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Criteria of the Dutch Clinical Network and genetic testing in familial hyperlipidemia in a group of Colombian patients

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ABSTRACT

Introduction: hyperlipidemia is a group of diseases, both hereditary and acquired, characterized by elevated levels of lipids in the human body, especially prevalent in the western hemisphere.

Methods: this study seeks to identify patients with familial hyperlipidemia using the criteria of the Dutch Clinical Network applied to the subsidized population of Bucaramanga, Colombia, and evaluate their individual profiles.

Results: the prevalence of heterozygous familial hypercholesterolemia (HeFH) is estimated to be 1 in 200 to 500 people, while the prevalence of homozygous familial hypercholesterolemia (HoFH) is 1 in 300,000 to 600,000 people. In Bucaramanga, it is projected that 240,000 people could have HeFH and from 160 to 300 cases of HoFH.

Conclusions: despite the estimates, the real prevalence of the disease in Colombia is unknown, which justifies carrying out this study to obtain more precise data on familial hyperlipidemia in the region.

INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic disorder manifested by persistently elevated LDL cholesterol (LDL-C) levels from an early age, which significantly increases the risk of premature atherosclerotic cardiovascular disease[1,2,3]. Its heterozygous form is estimated to affect approximately 1 in 200 to 500 individuals, and its homozygous form affects 1 in 300,000 to 600,000 individuals, although these data may vary by region and ethnic origin[4,5].

FH is primarily transmitted in an autosomal dominant manner and is associated with mutations in the LDLR, APOB, and PCSK9 genes, which alter LDL-C metabolism[2,6]. These mutations lead to a reduction in hepatic cholesterol uptake, elevating its plasma levels and accelerating the process of atherosclerosis[1,2,6]. The homozygous form of the disease, although less common, is associated with cardiovascular disease in children due to the almost complete absence of functional LDL receptors[3,6].

Most cases of FH remain undiagnosed, limiting the timely implementation of preventive measures[3,4,7]. Studies conducted in European and North American populations have reported prevalences of 1 in 217 in Denmark, 1 in 150 in Quebec, and up to 1 in 70 in Afrikaners in South Africa[5,6,7]. These differences highlight the importance of conducting local studies that consider the genetic and epidemiological characteristics of each region.

To improve identification, diagnostic tools such as the Dutch Clinical Network (DLCN) criteria have been proposed, which integrate personal and family history, LDL-C levels, physical signs, and genetic findings[2,8]. These criteria have demonstrated adequate sensitivity and specificity compared to molecular diagnosis, considered the gold standard[2].

In Colombia, the true prevalence of FH is unknown, and the application of standardized clinical criteria has been limited, especially in vulnerable populations such as those receiving subsidized healthcare. Bucaramanga, a mid-sized city in northeastern Colombia, has a population base that allows for the implementation of active screening strategies for FH[9,10].

The **objective** of this study was to identify patients with suspected familial hypercholesterolemia in a population of the subsidized healthcare system in Bucaramanga by applying the Dutch Clinical Network criteria and to evaluate their clinical, epidemiological, and genetic characteristics.

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METHODS

The present is an observational study that sought to identify the presence of FH based on the Dutch Clinic Network criteria. Patients aged 18-95 years who had a record of cardiometabolic risk variables including lipid profile and others were included in the study. Patients that did not have the variables as well as secondary causes of hyperlipidemia, such as hypothyroidism, nephrotic syndrome, cholestasis, and treatment with specific drugs (steroids, immunosuppressors, etc.) were excluded. The population that met the inclusion and exclusion criteria consisted of all health centers in the city of Bucaramanga, Santander, Colombia.

Socioeconomic level was classified according to the official Colombian stratification system, which groups the population into six levels based on the characteristics of their housing and surroundings. For this study, the classification was obtained from administrative health records, and strata 1, 2, and 3 were included, representing low to middle-low socioeconomic status.

Familiar Hyperlipidemia

To establish the clinical diagnosis of familial hyperlipidemia in the index case, the criteria of the Dutch Lipid Clinic Network (DLCN) are currently used in several countries. These criteria are based on a punctuation system according to personal and familial history of certain variables. Clinical diagnosis is certain when the score is ≥8 and likely when it is ≥6. The accuracy of the clinical criteria has been compared with the genetic diagnosis, which is the gold standard, with the DLCN criteria having the best overall sensitivity and specificity[10].

They should only be used for diagnosis of FH over the age of 18 years and never in their family members. To detect FH, an opportunistic search should be performed in patients with premature CVD and those with personal and/or family history of hypercholesterolemia and/or premature CVD[11].

Criteria for clinical suspicion of familial hypercholesterolemia[12].

1. Individual with LDL-c >250mg/dl and at least one of the following criteria
   a. Family member <18 years with LDL-c >150mg/dl
   b. Family member >18 years with LDL-c > 190mg/dl
   c. Presence of premature coronary heart disease in the index case and/or a first degree relative
   d. Presence of xanthomas in the index case and/or a first degree relative
2. If there is no family data available, familial hypercholesterolemia should be suspected in people with LDL-c > 300mg/dl.

