Revista da
SOCESP
Sociedade de Cardiologia do Estado de São Paulo

RISK FACTOR INTERVENTION IN CHILDREN AND ADOLESCENTS

INTERVENÇÃO SOBRE FATORES DE RISCO EM CRIANÇAS E ADOLESCENTES

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Received on 08/30/2018,
Accepted on 01/28/2019

ABSTRACT

Cardiovascular disease is one of the leading causes of mortality in the world and does not affect adults alone. Many papers have shown that it can already be seen in childhood. The most significant risk factors for cardiovascular disease include dyslipidemia, low birth weight and childhood obesity. Screening for dyslipidemia in childhood is crucial as this is considered a strategic phase for the implementation of measures aimed at preventing atherosclerosis in the population setting. Although environment or polygenic causes are the most common, it is important to identify genetic forms such as familial hypercholesterolemia and hypertriglyceridemia, since measures related to lifestyle and pharmacotherapy must be initiated early in life to avoid complications and change the natural history of clinical outcomes. Other studies have shown that low birth weight also contributes to the late development of hypertension, coronary artery disease and endothelial dysfunction, possibly due to injury to the developing vascular system. However, the mechanisms are still uncertain, and evidence suggests that some biomarkers, such as uric acid and homocysteine levels, and the low concentration of nitric oxide observed in low birthweight children, may be associated with deleterious changes in adulthood. Finally, the third factor to be considered is childhood obesity. This disorder has a multifactorial etiology and may favor the onset of the first stages of atherosclerosis, such as endothelial dysfunction, in young children. However, it is a modifiable risk factor, and prevention and intervention strategies are largely based on lifestyle changes such as healthy diet and exercise.

Keywords: Cholesterol; Triglycerides; Genetics; Diagnósis; Birth Weight; Endothelium; Pediatric Obesity.

RESUMO

As doenças cardiovasculares estão entre as principais causas de mortalidade no mundo e não afligem apenas os adultos. Muitos trabalhos têm demonstrado que elas já podem ser vistas na infância. Entre os fatores de risco para a doença cardiovascular, pode-se destacar a dislipidemia, o baixo peso ao nascer e a obesidade infantil. A detecção de dislipidemia na infância é crucial, por ser considerada a fase estratégica para a implementação de medidas de prevenção da aterosclerose no âmbito populacional. Embora as causas ambientais ou poligênicas sejam as mais frequentes, é importante a identificação de formas genéticas como a hipercolesterolemia familiar e hipertrigliceridemias de base genética, pois medidas relacionadas aos hábitos de vida e terapêutica medicamentosa devem ser iniciadas precocemente, evitando-se complicações e mudando a história natural dos desfechos clínicos. Outros estudos têm demonstrado que o baixo peso ao nascer também contribui para o desenvolvimento tardio de hipertensão arterial, doença coronariana e disfunção endotelial. Possivelmente, por conta das agressões ao sistema vascular em desenvolvimento. No entanto, os mecanismos ainda são incertos. Evidências sugerem que alguns biomarcadores, tais como os níveis de ácido úrico e homocisteína e a baixa concentração de óxido nítrico observados em crianças com baixo peso ao nascer, podem estar associados a alterações deletérias na vida adulta. Por fim, o terceiro fator que deve ser considerado é a obesidade infantil. Essa desordem tem causa multifatorial e pode favorecer o surgimento das etapas iniciais da aterosclerose, como a disfunção endotelial, já na infância. Porém, é um fator de risco modificável, e as estratégias de prevenção e intervenção baseiam-se, na maioria dos casos, em mudanças do estilo de vida, como alimentação saudável e exercício físico.

Descritores: *Colesterol; Triglicérides; Genética; Diagnóstico; Peso ao Nascer; Endotélio; Obesidade Pediátrica*

INTRODUCTION

Cardiovascular diseases (CVD) are a set of changes that affect the blood vessels, heart, and associated structures. These diseases are multifactorial in nature and contribute to mortality rates worldwide. In Brazil alone, more than 300,000 deaths per year from circulatory system diseases are recorded according to DATASUS mortality indicators.

