Dyslipidemias

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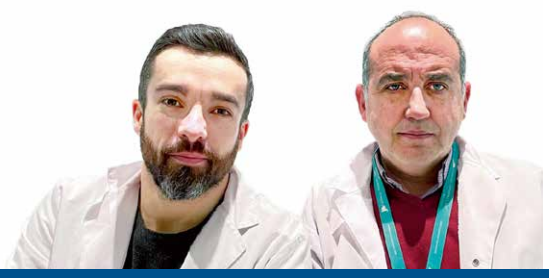

Abstract

Dyslipidemia is a major public health problem. Therefore, since the onset of the atherosclerotic process is known to occur early in children and is a key factor in cardiovascular morbidity and mortality in adulthood, it is essential to identify by means of population screening which patients are susceptible to diagnosis and thus to initial treatment of hypercholesterolemia. All this constitutes a great challenge for reducing cardiovascular mortality in the developed world, where the primary care pediatrician plays a key role. The aim of this review is to provide information on the basic hygienic and dietary measures for these patients, as well as first-line medical treatment. New therapies for the treatment of familial dyslipidemias are also discussed.

Resumen

Las dislipemias constituyen un problema de salud pública de primer orden. De esta forma, conociendo que el inicio del proceso aterosclerótico aparece ya de forma temprana en los niños y es un factor clave en la morbimortalidad cardiovascular en la vida adulta, resulta fundamental identificar mediante un cribado poblacional qué pacientes son susceptibles de un diagnóstico y con ello la instauración de un tratamiento precoz. Todo ello constituye un gran reto para reducir la mortalidad cardiovascular en el mundo desarrollado, donde el pediatra de Atención Primaria resulta clave. Mediante la presente revisión pretendemos dar a conocer las medidas higiénico-dietéticas básicas para estos pacientes, así como el tratamiento médico de primera línea. Asimismo, se comentan las nuevas terapias destinadas al tratamiento de las dislipemias familiares.

Key words: *Dyslipidemia; Hypercholesterolemia; Screening; Statins.*

Palabras clave: Dislipemia; Hipercolesterolemia; Cribado; Estatinas.

Introduction

Generally, dyslipidemia is defined as the following: total cholesterol ≥200 mg/dL, LDL-C ≥130 mg/dL, triglycerides ≥130 mg/dL, and HDL-C ≤45 mg/dL. However, it is important to note that the aforementioned parameters vary with age, particularly during puberty, and are influenced by sex. The atherosclerotic process begins at an early age when exposed to very high cholesterol levels. Therefore, classifying and diagnosing these patients is essential for the early initiation of healthy habits and pharmacological treatment, preventing the development of cardiovascular disease in adulthood.

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OBJECTIVES

- To be familiar with the normal lipid profile values by age group.
- To highlight the importance of early detection of familial dyslipidemias.
- To list the criteria for suspected genetic forms.
- To manage hypercholesterolemia in Primary Care and to identify the need for specialist assessment.
- To provide advice on the basic hygienic and dietary measures for these patients.
- To emphasize the indications and adverse effects of first-line treatments, as well as the use of second and third choice drugs.

Dyslipidemia is considered to be a value above the p95 for age and sex for total cholesterol (TC), low-density lipoproteins (LDL-C), triglycerides (TG) and below the p10 for high-density lipoproteins (HDL-C). As a guideline, TC ≥200 mg/dl, LDL-C ≥130 mg/dl, TG ≥130 mg/dl and HDL-C ≤45 mg/dl (Table I).

Plasma lipoprotein levels vary throughout childhood and adolescence. From birth, lipoprotein levels rise very slowly until they stabilize at age four, remaining almost unchanged during the prepubertal stage. Subsequently, TC and LDL-C levels decrease by up to 10% during the first years of puberty. These levels then rise at the end of puberty, stabilizing at adult levels after age 20. This increase is more attenuated in women.

HDL-C has a marked and sustained decline in males during puberty, which, together with the greater increase in

LDL-C, contributes to a more atherogenic pattern during adulthood.

Sustained exposure to elevated cholesterol levels, predominantly LDL-C, combined with environmental factors from an early age, manifests as small lipid striations in the arterial wall. These progress to thickening of the vascular intima and media, leading to an inflammatory process that causes atherosclerotic plaque, the main etiology of cardiovascular disease (CVD), which, in turn, is the leading cause of death in the developed world. Similarly, lowering cholesterol levels from an early age has demonstrated the reversibility of these initial structural alterations and a reduction in cardiovascular events in adulthood.

Although the onset of CVD before the age of 20 is uncommon, screening the pediatric population for the detection of genetically based dyslipidemia is important, since familial hypercholesterolemia is highly prevalent in our setting.

Early identification of these patients and the establishment of early treatment are essential pillars of preventive medicine for children and adults. If we add campaigns aimed at preventing smoking and excess weight, promoting physical exercise, and the early detection and treatment of high blood pressure, all of this contributes to a significant reduction in cardiovascular morbidity and mortality, improving quality of life and life expectancy[1].

