I Guideline for preventing atherosclerosis in childhood and adolescence

TRANSLATION OF THE PORTUGUESE TEXT, PUBLISHED IN ARQ. BRAS. CARDIOL. 2005;85(SUPPL. VI)

Background, definitions and guideline objective

Today we know that it is possible to decrease the incidence of atherosclerotic complications by adopting a healthy lifestyle and by the use of drug therapy. However, there is no consensus as to when or how prevention should begin. The concept that treatment should start during childhood became consolidated once the understanding of the mechanisms underlying atherosclerosis onset and development increased. Instead of substituting the clinical reasoning, this guideline intends to complement it and become a reference for the establishment of individual and population strategies that aim to control atherosclerosis risk factors in childhood and adolescence.

Methodology and evidence

The participants of this guideline were selected among health science experts with academic and hands-on experience in preventing atherosclerosis. The adopted methodology and evidence levels were the same used in previous documents by the Brazilian Society of Cardiology.

Epidemiology in Brazil

Hypertension

Epidemiologic studies done in Brazil on primary childhood and adolescent hypertension (HTN) demonstrated that its prevalence varied from 0.8 to 8.2%1,2. As with adults, many of these studies demonstrated a frequent association between HTN and overweight or obesity.

Overweight and obesity

In the last 30 years, childhood and adolescence malnutrition prevalence rapidly declined and adult overweight/obesity prevalence had an accelerated increase. The data on children and adolescents aged 2 to 17 years obtained from the Survey on Standard of Living (PPV) done in Brazil in 1997, showed that obesity prevalence was 10.1% and was higher in the Southeast (11.9%) than in the Northeast (8.2%); adolescent overweight prevalence was 8.5% (10.4% in the Southeast and 6.6% in the Northeast) and obesity 3.0% (4.2% in the Southeast and 1.7% in the Northeast)3. Excess weight prevalence was more common in families with higher income, except for Porto Alegre, where girls in public schools presented a higher BMI than those in private schools4.

Sedentary lifestyle

There are few studies on child and adolescent sedentary lifestyle prevalence in Brazil and its rate is estimated at 42 to 93.5%4,5 depending on the criterion used.

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Moura et al. (1998-1999) studied 1600 schoolchildren, aged 7 to 14 years, in Campinas, SP, and verified that the mean cholesterol, triglycerides, LDL cholesterol and HDL cholesterol levels were respectively, 160, 79, 96 and 49 mg/dL. The authors found a hypercholesterolemia prevalence of 35% when the 170 mg/dL cholesterol threshold was used. In 2001, Giuliano found mean total cholesterol, triglycerides, LDL cholesterol and HDL cholesterol levels of respectively 162, 93, 92 and 53 mg/dL for 1053 schoolchildren, aged 7 to 18 years, living in the municipality of Florianopolis. In this study, hypercholesterolemia was found in 10% of the children, hypertriglyceridemia in 22%, high LDL cholesterol in 6% and low HDL cholesterol in 5%.

Smoking

Until the 1980’s in Brazil, 1 to 34% of the interviewed elementary and high school students smoked. More recent surveys show that smoking rates among adolescents vary from 3 to 12.1%. However, it is important to point out that the surveys performed in 10 Brazilian capitals involving 24,000 elementary and high school students in the years 1987, 1989, 1993 and 1997 revealed that, in each of those capitals, the rate at which children were trying out cigarettes was increasing.

Long-term impact

Based on data from the Census of Brazil for 2000, the Brazilian population is expected to reach 259.8 million inhabitants by the year 2050; changes are also expected for the population pyramid since life expectancy will increase and female fertility rate will decrease, reflecting an aged population. To contextualize these facts in a global scenario, an international group has recently reviewed mortality data for many populous developing countries such as Russia, China, India, South Africa and Brazil; data from the State of Rio Grande do Sul was used for the Brazilian estimates. These authors demonstrated that the cardiovascular disease rate in Brazil is lower than those of the USA and Portugal, but when they took into account the fact that the Brazilian population is younger, this scenario changed. By extrapolating current mortality data by age group for the 2040 population pyramid, these authors found that Brazil presents the highest relative increase in mortality rate of all the reviewed countries.

Sociocultural changes in Brazil determine increased child and adolescent cardiovascular risk

The urbanization that occurred in the 20th century, not only in Brazil but worldwide, led to many changes, such as sedentary lifestyles, changes in eating habits with higher consumption of fats, fatty acids and sugars, lower consumption of fiber-rich foods, higher smoking and stress rates and women entering the workforce. Another change that has been observed was the preference for eating out, which calls for the need of promoting a healthy diet.

Evolution of the risk factors in the first three years of life

Intrauterine programming of the risk factors

The risk factors for atherosclerotic cardiovascular disease are present since intrauterine life and continue for life. When the intrauterine environment is unfavorable, the fetus may present intrauterine growth retardation or macrosomia. These clinical conditions were associated with the later development of diabetes, cardiovascular disease, dyslipidemia and hypertension. Epidemiological observations made in the last two decades demonstrated that there is an inverse relationship between birth weight and development of cardiovascular disease in adult life. These observations lead Barker et al. to formulate the hypothesis of intrauterine programming of cardiovascular diseases. At birth, these children present higher levels of blood pressure, ACTH and plasma endothelin and their number of nephrons was low for their gestational age. Although more emphasis has been given to fetal nutrition, other factors such as infections, season of the year and mother’s size and smoking status can also be related to the development of cardiovascular diseases.
Consequences for the small-for-gestational-age newborn: dyslipidemia, hypertension and endothelial function

Newborns are considered small for gestational age (SGA) when their weight is equal to or less than the 10th percentile of a population-specific weight versus gestational age plot. On the other hand, their weight is also considered low when their birth weight is below 2,500 g due to intrauterine growth retardation (IUGR). SGA newborns present a higher incidence of cardiovascular disease (systemic arterial hypertension and atherosclerosis) and glucose intolerance (type 2 diabetes or metabolic syndrome).

Consequences for the large-for-gestational-age newborn: macrosomia, obesity and metabolic syndrome

Macrosomia or fetal obesity is defined as a birthweight above the 90th percentile for the gestational age or birthweight >4 kg regardless of gestational age or gender. These infants present changes in carbohydrate and lipid metabolism that may persist after birth. Fetal macrosomia is associated with a later development of obesity, diabetes and dyslipidemia. These observations are in agreement with the epidemiological association made by Barker between fetal lipid levels and cardiovascular disease risk.

Among the detected changes, hyperglycemia, hyperinsulinemia and elevated serum levels of VLDL cholesterol, triglycerides and apoB-lipoprotein stand out. The main lipid atherogenic risk markers (apoB100/apo A-I, LDL cholesterol/HDL cholesterol and HDL3 cholesterol/HDL 2 cholesterol) are significantly high in macrosomic newborns when compared with a control group.

Programming in the first three years of life

The first three years of life are as important in health and disease programming as intrauterine life. Growth retardation during childhood can be associated with improper weight gain or growth. Both growth retardation and excessive growth (percentile crossing) can be risk factors for later development of chronic diseases. An association between growth retardation in the first year of life and high risk for coronary disease has been described, regardless of birth size. Higher levels of arterial blood pressure have been observed in children who presented intrauterine growth retardation and higher weight gain in childhood.

Breast milk and obesity, hypertension and dyslipidemia: myth or truth?

Exclusive breastfeeding of term and preterm infants is associated with significantly lower levels of arterial blood pressure during childhood. On the other hand, the preferential consumption of infant formulas resulted in high levels of diastolic and mean blood pressure but there is no consensus regarding these results. Observational studies indicate that infants who are exclusively breastfed (and breast milk is rich in saturated fats) can develop a regulation of hepatic lipoprotein metabolism, even though their cholesterol levels in early life are higher. Thus, breastfed children later developed a more favorable lipid profile (tending to remain at or below 150 mg/dL) than those who were fed infant formulas, and this favorable lipid profile continued during adolescence.

Genetics – importance of gene polymorphisms and genetic markers for preventing atherosclerosis in childhood and adolescence

The main causes for childhood genetic dyslipidemias and for dyslipidemias that present genetic and environmental components are listed in Table I. Childhood and adolescent familial hypercholesterolemia can be predicted using the criteria established by the family tracking program, Make Early Diagnoses Prevent Early Deaths (MEDPED), which are: total cholesterol >270 mg/dL or LDL cholesterol >200 mg/dL and first degree relatives with total cholesterol >220 mg/dL or LDL cholesterol >155 mg/dL.

Functional and genetic studies

Functional tests must be performed in order to precisely diagnose genetic dyslipidemias, such as LDL receptor studies in cultivated cells or lipoprotein lipase (LPL) activity after heparin in LPL or Apo CII defects that are associated with the chylomicronemia syndrome. Some diseases, such as familial hypercholesterolemia (FH), are determined by a large number of mutations (more than 700 have been described) and therefore, the gene of interest needs to be tracked by sequencing. Finally, it is possible to test a known mutation by polymerase chain reaction followed by enzyme restriction techniques.

Table I lists the dyslipidemias that are very likely to be genetic as well as their main characteristics.

