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Cardiovascular Risk Associated with Dyslipidemias in Children

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ABSTRACT

Atherosclerosis begins in childhood and can be aggravated by dyslipidemias, such as hypercholesterolemia and hypertriglyceridemia, especially in the presence of obesity and metabolic syndrome. The infant lipid profile should be assessed with a fast of 8 to 9 hours. Primary dyslipidemias, usually genetic, include heterozygous familial hypercholesterolemia and homozygous hypercholesterolemia, with diagnosis based on LDL-c levels and family history. Treatment involves diet, physical activity, and statins, and may include ezetimibe and PCSK9 inhibitors in more severe cases. Hypertriglyceridemia's can be mild to severe, with primary causes (such as familial chylomicronemia syndrome) or secondary causes (related to diet, endocrine disease, and medications). Combined dyslipidemia is common in children with obesity and insulin resistance. Treatment is based on lifestyle changes and, in more severe cases, the use of statins, fibrates, or omega-3s. Secondary dyslipidemias are associated with diseases such as diabetes, hypothyroidism, and lupus. Treating the underlying cause can normalize lipids, but medications may be indicated in cases of moderate or high risk. Early screening is essential and should be done universally between 9-11 and 17-21 years, and selectively between 2-8 and 12-16 years for children with risk factors. Early identification and management of these conditions are key to reducing cardiovascular risk in adulthood.

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Abbreviations

HDL-c: High Density Lipoprotein Cholesterol
LDL-c: Low Density Lipoprotein Cholesterol
PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9
TG: Triglycerides

Introduction

Atherosclerosis is a progressive process that begins in childhood, aggravated by high cholesterol, obesity and metabolic syndrome, increasing cardiovascular risk in adulthood. Knowledge about dyslipidemias in children has advanced, favoring more accurate diagnoses and effective treatments.

Child Lipid Profile

In children and adolescents, the lipid profile varies with age and sex. The analysis should be done after fasting for 8 to 9 hours, including total cholesterol, high density lipoprotein cholesterol (HDL-c), triglycerides (TG) and low-density lipoprotein cholesterol (LDL-c), which can be calculated or measured directly [1].

Primary Dyslipidemias

They are genetic, present from an early age, and are divided into monogenic or polygenic. The main ways are:

- Heterozygous familial hypercholesterolemia (HeFH) [2].
- Dominant genetic disease, with elevated LDL-c from birth.
- It affects 1 in 250-300 people and is among the most common inherited causes of cardiovascular disease [3].
- It is caused by mutations in the LDL receptor genes, Apolipoprotein B, Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9), among others [4].

Diagnosis: LDL-c \ge 190 mg/dL or \ge 160 mg/dL with a positive family history. Genetic testing is useful, but it can be replaced by phenotypic evaluation. LDL-c should be measured at least twice in three months [5].

Treatment: includes diet, physical activity, and statins, which should be started between 8 and 10 years old (or earlier in severe cases). Statins lower LDL-c by an average of 32% and are safe. Studies show that early initiation drastically reduces future cardiovascular events. The therapeutic goal is LDL-c \le 130 mg/dL [6-9].

Additional Therapies

- Ezetimibe lowers LDL-c by up to 27% and can be associated with statins [10,24].
- PCSK9 inhibitors (such as evolocumab and alirocumab) are indicated in cases that are resistant to or intolerant to statins.
- Evolocumab can reduce LDL-c by up to 44.5% in children. Both are approved for pediatric use [11-14].

Homozygous Familial Hypercholesterolemia (HoFH)

Severe and rare form (1:300,000), caused by mutations inherited from both parents [15,16].

LDL-c usually > 400 mg/dL, with early xanthomas and high risk of cardiovascular disease in childhood [16].
Diagnosis: based on extremely high LDL-c levels, clinical signs, and family history. Genetic testing confirms the condition and guides family treatment and screening [16].

Treatment
Early initiation with statins and ezetimibe (from 2 years old) [16].
LDL-apheresis is indicated before the age of 5 years, especially in severe cases [16].
PCSK9 inhibitors, lomitapide (not yet available for children), and evinacumab (effective even without LDL receptor action) are emerging options [17-21].
LDL-c target < 115 mg/dL, being lower in cases with established atherosclerotic cardiovascular disease, although difficult to achieve [16].

Hypertriglyceridemia's
They result from increased production of very low-density lipoprotein (VLDL) or reduction in lipolysis. TG levels between 175-885 mg/dL are mild to moderate; above 885 mg/dL are severe. Secondary causes include poor diet, endocrine disorders, medications, and alcohol [22-24].

Combined Dyslipidemia: Prevalent in children with obesity and insulin resistance. TG between 150-400 mg/dL, HDL-c < 40 mg/dL. LDL-c may be normal, but with small, dense particles that are more atherogenic [25,26].

Treatment
- Lifestyle: diet and physical activity.
- Pharmacotherapy: statins (reduce TG by up to 30%) from the age of 10; fibrates and omega-3s can be used at TG \g and 400 mg/dL [27].

Severe, Monogenic Hypertriglyceridemia
- Familial chylomicronemia syndrome: a rare, recessive disease caused by mutations in lipoprotein lipase and related genes. It manifests in childhood with TG > 1000 mg/dL, recurrent pancreatitis, retinal lipemia, and xanthomas. Treatment is based on a diet with severe fat restriction (8–10% of calories) and use of medium-chain fatty acids [28,29,30].
- Multifactorial chylomicronemia syndrome (MCS): caused by multiple genes and aggravated by factors such as diabetes, obesity, and certain medications. It is more common than familial chylomicronemia syndrome. It responds well to lifestyle changes and treatment of comorbidities [31].

Secondary Dyslipidemias
Caused by diseases or medications. The most common include [1]:
- Type 1 and 2 diabetes mellitus
- Hypothyroidism
- Chronic kidney disease
- Lupus
- Use of isotretinoin, corticosteroids, oral contraceptives
- Pregnancy
- Liver disease, among others

Treatment of the underlying condition usually normalizes the lipid profile. Lipid-lowering drugs are only indicated in patients at moderate or high risk. Statins can be initiated along with lifestyle changes in high-risk children (e.g., type 2 diabetes mellitus, end-stage renal disease), with a target LDL-c < 100 mg/dL. For moderate risk (e.g., obesity, hypertension), the goal is LDL-c \ le 130 mg/dL [9].

Tracing
It aims to detect dyslipidemia early and prevent cardiovascular events. Studies show that risk factors present in childhood, such as high body mass index, high cholesterol, and smoking, significantly increase cardiovascular risk in adulthood. Universal screening is recommended between 9-11 years and 17-21 years, preferably fasting, regardless of family history. Selective screening is indicated between 2-8 years and between 12-16 years for children with risk factors such as [32-34].
- Family history of hypercholesterolemia or premature cardiovascular disease
- Overweight/obesity
- Diabetes, hypertension or smoking

Conclusion
The early identification and management of pediatric dyslipidemias are essential for the prevention of atherosclerosis and cardiovascular diseases in adulthood. Early introduction of lifestyle interventions, judicious use of medications, and appropriate screening are proven strategies to reduce long-term risk.

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Conflict of Interest: None.

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