Etiology

Among the primary forms, the polygenic form stands out as the most common, but familial forms should be recognized due to the importance of early diagnosis. Secondary forms, also common, should always be included in the differential diagnosis.

Dyslipidemias are classified into primary forms, of genetic origin, and those secondary to a pathology or exogenous factors.

Primary forms

- **Familial hypercholesterolemia (FH):** of monogenic basis, with autosomal dominant inheritance, caused by mutations in the gene that codes for the C-LDL receptor in approximately 90% of cases (more than 2,000 mutations have been described, the severity of which depends on the amount of residual activity of the receptor). Much less frequently, mutations in *ApoB, PCSK9* and *LDLRAB1* have been described (which contribute to the decrease in c-LDL receptors in the hepatocyte or to its malfunction)[2]. A negative genetic study does not exclude the diagnosis, if it is very suggestive.
  - Heterozygous familial hypercholesterolemia (HeFH): autosomal dominant inheritance, prevalence of approximately 1 in 215-300 people. It should be suspected in patients with LDL-C ≥160-190 mg/dl along with a family history of cardiovascular events and/or hypercholesterolemia, plus skin or corneal lesions (these are often not present in children)[3].
  - Homozygous familial hypercholesterolemia (HoFH): autosomal recessive inheritance, approximate prevalence 1 in 400,000-1,000,000, its suspicion is based on LDL-C levels >330 mg/dL, skin lesions evident before the age of 10, and a history of both parents compatible with HeFH. The severity of the condition and the response to treatment will be guided by the residual activity of the LDL-C receptor, depending on the affected gene and the type of mutation. They usually develop atherosclerosis in the 1st or 2nd decade of life and die before the age of 30, if untreated.
- **Polygenic:** the most common, affecting 4-8% of the population, they present elevated LDL-C levels (130-160 mg/dL) and usually a family history of similar cholesterol levels. Currently, there is no known genetic basis. There is speculation about the interaction of several genes with environmental factors. Its onset usually occurs later than in the previous forms.
- **Familial combined hypercholesterolemia:** autosomal dominant inheritance, with more heterogeneous genetics, they usually present the combination of elevated TC, TG, LDL-C and apoB100 together with a first-degree relative with CVD and similar laboratory tests.
- **Much less frequent:**
  - *Sitosterolemia:* autosomal recessive inheritance with an affected *ABCG5/8* gene, involved in the intestinal transporter of non-esterified cholesterol. They present very high levels of plasma phytosterols along with elevated cholesterol levels. They are characterized by the early appearance of xanthomas. They respond well to dietary measures and treatments such as resins or ezetimibe.
  - *Dysbetalipoproteinemia:* of autosomal recessive inheritance, they present elevated cholesterol and triglycerides due to alteration in the *Apo E* gene.
  - *Familial hyperchylomicronemia:* in most cases, it is due to alterations in the lipoprotein lipase gene. It is characterized by very high triglyceride levels, which greatly increases the risk of hepatosplenomegaly and pancreatitis[4].

Table I. Normal values of the lipid profile

	Acceptable	*Limit*	*High*
Total cholesterol (mg/dl)	<170	170-199	≥200
LDL-C (mg/dl)	<110	110-129	≥130
Triglycerides 0-9 / 10-17 years (mg/dl)	<75	75-99	≥99
	<90	90-129	≥130
Non-HDL (mg/dl)	<120	120-144	≥145
HDL (mg/dl)	>45	40-45	<40
Lipoprotein a (mg/dl)			≥50

Table II. Causes of secondary dyslipidemias

Endocrinological	– Obesity (with a frequent pattern of hypertriglyceridemia and decreased HDL-C), type 1 and 2 diabetes, hypothyroidism, hypercortisolism, anorexia nervosa, and lipodystrophy
Drugs	– Corticosteroids, oral contraceptives, diuretics, retinoic acid, immunosuppressants, beta-blockers, anabolic steroids, and antipsychotics
Toxics	– Alcohol
Chronic diseases	– Storage diseases – Cholestatic syndrome and pancreatitis – Renal insufficiency, nephrotic syndrome and kidney transplant – Systemic lupus erythematosus and juvenile idiopathic arthritis – Autoimmune processes, Kawasaki disease and myelomas – Heart transplant

Secondary forms

The treatment will be directed towards the etiology of the pathologies that cause it (Table II).

Diagnosis

Screening

The benefit of an effective screening strategy lies in identifying patients with genetic forms for early treatment initiation and identification of at-risk relatives. Currently, a combination of universal screening before puberty with cascade screening would be desirable.

There are different screening strategies:

- **Universal:** it attempts to reach the entire population, recommended for ages 9-11 or after 17, acknowledging that 90% of FH cases can be detected[5].
- **Selective:** only if there is a history of cardiovascular events or familial hypercholesterolemia, or if the patient has risk factors (obesity, hypertension, smoking habits or other causes of secondary dyslipidemia). It is estimated that 60% of cases can be diagnosed using this model.
- **Cascade screening:** studying first-degree relatives for whom the genetic alteration is known. Considered the most cost-effective model.
- **Reverse cascade:** in the case where the child is the index case, the study of the parents is proposed in view of the suspicion of familial hypercholesterolemia.
- **Opportunistic screening:** targeting lipid abnormalities incidentally in the context of studying another pathology, estimating that approximately <10% of familial forms are identified.