Atherosclerosis as an early phenomenon

Postmortem autopsy studies in children and young adults who died unexpectedly showed that the presence and severity of atherosclerotic lesions positively and significantly correlate with cardiovascular risk factors. The accelerated progression of fatty streaks to fibrous plaques begins at 15 years of age.
Importance of venipuncture characteristics and clinical status of the child

In the presence of other factors (diabetes, hypertension, obesity, smoking and sedentary lifestyle), initially only the values for total plasma cholesterol can be obtained.\(^40,41\)

The requirements for collecting lipids in children are well defined:

- Stable metabolic state;
- Habitual diet and weight must be maintained for at least two weeks;
- Interval of at least eight weeks between surgery and venipuncture;
- No intense physical activity in the 24 hours preceding the examination;
- 12 to 14-hour fasting before the examination, although drinking water is allowed;

### Table I. Dyslipidemias with a strong genetic component and their association with atherosclerosis or pancreatitis

<table>
<thead>
<tr>
<th>Lipid phenotype</th>
<th>Genetic change</th>
<th>Mutation</th>
<th>Inheritance mode</th>
<th>Population frequency</th>
<th>Manifests in childhood</th>
<th>Outstanding clinical characteristics</th>
<th>Association with early atherosclerosis (+ or −) or pancreatitis (&amp;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL ↑↑↑ (CT ↑↑↑)</td>
<td>Familial hypercholesterolemia</td>
<td>LDH Receptor</td>
<td>Codominant</td>
<td>1:500 (heterozygous)</td>
<td>+</td>
<td>Tendinous xanthomas, xanthelasmas, early corneal arch</td>
<td>+++</td>
</tr>
<tr>
<td></td>
<td>Autosomal recessive sitosterolemia</td>
<td>APO B Arg 3500 Gln Peptide signal APO B Adapting protein ARH ABC G5/G8</td>
<td>Dominant Polymorphisms recessive</td>
<td>1:100,000,000 (homozygous)</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1:700</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;1%</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>rare, common in Sardinia</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>rare</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT ↑ or ↑↑ LDL ↑ or ↑↑</td>
<td>Polygenic hypercholesterolemia</td>
<td>?</td>
<td>Multiple genes</td>
<td>1:100 ou 5:100</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>LDL variable (CT ↓ or T)</td>
<td></td>
<td></td>
<td></td>
<td>−</td>
<td>APO E 2, E3, E4</td>
<td>Codominant</td>
<td>Up to 5% of the TC variation in the population</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL ↑↑↑ and/or LDL ↑↑↑ (TG and/or CT ↑)</td>
<td>Combined familial hyperlipidemia</td>
<td>APO AI-CIII-AIV ? LLP ? and others ?</td>
<td>Autosomal dominant segregation</td>
<td>0,5 – 1:100</td>
<td>+ or +/−</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td>VLDL ↑ or ↑↑ TG ↑ or ↑↑</td>
<td>Familial hypertriglyceridemia</td>
<td>Many</td>
<td>Autosomal dominant, (recessive or not mendelian)</td>
<td>1:300</td>
<td>+ or +/−</td>
<td>−</td>
<td>&amp;</td>
</tr>
<tr>
<td>VLDL ↑ and HDL ↓ LDL small and dense CT N or ↑ TG N or ↑</td>
<td>Metabolic syndrome</td>
<td>?</td>
<td>?</td>
<td>Frequent</td>
<td>+ /−</td>
<td>Insulin ↑, glucose intolerance, SAH obesity, microalbuminuria, fibrinogen ↑, PAI-1 ↑, Uric acid ↑</td>
<td>++</td>
</tr>
<tr>
<td>IDL ↑↑↑ (CT ↑↑↑ and TG ↑↑↑)</td>
<td>Dysbetalipoproteinemia (Fredrickson Type III)</td>
<td>APO E (E2E2) + other genetic defects LLP ?</td>
<td>Codominant not mendelian</td>
<td>Frequency of E2 1:100 (of lipemia 1:5000)</td>
<td>+ /−</td>
<td>Xanthoma striata palmaris</td>
<td>++</td>
</tr>
<tr>
<td>Qm ↑↑↑ (TG ↑↑↑)</td>
<td>Hyperchylomicronemia</td>
<td>LLP ↓↓ APO CII ↓↓</td>
<td>Recessive codominant</td>
<td>1:1,000,000</td>
<td>very rare</td>
<td>+</td>
<td>Pancreatitis eruptive xanthomas retinal lipemia</td>
</tr>
<tr>
<td>HDL ↓↓↓ HDL ↓↓↓ Fish-eye disease familial defic. LCAT</td>
<td></td>
<td>LCAT</td>
<td>Codominant?</td>
<td>Rare</td>
<td>+</td>
<td>Corneal opacification kidney disease</td>
<td>+ or −</td>
</tr>
<tr>
<td>HDL ↓ HDL ↓↓↓ Tanger familial hypalipoproteinemia</td>
<td></td>
<td>APO Al Milano / Al-CIII ABC1</td>
<td>Polymorphism Recessive Dominant</td>
<td>&gt;1% very rare</td>
<td>+</td>
<td>Lymphoid Infiltration</td>
<td>+</td>
</tr>
<tr>
<td>Lp (a) ↑ or ↑↑</td>
<td>Polymorphic Apo (a)</td>
<td></td>
<td>Codominan</td>
<td>?</td>
<td>+ or +/−</td>
<td>−</td>
<td>+ or ?</td>
</tr>
</tbody>
</table>

? = inconclusive data
Perform serial dosages in the same laboratory whenever possible.

The screening and follow-up algorithm for children with dyslipidemia can be found in Figure 1.

The clinical conditions and drugs that most affect the lipid profile are listed in Table II.42,43

### Table II. Drugs and diseases that interfere in the lipid profile 44.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive: thiazides, chlortalidone, spironolactone, beta-blockers</td>
<td>Hypothyroidism, hypopituitarism, diabetes mellitus, nephrotic syndrome, chronic renal failure, congenital biliary atresia, storage disorders, systemic lupus erythematosus, acquired immunodeficiency syndrome.</td>
</tr>
<tr>
<td>Immunosuppressives: cyclosporine, prednisolone, prednisone</td>
<td></td>
</tr>
<tr>
<td>Steroids: estrogens, progestogens, oral contraceptives</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants, acetylsalicylic acid, ascorbic acid, amiodarone, allopurinol, antiretroviral therapy.</td>
<td></td>
</tr>
</tbody>
</table>

### Determining the LDL Cholesterol Subfraction

When the lipid profile of a child needs to be determined, the LDL cholesterol subfraction is obtained by the Friedewald’s formula:

\[
\text{LDL cholesterol} = \text{TC} - \text{HDL cholesterol} - \frac{\text{Triglycerides}}{5}
\]

### Risk assessment

- **Total cholesterol determination**
  - **Acceptable total cholesterol**
    - <150 mg/dL
  - **Borderline total cholesterol**
    - 150 - 169 mg/dL
  - **High total cholesterol**
    - ≥170 mg/dL

- **1st degree relatives Total cholesterol ≥240 mg/dL**
  - Repeat cholesterol determination
    - <150 mg/dL
      - Repeat total cholesterol every 5 years
      - Follow dietary recommendations ↓ risk factors
    - ≥150 mg/dL
      - Lipoprotein analysis

- **Positive family history**
  - Lipoprotein analysis
This formula is valid for plasma concentrations of tri-
glycerides <400 mg/dL since higher values result in LDL
cholesterol underestimation. Fasting interferes with LDL
and triglycerides.

The environment determining the lipid profile

Changes in eating preferences and habits introduced
during childhood may become permanent. However, the
ingestion of fats during the breastfeeding period is essen-
tial for the myelination of the central nervous system and it
is only acceptable to recommend a diet low in saturated
fats and cholesterol for children older than two years.

Saturated fats are considered atherogenic since, when
consumed in excess, they are the main cause for increas-
sed plasma cholesterol and LDL cholesterol levels. Satura-
ted fats affect plasma cholesterol more than dietary cho-
lesterol. Trans fatty acids are unsaturated fatty acids for-
med when liquid vegetable oils are hydrogenated, as in the
production of margarine, and they help increase total cho-
lesterol and LDL cholesterol and decrease HDL choleste-
rol. The total amount of fat in a diet should be around 25
to 35% of the total amount of calories ingested per day,
where up to 7% may be saturated, up to 10% may be po-
lyunsaturated and as much as 20% may be monounsatu-
rated. The consumption of trans fatty acids should remain
below 1% and cholesterol below 200 mg per day.

Polyunsaturated fats are represented mainly by linoleic
(omega 6) and linolenic acids, EPA and DHA (omega 3);
monounsaturated fats are represented mainly by oleic acid
(omega 9). The omega-6 (ω6) fatty acids are found in
sunflower, canola, soybean and corn oils. The omega-3
(ω3) fatty acids are found soybean, canola and fish oils,
fish, especially those from cold waters, and in flaxseed.
Monounsaturated fats (ω9) are found mainly in olive and
canola oils, oily seeds, ginger, avocado and olives and they
have been shown to improve the lipid profile. An unbal-
anced intake of omega-6/omega-3 may have an athero-
genic effect, increasing the LDL cholesterol levels.

There is some evidence that other nutrients, such as
phytosterols and soluble fibers are likely to reduce car-
diovascular risk. Phytosterols are natural substances
found in vegetable oils such as soybean and sunflower oil.
Their main action is to reduce LDL cholesterol by inhibiting
intestinal absorption of cholesterol. Soluble fibers (psylli-
um, pectins, gums, mucilages and β-glucan) delay gastric
emptying and small intestinal transit, increase glucose tol-
eration and reduce increased cholesterol and LDL cho-
lesterol levels. Their main sources are oat and whole rye
flours, beans, apples, oranges and guava.

For smaller children, animal protein (skinned fowl, fish
and lean meats) are considered a complement to breast
milk or infant formulas. If the quality of the diet is adequa-
te, the use of skimmed foods and low fat dairy products
should be increased.

Endogenous sex hormones and lipid profile

Lipid and lipoprotein levels undergo important varia-
tions during human growth and development and they vary
according to age and sex. Serum levels of lipids and lipo-
proteins are higher in female children and adolescents,
and this difference is greater during adolescence. On aver-
age, girls present higher total cholesterol, HDL cholesterol
and LDL cholesterol levels.

Variations due to sexual maturation occur in both gen-
ders. In girls, a progressive increase in HDL cholesterol
starts at 10 years of age, and at the end of adolescence,
their levels of HDL cholesterol are much higher than those
of boys. LDL cholesterol and total cholesterol levels also
increase progressively starting at 14-15 years of age and at
17-18, they are higher than those of boys. It is possi-
ble that menarche plays an important role in triggering
this phenomenon during adolescence. Among boys, sexual
maturation results in a progressive decrease of total cho-
lesterol, LDL cholesterol and HDL cholesterol in function
of the Tanner pubertal stage development.

Determinants of carbohydrate metabolism and association
with other risk factors

Metabolic changes during growth and development

In puberty, insulin resistance is higher but compensat-
ed by increased secretion. The concentration of fasting
plasma insulin increases from two to threefold during the
growth peak period. In this phase, there is an associa-
tion between a relative resistance to insulin and facilitation
of the insulin response to glucose in the metabolism of
amino acids, increasing the anabolic effects of insulin on
protein metabolism.

Influence of sex hormones on glucose tolerance

Extensive changes in body composition and in hormo-
ne secretion profile occur during puberty because of the
increase in sex steroids. Increased growth hormone (GH)
levels may be the key to increased insulin resistance. Sus-
ceptible individuals may not adapt to this situation and if a
defect in insulin secretion is present, they may develop ty-
pe 2 diabetes mellitus during puberty.