Genetic test

Genetic testing for familial hyperlipidemia was performed using a kit from the Longwood Company (Lipid in Code®) and processed by molecular engineering DNA analysis using an Ion GeneStudio S5 Series device. The 7 genes involved in the following were analyzed: Familial hypercholesterolemia: LDLR, APOB, PCSK9, APOE and STAP1 genes, Autosomal recessive hypercholesterolemia: LDLRAP1 gene, Lysosomal acid lipase deficiency: LIPA gene.

Statistical analysis

The quantitative variables are presented as a median ± standard deviation or median (interquartile range) according to their distribution, and qualitative variables as percentages with confidence intervals (CI) of 95%. Student's t test was performed to evaluate the differences between two variables. All statistical analyses of the database results were performed using the Statistical Package for the Social Sciences (SPSS for Windows, v.20.1; Chicago, IL) and Microsoft Excel was used to tabulate the corresponding databases.

Ethical considerations

The ethical aspects of this research study were conducted based on the criteria of the Belmont Report, adjusted to its principles of respect to the person, benevolence, and justice and, the Helsinki declaration of the World Medical Association of 1964. Likewise, this work will be subjected to the national legislation and its code of medical ethics of 1985 (currently in force) in its title V, chapter 4, regarding research on human beings. The highest of standards were maintained that permitted the protection of the participant's privacy and physical integrity.

By means of informed consent, the objectives of this investigation were explained, in the same manner, the procedures performed, and their inherent risks and complications were explained in detail using clear and understandable language. The study was evaluated and approved by the ethics committee with the highest of standards.

RESULTS

Initially, we present the results of the epidemiological characterization after reviewing the statistics of the population of the cardiovascular risk programme of the subsidized population in Bucaramanga, Santander. *Table 1* presents the sociodemographic characteristics of the included population.

Table 2 depicts the principal comorbidities found in the population included in this study.

Table 3 shows the data corresponding to adherence, degree of control and mean lipid profile, renal function and glucose values of the patients included in the study.

After characterization of all the patients, the criteria for suspected familial hyperlipidemia of the Dutch Lipid Clinic Network were applied.

Genetic testing revealed various mutations: duplication of exons 13–15 with p.Asp47Asn and p.Ser326Cys in the LDLR gene; mutations p.Glu204* and Ile268Met in the APOE gene; and multiple substitutions in the PCSK9 gene, including T>A at nucleotide 621 and T>C at nucleotide 780. Among the patients, 15 were heterozygous, 2 were homozygous, 2 were compound heterozygous, and 1 was double heterozygous. Some PCSK9 mutations were of uncertain

significance, with limited prior documentation in the literature *(Table 4)*.

These findings support the utility of systematic screening using DLCN criteria in high-risk populations, and reveal a significant genetic burden of familial hyperlipidemia that remains underdiagnosed. The integration of genetic testing allowed for the identification of clinically relevant mutations, reinforcing the importance of targeted strategies in primary care for early detection and risk reduction.

DISCUSSION

As seen in *Table 1,* the majority of the total population were female (68.8%), which is consistent with prior national reports of higher healthcare-seeking behavior among women[10]. Additionally, most participants were single (85.7%), a finding previously associated with limited social support and potentially worse adherence to chronic disease management[11].

Regarding comorbidities in the overall sample *(Table 2),* hypertension (81.4%) and non-insulin dependent diabetes mellitus (28.2%) were the most common, followed by hypercholesterolemia and chronic kidney disease (both 24.3%). These findings are similar to those reported in studies from similar populations in Latin America and globally[12,13,14].

As shown in *Table 3,* adherence to treatment was high (91%) and overall control of metabolic indicators was achieved in 70.2% of cases, similar to previous reports[15,16]. However, these figures must be interpreted with caution, as they reflect the entire cohort and not specifically the subset of patients with suspected familial hypercholesterolemia (FH).

When focusing on the 20 patients who met the DLCN criteria for suspected FH *(Table 4),* the clinical profile was markedly different. This subgroup had a higher cardiovascular burden: 90% had very high cardiovascular risk and 70% had documented coronary artery disease, consistent with patterns described in other FH populations[17,18]. Hypertension, diabetes, and chronic kidney disease were also frequent comorbidities.

Interestingly, while adherence to lipid-lowering therapy was high (90%), only 30% of these high-risk patients achieved adequate LDL-C control. This therapeutic gap is well-documented in FH cohorts and is often due to both genetic resistance to standard therapies and delayed diagnosis[3,4,13].

Genetic analysis revealed mutations primarily in LDLR, along with variants in APOE and PCSK9, the latter often of uncertain significance. These findings align with the global literature, where LDLR mutations account for more than 80% of genetically confirmed FH cases[1,2]. The identification of compound and double heterozygous mutations also highlights the phenotypic and genetic complexity of FH.