Today, there is still considerable controversy between European and American models for establishing a cost-effective dyslipidemia screening strategy, without sufficient evidence to determine a model and the age at which it should be performed[6-8]. It is estimated that it is performed by 9% of primary care physicians[9].

The most widely accepted strategy appears to be one that combines cascade and universal screening before puberty (9-11 years of age)[10]; selective screening is considered only before age 9 or during puberty (Table III). Other authors consider that the best time for screening may be before age 9; however, the vast majority do not start drug treatment before that age[9].

Although the usefulness of selective screening is clear, relying on it alone would limit the number of patients recruited, since many relatives are unaware of their lipid profile and have not yet developed CVD, if they are young parents[1].

Diagnostic guidance

After diagnosing dyslipidemia, it is essential to identify cases of familial hypercholesterolemia. These patients should be referred to a specialist to consider the appropriateness of drug treatment.

Following one of the screenings described above, a child/adolescent with suspected dyslipidemia is identified. After a detailed history and a focused physical examination, we must try to differentiate between primary and secondary dyslipidemia.

The history will collect the following data:

- Family history: primary dyslipidemia (known or suggestive genetic cause with LDL-C ≥190 mg/dl), cardiovascular diseases (age of onset, giving

Table III. Proposal for screening for familial hypercholesterolemia

Age	*Type of screening*	*When?*
0-2 years	Not recommended	
2-8 years	Selective	History of cardiovascular events or familial hypercholesterolemia, or if the patient has risk factors (obesity, hypertension, diabetes, or other causes of secondary dyslipidemia)
9-11 years	Universal	
11-16 years old	Selective	History of cardiovascular events or familial hypercholesterolemia, or if the patient has risk factors (obesity, hypertension, diabetes, smoking habits, or other causes of secondary dyslipidemia)
>17 years old	Universal	

Cascade screening: anytime from age two onwards.

Table IV. Different scoring systems for the detection of familial hypercholesterolemia

	Simon Broome Register	*Dutch Lipid Clinic Network*	*American Heart Association*	*Canadian Criteria*
Lipid profile				
Total cholesterol (mg/dl)	>290 (adults) [a] >259 (children) [a]	–	–	–
LDL cholesterol (mg/dl)	>189 (adults) [a] >155 (children) [a]	≥330 [8] 250-329 [5] 190-249 [3] 155-189 [1]	>190 (adults) [a] >155 (children) [a]	>155 (children) [a] >172.5 (18-39 years) [a] >190 (>40 years old) >330 [b]
Physical examination				
Index case	Tendon xanthoma [b]	Tendon xanthomas [6] Corneal arcus <45 years [4]	–	Tendon xanthoma [c]
Relatives	Tendon xanthoma [b]	Tendon xanthoma or corneal arcus, first-degree relative [2]	–	–
Family history				
Cardiovascular disease	Myocardial infarction <50 years in two relatives or <60 years in one relative [d]	Early coronary artery disease (<55 years old men; <60 years old women) [2] Early peripheral vascular or cerebral disease (<55 years men; <60 years women) [1]	Early coronary artery disease in a relative [b]	Coronary artery disease in men <55 years and in women <60 years [d]
LDL cholesterol (mg/dl)	>290 in one or two family members [e]	First-degree relative ≥210 [1] Child with LDL >95th percentile [2]	One affected relative [c]	One relative with elevated LDL-C [d]
Genetics	–	–	–	A relative with mutation causing familial hypercholesterolemia [c]
Personal history				
	–	Early coronary artery disease (<55 years old men; <60 years old women) [2] Early peripheral vascular or cerebral disease (<55 years men; <60 years women) [1]	–	–
Genetic studies				
Genetic mutations	Mutations in *LDLR, APOB, PCSK9* [c]	Mutations in *LDLR, APOB, PCSK9* [8]	Mutations in *LDLR, APOB, PCSK9* [d]	Mutations in *LDLR, APOB, PCSK9* [c]
Diagnosis				
Diagnosis of familial hypercholesterolemia	Certainty: a + (b or c) Probable: (a + d) or (a + e)	Certainty: >8 Probable: 6-8 points	a + (b or c) or d	Certainty: (a + c) or b Probable: a + d

Modified from: Berberich AJ, Hegele RA. The complex molecular genetics of familial hypercholesterolaemia. Nat Rev Cardiol. 2019; 16: 9-20.

importance to men under 55 years of age and women under 65 years of age).

- Personal history: pathology causing secondary dyslipidemia or chronic pathology that increases cardiovascular risk (obesity, diabetes, high blood pressure, among others).

Within the physical examination, the following will be of great importance:

- Anthropometric data: weight, height, and body mass index. We will calculate percentiles and Z-score.
- Blood pressure.

