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FAMILIAL HYPERCHOLESTEROLEMIA IN YOUNG ADULTS: CHALLENGES IN DIAGNOSIS AND IMPLEMENTATION OF CURRENT GUIDELINES – A NARRATIVE REVIEW

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ABSTRACT

Background. Familial hypercholesterolemia (FH) is a common autosomal dominant genetic disorder associated with premature atherosclerotic cardiovascular disease. Despite established international guidelines, FH remains substantially underdiagnosed, particularly in young adults.
Aim. This narrative review summarizes current evidence on diagnostic challenges and barriers to guideline implementation in this population.
Methods. A narrative literature review was conducted using PubMed/MEDLINE, Scopus, and Web of Science databases. The review focused on evidence regarding FH epidemiology, diagnostic approaches, genetic testing, cascade screening, treatment strategies, and implementation gaps in young adults.
Results. Registry data indicate that the median age of FH diagnosis is 44.4 years, suggesting delayed identification and prolonged exposure to elevated low-density lipoprotein cholesterol levels during early adulthood. In young adults, diagnosis is often limited by the absence of overt clinical signs, reducing the utility of clinical scoring systems such as the Dutch Lipid Clinic Network criteria. As a result, diagnosis relies primarily on lipid measurements, family history, and genetic testing. However, genetic testing and cascade screening remain underutilized in routine clinical practice.
Conclusions. A persistent gap exists between guideline recommendations and real-world management of FH. Delayed diagnosis and suboptimal implementation of treatment strategies contribute to inadequate cardiovascular risk reduction in young adults. Improving early detection through enhanced use of genetic testing, optimization of cascade screening, and timely initiation of lipid-lowering therapy may reduce cumulative LDL-C exposure and improve long-term cardiovascular outcomes.

KEYWORDS

Familial Hypercholesterolemia, Young Adults, Cascade Screening, Genetic Testing, Early Diagnosis, Guideline Implementation, Lipid-Lowering Therapy

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1. Introduction

Cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality worldwide, with elevated low-density lipoprotein cholesterol (LDL-C) being one of the most important modifiable risk factors contributing to atherosclerotic disease development (1,2). Early identification and management of dyslipidaemia are therefore central to cardiovascular prevention strategies (1).

Familial hypercholesterolemia (FH) is a common autosomal dominant genetic disorder characterized by lifelong elevation of LDL-C, leading to accelerated atherosclerosis and premature cardiovascular events if left untreated. Despite its relatively high prevalence, FH remains substantially underdiagnosed and undertreated in routine clinical practice (3,4). Recent meta-analyses estimate the global prevalence of FH to be approximately 1 in 250 individuals, although detection rates remain low worldwide. (5,6).

The issue of underdiagnosis is particularly relevant in young adults, in whom FH is often clinically silent until the occurrence of premature cardiovascular events. Consequently, early detection in this population is essential to enable timely intervention and reduce long-term cardiovascular risk (3,7).

Current international guidelines provide structured recommendations for the identification and management of FH, including lipid screening, diagnostic criteria, cascade testing, and early initiation of lipid-lowering therapy. However, a persistent gap remains between these recommendations and their implementation in real-world clinical practice, contributing to delayed diagnosis and suboptimal treatment initiation despite available effective therapeutic options (8–11).

Therefore, this narrative review aims to evaluate the current evidence on familial hypercholesterolemia in young adults, with a particular focus on diagnostic challenges and barriers to the implementation of clinical guidelines in routine practice.

2. Methods

A narrative literature review was conducted to evaluate current evidence regarding familial hypercholesterolemia in young adults, with a particular focus on diagnostic challenges and barriers to the implementation of clinical guidelines.

2.1. Search strategy

A structured literature search was conducted in PubMed/MEDLINE, Scopus, and Web of Science databases. The search was conducted using combinations of keywords and Medical Subject Headings (MeSH), including: *"familial hypercholesterolemia", "young adults", "dyslipidaemia", "screening", "cascade testing", "diagnosis", "lipoprotein(a)", "apolipoprotein B", "guidelines", "genetic testing" and "PCSK9 inhibitors"*. Boolean operators (AND, OR) were used to optimize search sensitivity and specificity.

The search was limited to articles published in English. No restrictions were applied regarding study design in the initial search to ensure comprehensive coverage of the available literature.

2.2. Eligibility criteria

Studies were included if they met the following criteria:

1. Focused on familial hypercholesterolemia or severe dyslipidaemia relevant to FH.
2. Included populations of young adults or provided age-stratified data applicable to this group.
3. Addressed at least one of the following domains: epidemiology, diagnosis, screening strategies, diagnostic approaches, genetic testing, treatment, guideline implementation or implementation gaps.

