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Review Article

A mechanism-based operational definition and classification of hypercholesterolemia

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Abstract: In contrast to strong evidence-based clinical recommendations for lipid-lowering treatment, there is no analogous definitive diagnostic definition of hypercholesterolemia and its various subtypes. For many clinicians, guideline indications for hypolipidemic treatment can become broadly conflated with hypercholesterolemia in a non-specific sense. In this statement, we propose a unified definition and mechanism-based classification of hypercholesterolemia, which in turn should help to stratify patients and guide efficient diagnosis without interfering with the current strategies of ASCVD risk reduction.

Introduction

Plasma concentration of atherogenic cholesterol is mainly determined by circulating levels of the cholesterol transported within the apoB-containing lipoproteins represented by low-density lipoproteins (LDL) but also small very low-density lipoproteins (VLDL), intermediate-density lipoproteins (IDL) and lipoprotein(a) [Lp(a)].[1,2] These fractions of circulating cholesterol are recognized to be the causal factor for development of atherosclerotic cardiovascular disease (ASCVD).[3] Therefore, the precise blood lipid measurements and the reduction of circulating levels of atherogenic lipoproteins are key procedures to reduce the onset or recurrence of ASCVD. Notably, the benefit of cholesterol-lowering treatments is present also when the levels of plasma total cholesterol are not markedly elevated.[4] For this reason, pharmacological lipid-lowering interventions have provided earned position as a very useful tool to reduce ASCVD risk, even in the absence of obvious hypercholesterolemia[5,6] i.e. when stretching the concept of relative "hypercholesterolemia" down to an LDL cholesterol (LDLc) value of 55 mg/dL (1.4 mmol/L). Even at such low levels of LDLc, individuals continue to benefit from lipid-lowering. Setting the diagnostic threshold for "hypercholesterolemia" this low, the vast majority of the general

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population would necessarily be considered as "hypercholesterolemic" and this, in turn, would not be clinically pragmatic.

At present, there is no clear universally accepted definition of "hypercholesterolemia". The threshold value of LDLc that triggers initiation or intensification of lipid-lowering drug treatment in at-risk patients is quite different from the LDLc that defines a patient as having a diagnosis of clinical hyperlipidemia. However, subjects who receive lipid-lowering treatment are often misclassified or considered to have hypercholesterolemia even though their lipid profile does not actually conform to any particular objective criterion used to diagnose hypercholesterolemia or dyslipidemia, e.g. 95th percentile for age and sex.[7,8]

We mainly aim to define the different types of hypercholesterolemia, not in terms of the ASCVD risk they eventually may impart, but rather according to their underlying pathogenic mechanism. Our intention is not to perturb recommendations for lipid-lowering treatment from various expert panels of different scientific societies and jurisdictions.[9,10] The benefit of reducing cholesterol carried within atherogenic lipoproteins is independent of the underlying cause, and in relative terms, would be comparable whether the LDLc elevation is primary or results secondarily from diabetes, thyroid disease, liver disease, chronic renal disease or poor diet and lifestyle.[11,12] Current clinical practice guidelines provide indications for treatment based on threshold levels of LDLc concentration and the individual ASCVD risk, with comparatively little concern for the underlying mechanism(s) of the LDLc elevation. This new classification should help to better select different specialized diagnostic tests, improve knowledge of the pathogenic mechanism of hypercholesterolemia, and in some cases, favor the use of specific treatments, as is in the case of inherited enzyme deficiencies.

