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ANALYSIS OF PREVALENCE OF CARDIOVASCULAR RISK FACTORS IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA PHENOTYPE

ANÁLISE DA PREVALÊNCIA DOS FATORES DE RISCO CARDIOVASCULAR EM PACIENTES COM FENÓTIPO DE HIPERCOLESTEROLEMIA FAMILIAR

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ABSTRACT

Objective: To compare the prevalence of risk factors for cardiovascular disease in patients with FH phenotype with and without mutation. Methods: A cross-sectional study with patients who present LDL-c levels ≥190mg/dL and a personal or family history of hypercholesterolemia with positive or negative genetic diagnosis. We applied a standardized questionnaire to obtain information on cardiovascular risk factors (age, sex, biochemical profile, history of CVD, smoking, hypertension, type 2 diabetes mellitus and nutritional status). Anthropometric measurements and laboratory tests were also performed. The data were analyzed using version 21 of the IBM® SPSS® Statistics software and statistical significance was established as $p < 0.05$. Results: We studied 103 patients of both sexes (67% female) with a mean age of 55.27 ± 15.07 years. Thirty-three patients had a diagnosis of FH. The most prevalent comorbidity was systemic hypertension (65.05%), followed by overweight/obesity (57.28%) and type 2 diabetes mellitus (26.21%). Conclusion: The population with FH had lower cardiovascular RF prevalence when compared with patients without the mutation. However, they still merit differentiated care focused on the management of modifiable RFs, since the presence of at least one RF already significantly increases the CV risk in this population.

Keywords: Familial Hypercholesterolemia; Cardiovascular Diseases; Risk Factors for Cardiovascular Disease; Atherosclerosis and Anthropometry.

RESUMO

Objetivo: Comparar a prevalência dos fatores de risco para doenças cardiovasculares em pacientes com fenótipo de HF com e sem mutação. Métodos: Estudo transversal com pacientes que apresentam níveis de LDL-c ≥ 190 mg/dl e história pessoal ou familiar de hipercolesterolemia com diagnóstico genético positivo ou negativo. Foi aplicado um questionário padronizado para obtenção de informações sobre os fatores de risco cardiovascular (idade, sexo, perfil bioquímico, histórico de DCV, tabagismo, HAS, DM tipo II e estado nutricional). Também foram realizadas avaliações antropométricas e laboratoriais. Os dados foram analisados no software IBM® SPSS® Statistics versão 21 e o nível de significância estatística foi estabelecido em p < 0,05. Resultados: Foram avaliados 103 pacientes de ambos os sexos (67% mulheres) com média de idade de 55,27 ± 15,07 anos. Trinta e três pacientes tinham diagnóstico de HF. A comorbidade mais prevalente foi a hipertensão arterial sistêmica (65,05%), seguida de sobrepeso/obesidade (57,28%) e diabetes mellitus tipo II (26,21%). Conclusão: Portadores de HF apresentaram menor prevalência de FR cardiovasculares, quando comparados com pacientes sem a mutação. No entanto, eles ainda merecem atenção diferenciada e focada no manejo de FR modificáveis, uma vez que a presença de pelo menos um FR já aumenta significantemente o risco CV nessa população.

Descritores: *Hipercolesterolemia Familiar; Doença Cardiovascular; Fatores de Risco Cardiovascular; Aterosclerose e Antropometria.*

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INTRODUCTION

Familial hypercholesterolemia (FH) is a genetic disorder often associated with the development of premature coronary heart disease (<55 years) caused by high plasma concentrations of low-density lipoprotein cholesterol (LDL-c) since childhood.[1]

Heterozygous FH is the most recurrent form of this disease, affecting one in 200–500 individuals.[1] This disease is caused mainly by mutations in LDL receptors (LDLR) that decrease the transfer of LDL-c from the blood plasma to the liver. Thus, FH patients have very high LDL-c levels and tendon xanthomas and are at a high risk of developing cardiovascular disease (CVD) prematurely.[1] FH can also be caused by mutations in apolipoprotein B (ApoB) and proprotein convertase subtilisin/Kexin type 9 (PCSK9).[2]

FH patients are already at a high cardiovascular risk. However, it is known that the presence of classical risk factors (RF) for the development of CVD, such as smoking, type 2 diabetes mellitus (DMII), systemic arterial hypertension (SAH), low HDL-c levels, physical inactivity, obesity, advanced age, and male sex influence the prognosis of these individuals and contribute to further increasing this cardiovascular risk.[3,4]

In Brazil, studies describing populations with FH and the prevalence of modifiable and non-modifiable RF in this population remain scarce. Therefore, this study aimed to assess the prevalence of RF for CVD in patients with versus without an identifiable FH genotype.

