Diversitas Journal
ISSN 2525-5215
Volume 8, Número 4 (oct./dec. 2023) p. 2798 – 2810
https://diversitasjournal.com.br/diversitas_journal

LDLR rs2228671 gene polymorphism and relationship with the development of familial hypercholesterolemia and obesity in military police officers officers

Polimorfismo do gene *LDLR* rs2228671 e a relação com desenvolvimento de hipercolesterolemia familiar e obesidade em policiais militares

FERREIRA, Fábio Castro[1]; BARROS-SILVEIRA, Murilo[2]; COSTA, Iasmim Ribeiro da[3]; COSTA, Sérgio Henrique Nascente[4]; CASTRO, Frank Sousa[5]; GUILLO, Lidia Andreu[6]

[1] 0000-0001-9188-9105; Faculty of Inhumas. Inhumas, Goiás (GO), Brazil. E-mail: fabio.castrof@hotmail.com
[2] 0000-0003-1576-2844; Federal University of Goiás. Goiânia, Goiás (GO), Brazil. murilobarros@ufg.br.
[3] 0000-0003-3735-2803; Pontifical Catholic University of Goiás. Goiânia, Goiás (GO), Brazil. E-mail: iasmimribeirodacosta@gmail.com
[4] 0000-0002-4225-6368; Pontifical Catholic University of Goiás. Goiânia, Goiás (GO), Brazil. E-mail: sergionascente17@gmail.com
[5] 0000-0003-2293-5993; Pontifical Catholic University of Goiás. Goiânia, Goiás (GO), Brazil. E-mail: frank@pucgoias.edu.br
[6] 0000-0003-3220-6890; Pontifical Catholic University of Goiás. Goiânia, Goiás (GO), Brazil. E-mail: lidia.guillo@gmail.com

ABSTRACT

The polymorphism of the LDLR gene (LDL cholesterol receptor) is associated with lipid alterations, such as familial hypercholesterolemia (FH), caused by mutations in the genes that produce LDLR catabolic and uptake proteins. The objective of this study was to associate the polymorphism of the LDLR gene rs2228671 (C/T) with dyslipidemia in military police officers in the State of Goiás. The case-control study evaluated samples from 200 military police officers, by lipid profile measurement and by qPCR (real-time polymerase chain reaction) to identify possible associations between dyslipidemias, FH and LDLR gene polymorphism. Of the military police officers, 93% were male. In the lipid profile, 58% belonged to the group with the presence of a degree/class of dyslipidemia. The genetic analysis of the case group, the LDLR gene showed 68.1% of the CC genotype, 19.8% TC and 12.1% TT. In the control group, the genotype was CC in 82.1%, CT in 14.3% and TT in 3.6%. Lipid and BMI parameters were analyzed between the case and control groups. The dominant heterozygous genotype CT, 4.4% of the police officers exhibited TC ≥310 mg/dL with a positive diagnosis of FH and 95.6% CT <310 mg/dL, representing a probable diagnosis of FH. In the TT genotype, 100.0% of the police officers had TC <310 mg/dL, with a negative diagnosis for FH. The C allele of the LDLR rs2228671 gene in CC-dominant homozygosity and CT-dominant heterozygosity presents a high risk for the development of FH and obesity compared to the T allele.