Hypercholesterolemia

Any definition of hypercholesterolemia would be somewhat arbitrary since the blood cholesterol concentration is a continuous variable that varies by sex and age.[13] There is a large overlap in lipid levels across different metabolic states associated with hypercholesterolemia, and the levels merge with the upper range of the normal population distribution in healthy individuals.[14] Many years ago, the US National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) defined hypercholesterolemia as total cholesterol $>$ 200 mg/dL ($>$ 5.2 mmol/L),[15] and for decades this value was subsequently adopted and used across many settings and jurisdictions. However, this traditional definition of hypercholesterolemia has several limitations. First, it is arbitrary like any other definition, chosen in part because it is round number for American physicians. Second, the lipid profile varies according to age and sex; for example, average LDLc levels for a healthy 50-year-old man would be extremely elevated for an 18-year young man. Furthermore, young women with total cholesterol $>$ 200 mg/dL sometimes have elevated concentrations of high-density lipoprotein cholesterol (HDLc), with relatively normal concentrations of atherogenic lipoprotein concentrations. The prevalence of total cholesterol $>$ 200 mg/dL is sufficiently high in the general adult population as to be non-specific, with no implication of a particular etiological diagnosis. Individuals with total cholesterol concentrations between 200-250 mg/dL (5.2-6.5 mmol/L) usually do not have a discrete identifiable disorder of lipid metabolism. Levels in this range fall within the distribution of healthy normolipidemic people and are frequently the consequence of the combined small effects of multiple environmental and genetic factors that are not necessarily pathological. After assessment of global cardiovascular risk, many of such individuals might still benefit from lipid-lowering treatment but do not actually have a discrete or definable lipid metabolism disorder. By analogy with antiplatelet therapy, a patient may benefit from taking aspirin, without having an underlying discrete platelet disorder or syndrome.

We suggest that hypercholesterolemia is defined based on LDLc and non-HDLc concentrations, since these are the most abundant atherogenic lipoprotein fractions.[1] Most causes of hypercholesterolemia raise both LDLc and non-HDLc. Furthermore, as hypercholesterolemia due to high HDLc often has different clinical significance, etiology and prognosis, and its modulation does not alter ASCVD risk, it can be excluded from the definition of hypercholesterolemia.

We have chosen the threshold levels of LDLc and non-HDLc in the present document (130 and 160 mg/dL, or 3.4 and 4.1 mmol/L, respectively) in part because NCEP ATP III has already defined them in the past as being predictive of ASCVD risk.[15] The knowledge of LDLc and non-HDLc already have proven clinical utility; e.g. they demonstrate excellent sensitivity in screening of hypercholesterolemia of genetic origin in adults;[14] and the threshold level chosen for either elevated LDLc or non-HDLc divides the population into lower- and higher-risk groups associated with an approximate doubling of ASCVD risk.[16,17] However, the threshold levels of LDLc and non-HDLc chosen to define primary hypercholesterolemia are usually higher (see below), and are situated within the lower range of levels for most genetic hypercholesterolemias in adults.[14,18–20] As an example, among 8,577 CAD-free control participants from the Myocardial Infarction Genetics Consortium cohorts, the prevalence of a FH mutation increased across categories of LDLc levels, and especially when LDLc $\geq$ 190 mg/dL ($\geq$ 5 mmol/L).[14]

Lipid based definitions

Hypercholesterolemia: Defined as plasma concentration of LDLc $\geq$130 mg/dL ($\geq$3.4 mmol/L) and/or non-HDLc $\geq$160 mg/dL ($\geq$4.1 mmol/L).

Primary isolated hypercholesterolemia: LDLc $\geq$ 190 mg/dL ($\geq$ 5 mmol/L) and normal triglycerides ($<$150 mg/dL or $<$1.7 mmol/L). For practical purposes, we use to cut off levels of $<$150 mg/dl (or $<$1.7 mmol/L) for normotriglyc-

eridemia following the EAS recommendations[19] and in this way we differentiate isolated hypercholesterolemia from combined hyperlipidemia, since in many cases these have different etiologies, whose identification is essential in the diagnostic work up of hypercholesterolemia

Combined hyperlipidemia: Defined as non-HDLc ≥ 220 mg/dL (≥ 5.7 mmol/L) + triglycerides ≥ 150 mg/dL (≥ 1.7 mmol/L).