Despite being widely investigated in adults and the elderly, several studies have shown that risk factors for CVD can also be observed in children and adolescents[1,2]. Understanding these factors is vital to the implementation of preventive and interventional strategies as well as the reduction of mortality rates and costs generated in adulthood. Early intervention can also alleviate the burden that the disease can cause later, thereby improving overall quality of life and population survival.

Scientific evidence has shown changes in childhood that are indicators of the late development of more severe heart diseases such as dyslipidemia, low birth weight (LBW), and childhood obesity.[2-4] Dyslipidemia is characterized by abnormal serum lipid levels, mainly high levels of low-density lipoprotein cholesterol (LDL-c) and triglycerides (TG). LBW is a term used when a newborn baby does not weigh within the estimated normal range. According to the Ministry of Health (DATASUS), a weight < 2500 g is considered LBW. Obesity, on the other hand, is a condition indicated by excess body fat, which compromises the function of various body systems.

Thus, this article aimed to review the main evidence demonstrating the relationship between dyslipidemia, LBW, and childhood obesity with the development of CVD as well as possible preventive and interventional measures.

DYSLIPIDEMIA IN CHILDREN AND ADOLESCENTS

Epidemiological and etiological aspects

The prevalence of dyslipidemia in childhood and adolescence in Brazil is 10–23.5% according to the region and criteria used.[2,3,5] The detection of dyslipidemia in childhood is crucial since it is considered the strategic phase for the implementation of measures to prevent atherosclerosis in adulthood. Life habits can be more easily and effectively modified in this phase, preventing the integration of risk factors for CVD. Longitudinal studies show that interventions in children effectively prevent CVD in adulthood.[6,7]

The main causes of dyslipidemia in childhood and adolescence are primary (of genetic origin) or secondary (medications, lifestyle habits, or certain clinical conditions) (Chart 1). Every child with dyslipidemia should receive guidance regarding adopting a healthy lifestyle, but the opportunity to start treatment should be analyzed based on the stratification of cardiovascular risk in childhood and adolescence since treatment intensity varies with the risk and proposed lipid goals. The diseases and risk factors associated with atherosclerosis in childhood and adolescence are described in Chart 2.[8]

Chart 1. Classification of the main causes of dyslipidemia in childhood and adolescence.

Cause	Exemplos
Lifestyle habits	Inadequate diet, sedentary lifestyle, smoking, alcohol
Medication	Valproic acid, beta-blocker, contraceptives, corticosteroids, parenteral nutrition, amiodarone, isotretinoin, antipsychotics
Secondary and clinical conditions	Acquired immunodeficiency syndrome, chronic cholestasis, hypothyroidism, nephrotic syndrome, chronic renal failure, obesity, chronic inflammatory diseases, diabetes mellitus, deposit diseases, lipodystrophy
Genetic causes	Familial hypercholesterolemia, familial combined hyperlipidemia, familial severe hypertriglyceridemia

Adapted from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report.[8]

Chart 2. Clinical conditions and risk factors associated with atherosclerosis in childhood by severity.

High-risk diseases: Diabetes mellitus, chronic kidney disease, heart or kidney transplantation, Kawasaki disease with aneurysms
Moderate-risk diseases: Chronic inflammatory diseases (including Kawasaki disease with aneurysm regression), HIV infection, family history of early ischemic artery disease (men < 55 years of age and women < 65 years of age)
High-risk factors: Hypertension (above the 99th percentile + 5 mmHg) in use of medication, smoking, obesity (above the 97th percentile)
Moderate-risk factors: Hypertension without medication, obesity (between the 95th and 97th percentiles), HDL < 40 mg/dL

Adapted from Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report.[8]

CONSIDERATIONS OF LIPID PROFILE AND CONCENTRATION IN CHILDREN AND ADOLESCENTS

Data obtained from prevalence studies of lipid research clinics show that serum lipid and lipoprotein concentrations increase from early childhood and reached concentrations similar to those of adults at 2 years of life.[9] This knowledge is important because concentrations obtained before this point may not reflect values in subsequent years of childhood and adulthood. Population studies including the National Health and Nutrition Examination Surveys (NHANES)[10] provided important data on the distribution and trends of lipids and apolipoprotein in childhood and adolescence. NHANES data of 1988–1994 of children 4–19 years of age showed that the mean total cholesterol was 165 mg/dL, while those of children 9–11 years of age was 171 mg/dL, with a decrease during pubertal development and an increase thereafter. This information has implications regarding the timing of the lipid profile evaluation and the cut-off points used because lipid concentrations are related to age and sexual maturation stage.[11]