Importance of glucose and insulin in
childhood and adolescent atherosclerosis

Hyperglycemia can lead to an increased tissue uptake
and metabolism of glucose by, for instance, the polyol and glucosamine pathways. Furthermore, hyperglycemia can lead to glycosylation of extracellular proteins (such as more atherogenic LDL) and generation of free radicals (increase in oxidative stress) and advanced glycosylation end products. The binding of these end products to the endothelium, smooth muscle and fibroblast receptors may lead to increased vascular permeability, coagulation, cell proliferation, production of extracellular matrix proteins and decreased thrombolysis. Free radicals generated by hyperglycemia can promote atherogenesis by peroxidizing LDL (a more atherogenic molecule), oxidizing fibrinogen (increased coagulation), increasing platelet activation by collagen and decreasing the production of nitric oxide.

Hyperglycemia-associated processes are also involved in basal membrane thickening, extracellular matrix formation, angiogenesis, increased vascular permeability, smooth muscle cell proliferation, increased aggregation of inflammatory cells, decreased fibrinolysis and exacerbation of endothelial dysfunction.

Association with arterial hypertension

Young individuals with adequate weight and essential hypertension present higher plasma insulin concentration and lower total insulin-mediated glucose uptake. Many mechanisms have been proposed to explain the relationship between insulin resistance and hypertension: insulin-mediated vasodilation resistance, altered endothelial function, activation of the sympathetic nervous system, renal sodium retention, altered transmembrane cation transport, growth-promoting effects of vascular smooth muscle cells and vascular hyperreactivity.

Insulin/glycemic indices

Many indices have been developed to assess insulin sensitivity. By comparing the HOMA indices, fasting glucose/insulin ratio and QUICKI methods, Keskin et al. found that HOMA (Homeostasis Model Assessment - Insulin Resistance) had the highest sensitivity and specificity for measuring insulin resistance. They also determined that the HOMA cutoff point for adolescents when diagnosing insulin resistance is 3.16, different from that for adults.

Blood pressure in children and adolescents

Starting at 1 year of age, systolic blood pressure (BP) rises progressively until adolescence. Yet, diastolic BP starts rising after 5 or 6 years of age, proportionally to systolic BP. The correlation coefficients of systolic BP and age are higher than those observed for diastolic BP, as are other variables, such as anthropometric indices and heart rate. In younger children, the secondary causes for hypertension prevail. Starting at age 10 and especially during adolescence, the primary cause for increased blood pressure is more frequent. Table III shows the main causes for arterial hypertension by age group.

The child must remain sitting for at least 5 minutes before the first AP measurement is done. BP should be taken at least twice per visit, preferably on the right arm. The auscultatory is the method of choice and the sphygmomanometer should be that with a mercury column. For children younger than 3 years, it is preferable to use the oscillometric method. Inflation of the cuff should reach from 20 to 30 mmHg above the estimated systolic BP and deflation must be slow: 2 mmHg per second. Place the stethoscope over the brachial artery pulse, proximal and medial to the cubital fossa, and below the bottom edge of the cuff.

Use a cuff with an inflatable bladder width that is at least 40% of the arm circumference at a point midway through the arm.

<table>
<thead>
<tr>
<th>Age range</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns</td>
<td>Thrombosis and renal artery stenosis, congenital kidney malformations, coarctation of the aorta, bronchopulmonary dysplasia.</td>
</tr>
<tr>
<td>Infants – 6 years</td>
<td>Diseases of the renal parenchyma, coarctation of the aorta, renal artery stenosis.</td>
</tr>
<tr>
<td>6 – 10 years</td>
<td>Renal artery stenosis, diseases of the renal parenchyma, coarctation of the aorta; primary hypertension.</td>
</tr>
<tr>
<td>Adolescents</td>
<td>Primary hypertension, diseases of the renal parenchyma.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cuffs</th>
<th>Width (cm)</th>
<th>Length (cm)</th>
<th>Maximum arm circumference (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newborns</td>
<td>4</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>Infants</td>
<td>6</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Children</td>
<td>9</td>
<td>18</td>
<td>22</td>
</tr>
<tr>
<td>Small adult</td>
<td>10</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Adult</td>
<td>13</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>Large adult</td>
<td>16</td>
<td>38</td>
<td>44</td>
</tr>
<tr>
<td>Thigh</td>
<td>20</td>
<td>42</td>
<td>52</td>
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between the olecranon and the acromion; for such a cuff to be optimal for an arm, the cuff bladder length should cover 80% to 100% of the circumference of the arm. Always choose the larger cuff when in doubt. Table IV shows the available cuff sizes.

Systolic BP is determined by the onset of the “tapping” Korotkoff sounds (K1) and diastolic BP will correspond to the disappearance of Korotkoff sounds (K5). In some children, Korotkoff sounds can be heard to 0 mm Hg and when this happens, both Korotkoff K4 and K5 should be recorded for diastolic BP. For an adequate BP measurement, substances such as coffee, teas and certain drugs (beta-2 agonists, nonsteroidal anti-inflammatories, corticosteroids, nasal vasoconstrictors and oral anabolic steroids) should be avoided.

Ambulatory blood pressure monitoring (ABPM) presents good tolerability and reproducibility in the pediatric population. ABPM is recommended especially when there is suspicion of white coat hypertension, hypotension, resistance to antihypertensive treatment, target organ damage risk, chronic renal failure, diabetes mellitus and autonomic dysfunction. It is recommended to adopt the value corresponding to the 95th percentile for gender, age and height percentile as the threshold for the vigil period and 10% lower cutoffs for the sleeping period.

Hypertension can compromise many organs but changes in left ventricular mass (LVM) stand out. LVM assessment can be done by the indexation of height to the 2.7 power (m^2.7) with a cutoff point of 51 g/m^2.7 for boys and 64 g/m^2.7 for girls. All young individuals with established HTN should undergo an echocardiogram to verify the existence of left ventricular hypertrophy (Degree of Recommendation IIa; Level of Evidence D). The presence of left ventricular hypertrophy requires a stricter therapeutic approach and at least one echocardiogram per year. Among young individuals, structural changes of the left ventricle, such as increased mass or geometrical changes, are found earlier than diastolic function abnormalities. For children, blood pressure values have been associated with greater carotid intima-media thickening and lower arterial compliance. However, there is no evidence to support recommending these evaluations routinely when clinically approaching the young hypertensive population.

There is little evidence associating salt intake and blood pressure levels in children. Sodium sensitivity in children and adolescents seems to be related to family history and obesity. Potassium intake is inversely related to BP in children since potassium interferes in the regulation of BP by inducing natriuresis and suppressing renin production and release.

### Chart II. Factors associated with blood pressure levels in children and adolescents.

<table>
<thead>
<tr>
<th>Genetic factors</th>
<th>Arterial pressure from parents and siblings, salt sensitivity, obesity, deletion of polymorphism of the ACE gene.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental factors</td>
<td>Socioeconomic status, birth weight, physical activity.</td>
</tr>
<tr>
<td>Genetic and environmental factors</td>
<td>Height, weight, BMI, heart rate, somatic growth and sexual maturation, ingestion of sodium and other macronutrients, reactivity of the sympathetic nervous system, stress.</td>
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</table>

Besides gender and age, many factors correlate with BP in children and adolescents. These factors may be genetic or environmental and most are subject to the interference of both, as shown in Chart II. Weight and body mass index (BMI) are variables that present the strongest correlation with BP for this age group, especially with systolic BP. The differences observed between both genders are small and may represent different stages of sexual maturation. Synergistically to obesity, there is a strong correlation between the BP of parents and children, especially between mothers and sons, which justifies a more careful approach in families with HTN.

### Body composition, obesity and the association with other risk factors

**Correlation between childhood and adolescent obesity and obesity in adulthood**

There are reports of a direct relationship between the severity of childhood obesity and the risk of the child remaining overweight or obese in adult life. This association seems to be stronger than that between weight in adult life and parents’ weight. It is suggested that environmental factors may play a greater role in perpetuating obesity during growth and development than genetic factors. From the second decade of life on, this correlation becomes stronger and the risk of developing lipid metabolism abnormalities and hypertension later in life increases. Yet, a normal body mass index during childhood or adolescence is not a guarantee of protection against obesity in adulthood. When the association between mother’s weight and offspring gender is analyzed, girls from obese mothers present a higher risk of becoming obese adults than boys, maybe because they are more susceptible to their mother’s eating behavior and to the stimulus to consume more calories.
General obesity, distribution of body fat and other risk factors

**DYSLIPIDEMIAS** – There is a positive association between the incidence of obesity and dyslipidemia in children. A dyslipidemia prevalence of approximately 50% has been found among children with a body mass index above the 99th percentile for age, and obesity is considered a screening criterion for determining the lipid profile of children and adolescents. The mechanism that may explain this association could be the activation of the AMP-dependent kinase pathway, induced by increased levels of insulin and leptin and reduced activation of adiponectin, which, on its turn, increases fatty acid oxidation. In these children, adiponectin presents a positive association with insulin sensitivity and HDL cholesterol levels and a negative association with triglyceride levels. On the other hand, childhood dyslipidemia can be associated with the development of obesity in adulthood, especially among women. This may suggest that there is a genetically determined mechanism that explains the association between these variables.

As the size of the LDL particle decreases, its atherogenic potential is likely to increase. Obese children seem to have a higher percentage of LDL subclass pattern B (smaller particles) than children with normal weight-for-height. Therefore, even obese children with normal LDL cholesterol levels may present less favorable lipid profiles given the proportions of lipoprotein subclasses. Studies show that obese children present higher levels of lipoprotein (a) [Lp(a)] regardless of their family history. In obese children, there seems to be a direct relationship between homocysteine and insulin levels.

**HYPERTENSION** – The increased worldwide prevalence of child and adolescent primary arterial hypertension is directly related to the increased obesity prevalence. There is a direct relationship between the degree of obesity and the risk of childhood systemic hypertension. Many mechanisms try to explain the relationship between obesity and hypertension: insulin metabolism disturbances, increased sympathetic tonus, decreased vagal tonus, structural and functional vascular changes, increased platelet aggregation and oxidative stress with consequent decrease in nitric oxide levels and possible sleep disturbances, as previously reported in adults.