In the presence of hypertriglyceridemia, the calculation of LDLc is less reliable and the use of non-HDLc facilitates diagnosis in clinical practice. When triglycerides are normal (< 150 mg/dL or < 1.7 mmol/L) the amount of cholesterol in TG-rich particles is usually normal (<30 mg/dL or < 0.8 mmol/L) and can be reliably calculated using the Friedewald formula.[20] In this situation, the calculated LDLc concentration will better identify the presence of hypercholesterolemia. However, when triglycerides are elevated, cholesterol may be increased in VLDL, IDL and / or LDL fractions, and focusing only on LDLc may impair sensitivity for the diagnosis of different clinical subtypes of hypercholesterolemia that are concurrently associated with hypertriglyceridemia. The non-HDLc cut-off point for the diagnosis of combined hyperlipidemia adds 30 mg/dL (0.8 mmol/L) to the LDLc cut-off point used in treatment guidelines, and has been proven to have excellent sensitivity for the diagnosis of the different hypercholesterolemia associated with combined hyperlipidemia.[21–23]

Classification

Hypercholesterolemia can be primary, secondary to another disease or condition, or multifactorial. The primary forms, in turn, can be genetic or idiopathic (Table 1). All genetic hypercholesterolemia is primary, but not all primary presentations of hypercholesterolemia are genetic. There remains a subset of hypercholesterolemia patients in whom a clear primary cause cannot be identified[24] (Figure 1).

There are several clinical situations as well as commonly used drugs that can modify cholesterol levels.[25–27] The list is extensive, but in few cases an associated disease can be implicated for the altered lipid profile. Here we define two different situations. The former is secondary hypercholesterolemia that is entirely attributed to the associated disorder, such as pregnancy,[28] nephrotic syndrome,[29] hypothyroidism,[30] anorexia nervosa[31] or cholestasis,[32] very high saturated fat intake[33] or the use of certain drugs[34–37] (Table 1). These disorders usually result in an increase in LDLc concentration by > 20%, hence the presence of any of these factors often underlies hypercholesterolemia according to thresholds indicated above. By definition, the disturbance is secondary; upon correcting the underlying cause, the lipid profile should normalize. If hypercholesterolemia persists, it should prompt further assessment and possible reclassification as a primary condition.

A second group of factors can promote the development of hypercholesterolemia. These so called "promoting" factors include overweight, obesity, inactivity, metabolic syndrome or pre-diabetes, diabetes, diets rich in saturated fat, chronic kidney disease with GFR <30 mL/min, alcohol intake > 30 g/day, or use of certain drugs, e.g. estrogens, corticosteroids, thiazide diuretics, atypical antipsychotics, retinoids, progestogens, or interferons (Table 2). It must be pointed out that, though these factors may not be sufficient to cause a clinically relevant perturbation of cholesterol levels,[27,38] their presence on top of an endogenous background of predisposing polygenic risk, can trigger the clinical expression of hypercholesterolemia. However, the presence of promoting factors does not lead per se to the diagnosis of secondary hypercholesterolemia.

Certain promoting factors, particularly obesity, diabetes and diets rich in saturated fat frequently lead to a combined hyperlipidemia phenotype, which typically has an underlying polygenic basis.[39] When this phenotype clusters in families, it often gives the superficial and misleading appearance of Mendelian inheritance, which in turn has led to the erroneous designation of familial combined hyperlipidemia, implying a monogenic disorder, like familial hypercholesterolemia (FH). In fact, combined hyperlipidemia has a similar polygenic architecture to isolated hypertriglyceridemia.[39,40]