There are differences in cholesterol concentrations between the sexes and, according to NHANES data from 1988–1994, women have higher total and LDL-c cholesterol than men and a tendency to high-density lipoprotein cholesterol (HDL-c) also higher after puberty. Patterns of puberty also vary with ethnicity, with black girls reaching puberty sooner than white girls. There are also differences in TG concentrations among

ethnicities. Black children have higher HDL-c concentrations and lower TG concentrations than white non-Hispanic and Hispanic children.[10]

Lipid profile screenings should begin at the age of 10 years (universal screening) or in children 2–10 years of age when they[12] have parents or grandparents with a history of early ischemic arterial disease (Chart 1); have parents with total cholesterol > 240 mg/dL; have other diseases or risk factors for atherosclerosis (Chart 2); are carriers of diseases that course with dyslipidemia (Chart 1); use drugs that alter the lipid profile (Chart 1); have clinical manifestations of dyslipidemia (xanthomas, xanthelasma, corneal arch, recurrent abdominal pain, pancreatitis). Another strategy that could be implemented is opportunistic screening at the time of vaccination, when every child who receives a routine vaccine is submitted to a lipid profile analysis, or at least *point of care* test.

The non-HDL-c calculated must be calculated for each child at 9–11 years and at 17–21 years. Fasting is unnecessary. An abnormal value indicates the need to repeat the lipid profile between 2 weeks and 3 months. When genetically based dyslipidemia is suspected, a complete lipid profile (TC, LDL-c, HDL-c and TG) should be obtained.[13,14]

The reference and desirable values of the lipid profile in children and adolescents, with and without fasting, are described in Table 1.[15]

GENETIC HYPERCHOLESTEROLEMIA

When a child has dyslipidemia, primary (genetic) and secondary causes should be considered.[16] After ruling out possible secondary causes (Chart 1), primary forms of hypercholesterolemia should be considered. These can be mono- or polygenic. Most dyslipidemias are polygenic, resulting from a combination of genetic and non-genetic factors. Polygenic dyslipidemias are caused by the cumulative effect of genetic variants called single nucleotide polymorphisms (SNP). Individually they do not significantly alter the lipid profile, but the cumulative effect of various SNP within the genome is amplified, resulting in the clinical phenotype of dyslipidemia, often with skin stigma similar to that of familial hypercholesterolemia. These variants are segregated into independent chromosomes without classical Mendelian transmission patterns (transmission of characteristics from father to son).[17]

FAMILIAL HYPERCHOLESTEROLEMIA

Familial hypercholesterolemia (FH) is the most common form of inherited dyslipidemia. Its heterozygous form (HeFH) represents ~1 of every 200–250 individuals in the general population, occurring about twice as frequently as previously reported.[18] Of every 1,000 births, 5 babies are FH carriers.[19] Of a control population without coronary heart disease, 1 in 217 had a mutation in the gene that encodes the LDL receptor (LDLR) and an LDL-c > 190 mg/dL. Consequently, approximately 4.5 million individuals have HeFH in Europe alone, while there are approximately 35 million worldwide. Of those, about 20–25% are children and adolescents. Considering that there are 255 births per minute, 1 baby with FH is born per minute.[19]

Children with untreated FH will have a dramatic increase in the risk of premature atherosclerotic cardiovascular disease (ACD) after the age of 20 years.[20,21] In the homozygous form of FH (HoFH), a very rare form, the estimated prevalence is 1:160,000 to 1:300,000 in European populations. Individuals with HoFH are at extremely high risk of ACD, and many untreated individuals will experience coronary manifestations in childhood or adolescence.[19]

Childhood is the ideal time to discriminate between individuals with versus those without a mutation based on LDL-c values.[22] Children with two measurements of LDL-c > 190 mg/dL at 3-month intervals have a high likelihood of FH, while children with two measurements of LDL-c > 160 mg/dL combined with a family history of hypercholesterolemia or premature ACD are highly likely to have FH. On the other hand, children with an LDL-c > 130 mg/dL and a parent affected by FH have a high probability of inheriting the mutation (Table 2).[19,23]

