acute myocardial infarction. Echocardiographic studies have demonstrated a continuous increase in thickness of the left ventricular wall concomitantly to increasing arterial pressure levels in children and adolescents. These studies indicated that these alterations may accompany hypertension from the beginning. Increased ventricular mass and left ventricular mass index were observed in normotensive children of hypertensive parents.34

The diagnosis of lesions in target organs is an indication of premature AH. In this sense, data from necropsy studies were extremely important. Tracy et al.5 observed increased medial thickness in small renal arteries and fibroplasia of intimal coronary arteries in necropsies of children. In the PDAY study, the assessment of AH by measurement of intimal thickness in renal arteries indicated that AH starts to influence the development of AD (increasing extension of raised coronary lesions) in male subjects aged 25 to 29 years. This effect is up to three-fold more significant in subjects aged 30 to 34 years. The study showed that hypertension is involved in accelerating the atherosclerotic process in all parts of the arterial system.

The onset of primary arterial hypertension depends on genetic and environmental factors, with the earlier participating in 30 to 60% of cases. Studies that showed higher casual and pressure tests arterial pressure levels in children of hypertensive parents clearly demonstrate the family influence on arterial pressure. Brandão et al.34 reported higher blood pressure levels in siblings and mothers of children and adolescents with arterial pressure percentiles greater than or equal to 95 in comparison to those of siblings and mothers of children and adolescents with percentiles less than or equal to 50. The study demonstrated a pattern of familial aggregation in relation to arterial pressure. It is important to keep in mind that in addition to the genes, families also share the same social and cultural environment. The lifestyle and dietary habits can also be passed on from one generation to the next.35

Also in relation to dietary habits, the intake of salt is associated to an increase in arterial pressure in adults, adolescents, and children. Results from the Muscatine Study indicated that weight and weight gain are the main determinants of arterial pressure in childhood.30 An assessment of data provided by the Bogalusa Study shows similar results.5 Findings from a cross-sectional study indicated that the presence of overweight was related to the maintenance of a profile of high arterial pressure and that loss of weight determined a significant decrease in tension values of adolescents.36

Independently of age group, sedentariness presents adverse effects on pressure levels. In the case of children, an unsatisfactory physical conditioning is associated to an increase in blood pressure levels, whereas the improvement of the aerobic function is followed by a decrease in these levels.

**Unchangeable risk factors**

This group includes the factors of family history of AD, sex, and age.

**Family history**

Multi-factor diseases such as AD are influenced by different genetic and environmental variables. In general, establishing a detailed family history can reveal the genetic susceptibility for development of early coronary artery disease. The Brazilian Group of Studies and Research on Atherosclerosis8 considers that presence of CAD in first-degree relatives of the male sex aged less than 55 years, and of those of the female sex aged less than 65 years, represents a significant risk.

The association between family history of CAD and presence of cardiovascular risk factors in childhood and adolescence is well-documented in several epidemiological studies. Kaprio et al.37 observed a positive association between intimal thickening of the coronary arteries in children aged less than one year and family history of CAD.

Early onset of atherosclerotic events in parents constitutes an important piece of information for determining the cardiovascular risk in children. The earlier the manifestation of symptoms of AD, the greater the risk for the offspring.
Bao et al.\textsuperscript{38} were the first to study the association between clinically-diagnosed CAD parents and the cardiovascular risk profile in a cohort of offspring followed-up from childhood to young adult life. In the study, those who were born to parents with coronary disease presented higher weight, total cholesterol levels, LDL-C, glucose, and insulin in comparison to those born to parents without manifest AD. While differences in relation to weight were consistently manifest since childhood and became evident around 10 to 11 years of age, the differences in other variables appeared later on in life. Differences in total cholesterol appeared, on average, around ages 15 to 18 years; the differences in LDL-C and glucose at 18 years; and those in insulin at 21 years. The study also showed a greater coexistence of risk factors in the offspring of parents with family history of CAD. Moreover, it stressed the notion that the sum of risk factors affecting adults may have originated during childhood. Consequently, family history of AD, especially of parents, is considered a useful marker for the screening and guidance of children and adolescents who present a potential to develop AD later on in life.

Others have considered that surveying family history of atherosclerosis should be more comprehensive than just the matters related to coronary disease itself, and thus include the history of other well-known factors, such as: arterial hypertension, diabetes mellitus, obesity and other metabolic diseases.

The dyslipidemias are among the most widely studied family factors that predispose patients to AD. Numerous studies have shown a pattern of familial aggregation in relation to lipidic and lipoproteic levels. Different forms of dyslipidemia were diagnosed in approximately one third of children whose lipidic profile was investigated due to presence or history of CAD in parents and/or grandparents.

The genetic participation in determining the variability of lipidic profiles is of approximately 60%. In some families, the diseases involving lipidic and lipoproteic alterations can be monogenic or polygenic. When the genetic inheritance is determined by a single gene, or by a pair of genes, it is called monogenic. Such is the case of familial hypercholesterolemia (FH) and familial combined hyperlipidemia (FCH). FH is a hereditary and codominant disorder of lipoproteic metabolism, and it is caused by a mutation in the gene responsible for providing information regarding the LDL-C receptor. The disease is clinically characterized by a marked increase in plasma cholesterol levels and by premature CAD. The incidence of heterozygote FH individuals is elevated (1:500). Homozygosis, in turn, is rare (1:1,000,000). FCH is characterized by an increase in serum cholesterol and/or triglyceride levels and is the genetic condition responsible for approximately 4% of cases of premature CAD. While FH is responsible for approximately 4% of cases of premature CAD, FCH is responsible for around 11%.