Definitions

1. Secondary hypercholesterolemia: This is defined as hypercholesterolemia that occurs in the presence of pregnancy, nephrotic syndrome, hypothyroidism, anorexia nervosa or cholestasis, or certain drugs.
2. Primary hypercholesterolemia: This is defined as hypercholesterolemia that occurs in the absence of a secondary cause and fulfilling one the following categories:
   - 2.a Genetic hypercholesterolemia: Primary hypercholesterolemia with a diagnostic genetic study and/or strong family history and very high values of LDLc or non-HDLc. It can be defined by:
     - I) Hypercholesterolemia (LDLc ≥130 mg/dL [≥ 3.4 mmol/L] or non-HDLc ≥160 mg/dL [≥ 4.1 mmol/L]) plus a definitive diagnostic genetic study. Individuals with a "pathogenic" or "likely pathogenic" variant in a gene for monogenic hypercholesterolemia or those with a high polygenic score for LDLc (often set at >75th or >90th percentile of the distribution of such scores). or
     - II) Primary hypercholesterolemia with evidence of Mendelian inheritance in multigenerational families and LDLc ≥190 mg/dL ≥ (4.9 mmol/L) or non-HDLc ≥220 mg/dL (≥ 5.7 mmol/L). or
     - III) Primary hypercholesterolemia with lipoprotein(a) (Lp(a)) ≥ 100 mg/dL and LDLc ≥190 mg/dL (4.9 mmol/L) or non-HDLc ≥220 mg/dL (5.7 mmol/L).
   - 2.b Idiopathic primary hypercholesterolemia: Primary hypercholesterolemia with LDLc ≥190 mg/dL (4.9 mmol/L) or non-HDLc ≥220 mg/dL (5.7 mmol/L)

Table 1 Classification of hypercholesterolemias

1. Primary
   a. Genetic
      (a) Monogenic
         i. Dominant
            Familial hypercholesterolemia
               Heterozygous
               Homozygous
            Dominant dysbetalipoproteinemia
         ii. Recessive
            Autosomal recessive hypercholesterolemia
            Common dysbetalipoproteinemia
            Sitosterolemia
            Lysosomal acid lipase deficiency
         iii. Complex: **Hyperlipoproteinemia(a)**
      (b) Polygenic: **Polygenic hypercholesterolemia**
   b. Idiopathic
2. Secondary
   a. Hypothyroidism
   b. Nephrotic syndrome
   c. Cholestasis
   d. Pregnancy
   e. Anorexia nervosa
   f. Very high saturated fat intake
   g. Drugs:
      - Anabolic steroids
      - Protease inhibitors
      - Immunosuppressive agents
      - Corticosteroids (high dose)
3. Multifactorial
   a. Multifactorial isolated hypercholesterolemia
   b. Multifactorial combined hyperlipidemia

Table 2 Medications associated with hypercholesterolemia

Usually responsible	Promoting
Anabolic steroids	Retinoids
Protease inhibitors	Corticosteroids (low dose)
Immunosuppressive agents	Thiazides
Corticosteroids (high dose)	Antipsychotics
	Progestogens

in the absence of criteria for genetic hypercholesterolemia and any predisposing secondary condition or promoting factor.

3. Multifactorial hypercholesterolemia: Hypercholesterolemia with LDLc ≥130 mg/dL (3.4 mmol/L) or non-HDLc ≥160 mg/dL (4.1 mmol/L) and absence of criteria for primary and secondary hypercholesterolemia.

In the presence of an LDLc ≥130 mg/dL (≥ 3.4 mmol/L) or non-HDLc ≥160 mg/dL (≥ 4.1 mmol/L), the first step should exclude a secondary form. In its absence, assess whether there is a significant family history of hypercholesterolemia and very high levels of LDLc [≥190 mg/dL ≥ (4.9 mmol/L)] or non-HDLc [≥220 mg/dL (≥ 5.7 mmol/L)]. If both are present, we must analyze if the family history is compatible with a dominant monogenic disease, in which case we must analyze the candidate genes: *LDLR, APOB, PCSK9, APOE* for the diagnosis of FH; or a recessive disease, then test *APOE* for dysbetalipoproteinemia; *LDLRAP1* for ARH; *ABCG5/ABCG8* for sitosterolemia; and *LIPA* for LAL deficiency. If the genetic study is negative, analyze Lp(a) concentration and the polygenic score for the diagnosis of hyperlipoproteinemia(a) or polygenic hypercholesterolemia, respectively. In the absence of criteria for monogenic disease, hyperlipoproteinemia(a) or polygenic hypercholesterolemia, the diagnosis will be idiopathic primary or multifactorial hypercholesterolemia in the absence or presence of promoting factors, respectively.