The homozygous form of FH was the object of a consensus document.[24] LDL-c levels in children with HoFH are generally >500 mg/dL, although there is phenotypic variability and lower levels have been found using genetic testing.[25] The homozygous form should be suspected if both parents had LDL-c compatible with HeFH. If parents have normal values, the recessive form of FH due to two mutations in the *LDLRAP1* gene should be considered in addition to the exclusion of sitosterolemia. Xanthomas can appear in the first years of life and generally before 10 years of age,[24] and are the reason families seek medical attention. However, its absence or later onset does not exclude the diagnosis of HoFH.

Table 1. Desirable lipid profile reference values for children and adolescents.

Lipid	Fasting (mg/dL)	Non-fasting (mg/dL)
Total cholesterol*	< 170	< 170
HDL-c	> 45	> 45
Triglycerides (0-9a)**	< 75	< 75
Triglycerides (10-19a)**	< 90	< 90
LDL-c	<110	<110

*At a total cholesterol level > 230 mg/dL, familial hypercholesterolemia is possible. **At a triglyceride level > 440 mg/dL (without fasting), a new triglyceride level after a 12-h fast should be determined. Adapted from Scartezini et al.[15]

Table 2. Diagnosis of hypercholesterolemia in children and adolescents.

Hypercholesterolemia (high LDL-c) and a family history of premature atherosclerosis are two key criteria in the selection for screening (F+H).
The cholesterol value should be used for the phenotypic diagnosis.
Family history of premature atherosclerosis in close relatives and/or high LDL-c in one parent + LDL-c > 160 mg/dL indicates a high probability of FH. If the father is genetically diagnosed, an LDL-c > 130 mg/dL suggests FH in the child.
Secondary causes of hypercholesterolemia should be ruled out.
The genetic test establishes the diagnosis. If a pathogenic mutation in the LDLR is identified in a first-degree relative, the genetic test should be offered to the child.
If a parent dies of atherosclerosis, a child with even moderate hypercholesterolemia should be genetically tested for FH and high Lp(a).

Adapted from reference 19.

HYPERTRIGLYCERIDEMIA IN CHILDHOOD AND ADOLESCENCE

Plasma TG level is a biomarker of lipoproteins rich in circulating TG and their remnants. Hypertriglyceridemia is a frequent finding in clinical practice, but severe forms must be recognized because they increase the patient's risk of pancreatitis. After secondary causes such as hypothyroidism, decompensated diabetes mellitus, chronic nephropathy, and medications are ruled out, genetic and familial etiologies should be considered.[26] Mild and moderate primary hypertriglyceridemia is typically polygenic and results from the cumulative effect of common or rare genetic variants in more than 30 genes. However, there are rare severe forms of primary hypertriglyceridemia with an autosomal recessive inheritance mode. Phenotypically, hypertriglyceridemia is classified according to the primary lipoprotein abnormality (Chart 3) into combined familial hyperlipidemia (type 2b), dysbetalipoproteinemia (type 3), simple primary hypertriglyceridemia (type 4), and mixed primary hypertriglyceridemia (type 5), which have a multigenic or polygenic genetic basis that is consequent to additive effects of multiple alleles and the interaction with environmental factors. [27]

One type of hypertriglyceridemia is in fact monogenic: the so-called familial chylomicronemia, or type 1, which is characterized by the persistence of elevated chylomicrons after fasting for 12–14 hours with TG levels > 1,000 mg/dL that manifests in childhood or adolescence.[27,28] Five genes are responsible for causing lipid alterations: Three affect lipoprotein lipase (LPL) activity, while the other two affect LPL assembly and transport (Chart 4). Among the genes that affect LPL function are defects in the *LPL* gene, its cofactor *APOC-II*, or the *APOAV* gene, although the mechanism of hypertriglyceridemia is not well understood in this situation; the other two genes, lipase-1 maturation factor (*LMF-1*) and glycosylphosphatidylinositol-anchored HDL-binding protein (*GPIHBP-1*), affect LPL assembly and transport.[27,28] However, no mutations were found in any of these genes in about 30% of cases, suggesting that others not yet known may cause this phenotype.