Studies were excluded if they:

1. Focused exclusively on pediatric populations without relevance to transition-age or young adult patients.
2. Were not available in English.
3. Were case reports without broader clinical or methodological relevance.

2.3. Study selection

Titles and abstracts retrieved from the search were screened for relevance. Full-text articles were assessed when eligibility could not be determined based on abstract alone. Reference lists of included articles were additionally screened to identify further relevant publications (snowballing technique).

2.4. Data extraction and synthesis

Data from included studies were extracted and synthesized narratively. Due to the heterogeneity of study designs and outcomes, a meta-analysis was not performed. Evidence was organized thematically into the following domains: epidemiology and burden of FH in young adults, diagnostic strategies, cascade and genetic testing approaches, guideline recommendations, and implementation gaps in clinical practice.

2.5. Quality considerations

Given the narrative nature of this review, no formal risk-of-bias assessment was performed. However, preference was given to high-quality sources, including clinical guidelines, systematic reviews, meta-analyses, and large cohort studies when available.

2.6. AI

AI was utilized for two specific purposes in this research. Text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Assistance in refining the academic English language of the manuscript, ensuring clarity, consistency, and adherence to scientific writing standards. AI were used for additional linguistic refinement of the research manuscript, ensuring proper English grammar, style, and clarity in the presentation of results. It is important to emphasize that all AI tools were used strictly as assistive instruments under human supervision. The final interpretation of results, classification of errors, and conclusions were determined by human experts in clinical medicine and formal logic. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, rather than replacing human judgment in the analytical process.

3. Results

3.1. Epidemiology

Familial hypercholesterolemia (FH) is a relatively common genetic disorder, with an estimated prevalence of approximately 1:313 for heterozygous FH and 1:400,000 for homozygous FH in the general population (5). Prevalence estimates may vary depending on diagnostic criteria, population age, and ethnicity, and are notably higher among individuals with ischemic heart disease, premature ischemic heart disease, and severe hypercholesterolemia (5).

Despite its relatively high prevalence, FH remains markedly underdiagnosed, with less than 1% of affected individuals identified in most countries, leading to a substantial proportion of untreated patients (5,6,12).

The scale of this diagnostic failure is particularly evident in global registry data, which indicates that the median age of FH diagnosis is as late as 44.4 years (13). This delay suggests that the majority of affected individuals remain unidentified throughout their young adulthood, a critical period during which cumulative exposure to LDL-C significantly accelerates atherosclerotic progression and increased lifetime cardiovascular risk despite the absence of early clinical symptoms (1,13).

3.2. Diagnostic Approach and Genetic Testing

The diagnosis of familial hypercholesterolemia (FH) is primarily based on clinical criteria, including the Dutch Lipid Clinic Network (DLCN) score. This scoring system assigns weighted points based on personal and family history of premature cardiovascular disease, physical examination findings, LDL-C levels, and genetic testing results. The DLCN criteria are summarized in Table 1. Based on the total score, patients are classified as having possible (3–5 points), probable (6–7 points), or definite FH (≥8 points). Molecular genetic testing is generally recommended in individuals with a DLCN score ≥6 to confirm the diagnosis, support cascade screening strategies and facilitate earlier initiation of lipid-lowering therapy. (4,6,14).

In young adults, the diagnostic process may be particularly challenging due to the absence of overt clinical manifestations, which increases reliance on lipid levels, family history, and early use of genetic testing (1).

FH is caused by pathogenic variants in genes involved in LDL metabolism, most commonly LDLR, followed by APOB and PCSK9. Less frequently, variants in APOE and LDLRAP1 may also contribute to the phenotype. The majority of cases are inherited in an autosomal dominant manner, while autosomal recessive inheritance is rare and typically observed in populations with a higher degree of consanguinity. Among all genetic causes, LDLR variants represent the predominant molecular defect in FH patients (15).

Despite its diagnostic value, genetic testing remains underutilized in routine clinical practice. Wider implementation of molecular diagnostics in individuals with clinically suspected FH could improve diagnostic accuracy, facilitate earlier initiation of lipid-lowering therapy, and enhance cascade screening among family members, ultimately improving long-term cardiovascular outcomes (16,17).