Classification and definition of primary hypercholesterolemia

Monogenic

Heterozygous (mono-allelic) familial hypercholesterolemia (HeFH): Genetic hypercholesterolemia being heterozygous for a rare variant identified in *LDLR, APOB* or *PSCK9* genes classified as "pathogenic" or "likely pathogenic," according to the guidelines of the American

College of Medical Genetics and Genomics (ACMG)[41] or the p.(Leu167del) variant in *APOE*.[42]

In the absence of a definitive genetic study or an inconclusive result (e.g. for variants of uncertain significance (VUS) according to ACMG criteria) this condition can still be diagnosed clinically if there is severe hypercholesterolemia with tendon xanthomas in the proband or first degree relative, or in the presence of LDLc >250 mg/dL (6.4 mmol/L) in the proband or in a first-degree relative plus dominant hypercholesterolemia pattern, with vertical transmission in multigenerational pedigrees and approximately 50% affected first degree relatives, with only one affected parent.

Homozygous (bi-allelic) familial hypercholesterolemia (HoFH): Genetic hypercholesterolemia due to biallelic variants, incompletely covered by the term "homozygosity", which also includes compound heterozygosity or double heterozygosity for two pathogenic or likely pathogenic variants in *LDLR, APOB, PCSK9* or *APOE*.

Monogenic recessive hypercholesterolemia: Genetic hypercholesterolemia with homozygosity for two pathogenic or likely pathogenic variants in *LDLRAP1*.[43] Bi-allelic pathogenic variants in other genes that classically cause distinct dyslipidemias, such as *ABCG5/ABCG8* in sitosterolemia or *LIPA* in lysosomal acid lipase deficiency, can rarely produce a phenotype that resembles homozygous hypercholesterolemia.[44]

Dysbetalipoproteinemia: Dysbetalipoproteinemia (formerly type III hyperlipoproteinemia) is a severe combined hyperlipidemia caused by the accumulation of triglyceride-rich remnant particles in plasma, also called β-VLDL that can be visualized or isolated only by ultracentrifugation or another resource intensive fractionation method. It results most often from predisposition to abnormal particle catabolism due to homozygosity for receptor-defective binding apo E2 isoforms encoded by variation in the *APOE* gene.[45] Dysbetalipoproteinemia (DBL) represents 2-5% of patients with combined dyslipidemias treated in specialized lipid referral centers. DBL is highly atherogenic and predisposes to diffuse atheromatosis, and is associated with pathogenic features such as palmar, planar and tuberous xanthomatosis.[46] This condition is seen in ~ 1 in 10000 to 20000 individuals and is diagnosed based on clinical features, but also suggestive biochemical findings, including non-HDLc ≥160 mg/dL (4.1 mmol/L). Because the diagnostic β-VLDL subfraction cannot be routinely detected, variables that can help with diagnosis include a non-HDLc to apo B ratio >1.43 (in mg/dL) together with *APOE* genotyping showing homozygosity for *APOE* E2/2 genotype or very rarely heterozygosity for a dominant pathogenic *APOE* variant leading to dysbetalipoproteinemia.[47,23]

Sitosterolemia: Sitosterolemia, also called phytosterolemia, is a rare autosomal recessive disease caused by homozygous or compound heterozygous mutations affecting *ABCG5* or *ABCG8* genes, preventing the creation of heterodimers that efflux free sterols from hepatocytes and enterocytes into the bile and intestine, respectively.[48] Plant sterols are characteristically 30- to 100-fold elevated in plasma in sitosterolemia. Approximately one third of patients with sitosterolemia have biallelic (i.e. homozygous or compound heterozygous) pathogenic variants in the *ABCG5* gene while two thirds of patients have biallelic pathogenic variants in *ABCG8* gene. The most frequent clinical presentation includes moderate elevation of LDLc, tendon xanthomas, and premature ASCVD.[49] As the usual