Hypertriglyceridemia may be accompanied by eruptive xanthomas, *lipemia retinalis*, pancreatitis, or recurrent abdominal pain. In dysbetalipoproteinemia, tubero-eruptive xanthomas are characteristic. The appearance of the plasma left in the refrigerator for 24 hours is another finding in hypertriglyceridemia. It is turbid in hypertriglyceridemia. It may have a creamy layer when chylomicrons are present, or it may have two phases consisting of turbidity and a creamy layer in the presence of increased chylomicrons and TG. In severe genetic forms, such as familial chylomicronemia, recurrent abdominal pain and pancreatitis are frequent findings.

Chart 4. Genes associated with recessive forms of familial chylomicronemia.

Gene	Prevalência da doença	Age of appearance	Genetic basis
LPL	1:1 million	Childhood or adolescence	Very low or absent LPL activity
APOC-II	More than 20 families described	Adolescence or adulthood	Nonfunctional or absent ApoC-II
GPIHBP1	More than 5 families described	Adulthood	Disability or absence of GPIHBP1
APOA-V	More than 5 families described	Adulthood	Disability or absence of ApoA-V
LMF-1	More than 5 families described	Adulthood	LMF1 deficiency or absence

LPL, lipoprotein lipase; APOC-II, apolipoprotein C-II; GPIHBP1, glycosyl-phosphatidylinositol-anchored HDL-binding protein; ApoAV, apolipoprotein A-V; LMF-1, lipase-1 maturation factor. Adapted from Hegele et al.[27]

Chart 3. Classification of genetic hypertriglyceridemia by primary lipoprotein abnormality.

Type	Primary lipoprotein abnormality	Lipid profile	Clinical manifestation	Population prevalence
Familial chylomicronemia (type 1)	High CM	Increase in TG+++ Increase in TC+	Eruptive xanthomas, lipemia retinalis, recurrent abdominal pain, pancreatitis, hepatosplenomegaly, and focal neurological symptoms	1:1 million
Combined familial hyperlipidemia (type 2b)	High TG High LDL	Increase in TG++ Increase in TC++	Unusual findings of xanthomas or xanthelasmas	1:40
Dysbetalipoproteinemia (type 3)	High IDL remnants	Increase in TG++ Increase in TC++	Tuberous and palmar xanthomas; increased risk of CAD	1:10 thousand
Simple primary hypertriglyceridemia (type 4)	High VLDL	Increase in TG++ Increase in TC+	Increased risk of CAD, DM, obesity, hypertension, hyperuricemia, and insulin resistance	1:20
Mixed primary hypertriglyceridemia (type 5)	high CM high VLDL	Increase in TG+++ Increase in TC+++	Similar to type 1, but appears in adulthood and is exacerbated by secondary factors	1:600

CM, chylomicrons; TG, triglyceride; TC, total cholesterol; VLDL, very low-density lipoprotein; IDL, intermediate-density lipoprotein; CAD, coronary artery disease; DM, diabetes mellitus Adapted from Hegele et al.[27]

Monogenic recessive forms of hypertriglyceridemia (type 1) are very rare (1 case in every 1 million individuals) and characteristic of familial chylomicronemia. The genes associated with this condition are characterized by the absence or very low activity of LPL (mutations in the *LPL* gene), with manifestations in childhood or adolescence; absence of or nonfunctional ApoC-II or ApoC-II (mutations in the *APOCII* gene) with manifestations in adolescence or adulthood; deficiency or absence of *GPIHBP1*; and deficiency or absence of *ApoA-V* or *LMF-1* with manifestations in adulthood. Diagnosis is confirmed by testing for reduced post-heparin lipase activity.

TREATMENT OF DYSLIPIDEMIA IN CHILDHOOD AND ADOLESCENCE

In most cases, dyslipidemia is a result of poor lifestyle habits, including a diet rich in saturated or trans fats and a sedentary lifestyle. Obesity also has an unfavorable metabolic effect, increasing TG and LDL-c levels and decreasing HDL-c levels in addition to altering lipid subfractions, increasing the concentration of pro-atherogenic fractions.[16] Hypolipidemic therapy should be initiated after at least 6 months of intensive lifestyle modification. Chart 5 describes the doses of hypolipidemic drugs used in childhood and adolescence.