Taken together, these results reinforce the clinical utility of DLCN criteria in identifying suspected FH cases within primary care, especially in underserved health systems. The integration of targeted genetic testing not only confirmed diagnoses but also uncovered clinically actionable mutations, contributing to the growing body of data on FH in Latin American populations. Furthermore, our findings support expanding systematic screening strategies and cascade testing to improve early detection and cardiovascular prevention.

TABLA 1.
Características sociodemográficas de la población incluida

Variable		Valores	
Sexo	Mujeres	7256	68,8%
	Hombres	3285	31,2%
Edad promedio		65,67 años	
Estado civil	Casados	435	4,1%
	Otros	599	5,7%
	Separados	88	0,8%
	Solteros	9033	85,7%
	Unión civil	147	1,4%
	Viudos	110	1,0%
	Sin información	125	1,2%
Estrato socioeconómico	Estrato 1 (n: 5952) Estrato 2 (n: 3845) Estrato 3 (n: 744)		
Evaluación psicológica	24 / 10541		
Evaluación nutricional	3841 / 10541		
Evaluación odontológica	2150 / 10541		

TABLA 2.
Comorbilidades principales de los pacientes incluidos en el estudio

Variable	Valores n (%)
Hipertensión	8580 (81,4%)
Diabetes mellitus no insulinodependiente	2971 (28,2%)
Diabetes mellitus insulinodependiente	833 (7,9%)
Insuficiencia renal	2560 (24,3%)
Hipercolesterolemia	2560 (24,3%)
Enfermedad pulmonar obstructiva crónica	833 (7,9%)
Cáncer	21 (0,05%)

TABLA 3.
Adherencia, grado de control y perfil lipídico promedio, función renal y valores de glucosa de los pacientes incluidos en el estudio

Variable	Valores n (%)
Adherencia	9592 (91%)
Control	7380 (70,2%)
Promedio de colesterol total	168,353 mg/dL
Promedio HDL	42,735 mg/dL
Promedio LDL	111,919 mg/dL
Promedio función renal	194,906 mg/dL
Promedio triglicéridos	194,906 mg/dL

Future research should evaluate the cost-effectiveness of implementing routine FH screening in primary care settings using clinical algorithms and genetic tools. Such studies are necessary to validate the approach at a larger scale and determine its long-term impact on morbidity and mortality.

CONCLUSIONS

Familial hyperlipidemia (FH) remains significantly underdiagnosed and undertreated in clinical practice, particularly in low- and middle-income countries. This study identified patients with clinical suspicion of FH in a subsidized health population in Bucaramanga using the Dutch Lipid Clinic Network (DLCN) criteria, revealing a high burden of cardiovascular disease and a low rate of LDL-C control despite adequate treatment adherence. Genetic testing confirmed pathogenic variants—especially in the LDLR gene—reinforcing the role of molecular analysis as a complement to clinical screening.

These findings support the integration of standardized diagnostic tools and genetic testing into primary care, especially in resource-limited settings where specialized lipid clinics are not widely available. Primary care physicians are fundamental in the early recognition of red flags such as persistent hypercholesterolemia or premature cardiovascular events. However, gaps in knowledge and diagnostic capacity remain a barrier to early detection.

To address this challenge, educational programs, improved biochemical screening protocols, and support from multidisciplinary teams—including clinical geneticists—are needed[19]. Public awareness campaigns are also essential, particularly for families with a history of early cardiovascular disease or elevated LDL-C.

Future research should explore the broader implementation of systematic FH screening and its effect on cardiovascular outcomes. Advances in genomic technologies and their accessibility may further improve detection, risk stratification, and eventually, the development of personalized therapeutic strategies[20]. Characterizing the genetic and clinical profile of FH within the Colombian population remains a key priority for national health institutions.

TABLA 4.
Características clínicas y genéticas de pacientes con sospecha de hiperlipidemia familiar

Categoría	Variables	Valores n (%)
Demografía	Mujeres	17 (85%)
	Hombres	3 (15%)
	Rango de edad	46–88 años
Riesgo cardiovascular	Riesgo estimado muy alto	18 (90%)
	Riesgo estimado alto	2 (10%)
Comorbilidades	Hipertensión	17 (85%)
	Enfermedad coronaria	14 (70%)
	Diabetes mellitus	6 (30%)
	Patología cerebrovascular	4 (20%)
	Insuficiencia renal	4 (20%)
Indicadores terapéuticos	Adherencia a terapia hipolipemiante	18 (90%)
	Logro de control de c-LDL (<100 mg/dL)	6 (30%)
Hallazgos genéticos	Mutaciones LDLR	Variantes patogénicas (por ej., duplicación de exón 13–15, p.Asp47Asn, p.Ser326Cys); observado frecuentemente en casos de genética alterada.
	Mutaciones APOE	Mutaciones como p.Glu204* y Ile268Met; detectados en una minoría de pacientes.
	Variantes PCSK9	Sustituciones que incluyen nt. 621 T>A y nt. 780 T>C; principalmente clasificados

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