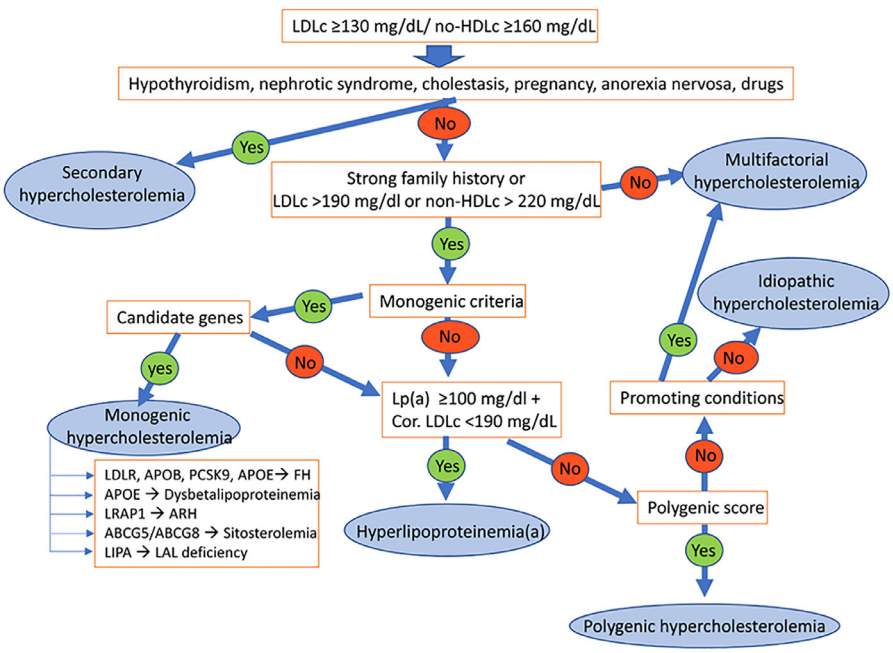

Figure 1 Diagnostic algorithm for hypercholesterolemia. LDLc denotes low-density lipoprotein cholesterol; HDLc, high-density lipoprotein cholesterol; Lp(a), lipoprotein(a); Cor. LDLc, LDL cholesterol corrected for the Lp(a) cholesterol content; FH, familial hypercholesterolemia; ARH, autosomal recessive hypercholesterolemia; LAL, lysosomal acid lipase.

enzymatic methods cannot differentiate between cholesterol and phytosterols, therefore the biochemical diagnosis of sitosterolemia requires gas chromatography or high-performance liquid chromatography to detect plasma plant sterols.[50] The definitive diagnosis of sitosterolemia requires identification of biallelic pathogenic variants in *ABCG5* or *ABCG8*, together with elevated plant sterols in plasma.

Lysosomal acid lipase deficiency: Lysosomal acid lipase deficiency (LALD) is a rare autosomal recessive disorder characterized by a huge accumulation of cholesterol esters and triglycerides in hepatocytes and macrophages in multiple organs, especially liver.[51] LALD is caused by biallelic loss-of-function variants in *LIPA*, the gene coding for LAL, an enzyme that hydrolyzes cholesteryl esters and triglycerides to produce free fatty acids and cholesterol intracellularly.[52] The clinical spectrum of LALD is varied in relation to the intensity of the deficiency of LAL. The most serious form associated with complete deficiency of the enzyme is called Wolman's disease and presents with severe liver disease from the first years of life. Less severe defects produce cholesteryl ester storage disease (CESD) resulting in a variable clinical presentation, including combined hyperlipidemia, hepatosplenomegaly, elevated liver enzymes and premature atherosclerosis.[53] Liver biopsy shows characteristic microvesicular steatosis and birefringent CE crystals. The suspected diagnosis is based on the presence of a combined hyperlipidemia, with elevated transaminases, hepatomegaly and hepatic steatosis in young patients without risk factors for a non-alcoholic steatohepatitis. Confirmatory diagnosis requires the presence of at least two of the following criteria: deficient LAL activity, usually measured in dried blood spot; biallelic (i.e. homozygous or compound heterozygous) pathogenic or likely pathogenic variants in *LIPA*; and microvesicular steatosis with birefringent CE crystals in the liver biopsy.[54]