In cases of FH, the early treatment of dyslipidemia can reduce carotid intima-media thickness.[29] The reduction in LDL-c with the early use of statins in FH (at 8–10 years of age) translated to improved cardiovascular outcomes in a cohort of 214 families with FH in which individuals treated with statins since childhood (n = 214) compared with their parents with FH treated since adulthood (n = 156) had 100% versus 92.9% event-free survival, respectively. The target for LDL-c in FH should be <135 mg/dL.[19] Multiple drugs, such as ezetimibe and nicotinic acid, may be necessary in the treatment of severe and homozygous forms. PCSK9 inhibitors are being studied in HeFH and HoFH. Mipomersen (anti-APOB antisense) and lomitapide (MTP inhibitor) are not approved in Brazil and are only indicated for the treatment of the homozygous form.[22,24]

The treatment of hypertriglyceridemia (TG < 500 mg/dL) should prioritize lifestyle changes, but in cases of TG > 500 mg/dL after lifestyle changes, fibrates are the first option. Severe hypertriglyceridemia (TG > 1,000 mg/dL) requires immediate measurements and intensive TG reduction to minimize the risk of pancreatitis; a diet restricted in simple fats and carbohydrates, use of fibrates, isolated or associated with fatty acids such as omega 3 (~ 4 g a day of marine EPA/DHA), and nicotinic acid (500 mg to 2.0 g a day) is indicated.[27,28] Some genetic forms, including familial chylomicronemia, are poorly responsive to the association of drugs. New therapies for these severe forms are being tested in clinical studies. The presence of abdominal pain or pancreatitis requires hospitalization, the interruption of oral eating, plasmapheresis (if available), and supportive measures that include fluid replacement and the treatment of triggering factors. In very severe cases, apheresis may be necessary.[16,27,28] Babies with chylomicronemia have milky serum and should not breastfeed due to the risk of pancreatitis.[16,27,28] Middle-chain TG are an alternative treatment for severe forms with careful supervision by a nutritionist and supplementation of fat-soluble vitamins.

Chart 5. Doses of hypolipidemic drugs used in children and adolescents.

Drug	Dosage (mg/day)
Lovastatin	10-40
Pravastatin	10-40
Simvastatin	10-40
Rosuvastatin	5-20
Atorvastatin	10-40
Cholestyramine	4.000-16.000
Ezetimibe	10
Bezafibrate	200
Fenofibrate	200
Omega-3	2.000 a 4.000
Phytosterols	1.200-1.500

Adapted from Faludi et al.[16]

BIRTH WEIGHT AND LATE DEVELOPMENT OF ENDOTHELIAL DYSFUNCTION

At least three decades ago, a group of British researchers led by epidemiologist David JP Barker started a series of studies that identified the possible importance of events occurring during fetal life in the pathogenesis of some CVD.[30-33] These authors reported that individuals with a history of LBW had a higher incidence of hypertension and mortality due to coronary artery disease and ischemic heart disease when they reached maturity.[30-33] Based on these first observations, studies were conducted in different populations that proved the existence of a correlation between adversities in fetal life and the late development of CVD. A recent prospective study followed newborns with LBW for 30 years and verified a significant increase in pressure levels.[34] Another longitudinal study also described the presence of an inverse correlation between birth weight and systolic blood pressure. These authors evaluated 252 men and 231 women over 14 years and demonstrated that this association persisted from adolescence to adulthood.[35] These data are corroborated by findings of a prospective study that observed a significant correlation between LBW and the late development of coronary disease even after the adjustment for smoking, a sedentary lifestyle, poor eating habits, and socioeconomic aspects.[36]

Development of the vascular system is one of the first events that occurs during organogenesis. Its formation begins in the embryonic period from the differentiation of angioblasts into endothelial vascular and smooth muscle cells, forming the primary vasculature in a process called vasculogenesis.[37,38] Occurring parallel to this process, angiogenesis plays an important role and extends the vessels into a more complex network, thus establishing the formation of the vascular system. Therefore, insults during fetal life may program the formation of this system, contributing to the emergence of vascular changes in adult life.