- Skin lesions: tendon xanthomas (more frequent in extensor tendons, such as the Achilles tendon), tuberous xanthomas (in elbows and knees), plantar or palmar xanthomas, xanthelasmas in the eyelid region or corneal arcus lesions.

Initially, a blood test will be requested, including a complete lipid profile (TC, TG, HDL-C and LDL-C) together with lipoprotein A if available (especially in family cases or events), useful as a predictor of premature cardiovascular events, maintaining similar levels in childhood and adulthood[1].

Non-HDL cholesterol (TC minus HDL-C) can be a very practical marker, as it is a value independent of fasting, and provides information on all "atherogenic" lipoproteins. It is currently used as an additional cardiovascular risk parameter. Thus, a high value of ≥145 mg/dL is considered elevated.

In the event of elevated levels or those at the limit of the ranges suggested below, where interindividual variability (up to 20% of the normal value) must be assessed, it is advisable to repeat the analysis (between 3 and 6 months later), ensuring strict fasting conditions (at least 12 hours, knowing that this particularly affects triglycerides), with initial guidance on diet and exercise, and within a two-month period free of acute illness and/or surgery. In addition, kidney and liver function, total protein/albumin, and thyroid function will be assessed (see Algorithm at the end of the article).

Based on the history, physical examination, and laboratory data, we may have the following suspicions:

- Secondary dyslipidemia.
- Primary dyslipidemia:
  - Polygenic hypercholesterolemia: slightly elevated LDL-C values (130-160 mg/dl), with similar levels in family members.
  - HeHF: LDL-C values greater than 190 mg/dl, with familial cases of both marked hypercholesterolemia and CVD, may be associated with skin/eye lesions.
  - HoFH: LDL-C values greater than 500 mg/dl, family history compatible with or diagnosed with HeFH/HoFH, and present skin/ocular lesions.

Various clinical scoring systems have been used to detect familial hypercholesterolemia (Table IV)[2]. In our setting, the criteria proposed by the Dutch Lipid Clinic Network[2], recommended by the WHO, have been most frequently used, extrapolated to pediatric patients. In recent years, genetic diagnosis has been incorporated into these clinical scales. It should be noted that these scoring systems are also used in most Spanish autonomous communities to request a reduction in the price of pharmacological treatment.

If familial hypercholesterolemia is suspected, these patients should be referred to a hospital with a pediatric specialist experienced in the treatment of dyslipidemia, as they will likely require medical treatment from the moment of diagnosis.

Which patients would be recommended for genetic testing? Based on the most recent scientific evidence, genetic testing would be advisable for all patients with a high probability of familial hypercholesterolemia[2]. If there is a first-degree family history of genetic mutations causing FH, genetic testing should be directed. Furthermore, genetic analysis can determine the residual activity of the LDL receptor, facilitating the implementation of personalized medicine[3].

Treatment

After confirming our patient's dyslipidemia, it is advisable to refer to specialized consultations in the following cases (see Algorithm at the end of the article):

- LDL-C values ≥190 mg/dl.
- LDL-C values ≥160 mg/dl with a family history of dyslipidemia or CVD and/or chronic disease (obesity, diabetes mellitus, chronic kidney disease, organ transplant, and history of Kawasaki disease with aneurysms).
- As long as they have a known genetic defect.

In patients with LDL-C ≥130 mg/dL, it seems reasonable to continue follow-up in Primary Care, with a repeat laboratory checkup in 6-12 months after implementing health and dietary measures and reviewing the patient's current level of physical activity. Along these lines, we recommend considering supplementation with plant sterols.

In the various guidelines on familial hypercholesterolemia in childhood and adolescence, the goal is to achieve LDL-C levels below 130 mg/dL. In our opinion, each patient should be treated individually, taking into account genetic factors, family history of CVD, and the presence of chronic disease. The most effective possible dose of the drug used without adverse effects should also be considered.

Nutritional and exercise recommendations

Although drug therapy is necessary in the vast majority of cases, dietary measures and physical exercise should be a fundamental pillar at all stages of treatment.

- **Diet:** it can reduce LDL-C by 10-15%. It should be indicated as a general measure in children from the age of two, along with the goal of maintaining BMI within normal ranges (<85p).
  Two levels of restrictive diets can be established, being the most basic level (based on CHILD –1 recommendations):
  - Fats should be 25-30% of total calories.
  - Saturated fatty acids: 8-10% of total calories.
  - Polyunsaturated fatty acids: 10% of total calories.
  - Monounsaturated fatty acids: 10% of total calories.
  - Trans fatty acids: <1%.
  - Cholesterol: <300 mg/day.

  After 3-6 months on this diet, you can consider moving to a second level of restriction (based on CHILD-2 guidelines), not being used routinely due to its difficult adherence:
  - Fats should be <25% of total calories.
  - Saturated fatty acids: <7% of total calories.
  - Polyunsaturated fatty acids: 10% of total calories.
  - Monounsaturated fatty acids: 10% of total calories.
  - Trans fatty acids: <1%.
  - Cholesterol: <200 mg/day.