Hyperlipoproteinemia(a): Defined as genetic hypercholesterolemia with Lp(a) $\geq$100 mg/dL (or 214 nmol/L) + adjusted for Lp(a) LDLc < 190 mg/dL (< 4.9 mmol/L) and non-HDLc < 220 mg/dL (< 5.7 mmol/L). Certain subjects with very high concentrations of Lp(a) have a biochemical, although not clinical phenotype, that resembles HeFH.[55,56] The concentration of Lp(a) is > 90% genetically determined by both size polymorphism and small single nucleotide polymorphisms at the *LPA* locus on chromosome 6, and varies little throughout life. Elevated Lp(a) can thus justifiably be considered as a genetic hypercholesterolemia.[57] Its inheritance does not correspond clearly to a typical dominant or codominant Mendelian pattern, since the Lp(a) concentration is not the simple arithmetic sum of the effect of the two alleles of *LPA* separately. For this reason, we suggest that hyperlipoproteinemia(a) should be defined as a complex genetic hypercholesterolemia (Table 1).

Non-HDLc and LDLc are adjusted for the Lp(a) cholesterol content by subtracting 30% of the individuals' Lp(a) total concentration,[58] although there is substantial variability among individuals when this simple correction factor is applied.[59,60] There is an important scientific need to reliably quantify the amount of cholesterol transported by Lp(a).

Polygenic hypercholesterolemia (PH)

Polygenic hypercholesterolemia (PH): This is defined as a genetic hypercholesterolemia that does not meet criteria for monogenic disorder, e.g. HeFH, with a hypercholesterolemia polygenic score (PS) >75th percentile of the distribution. A polygenic score to explain the case of apparent HeFH but in which no pathogenic or likely pathogenic variant was found, was first described by Talmud, Humphries et al, and represented an extraordinarily important conceptual advance in the diagnosis of genetic hypercholesterolemias.[61] They clearly demonstrated that some forms of primary hypercholesterolemia that fulfilled clinical criteria for HeFH did not have a pathogenic variant in any of the candidate genes, but instead had inherited an excessive burden of common, small effect variants from different chromosomes throughout the genome, which individually only slightly raise LDLc but which in aggregate raise LDLc into the range that would prompt consideration of HeFH as a possible diagnosis. This has been confirmed in different massive sequencing studies of all coding exons screening for new putative FH genes, which confirm that many presumed HeFH patients do not have a single monogenic variant, but instead have accumulated a large burden of small effect variants that are quantified using a polygenic score. A high polygenic score is defined from the distribution in the general population: a high score is often at the 75th or 90th percentile of scores.[62]

Idiopathic primary hypercholesterolemia (IPH)

Primary hypercholesterolemia in the absence of compatible genetic hypercholesterolemia criteria and LDLc >190 mg/dL (4.1 mmol/L) and/or non-HDLc >220 mg/dL (5.7 mmol/L) and any predisposing secondary condition or promoting factor. Diagnosis of FH and PH should be restricted to those in whom a genetic study confirms the diagnosis. Probably, many cases of IPH have a polygenic basis. However, the current available polygenic scores have different limitations (Table 3)[63–67] and they are not available to many laboratories. For these reasons, some authors consider that a hypercholesterolemia due to an increase in LDLc in which secondary causes are excluded, with family presentation and which excludes mutations in FH genes should be considered as polygenic.[68,69] This document prefers to limit the concept of PH to those cases in which it is specifically confirmed by genetic testing, rather than a diagnosis of exclusion. Other possible causes for hypercholesterolemia that is neither monogenic FH or polygenic include undetected monogenic hypercholesterolemia due to variants inaccessible by current sequencing approaches, variants in as yet unidentified genes, gene-gene or gene-environment interactions, epigenetic imprinting or yet unknown genetic or non-genetic mechanisms.[26]