Table 1. Dutch Lipid Clinic Network (DLCN) criteria.
LDL-C – low-density lipoprotein cholesterol; CAD – coronary artery disease; LDLR – low density lipoprotein receptor; APOB – apolipoprotein B; PCSK9 – proprotein convertase subtilisin/kexin type 9

Category	Points
First-degree relative with tendinous xanthomata and/or arcus cornealis, OR children <18 years with LDL-C level above the 95th percentile	2
First-degree relative with known premature (<55 years in men; <60 years in women) coronary and vascular disease, OR first-degree relative with known LDL-C level above the 95th percentile	1
Personal history of premature (<55 years in men; <60 years in women) coronary artery disease	2
Personal history of premature (<55 years in men; <60 years in women) cerebral or peripheral vascular disease	1
Tendinous xanthoma	6
Arcus senilis at age <45 years	4

Category	Points
LDL-C level > 8.5 mmol/L (>325 mg/dL)	8
LDL-C level: 6.5-8.5 mmol/L (251 – 325 mg/dL)	5
LDL-C level: 4.9-6.5 mmol/L (191 – 250 mg/dL)	3
LDL-C level: 4.0-4.9 mmol/L (155 – 190 mg/dL)	1
DNA analysis - functional mutation in LDLR, APOB and PCSK9 gene	8

However, genetic testing has important limitations. A proportion of patients with a clinically definite FH phenotype do not have an identifiable pathogenic variant using current testing methods. In addition, variants of uncertain significance (VUS) are frequently detected and may require reclassification over time as additional genomic and clinical data become available. These factors limit the ability of genetic testing to fully replace clinical diagnostic criteria and highlight the continued importance of phenotype-based assessment (16).

3.3. Screening strategies in FH

Screening strategies for familial hypercholesterolemia aim to identify affected individuals early, particularly in asymptomatic young adults, to enable timely initiation of lipid-lowering therapy and reduce long-term cardiovascular risk. (3,6).

Cascade screening, based on systematic lipid and/or genetic testing of first-degree relatives of index cases, is currently considered the most cost-effective approach for identifying additional FH cases within affected families (6,8,18–20).

However, implementation of cascade screening remains inconsistent across healthcare systems, with significant variability in organization, uptake rates, and access to genetic testing (4,9,10).

Alternative strategies, including universal or opportunistic screening in young populations, have been proposed; however, their feasibility and cost-effectiveness remain debated despite promising results from selected healthcare settings (3,9).

3.4. Treatment

Lipid-lowering therapy remains the cornerstone of treatment in patients with familial hypercholesterolemia, with the primary therapeutic goal of achieving substantial and sustained reductions in low-density lipoprotein cholesterol (LDL-C) to reduce lifetime atherosclerotic cardiovascular risk (1).

Early initiation of lipid-lowering interventions is emphasized in current guidelines, highlighting the importance of reducing cumulative exposure to atherogenic lipoproteins over the lifespan. In this context, lifestyle modification and health behavior counseling should begin in youth, with early consideration of pharmacotherapy in individuals with familial hypercholesterolemia and in young adults with low-density lipoprotein cholesterol (LDL-C) ≥160 mg/dL or a strong family history of premature atherosclerotic cardiovascular disease (2)

High-intensity statins are recommended as first-line pharmacological therapy in young adults with FH and are typically initiated as early as possible following diagnosis, including during late adolescence or early adulthood, depending on individual risk stratification and LDL-C levels (1,7,14).

In cases where LDL-C targets are not achieved with maximally tolerated statin therapy, combination treatment with ezetimibe is commonly used, while PCSK9 inhibitors represent an effective additional therapeutic option for patients with persistently elevated LDL-C or those at very high cardiovascular risk (21).

Despite the availability of effective lipid-lowering therapies, treatment uptake and attainment of guideline-recommended LDL-C targets remain suboptimal in young adults with FH, largely due to delayed diagnosis, treatment inertia, and variability in clinical practice implementation (1,6,10).

3.5. Implementation gap

Despite advances in diagnostic and therapeutic strategies, significant gaps remain in the real-world management of familial hypercholesterolemia, particularly in young adults (1).

Underdiagnosis remains a major barrier, limiting the initiation of cascade screening and delaying identification of affected relatives, which reduces the overall effectiveness of preventive strategies at the population level (6,10).

In addition, treatment initiation is often delayed, and many patients fail to achieve guideline-recommended LDL-C targets despite the availability of effective lipid-lowering therapies, reflecting therapeutic inertia and variability in clinical practice (1).

Finally, cascade screening programs remain inconsistently implemented across healthcare systems, with variability in organization, patient engagement, and access to genetic testing contributing to unequal identification of affected individuals (8,9).