Restrictive diets, mainly CHILD-2, present enormous adherence problems and can sometimes lead to an abnormal eating behavior. Therefore, for most authors today, nutritional advice based on food choices is more useful:

- Reduce consumption of red meat to once a week. Currently, there is no scientific consensus on egg consumption. In our opinion, it would be reasonable not to exceed 4 units per week (although the amount of egg whites could be increased).
- Eat fish twice a week, one of which should include blue fish.
- Avoid cooking in oil, prioritizing grilling, steaming, or boiling. Limit batters or sauces.
- Remove visible fat from food.
- Skimmed dairy products from the age of two.
- Prioritize the use of vegetable oils, especially olive oil. Very occasional consumption of butter and margarine.
- Consume fruits, vegetables, and whole grains daily. Include legumes and nuts several times a week, ensuring your daily intake of 6-20 g of fiber.
- Restrict refined sugars and added salt.
- Restrict the consumption of pastries, *snacks*, sausages, industrial pastries and pre-cooked/processed foods.

- **Nutritional supplements:**
  - Sterols/plant stanols: in addition to those naturally present in the diet and enriched foods, their use as supplements from the age of 6, at doses of 1.5-2.2 g/day, decreases intestinal fat absorption if used during main meals. Different clinical trials have demonstrated their usefulness, since they are capable of reducing LDL-C values by 8-16% in addition to the implemented diet. They have no significant side effects, and the concomitant intake of fat-soluble vitamins in the diet should be ensured[12]. In our experience, the use of plant sterols together with nutritional recommendations is a very effective measure in the treatment of polygenic hypercholesterolemia.
  - ω-3 acids at high doses can be useful in the treatment of hypertriglyceridemia. Paradoxically, on occasions, they can produce elevation of LDL-C.
  - If dietary measures are followed, it is not necessary to add fiber supplements[13].
  - Currently, there is not enough scientific evidence to systematically recommend supplementation with garlic, soy derivatives, red yeast rice or probiotics in the pediatric age[14].
- **Exercise:** ensure moderate-intensity aerobic activity a minimum of three days per week (ideally five) lasting 60 minutes each. It is also advisable to combine this with strength training if the child is mature enough. In short, non-sedentary activities should be encouraged.
- Prevention of non-exposure and initiation of tobacco habit and alcohol abuse is essential.

Medical treatment (Table V)

Indicated if:

- LDL-C ≥190 mg/dl.
- LDL-C ≥160 mg/dl with family history of dyslipidemia or premature CVD.
- LDL-C ≥160 mg/dl with risk factors (obesity, diabetes mellitus, chronic kidney disease, organ transplant, and Kawasaki disease with aneurysms).

Table V. Drugs used in the treatment of hypercholesterolemia

Statins	Rosuvastatin	From 6 years old	Start 5 mg/day, maximum 10 mg/day (20 mg if >10 years)
	Pitavastatin		Start 1 mg/day, maximum 2 mg/day (4 mg if >10 years)
	Pravastatin	From 8 years old	Start 10 mg/day, maximum 20 mg/day (40 mg if >13 years)
	Fluvastatin	From 9 years old	Start 10 mg/day, maximum 20 mg/day (40 mg if >13 years)
	Atorvastatin	From 10 years old	Start 10 mg/day, maximum 20 mg/day
	Simvastatin		Start 10 mg/day, maximum 40 mg/day
Ezetimibe		From 10 years old	10 mg/day
Resins	Cholestyramine	From 6 years old	Start 2 mg/day, maximum 4 mg/day (8 mg if >10 years)
	Colestipol*	From 6 years old	Start 2 mg/day, maximum 10 mg/day
	Coleveselam*	From 10 years old	Start 1.25 mg/day, maximum 3.75 mg/day
PCSK9 inhibitors	Evolocumab	From 10 years old	140 mg every 2 weeks or 420 mg every 4 weeks (equivalent dose)
	Alirocumab	From 8 years old	150 mg every 4 weeks (300 mg if >50 kg) (the dose can be divided every 15 days, if more effect is needed)

**Drugs whose indication is outside of normal clinical practice (off-label).*

Statins are the first-line treatment. These drugs inhibit the HMG-CoA reductase enzyme, decreasing hepatic cholesterol biosynthesis and reducing LDL-C receptors on the cell membrane. They can reduce LDL-C levels by up to 50%, secondarily triglycerides by 30%, and increase HDL-C levels by 10%.

The FDA (US Food and Drug Administration) and the EMA (European Medicines Agency) have approved rosuvastatin and pitavastatin for use in children 6 years and older, pravastatin for children 8 years and older, fluvastatin for children 9 years and older, and atorvastatin and simvastatin for children 10 years and older.

It should be started with the lowest possible dose, preferably at bedtime, monitoring its effect after two months and, subsequently, every 6 months, including the transaminase and creatine kinase profile in the analysis, given the possible appearance of adverse effects at the muscular and hepatic level (a 3-fold increase in the transaminase level or 10-fold the previous CPK level is an indication to suspend treatment with statins and consider resuming treatment after two weeks of absence of symptoms).