A family history of hypertension seems to have a synergistic effect on the impact of obesity on child and adolescent blood pressure levels. The following factors also seem to be associated with hypertension in obese children: hyperinsulinemia, hyperleptinemia and central distribution of body fat. Hypertension can bring about cardiovascular complications already in childhood and adolescence, such as left ventricular hypertrophy. This risk seems to increase as the percentile of body mass index increases, showing that both obesity and hypertension add to this outcome.

**INFLAMMATION AND EARLY ENDOTHELIAL DYSFUNCTION** – The serum levels of high sensitivity C-reactive protein present a direct relationship with severity of childhood obesity and can be a marker for an accelerated atherosclerosis progression rate. This does not mean that obese children should undergo routine hs-CRP determination.

Early endothelial dysfunction has been reported among obese children and adolescents. This dysfunction seems to be more strongly associated with serum leptin levels than with severity of obesity. Children who are severely obese present carotid intima-media thickness significantly greater than those with normal weight. The factors that seem to be associated with this thickening are: increased insulin levels, hypertension, low apolipoprotein A-1 levels and central obesity.
## Table VII. BP percentiles for males according to age and height percentile.

<table>
<thead>
<tr>
<th>Age in years</th>
<th>BP percentile</th>
<th>SBP, mm Hg Height percentile</th>
<th>DBP, mm Hg Height percentile</th>
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Obs: Adapted from “The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents”660
Table VIII. BP percentiles for females according to age and height percentile.

<table>
<thead>
<tr>
<th>Age in years</th>
<th>BP percentile</th>
<th>SBP, mm Hg</th>
<th>DBP, mm Hg</th>
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<td>Height percentile</td>
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Obs.: Adapted from "The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents"\(^{(2)}\)
Methods for diagnosing the risk factors
Dyslipidemia

Children whose parents present hypercholesterolemia are more likely to present this dyslipidemia. Children with the following characteristics should have their lipid profile verified:

- Parents or grandparents have a history of atherosclerosis before the age of 55 years;
- Parents with TC >240 mg/dL;
- Other risk factors present, such as hypertension, obesity, smoking or a diet rich in saturated fats and/or trans fatty acids;
- Take drugs or have diseases that present dyslipidemia as a clinical manifestation (AIDS, hypothyroidism etc);
- Present clinical manifestations of dyslipidemias (xanthomas, xanthelasmata, corneal arcus, recurrent abdominal aches, pancreatitis).

Starting at 10 years of age, every child should undergo blood TC determination. The parents of children whose TC is greater than 150 mg/dL need to be advised to make changes in their lifestyle, and lipid screening should be repeated annually; children with TC >170 mg/dL should be submitted to a full lipid screening after a 12-hour fasting period (Degree of Recommendation IIb; Level of Evidence D).

The proposed reference values for child and adolescent serum lipids are given in Table V (Degree of Recommendation IIb; Level of Evidence D). With regard to childhood hypertriglyceridemia, triglyceride levels between 100 and 200 mg/dL are generally related to obesity and, levels above 200 mg/dL, to genetic alterations.

Hypertension

Table VI shows arterial pressure classification for children and adolescents. Arterial hypertension is present when systolic and/or diastolic arterial pressure is equal to or greater than the 95th percentile for gender, age and height percentile on three distinct occasions. Strict preventive measures should be taken when a child is found to be in the prehypertensive range.

The values corresponding to the different BP percentiles for gender, age and height percentile are given in Tables VII and VIII. Be aware that these values regard the North American population. Representative data for the Brazilian population are not available; therefore, this Table should be used as reference. To determine the BP values corresponding to the 90, 95 and 99th percentiles for a given individual, follow these steps:

- Use the correct Table for the child's or adolescent's gender;
- Find the line that corresponds to age;
- Determine the height percentile for the child or adolescent using the stature graphs found in the following Internet sites:

**BOYS**
- i. from 0 to 36 months
  http://www.cdc.gov/nchs/data/nhanes/growthcharts/set1clinical/cj41c017.pdf
- ii. from 2 to 20 years
  http://www.cdc.gov/nchs/data/nhanes/growthcharts/set1clinical/cj41c021.pdf

**GIRLS**
- i. from 0 to 36 months
  http://www.cdc.gov/nchs/data/nhanes/growthcharts/set1clinical/cj41c018.pdf
- ii. from 2 to 20 years
  http://www.cdc.gov/nchs/data/nhanes/growthcharts/set1clinical/cj41c022.pdf

- Find the column corresponding to the height percentile;
- Note the value related to the desired percentile in the corresponding line for age and height percentile.

Children older than 3 years should have their BP checked at every visit, at least once a year (Degree of Recommendation IIb; Level of Evidence D). Children who present risk factors for hypertension should have their BP checked earlier. If arterial pressure is within the prehypertensive range, BP determination should be repeated within six months at most. If the child or adolescent presents an abnormal BP, blood pressure should be taken again on two other occasions. If their BP is indeed abnormal, they must be referred to treatment as described previously.

Obesity

Body mass index (BMI) is defined by the weight in kilograms divided by the square of the height in meters and is the primary diagnostic criterion for overweight and obesity. Although this index presents high association with adiposity in childhood and adolescence, it is important to point out that it also presents variation according to age and gender; therefore, specific curves are necessary for a correct assessment. Abdominal circumference has recently been proposed as a better means of assessing visceral obesity.

The National Center for Health Statistics (NCHS) has recently elaborated reference graphs and recommended that children with BMI above the 95th percentile be classified as obese and children with BMI between the 85 and...
95th percentiles as overweight. BMI curves with reference values for children aged from 2 to 20 years, of both genders, can be found at the CDC-NCHS Internet site:

**BOYS**
http://www.cdc.gov/nchs/data/nhanes/growthcharts/set1clinical/cj41c023.pdf

**GIRLS**
http://www.cdc.gov/nchs/data/nhanes/growthcharts/set1clinical/cj41c024.pdf

Obese children and adolescents must have their lipid, fasting glycemia and insulinemia profiles and BP determined. Furthermore, this population should be screened for diseases associated with sleep apnea and hypoventilation, menstrual changes such as oligomenorrhea and amenorrhea, streaks, hirsutism and skin changes such as acanthosis nigricans, orthopedic diseases, steatohepatitis, hypothyroidism and psychological disorders; many times it is recommendable to refer the child/adolescent to a specialist (Degree of Recommendation IIb; Level of Evidence D).

**Insulin resistance**

Insulin resistance syndrome should be considered a developing theme; thus, its diagnostic criteria are still preliminary. The first step is to identify the children and adolescents who will benefit from intervention and who are at risk for developing diabetes:

- Children who are obese or overweight;
- Those with a family history of type 2 diabetes mellitus;
- Those belonging to ethnic groups that are more prone to develop type 2 diabetes (Native Indian, African, Asian and Hispanic populations);
- Those who present signs or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome).

In these situations, determination of the fasting glycemia level (Degree of Recommendation IIb; Level of Evidence D) is recommended. Determining insulin resistance, however, is more complex and involves techniques applied only in research, such as the euglycemic clamp. The alternative has been to determine the fasting plasma insulin level (normal <15 mU/L, high/borderline from 15 to 20 mU/L, high >20 mU/L). Additionally, associations between glycemia and oral glucose tolerance test have been suggested.

Given the important role obesity plays in this syndrome, there should be special emphasis on preventing overweight and obesity. Since this is a complex syndrome, endocrine and lipid disorders, hypertension, obesity or psychological disorders may require specialized assessment.

**Atherogenic diet**

The 24-hour or 3-day food diary can be used to diagnose an atherogenic diet (two weekdays and one weekend day), and consists in defining and quantifying the foods or drinks consumed during that period. The eating frequency questionnaire also allows to obtain additional information on particular food groups that are ingested regularly. It is important to detect an excessive consumption of saturated and trans fatty acids, sodium, simple carbohydrates and fried and competitive foods.

**Sedentary lifestyle**

When assessing the level of physical activity, it is necessary to verify the duration and level of exercise, as well as the time spent in physical activities with the family. On the other hand, it is also convenient to verify the time spent playing video games, watching television and using the computer. The duration of recreational inactivity should be limited, for example, the child should not be allowed to watch more than 2 hours of TV/day. The International Physical Activity Questionnaire (IPAQ) should be used, where total physical activity is assessed by MET/minute/week and the total sitting time is also recorded. Daily physical activity is considered moderate when it corresponds to an energy expenditure varying from 3.3 to 4.0 MET and vigorous when above 5.5 MET (1 MET=3.5 ml O2/kg/minute). Currently, it is recommended that children should practice moderate physical activity for approximately 30 minutes per day on most days (150 minutes/week), but ideally this time should be of approximately 60 minutes per day.

Some studies show that the diet of a child is influenced by TV, leading to an excessive consumption of salt, simple carbohydrates and saturated or trans fats. This influence also ends up determining the snacks a child eats at school.

**Physical activity in preventing childhood atherosclerosis**

From the point of view of atherosclerotic disease prevention, studies involving youngsters and physical activity investigated their levels of physical activity, the results obtained by giving education on health in schools and communities, strategies that increase physical activity and the results regarding physical activity and cardiovascular risk factor prevention or control. Therefore, studies associating childhood and adolescent physical activity interventions and decreased atherosclerotic disease rates in adulthood still do not exist.
It is important to point out that in 1996, a report from the United States Department of Health made clear that the benefits of physical activity are not limited to adults, since regular physical activity helps children and adolescents develop and maintain healthy joints, muscles and bones; helps control weight by reducing fat and increasing muscle mass; prevents or delays the development of hypertension, helps to reduce arterial pressure levels of hypertensive adolescents and additionally, decreases feelings of anxiety and depression. Children should be motivated to adopt an active lifestyle as early as possible (AHA recommends to start at age 2), and proper activity levels should continue through adolescence and on to adulthood.

As a general guideline, healthy children should be motivated to practice physical activity in a pleasant fashion during their recreational time or as programmed physical exercises or sports, for at least 30 minutes per day and from three to four times per week to become and remain physically fit. Individual needs with respect to gender, age, degree of sexual maturation, presence of physical or mental limitations that prevent the child from practicing physical activity, economic status and family and environmental factors must be respected.