MATERIAL AND METHODS

Sample

This descriptive observational cross-sectional study included a convenience sample of patients of both sexes with severe hypercholesterolemia treated at the National Institute of Cardiology. Individuals over 18 years of age with an LDL-c ≥ 190 mg/dL and suspected familial hypercholesterolemia who were taking lipid-lowering drugs were selected after medical record assessment. These patients were contacted by telephone and invited to participate in the study. Those with acute coronary syndromes, congestive heart failure, coronary angioplasty, a history of any surgical procedure in the 30 days prior to the consultation, rheumatic or systemic connective tissue disease, untreated hypothyroidism or hyperthyroidism, chronic renal failure, liver disease, or cancer; who were taking corticosteroids; or who were pregnant or breastfeeding were excluded.

The participants were clinically assessed through blood collection, anthropometric assessment, and the administration of a standardized questionnaire to obtain sociodemographic data.

Information related to previous cardiovascular diseases (angina pectoris, acute coronary syndrome, or stroke), the presence of DMII, smoking, and SAH were obtained from each participant's medical record.

This study followed the ethical standards for research according to Law No. 466/2012 concerning humans and all participants authorized the use of the data for research purposes by signing the Informed Consent Form. This study was approved by the Ethics and Research Committee of the National Institute of Cardiology under protocol No. 26802514.4.0000.5272.

Biochemical analysis

For the biochemical analyses, blood samples were collected after a 12-hour fast. Laboratory tests were performed by an automated method (ARQUITECTO ci8200; Abbott, Abbott Park, IL, USA) using commercial kits (ARQUITECTO c8000®; Abbott). Serum levels of glucose, triglycerides (TG), total cholesterol (TC), LDL cholesterol (LDL-c), HDL cholesterol (HDL-c), apolipoproteins A and B, and uric acid were measured.

For the genetic analysis, peripheral blood was collected in a tube containing EDTA, and genomic DNA was extracted from leukocytes.[5] The regions of interest of the studied gene(s) were amplified by polymerase chain reaction (PCR). Amplification products obtained by PCR were analyzed by electrophoresis and digested with restriction enzymes or sequenced.[6] Patients with mutations in one of the analyzed genes (*LDLR, APOB, PCSK9, LDLRAP1, LIPA*, and *APOE*) were diagnosed with genetically confirmed FH.

Anthropometric assessment

Body mass in kilograms and height in meters were measured using a digital platform scale with a stadiometer (Filizzola®), with a capacity of 180 kg and a precision of 100 g, positioned on a flat surface. Height was measured with the individuals barefoot, the head in the Frankfurt position, and arms extended along the body. Waist circumference (WC) was measured at the midpoint between the lower costal margin and the iliac crest using a Sanny flexible anthropometric measuring tape (SANNY, Brazil) with a scale of 0.1 centimeters and was classified according to the International Diabetes Federation.[7] Body mass index was calculated as body mass (kg)/height (m^2) and classified according to the World Health Organization for adults[8] and according to the PAHO for the elderly.[9] The waist-to-height ratio (WHtR) was calculated as the ratio between WC (cm)/height (m); values higher than 0.5 indicated an increased risk of developing metabolic disorders.[10]

Statistical analyses

The data were summarized in an Excel spreadsheet (Windows Office 2010; Microsoft,) and analyzed using SPSS® Statistics version 21 software (IBM,). Initially, the normality of the data was verified using the Kolmogorov-Smirnov test. Continuous variables are described as mean ± standard deviation, whereas categorical variables are presented as percentages.

The chi-square test was used to analyze categorical variables. Student's t-test was used for normally distributed continuous variables, while the Mann-Whitney U-test was used for non-normally distributed continuous variables. A statistical significance level of 5% was considered.

RESULTS

A total of 103 patients with LDL-c > 190 mg/dL and a mean age of 55 ± 15 years were included; 67% (n = 69) were women and 50.5% (n = 52) were taking statins. The study group had a high mean TC (346.47 ± 102.75 g/dL) (Table 1). A total of 32% (33) of the patients were diagnosed with genetically confirmed FH.

Table 1. Demographic data and clinical, biochemical, and anthropometric characteristics of individuals with a FH phenotype.