The occurrence of adverse effects is much more common in adults, especially due to interactions with other drugs. It should be noted that no impact on growth, pubertal development, or absorption of fat-soluble vitamins has been demonstrated; however, there is controversy in the literature regarding a possible increased predisposition to type 2 diabetes. They should not be used during breastfeeding or pregnancy[15].

If the use of statins at maximum doses does not improve the lipid profile or if the treatment is not well tolerated, second-line drugs may be used:

- Ezetimibe: Selectively inhibits intestinal absorption of both dietary and biliary cholesterol (NPC1L1 blockade). It reduces LDL-C levels by 20-27% in monotherapy, with reports of up to 90% reduction in LDL-C when combined with statins. It can be used from the age of 10, usually at a dose of 10 mg/day, regardless of food intake. The main adverse effects are diarrhea and abdominal pain.
- Ion-exchange resins: by interfering with bile acid absorption, they reduce LDL-C by 10-20%. They can be started from age 6 (colestipol and cholestyramine) or 10 (coleveselam), preferably before dinner. They are very safe options due to the lack of drug absorption; however, adherence is very difficult due to their poor palatability. Because the absorption of other drugs is impaired, they are often used as monotherapy, and the absorption of fat-soluble vitamins must also be monitored.

As a third-line treatment in pediatric patients, PCSK9 inhibitors are available. These monoclonal antibodies act on this protein in the liver, reducing the number of LDL receptors that are targeted for degradation and, consequently, increasing its availability in the membrane. Different studies have shown LDL-C reductions ranging from 24% to 30%. In Spain, evolocumab (from 10 years of age in cases of HeFH and HoFH) and alirocumab (from 8 years of age in cases of HeFH) are available. They are used in children who do not respond to treatment at maximum tolerated doses of statins or when contraindications to their use arise. They are usually administered subcutaneously every 2-4 weeks. They are relatively safe drugs, limiting their adverse effects to local reactions, arthralgia, myalgia, headache, and a possible increase in upper respiratory symptoms.

Specific forms

HeFH

Follow-up by a pediatric specialist with experience in dyslipidemia is recommended. In most cases, a combination of drug therapy and dietary measures will be necessary. As mentioned, the medical treatment of choice will be statins. The choice of these will depend on the patient's age and the experience of the center. An initial approach would be to prescribe rosuvastatin at a dose of 5 mg/day starting at age six. This could be increased to a maximum dose of 10-20 mg/day (depending on age), with the goal of lowering LDL-C levels below 160 mg/dL. However, as previously mentioned, we should advocate for precision medicine tailored to each patient[1]. Depending on the degree of response, the addition of ezetimibe at a dose of 10 mg/day may be considered[2]. PCSK9 inhibitors may be a good option in cases of poor tolerance to statins or difficulty achieving the set goals. The importance of good adherence to treatment, along with maintaining dietary and exercise recommendations, should be communicated to the family.

HoFH

Follow-up should be in a center specializing in primary dyslipidemias, with the option of performing apheresis. In these cases, the response to treatment will depend on the residual LDL receptor activity (in patients with zero residual activity, PCSK9 inhibitors will not be effective). From the moment of diagnosis, a combination of statin therapy with second- or third-line drugs will be necessary, achieving a 20-30% reduction in LDL-C. Therefore, in most cases, apheresis treatment will be necessary. This can be initiated as early as 5 years and no later than 8 years, and biweekly treatment can reduce LDL-C levels by up to 75%. This response to apheresis has led to a significant change in the prognosis of these patients. Ultimately, it is important to note that these patients may require liver transplantation.

Hypertriglyceridemia

Initial treatment will consist of implementing the aforementioned dietary recommendations, with special emphasis on fish consumption, including oily fish (sardines, salmon, tuna, mackerel, etc.), and restricting processed baked goods, animal fats, and refined sugars.

If, despite implementing the aforementioned measures, triglyceride levels remain above 200 mg/dL, supplementation with ω-3 fatty acids containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) is recommended. Initially, use a dose of 500-1,000 mg/dL and monitor for response (they can reduce triglyceride levels by up to 45%).

If, despite both measures, the triglyceride level remains above 200 mg/dl and an elevation in TC and LDL-C is observed, we should suspect familial combined hyperlipidemia and it would

be advisable to add a statin to the ω-3 fatty acid supplements.

If, despite implementing health and dietary measures along with ω-3 fatty acid supplements, triglyceride levels remain above 500 mg/dL, treatment with fibrates should be considered. Fenofibrate is the most commonly used at doses of 70-145 mg/day (maximum 200 mg/day). These drugs have frequent and significant adverse effects: rhabdomyolysis, hypertransaminasemia, dyspepsia, anemia, etc. However, the high risk of developing pancreatitis with these triglyceride levels may justify starting this therapy. Furthermore, it should be noted that in these cases, with such high triglyceride levels, there is a greater likelihood of genetically caused hypertriglyceridemia. Therefore, family history is important in guiding genetic testing.