The physician’s role in promoting physical activity during childhood
Health professionals, physicians included, play an important role in promoting health among children and adolescents through education, especially when it comes to physical activity and other healthy behaviors. In order to program the practice of physical activity for the child and family, in routine visits of healthy individuals (without limitations), individuals with chronic diseases (physical or mental), cardiovascular risk factors or special needs, the following should be investigated:

- Physical activity in school or elsewhere;
- How the family feels about exercise programs, games and sports, and the time spent by the child in sedentary activities;
- If the child has access to places that are adequate for practicing physical activities inside or outside the school;
- If and how the family encourages the child to practice physical activity.

Recommendations to the health professional

- Routinely advise your clients to practice physical activity;
- Emphasize the benefits of regular physical activity to the family;
- Identify, through clinical history, physical examination and complementary evaluation when necessary, the existence of diseases where physical exercises are not recommended;
- Motivate the child and adolescent to participate actively and enthusiastically in unstructured activities, games and organized sports;
- Advise the children to practice physical activities that are appropriate for their age and developmental phase, for at least 30 minutes per day, 7 days per week;
- Advise the adolescents to practice at least three sessions of moderate or intense physical activities per week, for at least 20 minutes at a time;
- Motivate the children and adolescents who already practice physical activities, to continue practicing physical activities;
- Instruct and motivate children and adolescents who present cardiovascular risk factors to practice physical activities in order to help control these risk factors;
- Advise adequate physical activities for children with limitations or special needs;
- Instruct the parents to plan physical activities (games, sports) instead of meals as part of the reward for the good performance of the child;
- Instruct the parents on how important it is to be an example of active lifestyle and to give their children opportunities to continuously increase their levels of physical activity.

Family’s role in promoting physical activity during childhood

The parents’ level of physical activity is positively associated with that of the children during the preschool and adolescent phases. The aid and motivation given by the parents, either by organizing activities or by providing transportation and access to the chosen activities, also present a positive association with the physical activity levels of their children. Other studies, however, have not shown this same relationship for children in elementary and high schools. In conclusion, despite the lack of compelling scientific evidence the family plays a critical role in the attitude of a child towards physical activity since the first opportunities and motivations for someone to become physically active begin at home.

Recommendations to the family

- Encourage children and adolescents to practice regu-
lar physical activity, helping them to engage in fun activities at school or in the community;
• Plan and participate in family activities that involve physical activity, for example, parties and field or vacation trips;
• Be an example of an active lifestyle and offer your children opportunities to continuously increase their physical activity levels;
• Establish time limits for activities that do not require a greater energy expenditure, for example, watching television for no more than two hours per day;
• Demand that the school and community set up quality physical activity programs;
• Help choosing places that provide proper space, temperature/ventilation, safety and equipment for practicing physical activities.

Society’s role in promoting physical activity during childhood

Potentially, schools and community have the capacity to improve the quality of child and adolescent health promotion by creating programs and services that promote youth education and motivate them to engage in fun physical activities that may become indefinitely incorporated in their lives. Most of the intervention works done on promoting physical activity among the youngsters were developed in schools and the results were promising; this demonstrates that the school can function as the most encompassing instrument of health education.

Taking into account that health authorities are already aware of the benefits of regular physical activity for health promotion and prevention and rehabilitation of chronic-degenerative diseases, it is up to them to include, among their actions, educational campaigns on the theme, instructing health professionals to advise the population on the importance of physical activity and create community health education programs targeting the young.

Recommendations to the community83-86

• Demand from the competent authorities the development, maintenance and evaluation of a health promotion policy that includes physical activity as an element to be worked at all levels of education, sport and health care;
• Demand that the schools comply with government decisions that incorporate physical activity in the educational process;
• Participate in the physical activity programs offered in the community, incorporating an active lifestyle that can serve as an example for children and adolescents;
• Make sure all children and adolescents have access to physical activity programs, regardless of their education level, religious beliefs or social status;
• Establish advertising campaigns that motivate people to practice physical activities, using a language that children and adolescents can understand;
• Demand the creation of areas in the community that are safe and adequate for practicing physical activities, with proper construction and temperature/ventilation.

Recommendations to the school83-86

• Comply with the determination of the third paragraph in article 26 of the Brazilian Education Guidelines, LDB (number 9394 from December 20, 1996) that states: “physical education, incorporated in the pedagogical proposal of the school, is a mandatory component of basic education,” where basic education comprises kindergarten, elementary and high schools.
• Offer good quality and daily physical activity programs in the curriculum and after school, where students may choose among different activities, helping the student develop the necessary knowledge and confidence to adopt and maintain an active lifestyle;
• Promote health education as part of the knowledge the students will acquire during their school years;
• Identify the specific needs of the students, especially of those who are not inclined to practice sports;
• Take into account student gender and cultural differences when programming physical activities in schools;
• Motivate and allow students to practice physical activities inside and outside the school;
• Do not use physical activity as punishment but as a fun activity that is part of the daily routine of the student;
• Allow teachers to acquire knowledge in health education and to include whenever possible health education in the specific content of the subject they teach;
• Allow the physical education teachers to undergo continuous training in different modalities of physical activity in order to increase the number of physical activities offered by the school;
• Offer the necessary space, equipment and anything else that is necessary for the practice of good quality physical activity;
• Allow the community to use the school facilities to practice their preferred physical activities and create physical activity programs for the community;
• Include the parents in the physical activity programs offered after school.

Recreational inactivity as cardiovascular risk factor

Although there are no studies showing that physical activity during childhood and adolescence reduces the frequency and severity of cardiovascular disease during adulthood, less active individuals are more prone to smoking,
obesity, hypertension, high triglyceride and insulin levels, and lower levels of HDL cholesterol. There is evidence that physical activity during this time of life is beneficial for controlling cardiovascular risk factors such as obesity, dyslipidemia, diabetes mellitus, smoking and hypertension; it also improves aerobic functional capacity, helps prevent osteoporosis and promotes psychological health87.

Studies on physical activity in children and adolescents and have become considerably important in the last decades, especially because of the increased overweight and obesity rates observed in these age groups worldwide and of the hypothesis that this may have happened because of decreased physical activity and increased consumption of high-energy foods. Population studies have analyzed how much physical activity children and adolescents perform in school and during their free time and how much time they spend on sedentary activities (television, computer or telephone). These studies have revealed that children and adolescents are spending less energy than they should according to the current recommendations, and much of their time is spent on sedentary activities88.

Since 81.7% of the children aged 5 to 17 years in Brazil go to school (95.7% of the children aged 7 to 14)89, the school is a powerful and efficient vehicle for implementing physical activity programs as it reaches most of the children and adolescents. However, since most of the physical activity is done outside the school, it is the free time that ends up decisively influencing the amount of physical activity performed daily by youngsters.

Preventing bad habits when preventing atherosclerosis
Who is the child at risk for smoking?

In Brazil, according to Conprev/Inca/MS data and to the Brazilian Center of Information on Drugs (Cebrid), 90% of the smokers try their first cigarette before the age of 13 years. In 1989, a study was conducted on tobacco use among elementary and high school students in state schools covering 10 Brazilian capitals. The results showed that 19.5% of the interviewed students had already smoked at some point in their lives, 15.9% had used tobacco in the previous year and 10.5% had used tobacco in the previous week90.

Sociocultural, environmental, family, individual, genetic and psychopharmacological variables may influence someone to start smoking and/or make it harder for someone to give up smoking. Studies show the importance of factors with a psychosocial nature, such as dynamics of family interaction, imitation of parents and third-party influences, such as relatives, friends and schoolmates. There is also the conditioning that results from the advertising by the tobacco industry and the media, among other diverse factors90.

Genetics

Studies in twins and animals show that genetics has a substantial influence on the development of nicotine dependency. Although definite results do not exist, the evidence is consistent with the genes coding for the CYP group of enzymes, which lead to an increased nicotine metabolism, and the genes DRD2 that regulate dopamine function. Further studies on genetic contributions to smoking may lead to more effective strategies to reduce smoking rates9091.

Psychiatric comorbidity and smoking

Patients with certain psychiatric disorders use nicotine as medication, thus they become more upset with abstinence. Statistics from the USA show that 50% of psychiatric patients smoke compared with 25% of the general population; 50% of the general population manage to stop smoking, while only 15% of psychiatric patients manage to stop. Attention deficit and hyperactivity disorder (ADHD) is a chronic disorder that affects children and adolescents, placing them at risk for substance use, and smoking prevails. One hypothesis to explain the high prevalence of tobacco use among these patients is self-medication. The action of nicotine on concentration capacity, attention and memory turns it into a beneficial substance for overcoming the symptoms associated with ADHD. Therefore, it is particularly important to prevent patients with ADHD from smoking. Other comorbidities more frequently associated with smoking are depression, anxiety disorders and schizophrenia9092.

Passive smoking

Non-smokers that are exposed to tobacco smoke are called passive or involuntary smokers. The effects of passive smoking increase as the ventilation of a given environment decreases. Environmental tobacco smoke (ETS) has two components: the smoke exhaled by the smoker and the smoke generated by burning tobacco derivatives, which represents 96% of the ETS. ETS is particularly harmful to children because their lung airways are more vulnerable and especially because the younger children remain confined to their homes for longer periods93.

Effects of ETS

The most frequent and immediate symptoms of acute ETS effects are eye irritation, nasal manifestations, headache and coughing. Atopic individuals are more sensitive to
ETS with exacerbation of their allergic respiratory conditions. Children, especially the very young ones, are greatly affected by the ETS generated by their parents’ smoking. Many studies have already demonstrated the relationship between passive smoking and diseases such as pneumonia, acute bronchitis, bronchopneumonia, middle ear infection and exacerbation of asthma attacks. Sudden death syndrome in children is more frequent when their mothers smoked during gestation and it has also been described for children who were exposed to their parents’ smoking after birth and not during gestation. The exposure of previously asymptomatic children to the ETS of mothers who smoke at least 10 cigarettes per day results in almost two times the number of chronic bronchitis and pneumonia episodes if there is a smoker in the house and almost three times if there are two smokers in the house.

Smoking and women in childbearing age
Tobacco can affect those that are around smokers in two ways: via blood, in the case of pregnant women, and through breast milk, in the case of nursing women. The toxic components of tobacco found in the mother’s circulation cross the placenta. These substances cause immediate and late disturbances in the fetus. Placental complications, vasoconstriction, anoxia and difficulty with thoracic movements have an unfavorable effect on fetal development and on their respiratory nervous centers. There is an increased risk of miscarriage, natimortality, neonatal mortality, preterm birth, low birth weight, shorter stature when school-aged and relative mental delay regarding general capacity, reading comprehension and mathematics. The frequency of schoolchildren with IQ below average was also higher among children whose mothers smoked during gestation. Studies have also revealed that the urine of breastfeeding infants whose mothers smoked contained high concentrations of cotinine, the active metabolite of nicotine, after each nursing session.