Variable	Total (n = 103)
Age (years)	55.27 ± 15.07
Women	69 (67)
History of angina	43 (41.75)
History of acute myocardial infarction	38 (36.89)
History of stroke	3 (2.91)
Type II diabetes mellitus	27 (26.21)
Smoking	46 (44.66)
Systemic arterial hypertension	67 (65.05)
Systolic blood pressure (mmHg)	139.80 ± 27.50
Diastolic blood pressure (mmHg)	78.92 ± 11.64
Total cholesterol (mg/dL)	346.47 ± 102.75
LDL-c (mg/dL)	158.02 ± 58.83
HDL-c (mg/dL)	46.98 ± 12.10
Triglycerides (mg/dL)	151.06 ± 74.74
Apolipoprotein A1 (mg/dL)	141.87 ± 24.36
Apolipoprotein B (mg/dL)	116.69 ± 37.45
Fasting glycemia (mg/dL)#	98.00 (75 – 110)
Uric acid (mg/dL)	5.31 ± 1.77
Body mass index (kg/m²)	28.19 ± 5.50
Waist circumference (cm)	95.23 ± 13.48
Waist-to-height ratio	0.59 ± 0.08
Overweight and obesity	59 (57.28)

Values are expressed as n (%), mean ± SD, or median (P25 - P75). LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol. #Variable with a non-normal distribution.

Comparison of patients with versus without the FH mutation (Table 2) showed that the first group had higher levels of TC ($p < 0.001$) and LDL-c ($p = 0.032$) and lower mean systolic blood pressure ($p = 0.018$), TG ($p < 0.001$), WC ($p = 0.016$), and WHtR ($p=0.002$). Patients without the FH mutation were also significantly older ($p = 0.003$) and had a higher prevalence of SAH ($p = 0.006$) and tobacco use ($p = 0.026$).

DISCUSSION

According to the World Health Organization (WHO), in 1997, FH was already considered a global health problem with approximately 15 million affected men and women.[11] The main cause of the reduced life expectancy of these patients was CVD, accounting for 31% of deaths worldwide.[12]

According to the Global Health Risks, one-third of all deaths worldwide can be attributed to a small number of RF, including age, male sex, dyslipidemia, DMII, smoking, SAH, physical inactivity, overweight, and obesity.[13] The incidence of cardiovascular disease in adults tends to double with each decade of life, possibly because of the longer exposure to RF and atherogenesis, with synergism between several RF.[14] However, cardiovascular events occur at an earlier age in patients with an FH mutation, usually between 30 and 45 years.[15]

In this study, FH patients were a mean 48.60 ± 17.45 years of age. Compared with the population without an FH mutation, participants with FH had a significantly lower mean age, which is explained by the fact that individuals with FH tend to suffer from early cardiovascular events,[16,17] highlighting the importance of cascade genetic screening for early identification of patients with the disease.

Regarding sex, although men showed a positive correlation with the early development of CVD, a higher prevalence of women was observed in both populations (67%), with no significant intergroup differences. Studies on FH populations are predominantly composed of women,[17-19] which corroborates data showing that women are currently the main users of private and public health services.[18]

Biochemical analyses revealed that the levels of TC and LDL-c were higher participants with an FH mutation than in those without (411.15 ± 109.28 vs. 317.37 ± 85.73, $p < 0.001$, and 179.14 ± 65.48 vs. 149.37 ± 54.10, $p = 0.032$, respectively) a well-described feature of the disease caused by the mutation in LDLR that leads to increased plasma LDL-c levels.[11] Conversely, the population without the FH mutation had higher TG levels (168.85 ± 75.63 vs. 108.36 ± 52.91, $p<0.001$), which can be directly related to an unbalanced diet, in addition to the presence of some factors such as overweight, high WC, physical inactivity, and older age.[20]

Patients with a genetic mutation, due to a worsening of the pathophysiology of atherosclerosis and premature coronary artery disease, presented a significantly higher percentage of acute myocardial infarction (AMI) compared to the population without FH (45.71% vs. 18.18%, $p=0.005$). However, there were no differences between groups regarding cases of angina and stroke. Studies with FH patients in the Netherlands also found a high percentage of cardiovascular events in this population, as the cohort study with 2,400 patients with a LDLR mutation that found a prevalence of CVD of 32.60%[21] and a cross-sectional study of 526 patients diagnosed with FH that found a prevalence of 65.8%.[16]

It is known that DMII can increase the risk of AMI by up to five times, usually as a result of factors such as obesity, inadequate diet, physical inactivity, SAH, and dyslipidemia.[22] In this study, the prevalence of DMII was high in both groups, with values of 18.18% and 30% in the groups with and without FH, respectively, with no statistical intergroup difference.[23,24]

Although smoking is an important RF for CVD, as it worsens the atherosclerotic process[25], the prevalence found in the population with the mutation, although similar to previous studies such as the Dutch studies of Bessiling et al.[24] and Nolting et al.[16] that reported percentages of 26.7% and 26.8%, respectively, was still high (33.30%). However, this percentage was still significantly higher in the population without the mutation (51.43%, $p = 0.026$).