Table 3 Important facts of polygenic scores (PS) in the diagnosis of hypercholesterolemia

Polygenic scores (PSs) measure the aggregated effect of common alleles identified in genome-wide association studies (GWAS) on low-density lipoprotein cholesterol (LDLc) concentration.
Subjects in the upper extreme of PS may have a severe hypercholesterolemia resembling monogenic familial hypercholesterolemia (FH).
Multiple PSs have been used with variable number and different genetic variants, but there is no consensus on which to use in clinical practice.
Different cut-offs from above 75th to above 90th percentiles of the PS have been used in research studies to define polygenic hypercholesterolemia, but there is no consensus for clinical use.
PSs, even including hundreds of genetic variants, explain no more than 10% of LDLc variance
PSs should be adapted to the genetic background of the population to study.
A high PS does not exclude FH: there are many patients who have both a pathogenic rare variant in a canonical gene plus a high PS. These patients have a more severe hypercholesterolemia phenotype.
Patients with polygenic hypercholesterolemias have a risk of ASCVD that is intermediate between those FH and those with no identified genetic cause of hypercholesterolemia.

Multifactorial hypercholesterolemia (MH)

Multifactorial hypercholesterolemia (MH): This is defined as hypercholesterolemia with LDLc $\geq$ 130 mg/dL ($\geq$ 3.4 mmol/L) or non-HDLc $\geq$ 160 mg/dL ($\geq$ 4.1 mmol/L) and absence of criteria for primary or secondary hypercholesterolemia as predominant contributor. MH is the most common form of hypercholesterolemia and is the result, in most cases, of the combination of unidentified polygenic factors and promoting factors, such as overweight and obesity, which act as promoters of the phenotype. Often, both genetic and environmental factors coalesce in families, resulting in confusion of this situation with a monogenic phenotype. When this hypercholesterolemia presents in combination with hypertriglyceridemia, it has been traditionally called familial combined hyperlipidemia.[70] This document prefers the term multifactorial isolated hypercholesterolemia or multifactorial combined hyperlipidemia, since it better responds to its etiology and can help patients and physicians to be aware of the importance of suppressing the promoting environmental factors.[71]

Conclusion

A diagnosis of hypercholesterolemia is more complicated and has deeper clinical implications than simply exceeding a threshold value to trigger therapy to prevent ASCVD according to clinical practice guidelines. When hypercholesterolemia occurs as a result of a secondary cause, it is essential to know these causes since intervening on them can help ameliorate the lipid disturbance. Similarly, knowing that a patient has a primary hypercholesterolemia such as FH implies that more intensive treatment, including combination treatment and use of novel therapies such as inhibitors of proprotein convertase subtilisin kexin 9 will be required to help the patient achieve target or threshold lipid values. Also, diagnosing certain hypercholesterolemia patients who actually have sitosterolemia or lysosomal acid lipase deficiency directs the treatment towards tailored pathways instead of simply statins. Similarly, hypercholesterolemia patients who have dysbetalipoproteinemia or combined hyperlipidemia might require combination therapy with triglyceride lowering agents in addition to statin therapy. Thus, while lipid lowering guidelines to prevent ASCVD remain paramount for evidence-based medical practice, a mechanism-based diagnostic structure for various etiologies of hypercholesterolemia such as that proposed here can help with selection and timing of appropriate treatment regimens to help with the main goal of LDLc reduction.

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