Family’s and teacher’s role in preventing smoking
The earlier children have access to information concerning the harms caused by the tobacco industry, the less likely they will be to accept cigarettes socially. Therefore, the school is the ideal place for health education programs that aim at a better quality of life. The Ministry of Health (via Inca-Conprev) developed a program called Saber Saúde (Know Health) given in schools using material that can be easily understood by the children. This program should include information on the social consequences and short-term psychological effects of tobacco use, the social and affective influences caused by parents who smoke and by the media and training in cigarette refusal capacities. Another important initiative is to create in schools, especially inside the classrooms, an environment free of tobacco and of its advertising.

Professionals who work with children should also act as counselors and provide advice on the dangers of tobacco use, with messages that are adequate for each age group and developmental phase. Orientation given by parents, teachers and health professionals can influence changes of attitude in the community by intervening when a child starts smoking.

Pediatrician’s role when dealing with parents and children who smoke
Individuals in the 20 to 35 years age range usually go to a physician only to accompany their children. Not to talk about smoking can be interpreted by the parents as consent to smoking. Physicians, especially pediatricians and adolescent physicians have an important role in preventing tobacco use and passive exposure to tobacco smoke, especially when younger individuals are involved. Two age groups show different approach perspectives: from birth to four years of age and from five to twelve years of age. Conprev/Inca strongly recommends the following:

FROM BIRTH TO FOUR YEARS OF AGE
(INFANTS AND EARLY CHILDHOOD)
• Ask the parents about tobacco use in their home and in the child’s environment. Try to find out if the child is constantly exposed to tobacco smoke.
• Advice all parents who smoke to quit smoking. Inform them about the respiratory allergies and infections that result in countless hospitalizations of children because of their involuntary exposure to tobacco smoke. Emphasize the importance of guaranteeing a smoke-free environment for the child’s growth and development.
• Prepare or refer the parents to give up smoking, identifying strategies that are efficient for this purpose and offer follow-up.
• Follow and show interest for these families’ progresses regarding tobacco use during the follow-up visits.

FROM FIVE TO TWELVE YEARS OF AGE
(MIDDLE AND LATE CHILDHOOD)
It is important to alert parents that children are more aware of their surroundings. Smoking can start early, as early as five years of age, especially in rural areas and in areas where tobacco is cultivated, yet most children start
smoking during the preadolescent period. The likelihood of children becoming smokers is directly related to their role models, i.e., having parents, siblings and friends who smoke and display positive attitudes toward smoking. It is important to remember that the parents’ beliefs and practices regarding smoking influence the child; therefore they should be encouraged to reevaluate their behaviors.

Children should be encouraged to participate in discussions on smoking and tobacco use. The active involvement of children in caring for their own health helps them to be responsible and self-controlled when they have to make decisions regarding healthy behaviors. The child's personal empowerment (the ability to say “no”) should be encouraged so that the child is more able to make choices. This favors the child’s self-esteem, emotional maturation and improves its capacity to deal with frustration.

- Ask the child if it smokes or smoked and about the use of tobacco derivatives by friends and family. Try to find out if the child knows what tobacco is and the damages it causes. Frequently ask about the child’s school performance since tobacco may decrease its performance if there are smokers in the school environment.
- Advise children who are trying cigarettes to quit immediately and those who have not yet tried, to refuse when offered. Warn the child about the short-term effects of tobacco use: bad smell in hair and on clothes, darkening of the teeth, difficult breathing, decreased athletic and school performance, and drug addiction - nicotine. The parents should be warned about how role models work and about passive smoking. Parents should also discourage the child from using tobacco-related products such as candy cigarettes and clothes that advertise cigarette brands, since these objects help promote smoking.
- Prepare the child to be more and more responsible for its healthy behavior. Congratulate the children who do not use tobacco and advise those who do or who are subject to a strong influence from their role models to develop their personal empowerment; tell them about the importance of their right to choose and say "no" and to value their self-esteem.
- Follow the children who are smoking by arranging more frequent visits or by sending them to smoking cessation programs that, whenever possible, are linked to their school; the same should be done for their parents.

**Education starting in preschool on the dangers of drugs**

The existing prevention programs are directed only to children in elementary and middle schools. In 1998, the Brazilian National Cancer Institute developed the Program *Saber Saúde* (Know Health) whose aim is to inform and educate the children in Brazilian schools about tobacco and other cancer risk factors. However, specific programs containing fun activities such as stories, puppet plays, storytellers etc. associated with a long-term follow-up are needed for preschool.

**Practices in maintaining behavior during adolescence**

Differently from adults, one of the aspects of smoking among adolescents is that their habits are irregular. This characteristic may be favorable for prevention initiatives and strategies. However, many youngsters also become addicted to alcohol and other drugs. When dealing with an adolescent, it is important to establish trust, respect and confidentiality, and try to understand that adolescence means rupture, self-affirmation and questioning. Frequently, adolescents start smoking out of curiosity or to imitate parents and friends, express independence, overcome shyness, acquire confidence. There is also a need to follow some ritual, reinforcing behavioral dependence. Some factors contribute to an increasing consumption of tobacco among adolescents:

- They believe they can quit whenever they want;
- They use tobacco as a way to contest family and social values;
- They believe they seem more attractive;
- There may be an absence of future perspectives and role models or they may be in need of affection and unsatisfied: tobacco becomes an interesting source of new pleasures, happiness and excitement;
- Messages in the media linking smoking to success (for example, car racing).

In this population group, purely informative antitobacco campaigns have little effect. The efforts in guiding the adolescents to resist the social pressures that lead them to smoking are more effective. Although the health risks caused by smoking play an important role in tobacco refusal, they are not enough to keep someone from smoking. Among adolescents, affectivity is one of the main factors in choosing to use tobacco derivatives. Youngsters whose friends smoke are more likely to smoke and those whose friends do not smoke will likely not smoke. The stress relief obtained when being accepted by a group, in addition to some self-image characteristics (rebelliousness, sociability, precocity) have also been associated with a tendency to smoke. Among women, smoking is a means to control weight since “the obsession with looks” is so stimulated by the western society. Another important fact is that, according to the WHO, smoking is considered as the
first step to becoming addicted to other drugs. There are few studies in the literature on preventing tobacco use among adolescents. Adult campaigns modified for adolescents do not present promising results. Brief and reiterated advice given to smoking adolescents during appointments with health professionals, especially if these adolescents present tobacco-related diseases, may lead to smoking cessation. On the other hand, brief interventions at school have short, but not long-term effect. A review made by Sowden and Arblaster based on a small number of studies showed that mass-media antitobacco campaigns could have a positive influence on youngsters under 25 years of age.

Preventing tobacco use in clinical practice

Physicians need to determine how likely it is for an adolescent to start smoking and this can be done by using some important predicting factors listed in Table IX. The answers can help the physician decide on where to intervene in order to increase the level of prevention. Adolescents’ peculiar characteristics can be explored in a positive way by tobacco control actions. Information, such as difficult breathing, darkening of the teeth and decreased athletic performance should be explored for a good part of the visit. Constant counseling is important as adolescents feel more motivated to quit smoking than adults, but relapses are also frequent.

Treatment strategies

Health professionals should encourage and support quit-smoking initiatives, especially when dealing with parents of children and adolescents, since this attitude causes a double impact on the treatment and prevention of active and passive smoking among children. The young smoker in particular, should be treated in a slow and progressive fashion at each visit. Cognitive-behavioral group therapy is the therapy of choice for young smokers. Counseling must be adequate for the young public with adolescent-targeted dynamics, language and teaching material. The following topics should be emphasized: physical activities, loss of ability to choose caused by tobacco dependency, illusory aspects of tobacco advertising, caring for the body and looks and sexual performance.

Treatment using drugs

There is a lack of randomized, placebo-controlled studies on the use of nicotine replacement therapy (NRT) and bupropion in children and adolescents. In the UK and USA, these drugs cannot be used in children under 16 years. Therefore, it is necessary to develop alternative methods to aid smoking youngsters.

<table>
<thead>
<tr>
<th>Table IX. Questionnaire for smoking risk assessment.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Risk factor</strong></td>
</tr>
<tr>
<td>Friend smokes</td>
</tr>
<tr>
<td>Parents smoke</td>
</tr>
<tr>
<td>Supervised programs</td>
</tr>
<tr>
<td>Antitobacco</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>School performance</td>
</tr>
<tr>
<td>Susceptibility attitude</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Psychological aspects in preventing atherosclerosis

Psychological aspects interact with other factors, creating a vicious cycle that may result in coronary disease. There are five classes of physiological aspects that may contribute to the pathogenesis of coronary artery disease: depression, anxiety, personality characteristics, social isolation and chronic stress. Among the mechanisms involved in the development of atherosclerosis are the excessive sympathetic nervous system activation and platelet activation.

Personality formation in childhood

Ideally, one should promote prophylactic interventions that make sure that the child acquires a lifestyle that contemplates healthier choices. Interventions done during childhood and adolescence are more likely to succeed since old habits die hard.

Masked depression and risky behavior (smoking, illicit drugs)

The symptoms of depression range from a stumped posture, sad facial expression, motor agitation and hyperactivity to aggressive and destructive behaviors. Risky behaviors such as smoking, drinking, sexual promiscuity, use of illicit drugs, vandalism and aggressive acts are often compensatory mechanisms of emotional states compromised by depression and emotional stress. Taking action to prevent the factors that trigger depression, such as lack
of life goals, feeling of uselessness, lack of perspective, lack of strategies to deal with the tensions of life and lack of knowledge on healthy life habits to maintain health can help people become less sedentary and reduce the use of tobacco and illicit drugs. Charts III and IV describe the most common symptoms and indicators of masked depression in children and adolescents.

**Self-esteem and the adoption of healthy habits**

Atherosclerosis prevention programs should focus on controlling obesity and metabolic dysfunctions by changing the eating habits and increasing the physical activity levels of an individual. In this age group, besides the numerous factors of modern life, emotional stress together with the preference for sugar and fat-rich foods represent an obstacle when trying to change a lifestyle. Behavioral psychological intervention is currently acknowledged as the intervention that offers the highest success rates regarding lifestyle changes, emotional stress, joining physical activity programs, changing eating habits, reducing obesity, doing more physical activity during leisure time, reducing isolation and increasing compliance with drug therapies.