The literature suggests that SAH is an important risk factor for CVD and can increase atherosclerosis in FH through neurohormonal effects on angiotensin II and noradrenaline and the activation of cytokines in the vasculature.[26] Studies by Jansen et al.[21] and Bessiling et al.[24] showed that SAH is associated with increased CVD in FH patients. The present study showed a significantly higher percentage of SAH in the population without the mutation (72.86% vs. 48.48%, $p = 0.006$), which is very close to the value found in the Brazilian study of Tamayo[27] that analyzed patients with SAH and hypercholesterolemia treated at a health clinic in Minas Gerais and found a percentage of 68.1%, with the hypothesis that differences in lifestyle habits among populations were causing this high prevalence of SAH.

Table 2. Demographic data and clinical, biochemical, and anthropometric characteristics of individuals with an FH phenotype, with and without genetic mutation.

Variable	Group without the FH mutation (n=70)	Group with the FH mutation (n= 33)	P value
Age (years)	58.33 ± 12.85	48.60 ± 17.45	0.003
Female sex	46 (65.71)	23 (69.70)	0.688
History of angina	33 (47.14)	10 (33.30)	0.085
History of AMI	06 (18.18)	32 (45.71)	0.005
History of stroke	02 (2.86)	01 (3.30)	0.968
Type II diabetes mellitus	21 (30)	06 (18.18)	0.171
Smoking	36 (51.43)	10 (33.30)	0.026
Systemic arterial hypertension	51 (72.86)	16 (48.48)	0.006
Systolic blood pressure (mmHg)	144.40 ± 27.68	129.43 ± 24.52	0.018
Diastolic blood pressure (mmHg)	79.55 ± 11.52	77.50 ± 11.98	0.449
Total cholesterol (mg/dL)	317.37 ± 85.73	411.15 ± 109.28	< 0.001
LDL-c (mg/dL)	149.37 ± 54.10	179.14 ± 65.48	0.032
HDL-c (mg/dL)	46.21 ±12.27	48.84 ± 11.71	0.364
Triglycerides (mg/dL)	168.85 ± 75.63	108.36 ± 52.91	< 0.001
Apolipoprotein A1 (mg/dL)	141.27 ± 54.10	143.64 ± 20.06	0.733
Apolipoprotein B (mg/dL)	112.76 ± 36.27	128.26 ± 39.57	0.142
Fasting glycemia (mg/dL)#	101 (90 – 116.2)	93 (92 – 101.0)	0.070
Uric acid (mg/dL)	5.55 ± 1.68	4.68 ± 1.88	0.057
Body mass index (kg/m²)	28.79 ± 4.95	26.87 ± 6.44	0.115
Waist circumference (cm)	97.50 ± 12.05	90.39 ± 15.24	0.016
Waist-to-height ratio	0.61 ± 0.07	0.56 ± 0.08	0.002
Overweight and obesity	43 (61.43)	16 (48.48)	0.430

Values are expressed as n (%), mean ± SD, or median (P25 - P75). The chi-square test, Student's t-test, and Mann-Whitney test were performed. LDL-c, low-density lipoprotein cholesterol; HDL-c, high-density lipoprotein cholesterol; AMI, acute myocardial infarction.

Regarding the anthropometric measurements, more than half of our patients were overweight or obese with visceral fat accumulation. When patients with and without the mutation were compared, the latter showed significantly higher WC and WHtR (97.50 ± 12.05 vs. 90.39 ± 15.24, p = 0.016 and 0.61 ± 0.07 vs. 0.56 ± 0.08, p = 0.002, respectively); these important RF were associated with the progression of atherosclerotic disease and the development of non-transmissible chronic diseases.[13]

The objective of cascade screening in the FH population is to enable the early identification of individuals and their relatives who can have the mutation for the disease. This early identification allows these individuals to receive appropriate drug treatment as well as relevant lifestyle guidelines such as those on a balanced diet, physical activity, and smoking cessation to control the development of cardiovascular disease RF.

Moreover, as they are a group at high CV risk, patients with FH are more carefully followed by health professionals, which can account for the lower prevalence of RF in this population. It is also believed that individuals with FH are aware of the severity of the disease and its possible impacts on their health because they are in contact with relatives who also have the disease and developed CVD prematurely and are thus more cautious about their lifestyle choices.

This study provides important data related to a population that has not yet been thoroughly studied in Brazil. However, as it is a cross-sectional study, retrospective data collection using medical records can represent a bias in the standardization of the information. In addition, the small sample size compared to that in other international studies is a limitation.

CONCLUSION

Patients with FH had a lower prevalence of cardiovascular RF than those without the mutation. However, they still require differentiated and focused attention on modifiable RF management, as the presence of at least one RF already significantly increases the CV risk in this population.

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CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

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