RESUMO

O polimorfismo do gene *LDLR* (receptor de LDL colesterol) está associado com alterações lipídicas, como a hipercolesterolemia familiar (HF), provocada por mutações nos genes que produzem as proteínas catabólicas e de captação do *LDLR*. O objetivo deste estudo foi associar o polimorfismo do gene *LDLR* rs2228671 (C/T) com quadros de dislipidemia em policiais militares do Estado de Goiás. O estudo de caso-controle avaliou amostras de 200 policiais militares, pela dosagem do perfil lipídico e por qPCR (reação em cadeia da polimerase em tempo real) para identificar possíveis associações entre dislipidemias, HF e polimorfismo do gene *LDLR*. Os policiais militares, 93% eram do sexo masculino. No perfil lipídico, 58% pertenciam ao grupo com presença de grau/classe de dislipidemia. A análise genética do grupo caso, o gene LDLR evidenciou 68,1% do genótipo CC, 19,8% CT e 12,1% TT. No grupo controle, o genótipo CC em 82,1%, CT em 14,3% e TT em 3,6%. Executou-se análises entre os parâmetros lipídicos e do IMC entre o grupo caso e controle. O genótipo heterozigoto dominante CT, 4,4% dos policiais exibiram CT ≥310 mg/dL com diagnóstico positivo de HF e 95,6% CT <310 mg/dL, representando provável diagnóstico de HF. O genótipo TT, 100,0% dos policiais apresentaram CT <310 mg/dL, com diagnóstico negativo para HF. O alelo C do gene *LDLR* rs2228671 em homozigose dominante CC e heterozigose dominante CT apresenta elevado risco para o desenvolvimento de HF e obesidade frente ao alelo T. O alelo T mostra-se protetor na redução dos níveis de colesterol LDL.

INFORMAÇÕES DO ARTIGO

Histórico do Artigo:
Submitted: 16/05/2023
Approved: 07/11/2023
Published: 20/11/2023

Keywords:
LDLR gene, familial hypercholesterolemia, genetic polymorphism

Palavras-Chave:
Gene LDLR, hipercolesterolemia familiar, polimorfismo genético

DOI: 10.48017/dj.v8i4.2682

Introduction

Chronic non-communicable diseases (NCDs) are a class of pathologies with a prolonged character, long latency time and the presence of several risk factors such as cardiovascular diseases (CVD), malignant neoplasms, diabetes and chronic respiratory disease. Among these, CVDs are responsible for 17.9 million deaths annually, being classified as one of the most serious morbidities that lead to death worldwide (Ministério da Saúde [MS], 2008; Ministério da Saúde [MS], 2021).

Characterized as one of the occupations with extremely high levels of stress, the position of police officer, especially military police officer, presents several conditions that contribute to psychological and metabolic changes, being one of the classes most affected by CVD (Oliveira et al., 2010). The police are responsible for maintaining public order and safeguarding the safety of citizens in order to maintain social stability. Due to the uniqueness of the role of the military police officer, which requires unpredictable, mentally and physically exhausting work, special attention should be given to the risk factors for occupational illness specific to this group of professionals, and measures should be adopted to reduce the number of risk factors (Liu et al., 2006; Garbarino, 2014; Magnavita & Garbarino, 2017; Taylor et al., 2019).

Several aspects contribute to the organic disorders of the police force, such as life-threatening situations, excessive work demands, poor diet, continuous supervision, hierarchical rigor and military discipline. These and other qualities intrinsic to the police force expose these individuals to various health problems, such as elevated lipids in the bloodstream (Paulino & Lourinho, 2014).

Dyslipidemia is caused by metabolic alterations that interrupt certain processes in lipid metabolism and is prevalent in the police force. The main increased lipids in the blood of these blood individuals are mainly total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-c) and decreased high-density lipoprotein cholesterol (HDL-c) (Baynes & Dominiczak, 2011; Faludi et al., 2017).

Hyperlipidemias (high levels of lipoproteins) and hypolipidemias (low levels of lipoproteins) are two subtypes of dyslipidemias, which can be linked to genetic-based causes, as well as secondary factors related to lifestyle and medication use (Faludi et al., 2017). A frequent dyslipidemia is hypercholesterolemia, which develops when cholesterol-rich lipoproteins, such as LDL, accumulate in the plasma compartment. This accumulation can be caused by monogenic diseases, by mutations in the Apo B100 genes. Numerous mutations of the LDL receptor (LDLR) gene have been found in individuals with hypercholesterolemia, some of which have deformed the structure and function of the receptor, while others have reduced its expression in the membrane (Mion et al., 2004).