One aspect that should be taken into account is how programs that aim to reduce childhood obesity are set up. Even though there is a clear need for these programs, dissatisfaction with body image, low self-esteem, body dysmorphic disorder and even bulimia and anorexia should be avoided.

**Stress as a cause of atherosclerosis risk factors**

Stress has been described as one of the possible factors directly contributing to atherosclerosis development and also contributing to the etiology of other risk factors, such as obesity, depression, hypercholesterolemia and sedentary lifestyle. The incidence of childhood stress is very worrisome. Stress rates of 23% among first-graders and of roughly 65% among twelfth-graders have been reported, and these rates may reach 83% at the time of the college entrance examinations. Chart V lists the most frequent symptoms of stress in children and Chart VI lists the symptoms in adolescents.

When we take into account the association between acute or chronic stress and physical and mental diseases, we realize that family and society-oriented actions are needed in order to alleviate the child and adolescent exposure levels to emotional tension.

**Treating the risk factors**

**Dyslipidemias**

In 2002, the American Heart Association, based on recommendations made by the Committee on Atherosclerosis, Hypertension and Obesity in the Young (AHOY), suggested an algorithm to treat dyslipidemias according to the individual risk and lipid profile (Figure 2). Thus, all children with LDL cholesterol >130 mg/dL should be followed. The first option should be low dietary intake of saturated fat and cholesterol. The use of drugs is only recommended for children >10 years of age whose LDL cholesterol is persistently high, regardless of proper diet. The LDL cholesterol reference values for intervention with lipid-lowering drugs depend on the present risk factors, family history and magnitude of LDL cholesterol levels.
**PHARMACOLOGICAL TREATMENT IN CHILDHOOD AND ADOLESCENCE** – Pharmacological treatment has been recommended preferentially for higher risk situations, when changes in lifestyle fail to reach ideal LDL cholesterol levels, when there is a family history of high LDL cholesterol and when there are risk factors present\(^8^0\). Table X presents the cutoff points for the use of lipid-lowering drugs in children (Degree of Recommendation IIb, Level of Evidence D).

**BILE ACID SEQUESTRANTS** – Colestipol and cholestyramine are resins that have been approved for use in children\(^1^0^2\),\(^1^0^3\). By decreasing the intestinal absorption of bile acids, they increase the expression of hepatic LDL receptors, consequently lowering serum cholesterol. The LDL cholesterol level reductions obtained with the use of these resins are relatively modest: cholestyramine (8 g/day) or colestipol (10 g/day) decreased LDL cholesterol levels by roughly 19% in children and adolescents with familial hypercholesterolemia\(^1^0^4\), but colestipol is not available in Brazil. Higher doses increase the incidence of gastrointestinal side effects and do not reduce cholesterol levels any further since compensatory mechanisms come into play, such as increased hepatic synthesis of cholesterol. Resins may increase triglyceride levels (increased VLDL synthesis) and decrease the absorption of fat-soluble vitamins and folic acid. The association of resins with ezetimibe to increase the effectiveness of resins has been tested and this double intestinal-interference route in the metabolism of cholesterol (absorption of bile salts and cholesterol) resulted in additional benefits\(^1^0^5\).

**STATINS** – The experience with statins is limited since there are no long-term studies evaluating their clinical outcomes and safety in children and adolescents. Studies with lovastatin, simvastatin, pravastatin and atorvastatin showed that these substances significantly reduced LDL.

<table>
<thead>
<tr>
<th>LDL – C (mg/dL)</th>
<th>Clinical condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;190</td>
<td>Dyslipidemia of genetic origin</td>
</tr>
<tr>
<td>&gt;160</td>
<td>Family history of early CAD or two or more risk factors (HDL-C &lt;35 mg/dL, smoking, hypertension, obesity, diabetes)</td>
</tr>
</tbody>
</table>

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**Table X. Reference values for using lipid-lowering drugs in children aged ≥10 years according to the clinical condition\(^8^0\).**

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**Figure 2. Algorithm for treating child and adolescent dyslipidemias\(^8^0\).**

*FH+ = Positive Family History; RF = Risk Factor.*
cholesterol levels and presented good tolerability. All these drugs have been used in the USA for some time now and the last two already have recommendations for their use in Brazil, especially in children >10 years of age, including postmenarche girls. However, they are not recommended during gestation and to adolescents and women in childbearing age who are not using adequate contraceptive methods since their use may be associated with fetal malformations, especially in the central nervous system. Dosage varies according to the basal level of LDL cholesterol; in the more severe cases of familial hypercholesterolemia, the association of resins with statins and more recently, with ezetimibe, has been suggested. Statins can induce a slight and transitory increase of liver enzymes and myositis, therefore it is recommended to monitor liver enzymes (ALT and/or AST) and creatine phosphokinase (CK), especially if muscle symptoms are present.102,103.

### EZETIMIBE

Ezetimibe specifically inhibits cholesterol absorption. The dose is 10 mg/day and it does not present the gastrointestinal discomfort seen with resins. It is preferably used in association with statins because of the advantage obtained from the double cholesterol-lowering mechanism. Its use in children >10 years of age has already been approved in the USA in cases of severe hypercholesterolemia. The effectiveness of atorvastatin and simvastatin associated with ezetimibe has been tested in people with homozygous familial hypercholesterolemia. Even among this group of patients, this association was well tolerated and promoted an important reduction of LDL cholesterol, at least 20% greater than that obtained with statins alone.106. In severe autosomal recessive hypercholesterolemia, there is a report stating that the association of rosuvastatin with ezetimibe resulted in normal LDL cholesterol level, regression of xanthomas and elimination of the need for LDL cholesterol apheresis. However, experience with this association is still limited, especially regarding the long-term safety profile, and these cases should, whenever possible, be referred to a dyslipidemia reference center.102,103.

Sitosterolemia, the rare mutation of the ABCG5/G8 gene, causes the hyperabsorption of dietary sterols, marked increase in plasma and tissue sitosterol and in plasma levels of campesterol, associated with the early development of atherosclerosis. Since ezetimibe inhibits the intestinal absorption of both cholesterol and of vegetable ste-
Table XII. Drugs used for treating systemic arterial hypertension in childhood.

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dosage</th>
<th>Interval</th>
<th>DR/LE</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>Benazepril</td>
<td>Initial: 0.2 mg/kg/d to 10 mg/d</td>
<td>1 x d</td>
<td>II/B</td>
<td>All ACE inhibitors are contraindicated in pregnancy or in women who might become pregnant</td>
</tr>
<tr>
<td></td>
<td>Captopril</td>
<td>Initial: 0.3-0.5 mg/kg/dose</td>
<td>3 x d</td>
<td>IIa/B</td>
<td>Monitor potassium and creatinine</td>
</tr>
<tr>
<td></td>
<td>Enalapril</td>
<td>Initial: 0.08 mg/kg/d to 5 mg/d</td>
<td>1 a 2 x d</td>
<td>II/B</td>
<td>Coughing and angioedema are more common with captopril</td>
</tr>
<tr>
<td></td>
<td>Fosinopril</td>
<td>Initial: 0.07 mg/kg/d to 40 mg/d</td>
<td>1 x d</td>
<td>II/B</td>
<td>Benazepril, enalapril, lisinopril and captopril are available for suspension preparation</td>
</tr>
<tr>
<td></td>
<td>Lisinopril</td>
<td>Initial: 0.07 mg/kg/d to 40 mg/d</td>
<td>1 x d</td>
<td>II/B</td>
<td>FDA has approved its use in children above 6 years of age and creatinine clearance of &gt;30 ml/m in</td>
</tr>
<tr>
<td></td>
<td>Quinapril</td>
<td>Initial: 0.5-10 mg/kg/d to 40 mg/d</td>
<td>1 x d</td>
<td>II/B</td>
<td>Same recommendations as for the ACE Inh.</td>
</tr>
<tr>
<td>AT2 blockers</td>
<td>Irbesartan</td>
<td>6-12 y: 75-150 mg/d to 1200 mg/d</td>
<td>2 x d</td>
<td>IIa/C</td>
<td>Contraindicated in HF, asthma and insulin-dependent diabetes; Titrated according to HR; can worsen systolic performance</td>
</tr>
<tr>
<td>Alpha and beta blocker</td>
<td>Labetalol</td>
<td>Initial: 1-3 mg/kg/d to 1200 mg/d</td>
<td>2 x d</td>
<td>IIa/C</td>
<td>Not cardioselective (propranolol) are contraindicated in asthma and HF</td>
</tr>
<tr>
<td></td>
<td>Atenolol</td>
<td>Initial: 0.5-1 mg/kg/d to 100 mg/d</td>
<td>1 a 2 x d</td>
<td>IIa/C</td>
<td>Titrate dose according to HR; can worsen systolic performance</td>
</tr>
<tr>
<td></td>
<td>Bisoprolol + HCTZ</td>
<td>Initial: 2.5/6.25 mg/d to 10 mg/d</td>
<td>1 x d</td>
<td>IIb/2</td>
<td>Should not be used if insulin-dependent diabetes is present</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>Initial: 0.5-2 mg/kg/d to 1200 mg/d</td>
<td>2 x d</td>
<td>IIa/C</td>
<td>Time release formulation of propranolol</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>Furosemide</td>
<td>Initial: 0.5-20 mg/kg/d to 62 mg/d</td>
<td>1 x d</td>
<td>IIa/B</td>
<td>Amlodipine and isradipine are available for suspension preparation</td>
</tr>
<tr>
<td></td>
<td>Permoxazone</td>
<td>Initial: 0.5 mg/kg/d</td>
<td>1 x d</td>
<td>IIa/B</td>
<td>The tablet must be swallowed whole</td>
</tr>
<tr>
<td></td>
<td>Nifedipine GITS</td>
<td>Initial: 0.25-0.5 mg/kg/d to 120 mg/d</td>
<td>1 a 2 x d</td>
<td>IIa/C</td>
<td>Central agonist</td>
</tr>
<tr>
<td></td>
<td>Clonidine</td>
<td>Initial: 0.2 mg/kg/d to 4 mg/d</td>
<td>2 x d</td>
<td>IIb/D</td>
<td>Cough, sedation and rebound hypertension; Transdermal preparation</td>
</tr>
<tr>
<td></td>
<td>HCTZ</td>
<td>Initial: 0.3 mg/kg/d to 50 mg/d</td>
<td>1 x d</td>
<td>IIa/C</td>
<td>Monitor electrolytes</td>
</tr>
<tr>
<td></td>
<td>Chlortalidone</td>
<td>Initial: 0.3 mg/kg/d to 50 mg/d</td>
<td>1 x d</td>
<td>IIa/C</td>
<td>Useful when associated with other drugs</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Furosemide</td>
<td>Initial: 0.5-20 mg/kg/d to 62 mg/d</td>
<td>1 a 2 x d</td>
<td>IIa/C</td>
<td>Useful in resistant hypertension and in RF</td>
</tr>
<tr>
<td></td>
<td>Spironolactone</td>
<td>Initial: 0.3 mg/kg/d to 100 mg/d</td>
<td>1 a 2 x d</td>
<td>B1/3</td>
<td>Caution with K sparing diuretics + ACE inh.</td>
</tr>
<tr>
<td></td>
<td>Amiloride</td>
<td>Initial: 0.4-0.625 mg/kg/d to 20 mg/d</td>
<td>1 x d</td>
<td>IIa/C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Doxazosin</td>
<td>Initial: 1 mg/kg/d to 4 mg/d</td>
<td>1 x d</td>
<td>IIb/D</td>
<td>Postural hypotension and syncope in 1 dose</td>
</tr>
<tr>
<td></td>
<td>Prazosin</td>
<td>Initial: 0.05-0.1 mg/kg/d to 5 mg/d</td>
<td>3 x d</td>
<td>IIb/D</td>
<td>Tachycardia and liquid retention Lupus-like syndrome</td>
</tr>
<tr>
<td></td>
<td>Hydralazine</td>
<td>Initial: 0.075 mg/kg/d to 200 mg/d</td>
<td>7/B</td>
<td>IIb/D</td>
<td>Reserved for resistant HTN; Prolonged use may cause hypertrichosis</td>
</tr>
<tr>
<td>Vasodilators</td>
<td>Minoxidil</td>
<td>Initial: 0.2 mg/kg/d to 50 mg/d</td>
<td>1 x d</td>
<td>IIc</td>
<td></td>
</tr>
</tbody>
</table>