Role of the Primary Care pediatrician

It is essential to detect these patients at a key age for preventive medicine, based on the screening strategies described above. Therefore, it is important to screen patients who are candidates for genetic testing and initiate early medical treatment.

An even more important function is to teach proper eating and exercise habits, which is the first step in any type of pediatric hypercholesterolemia.

Conflict of interest

There is no conflict of interest in the preparation of this manuscript nor source of funding.

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The asterisks indicate the authors' opinion of the article's interest.

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Recommended bibliography

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Essential reading for complete training in the study of dyslipidemia, with special emphasis on diagnostic guidance and treatment.

– Mainieri F, Tagi VM, Chiarelli F. Recent Advances on Familial Hypercholesterolemia in Children and Adolescents. Biomedicines. 2022; 10: 1043.

Update on new treatments, along with guidelines for managing familial forms.

– Fogacci F, ALGhasab NS, Di Micoli V, Giovannini M, Cicero AFG. Cholesterol-Lowering Bioactive Foods and Nutraceuticals in Pediatrics: Clinical Evidence of Efficacy and Safety. Nutrients. 2024; 16: 1526.

Extensive review of the existing literature on supplements in pediatric age.

Clinical case

Reason for consultation: the parents of a 7-year-old boy came to the Health Care Center, requesting information, since both report having hypercholesterolemia and were unsure of any possible effects on their children.

Family history: mother: 35 years old, normal weight, diagnosed with hypercholesterolemia at age 25, treated with statins since age 28 (last check-up: TC: 245 mg/dl; LDL-C: 178 mg/dl), with no other pathology of interest. Father: 38 years old, overweight, hypercholesterolemia (last check-up: TC: 215 mg/dl; LDL: 143 mg/dl), treated exclusively with diet, with no other pathology of interest.

Maternal grandmother: suffered a myocardial infarction at age 54 and was on statin therapy since age 30.

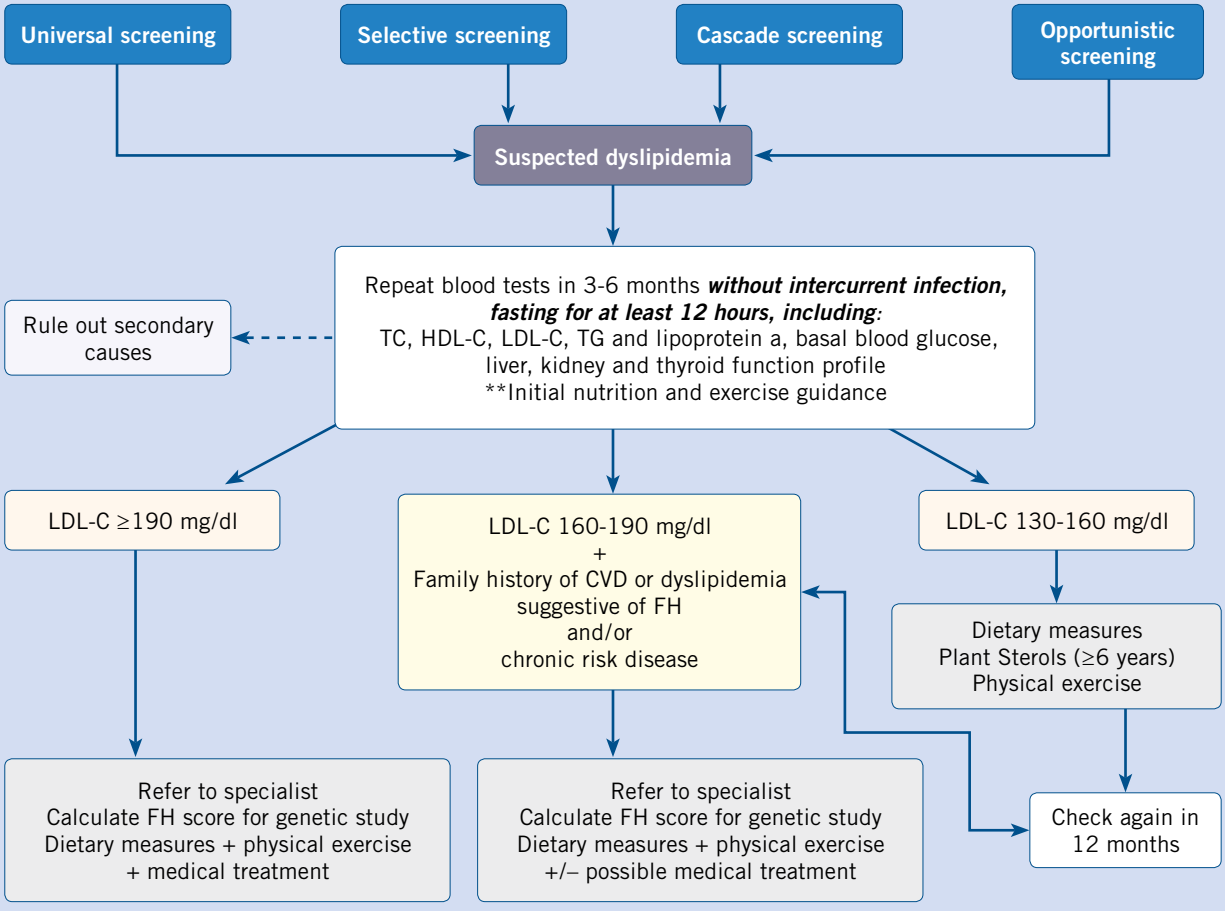
Personal background: healthy child, well vaccinated, with no known allergies.