Since most cases of dyslipidemia in children whose families presented cases of premature CAD cannot be attributed to monogenic disorders, Goldstein and Brown introduced the concept of polygenic hypercholesterolemia. The polygenic disorders are a result of the expression of several genes with small, but cumulative, effects that interact with environmental factors; for example, a diet rich in saturated fat and cholesterol and a sedentary lifestyle.\textsuperscript{9}

Several studies have shown that family lifestyles and behavior patterns that favor the development of AD are passed on from one generation to the next, owing to the fact that they share the same social and cultural environment. These patterns include inappropriate dietary habits, smoking, sedentariness, and so on.

**Sex and age**

Age is one of the main unchangeable risk factors for AD. It is estimated that mortality due to cardiovascular disease (including CAD), cerebral vascular accident, and peripheral artery disease increases 2.5 times every 10 years. The risk for nonfatal cardiovascular events also increases progressively with age, even in low-risk individuals. Nevertheless, the presence of other risk factors in any age group determines a greater susceptibility to these events.

Atherosclerotic lesions evolve with age in extension, number, and severity in both sexes. However, the increase in magnitude of cardiovascular risk factors and the occurrence of subsequent clinical events occur later in women.

Data from the PDAY study revealed that male individuals aged 30 to 34 years presented more extensive atherosclerotic lesions and a greater prevalence of raised lesions in the right coronary artery in comparison to female individuals of the same age group. Women presented a delay of approximately 5 years in comparison to men regarding the development of raised atherosclerotic lesions. This variance was not explained by the differences in lipidic profile, smoking habits, increase in glycosylated hemoglobin and/or hypertension.\textsuperscript{4}

Still, others understand that the greater extension of the atherosclerotic process in males at a younger age is related to the more marked expression of risk factors between men, and to the hormonal differences between men and women. Findings of the Bogalusa Heart Study indicated a significant increase in LDL-C levels and a decrease in HDL-C levels in boys during adolescence and post-adolescence, whereas in girls, the variations in levels of these lipoproteins were small during the same period.\textsuperscript{39} As a result, young males presented an unfavorable LDL-C:HDLC ratio in comparison to young females. Data from the Coronary Artery Risk Development in Young Adults Study (CARDIA)\textsuperscript{40} suggest that young adult women present a favorable lipoproteic profile regarding cardiovascular risks. There are also differences in relation to pressure levels according to sex in young subjects. The prevalence of
hypertension is lower in young women in comparison to young men.

The differences in lipidic profile before and after menses reflect the influence of sexual hormones, especially estrogen. This hormone exerts a favorable effect on lipoproteins. The action of estrogen contributes to an increase in HDL-C levels and to a decrease in LDL-C and fibrinogen. The levels of triglycerides, in turn, tend to increase. The incidence of CAD in women before menopause is much lower than that of men. After the age of 50, when menopause usually occurs, the morbidity rates for CAD become closer to those of male individuals.

There is a lot of controversy with respect to the increase in risk for nonfatal and fatal infarction in women who use oral contraceptive methods. In relation to the lipidic profile, the progestagens presenting greater androgenic potential can attenuate the cardioprotective effect of estrogen and exacerbate insulin resistance. While passing through the kidneys, the estrogen stimulates the production of certain coagulation factors and should be used with caution in patients with thrombogenic risk.

These findings lead to changes in the formulation and indication of birth control pills. The hormonal dosages became lower and the new progestagens presented less deleterious effects on the metabolism of lipids and carbohydrates, not allowing for an increase in risk for CAD.

The increase in risk for CAD in women who use birth control pills increases if they are smokers. In young women taking birth control pills, smoking causes a three-fold increase in the risk for acute myocardial infarction.

**Conclusions**

Despite the advancements in the areas of diagnosis and therapeutics, cardiovascular diseases remain as one of the main causes of mortality in developed and developing countries. According to several epidemiological studies, measures aimed at intervening on factors responsible for the onset of the atherosclerotic process would have an impact on both mortality and costs of treatment of cardiovascular diseases.

The influence of the environment is extremely important. Certain individuals can have a genetic predisposition to the development of several risk factors for AD; however, this predisposition seemingly plays more of a permissive than a determinant role. Often times, it is necessary that individuals be exposed to an inappropriate lifestyle for their predisposition to become manifest. Some individuals reach an advanced age with few signs of AD, thus showing that this disease is not unavoidable with age. In addition to that, the morbidity and mortality rates vary according to geographical regions and change with migration of individuals. In this sense, preventive measures should include reduction of exposure to well-established risk factors, selective identification of individuals with an elevated potential of developing the disease, and the adoption of more aggressive measures aimed at decreasing risks. Intervention measures as early as during childhood and adolescence have been reported feasible, safe, and effective.

Consequently, with the objective of ensuring a healthier childhood and avoiding future cardiovascular diseases, several researchers have emphasized the need for adopting preventive healthcare programs as soon as possible. The fact that younger individuals are still developing their habits can help to increase the compliance with changes proposed towards a healthier lifestyle.

Finally, the assessment of one’s lifestyle should be a part of pediatric consultations, similarly to the case of analysis of family history for stratification of cardiovascular risk in adolescents. The active participation of parents in the design of a diet plan and in the choice of physical activities is fundamental for the success of, and compliance with, a preventive and/or therapeutic program.

**References**

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