DR= Degree of recommendation; LE = Level of evidence; HF = Heart failure; DM = Diabetes mellitus; HR = Heart rate; RF = Renal failure.
rols, the use of this drug results in an effective reduction of sitosterolemia.\(^{107}\)

**FIBRATES AND NICOTINIC ACID** – The use of fibrates in children and adolescents has been described in small studies and resulted in moderate reductions of total and LDL cholesterol and good tolerability. Their use in this age group awaits further experience. Nicotinic acid is not usually recommended for children and adolescents given its potential to cause side effects and the absence of tolerability data for these age groups.\(^{102,103}\)

**NUTRACEUTICALS AND DIETARY SUPPLEMENTS** – The omega-3 fatty acids can contribute to decrease triglycerides while plant stanols and soybean protein may slightly reduce LDL cholesterol levels (Degree of Recommendation IIb, Level of Evidence D). Stanols and phytosterols are not recommended in cases of sitosterolemia.\(^{102,103}\)

**Hypertension**

The use of drugs to treat hypertension in these age groups is still controversial and the most relevant issue regards the long-term use of drug therapy and the possible effects on the physical development and quality of life of these individuals. More than in any other age group, the adoption of healthy habits to fight the factors associated with increased blood pressure is totally justified.\(^{60}\)

**THERAPEUTIC LIFESTYLE CHANGES** – It is recommended that all children with SBP and/or DBP greater than or equal to the 95th percentile in 3 or more occasions (established arterial hypertension) or with SBP and/or DBP greater than or equal to the 90th percentile and below the 95th percentile (prehypertension) comply with a healthy diet, rich in fruits, vegetables, whole grains, white meat and restricted in saturated fat (<10% calories/day), cholesterol (<300 mg/day), sugar and salt (<6 g/day), given the general health benefits of this diet and despite the limited evidences. For those individuals whose BP is in the prehypertensive range, the first step of treatment is to recommend the initiation of lifestyle intervention measures (Degree of Recommendation IIa, Level of Evidence D).\(^{60,83}\)

While the ingestion of salt only modestly affects BP in this age range (reduction of 1 to 3 mmHg), data from a controlled clinical study showed that reducing salt ingestion during childhood affected BP during adolescence. Given these facts, the ingestion of salt should be limited to 1.2 g/day for children ranging from 4 to 8 years and 1.5 g/day for children above 8 years 60,108 (Degree of Recommendation IIa, Level of Evidence D).

Regarding potassium, calcium and magnesium, there is evidence of an association between increased consumption of these minerals and lower BP. However, the number of studies that report these associations is still insufficient to justify recommending dietary supplementation of these nutrients (Degree of Recommendation III, Level of Evidence D). Supervised nutritional guidance can be useful when elaborating a diet, as it may increase the likelihood that one will comply with the proposed measures.\(^{60,108}\) (Degree of Recommendation IIa, Level of Evidence D).

Weight loss should be emphasized since excess weight correlates strongly with higher BP.\(^{1,2,5,10-12}\) Clinical studies in children have shown that BP tracking is strongly associated with weight throughout life.\(^{60,110}\) On the other hand, it has been demonstrated that losing weight is a very effective way of lowering BP, and in addition it also reduces salt sensitivity, insulin resistance and other risk factors associated with elevated BP, such as dyslipidemia. A weight loss of 10% is capable of reducing BP in 8 to 12 mmHg in adults.\(^{65,110}\) For these reasons and in the absence of other risk situations, treating overweight/obesity is the first step in treating childhood hypertension. If BP does not improve with weight loss, then drug therapy is recommended (Degree of Recommendation I, Level of Evidence D). The presence of overweight/obesity was a variable included in the algorithm of childhood SAH evaluation and treatment.

The implementation of regular physical activity should also be emphasized and it is an important component in treating childhood obesity. Exercises should be done for one hour per day, the activities should be fun and leisure time should not include sedentary activities for more than 2 hours per day.\(^{111}\) (Degree of Recommendation I, Level of Evidence D). Smoking habit should be strongly discouraged, and adult smokers in the child’s or adolescent’s environment should also be strongly discouraged to smoke.\(^{83}\) (Degree of Recommendation I, Level of Evidence D). It is important to point out that childhood and adolescence are the perfect times to establish healthy life habits so that no changes are required later on. Everyone agrees that these measures are likely to be successful if the family, school, community and government implement them in a joint effort, obviously taking into account the diversities of each population.

**PHARMACOLOGICAL TREATMENT OF HYPERTENSION** – The use of medication should be considered when other measures do not succeed in controlling BP and/or when there is evidence of target organ compromise, such as left ventricular hypertrophy, microalbuminuria or retinal vascular changes. These conditions are generally present in symp-
tomatic hypertension, in the secondary forms of hypertension or in individuals who present multiple cardiovascular risk factors (Degree of Recommendation IIa, Level of Evidence C).

Clinical studies have expanded the number of drugs used for hypertension treatment in this age group. However, studies that compare the many classes of drugs and their impact on clinical outcomes do not exist. Thus, it is up to the specialist to choose the best drug for each case. The treatment objective is to lower blood pressure to values below the 95th percentile for age, gender and height in cases of hypertension without complications, or below the 90th percentile when there is target organ damage, type 2 DM or kidney disease (Degree of Recommendation IIa, Level of Evidence D). It is recommended to start treatment using only one of the following drugs: angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB), calcium channel blockers, beta-blockers and diuretics. Specific classes are used preferentially in the presence of special conditions, such as ACE inhibitors or ARB when diabetes and/or microalbuminuria are present and beta-blockers or calcium channel blockers in people with hypertension and migraines (Degree of Recommendation I, Level of Evidence B). Drugs with complementary mechanisms can be associated but since data on drug associations in this age group are scarce, associations are usually not recommended (Degree of Recommendation IIb, Level of Evidence B). Table XII lists the drugs that have been approved for use in children and Figure 3 shows the SAH treatment algorithm.

Metabolic syndrome

**TREATMENT ALGORITHM** – There is no consensus regarding the metabolic syndrome definition criteria for children.
Figure 4. Algorithm for treating child and adolescent metabolic syndrome and/or diabetes.

Figure 5. Algorithm for treating obesity in childhood and adolescence.
and adolescents although some studies already use the term for this population group. Contrary to diabetes, there is no evidence showing that treating this syndrome is beneficial to prevent cardiovascular diseases. For this reason, metabolic syndrome treatment should be based on lifestyle changes, emphasizing the need for proper eating habits and regular physical activity. The treatment objectives are to reach normal glycemia, BP and serum lipid levels and adequate body weight. Dietary intervention aims to reduce calorie, fat and simple sugar intake and increase fiber consumption. Pharmacological treatment is reserved for those cases where there is a diagnosis of diabetes. Figure 4 summarizes the management of these patients (Degree of Recommendation IIA, Level of Evidence D).

**DRUGS USED IN ADOLESCENTS** — The only FDA-approved drug for use in children and adolescents when treating type 2 diabetes is metformin. Metformin has proven efficacious in controlling glycemia and in improving the lipid profile by lowering triglyceride, VLDL and LDL cholesterol levels and slightly increasing HDL cholesterol levels. It has an anorectic effect\(^ {112} \).

**Obesity**

**OBESITY TREATMENT ALGORITHM** — Treating obesity is complex given the number of factors implied in its genesis. However, there is consensus that healthy eating habits and regular physical activities are essential. Treatment aims at achieving proper weight, controlling the associated comorbidities and acquiring healthy life habits\(^ {113} \).

**Drugs used in childhood and adolescence**

The small number of long-term controlled studies demonstrating the safety and efficacy of using drugs in the pediatric age range to achieve weight loss has limited their recommendation. Two drugs have been approved by the FDA for this age group: orlistat (pancreatic lipase inhibitor)\(^ {114} \) and sibutramin (serotonin and noradrenaline reuptake inhibitor)\(^ {115} \). These drugs have proven efficacious in adolescence. Therefore, treatment should be individualized and address specific causes in order to limit the onset of complications and to avoid obesity in adulthood\(^ {116} \).

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