Physical examination: weight: 28 kg (50-75 kg); height: 126 cm (50-75 kg); BMI: 17.64 kg/m^2 (50-75 kg); BP: 105/64 mm Hg; no skin lesions or eye abnormalities, Tanner stage I.

A 12-hour fasting lipid profile was performed through a selective screening test, which revealed: TC: 287 mg/dl; LDL-C: 198 mg/dl; HDL: 67 mg/dl; triglycerides: 75 mg/dl; thyroid profile: normal; basal glucose: 95 mg/dl; and HbA1c: 5.4%.

The primary care pediatrician decides to send him to a specialized lipid unit, where his family members say they have also started drug treatment.

Algorithm. Diagnostic and therapeutic guidance for dyslipidemia in childhood



CVD: cardiovascular disease; FH: familial hypercholesterolemia; TC: total cholesterol; TG: triglycerides.

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Accreditation quiz

Subsequently, the following accreditation quiz of Pediatría Integral collects questions on this topic, which must be answered online through the website: www.sepeap.org.
In order to obtain certification by the Spanish "formación continuada" national health system for health professionals, 70% of the questions must be answered correctly. The accreditation quizzes of the different numbers of the journal may be submitted during the period indicated in the "on-line" quiz.

Dyslipidemias

25. What is the MOST COMMON form of primary dyslipidemia?

a. Heterozygous familial hypercholesterolemia, alteration in PCSK9 and autosomal recessive inheritance.
b. Homozygous familial hypercholesterolemia, alteration in LDL receptor and autosomal recessive inheritance.
c. Heterozygous familial hypercholesterolemia, alteration in LDL receptor and autosomal dominant inheritance.
d. Familial hyperchylomicronemia.
e. Polygenic hypercholesterolemia.

26. Which of the following findings seems MORE SUGGESTIVE of familial hypercholesterolemia to you?

a. Triglycerides of 120 mg/dl.
b. LDL-C of 250 mg/dl.
c. Maternal grandfather with stroke at 87 years old.
d. Mother with LDL-C at 145 mg/dl.
e. Total cholesterol (TC) of 210 mg/dl.

27. In the context of a laboratory study for morning fatigue in a 7-year-old girl, an LDL-C level of 210 mg/dL was found, with normal laboratory results. This value, suggestive of possible genetic dyslipidemia, was detected. WHAT TYPE OF screening is used?

a. Universal screening.
b. Selective screening.
c. Reverse cascade screening.
d. Cascade screening.
e. Opportunistic screening.

28. Of the following, which is the MAIN adverse effect of statins?

a. Pubertal delay.
b. Rhabdomyolysis.
c. Poor growth.
d. Induction of type 2 diabetes.
e. Incompatibility of use with other drugs.

29. The use of ion exchange resins is not usually a common practice in Pediatrics. What IS IT DUE TO?:

a. It is a drug with numerous adverse effects.
b. The high absorption of the drug increases its side effects.
c. Adherence to treatment is usually reduced due to its poor palatability.
d. They are not approved by the EMA and are used outside of standard recommendations.
e. Its use is limited in Pediatrics, due to decreased absorption of vitamin D.

Clinical case

30. Regarding the follow-up of the patient in the clinical case, indicate the CORRECT answer:

a. The LDL-C value is most likely in the context of dyslipidemia of secondary cause.
b. LDL-C level, family history of dyslipidemia and cardiovascular disease are highly suggestive of familial hypercholesterolemia and should be evaluated by a specialist.
c. This patient most likely does not need medical treatment, so it should not be referred.
d. Only dietary measures and repeated analytical monitoring in Primary Care will be necessary.
e. The absence of skin lesions excludes the possibility of familial hypercholesterolemia.

31. Until the patient is evaluated by a specialist, dietary and exercise measures are proposed. Of the following statements, which do you consider INCORRECT?

a. It is advisable to avoid processed foods for breakfast.
b. The amount of vegetables per meal and the number of days its eaten should be increased.
c. They should ensure three days of moderate activity exercise.
d. You recommend starting red yeast rice supplements.
e. Along with dietary measures, treatment with plant sterols will be recommended.

32. In the hypothetical case of recommending the start of medical treatment in this patient, what do you consider to be the BEST OPTION?

a. The start of ezetimibe at a dose of 10 mg/day.
b. He is too young to start medical treatment; he should continue with dietary measures, exercise and plant sterols.
c. Rosuvastatin 5 mg/day orally.
d. Fenofibrate 70 mg/day orally.
e. Evolocumab at 140 mg/2 weeks, subcutaneously.