Several clinical studies demonstrated modifications in the vascular system that may compromise its functionality in individuals with LBW. In fact, it was observed that newborns with LBW already had a significant endothelium-dependent decrease in the vasodilator response at 3 months of age.[39]

Other studies conducted in children with a history of LBW also found a decrease in endothelium-dependent vasodilation in different vascular beds such as the brachial artery,[40-42] carotid artery,[41,43] and peripheral microcirculation.[43] Some authors recently started to explore this relationship between birth weight and the development of endothelial dysfunction by focusing on the importance of endothelial progenitor cells (EPCs).[44-47] Ligi et al. demonstrated that LBW may be a prenatal factor capable of promoting deleterious changes in EPCs. In fact, these authors found less functionality in EPCs that were isolated from the umbilical cord blood of newborns with LBW.[44] In subsequent studies, these authors found that these EPCs in culture also showed reduced angiogenic capacity and increased senescence.[45,47]

Although the correlation between LBW and changes in endothelial function is well established, the question still remains as to what mechanisms are involved. In recent decades, evidence has indicated that several biomarkers could be involved that act in conjunction with other already established risk factors. Increasing attention has been paid to uric acid, homocysteine, and nitric oxide (NO) as biomarkers associated with a higher incidence of cardiovascular events such as arterial hypertension and endothelial dysfunction in individuals with a history of LBW. Elevated serum concentrations of uric acid are commonly seen in association with several CVD.[48] Studies in the literature have observed, both in children and adolescents, an inverse correlation between birth weight and circulating uric acid levels.[42,49-52] A cohort study involving 5,309 American adolescents aged 12–15 years reported that for every 1 kg of birth weight gain, a reduction of 0.11 mg/dL of uric acid occurred.[52] In addition, some authors reported that uric acid levels correlated inversely with the endothelium-dependent vasodilator response[42] and systolic blood pressure levels[52] only in individuals with a history of LBW.[42]

Homocysteine increases the risk of CVD due to its direct effect on the endothelium in which it acts on the oxidation of LDL cholesterol, promoting the proliferation of vascular smooth muscle cells and deterioration of the elastic material of vasculature and consequently leading to gradual vascular stiffening.[53] Considering its relationship with birth weight, studies have shown an inverse correlation between homocysteine levels and birth weight in newborns[54] and children.[55] Homocysteine levels were positively correlated with systolic blood pressure in children with LBW.[55] On the other hand, changes in the homocysteine pathway are closely related to injuries in NO synthesis and/or bioavailability. This fact suggests that the latter route may also be altered in individuals with LBW. Studies have demonstrated a significant reduction in NO activity in the umbilical artery and the fetal-placental circulation of pregnancies affected by low fetal weight.[56] Other findings in the literature showed that children with LBW showed lower NO concentrations.[56] In these children, it was observed that the decrease in flow-dependent vasodilation was correlated with lower NO levels, suggesting that changes in this pathway persist during childhood and may play an important role in the late development of vascular disorders in individuals with LBW. Another study showed similar results in which adolescents with a history of LBW showed reduced circulating levels of NO associated with increased levels of asymmetrical dimethylarginine, an endogenous inhibitor of the NO synthase enzyme. [57]

Although several studies have attempted to identify the mechanisms related to the loss of modulating function of the endothelium in response to insults during fetal life, a better understanding of these mechanisms is needed to establish better strategies to prevent potential complications in the progression of cardiovascular changes that occur during adulthood.

CHILDHOOD OBESITY AND CARDIOVASCULAR RISK FACTORS

The prevalence of overweight and obesity in children has reached alarming levels in recent years in both developed and developing countries. The prevalence of childhood obesity worldwide increased an estimated 47.1% between 1980 and 2013.[58] According to the Brazilian Association for the Study of Obesity and Metabolic Syndrome, obesity rates in Brazil have accompanied this growth, and approximately 15% of Brazilian children can now be considered obese or overweight.