4. Discussion

This narrative review highlights that familial hypercholesterolemia remains insufficiently recognized, largely due to its clinically silent course, particularly in young adults. The scale of this diagnostic gap is reflected in global registry data, which indicate that the median age at diagnosis remains as high as 44.4 years, suggesting that many affected individuals remain unidentified throughout early adulthood - a critical period of lifelong atherogenic burden of elevated LDL-C levels (13). Despite the availability of well-established diagnostic criteria and clear clinical guidelines, a significant gap persists between recommendations and their implementation in routine clinical practice. Early identification of FH is therefore essential, as it enables early deployment of lipid-lowering agents and reduces lifetime exposure to atherogenic lipoproteins, ultimately lowering cardiovascular risk (1). Furthermore, underdiagnosis limits the effectiveness of cascade screening strategies, reducing the likelihood of identifying affected individuals within families.

Genetic testing plays an important role in improving the diagnostic accuracy of familial hypercholesterolemia and is recommended in individuals with a high clinical probability of disease, such as those with a Dutch Lipid Clinic Network score ≥6. Its use supports diagnostic confirmation and facilitates cascade screening; however, its implementation in routine clinical practice remains limited. Importantly, genetic testing has several inherent limitations. A proportion of patients with a clear clinical FH phenotype do not have an identifiable pathogenic variant using currently available methods, while others may carry variants of uncertain significance (VUS), which complicate interpretation. The presence of VUS introduces diagnostic ambiguity and may affect clinical decision-making, particularly with regard to risk stratification and treatment initiation. These limitations highlight the continued importance of integrating genetic testing with clinical criteria and phenotypic assessment rather than relying on molecular findings alone. Furthermore, the uncertain nature of VUS may also have psychological implications for patients, as inconclusive results can contribute to uncertainty regarding diagnosis and long-term management (16).

Early detection strategies, particularly cascade screening of relatives of affected index cases, represent a cornerstone of effective familial hypercholesterolemia management and are considered the most cost-effective approach for identifying additional cases. This strategy is especially relevant in young adults, in whom FH often remains asymptomatic, enabling earlier diagnosis and timely initiation of lipid-lowering therapy, thereby reducing long-term cardiovascular risk. However, despite strong evidence supporting its effectiveness, the implementation of cascade screening remains suboptimal across healthcare systems, reflecting a persistent gap between guideline recommendations and routine clinical practice, which contributes to ongoing underdiagnosis of FH (8,10,18,20).

Lipid-lowering therapy plays a central role in the management of familial hypercholesterolemia, with statins forming the foundation of pharmacological treatment, followed by combination approaches including ezetimibe and, in selected cases, PCSK9 inhibitors. The therapeutic objective extends beyond short-term lipid reduction and focuses on limiting cumulative exposure to elevated LDL-C levels over the lifespan. However, in clinical practice, treatment initiation is frequently delayed, particularly in young adults, primarily due to underdiagnosis and therapeutic inertia. This remains concerning in light of current recommendations emphasizing early intervention, including consideration of pharmacotherapy in individuals with FH and in young adults with LDL-C ≥160 mg/dL or a strong family history of premature atherosclerotic cardiovascular disease. These observations highlight the need to shift clinical practice toward earlier and more proactive management strategies in younger populations (1,2).

This study has several limitations that should be acknowledged. As a narrative review, it does not follow a systematic methodology, which introduces a potential risk of selection bias and limits the reproducibility of the findings. In addition, the heterogeneity of included studies, particularly in terms of populations, diagnostic criteria, and healthcare settings, may affect the generalizability of the conclusions. Future research should focus on improving the implementation of established diagnostic and screening strategies, particularly in younger populations, as well as on refining the role of genetic testing, including the clinical interpretation of variants of uncertain significance. Strengthening early detection programs and integrating guideline-based care into routine clinical practice remain key priorities.

5. Conclusions

Familial hypercholesterolemia remains an insufficiently recognized condition, particularly in young adults, despite the availability of effective diagnostic tools and evidence-based treatment strategies. Early identification and timely initiation of lipid-lowering therapy are essential to reduce cumulative exposure to atherogenic lipoproteins and lower lifetime cardiovascular risk. However, significant gaps persist between guideline recommendations and their implementation in clinical practice, especially in the areas of cascade screening and early treatment initiation. Addressing these gaps through improved awareness, broader use of diagnostic tools, and earlier intervention strategies may significantly enhance long-term outcomes in individuals with familial hypercholesterolemia.

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