Obesity, a state of excess body fat, is associated with several comorbidities. Because of the high cost of techniques that more accurately assess body fat, body mass index (BMI) has been used as a metric. Despite the advantages and disadvantages of this method, BMI has been used as a standard measure to estimate overweight and obesity rates in children $>$ 2 years of age.[59,60]

The cause of childhood obesity is multifactorial and involves a complex interaction between several factors such as food, genetics, family, and the school environment. Environmental factors such as an increased consumption of fast food and processed foods rich in sugar, salt, and fat have contributed to this scenario. The amount of time children spend in front of the television, tablets, and cell phones is also related to the prevalence of overweight and obesity, mainly because it predisposes individuals to a decreased energy expenditure and increased time spent in sedentary activities. [61,62]

Obesity is a modifiable risk factor that affects the endocrine, gastrointestinal, pulmonary, musculoskeletal, and cardiovascular systems. However, the most serious complications are cardiovascular changes that favor the emergence of other diseases.[59,62,63] It was once believed that the manifestations of the clinical symptoms of CVD only appeared in adulthood and were not observed in children. Atherosclerosis, for example, was considered a degenerative disease of the elderly, but studies have shown that the atherosclerotic process begins in childhood. Thus, this concept has changed, and today it is considered a chronic subclinical inflammatory disease that starts in childhood.[63,64]

Many other comorbidities that were considered "adult diseases," including type 2 diabetes, dyslipidemia, obstructive sleep apnea, and insulin resistance, are now observed in children and adolescents. The risk of these comorbidities manifesting increases with the severity of obesity.[62,65]

Endothelial dysfunction is one consequence of obesity and a key event in the development of CVD. It precedes the evolution of atherosclerosis and can already be seen in children 9–12 years of age.[66] A study of obese children and young adults observed a progressive deterioration in arterial stiffness and endothelial function.[67] It has also been demonstrated that intima-medial layer thickness, a marker for coronary and carotid atherosclerosis, is increased in children at high risk for CVD.[59]

The accumulation of risk factors that accompany obesity can trigger the early stages of atherosclerosis, which includes endothelial dysfunction, arterial stiffness, expression of adhesion molecules, and proliferation of smooth muscle cells, as well as late events such as atheroma plaque rupture and thrombosis. More recent studies have focused on new mediators of cardiovascular dysfunction in obesity. Among them are the adipocytokines that can act as mediators of the inflammatory process. Several studies have examined different adipocytokines, whereas others have focused on the role of adiponectin, a protein that is produced mainly by white fat tissue but is found at low levels in obese versus non-obese individuals. In human studies, low levels of adiponectin have been related to endothelial dysfunction in children and adults and increased carotid intima-media layer thickness in adolescents. These studies have consistently demonstrated an anti-atherosclerotic action of adiponectin.[59,66-68] Therefore, low levels of this protein in obese people, including children, may favor the development of atherosclerosis and other cardiac alterations.

The increase in childhood obesity rates may accompany this start of atherosclerosis, a gateway to other cardiac dysfunctions. The progressive accumulation of cardiovascular risk factors may contribute to the persistence of these changes until adulthood, contributing to the increased incidence of CVD worldwide.

Considering these developments associated with the prevalence of childhood obesity, the *Endocrine Society* published a new guideline to guide physicians in the diagnosis, treatment, and intervention of childhood obesity. To guide the diagnosis of childhood overweight and obesity, the use of BMI and the corresponding normative percentiles is recommended for children > 2 years of age and adolescents. According to this classification, the diagnosis of overweight is given if the BMI is equal to or greater than the 85th percentile; a measurement above the 95th percentile is considered obesity, while one exceeding the 120th percentile is considered extreme obesity.[60]

As an intervention strategy, the guideline highlights the relevance of lifestyle changes to prevent and treat obesity and emphasizes as a primary measure the inclusion of healthy eating and regular physical activity in the daily life of children or adolescents as well as a reduction in the intake of fast food and processed foods. In cases in which changing one's lifestyle is insufficient, the use of drugs to reduce BMI and even bariatric surgery in extreme cases can be implemented.[60]

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

AUTHORS' CONTRIBUTIONS: All authors (MCOI, MCI, RP, and MCF) contributed individually and significantly to the development of this work.

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