The LDLR gene is located on the short arm p, of chromosome 19, region 13, band 2, and is composed of about 45,000 base pairs of DNA and consists of 18 exons and 17 introns (Faludi et al., 2017). The LDLR gene has a single nucleotide polymorphism (SNP), a variation in the DNA sequence that affects only one base in the genome sequence. SNP rs2228671 is associated with decreased LDC-c rates.

Familial hypercholesterolemia is autosomal dominant, since it has a significant genetic cause for the development of early coronary heart disease, including myocardial infarction, as a result of lifetime exposure to high levels of low-density lipoprotein cholesterol (LDL-c). It stands out for having a severe form of genetically-based dyslipidemia, which, if left untreated, can cause coronary artery disease (CAD) in up to 85% of men and 50% of women (Izar et al., 2021).

Most of the time, familial hypercholesterolemia (FH) is caused by mutations in the genes that produce the catabolic and LDLR uptake proteins. The LDLR, apolipoprotein-B (APOB), and PCSK9 genes are thought to be genes linked to FH onset, which results in decreased LDL particle homeostasis and, as a result, increased plasma LDL-c concentrations. Consequently, pathogenic mutations in the LDLR gene are commonly found in individuals with a molecular diagnosis of FH (Faludi et al., 2017; Izar et al., 2021).

The objective of the present study was to associate the polymorphism of the LDLR gene rs2228671 (Cytosine/Thymine - C/T) with dyslipidemia and obesity in military police officers in the State of Goiás.

Procedures

A case-control study was carried out through a convenience sampling of 200 military police officers treated at the Military Police Comprehensive Health Center (CSIPM), located at Av. Eng. Atílio Corrêa Lima - Cidade Jardim neighborhood, in the city of Goiânia - Goiás. As an inclusion criterion for the study, the patient was over 18 years of age and voluntarily agreed to participate in the study and in the annual check-up suggested by the CSIPM. About 10 percent of police officers declined to participate in the survey because they felt uncomfortable answering the questions.

Participants who consented to participate in the study as volunteers filled out the Free and Informed Consent Form (ICF). The research was authorized by the Research Ethics Committee of the Federal University of Goiás (*Universidade Federal de Goiás*) through Consolidated Opinion No. 608.207.

The group of cases was composed of individuals who presented the following profiles in the lipid profile results: Isolated hypercholesterolemia (LDL-C ≥ 160 mg/dL); isolated hypertriglyceridemia (triglycerides ≥ 150 mg/dl); mixed hyperlipidemia (LDL-C ≥ 160 mg/dL and triglycerides ≥ 150 mg/dl, if TG ≥ 400 mg/dL, total cholesterol is considered > 200 mg/dL, instead of LDL-C); and HDL < 40 mg/dL in men and less than 50 mg/dl in women (FALUDI

et al., 2017).

The control group consisted of 84 individuals from the same target audience as the study, who met the following inclusion criteria in all lipid profile results: LDL cholesterol < 130 mg/dL, triglycerides < 150 mg/dL, and HDL > 60 mg/dL.

Initially, serum samples were collected in 4 mL vacuum tubes with separator gel, which after centrifugation were used to perform the lipid profile, using enzymatic and direct methodologies in automated equipment A15 (Biosystems®), at the Clinical Laboratory of the Military Police Hospital of the State of Goiás. All quality assurance requirements have been met.

Whole blood samples were collected in 4 mL vacuum tubes with EDTA anticoagulant, from which DNA extraction was performed. The biological samples were aliquoted at 2 mL and properly preserved in a freezer at -20°C until the moment of use. The DNA of the samples was extracted with the commercial kit IlustraBloodGenomicPreMini Spin® (GE Healthcare, UK), according to the manufacturer's instructions GE Healthcare. The isolated DNA was properly identified and stored at -20°C for the genotyping of the SNP LDLR 27208873_10 rs2228671. The LDLR allelic distribution sequence [VIC/FAM] consists of forward and reverse primers CCTCTCTCTCAGTGCCGCACAGATG[C/T]GAAAGAAACGAGTTCCAGTGCCAAG.

Genotyping was performed using the TaqMan Real Time PCR® kit (SNP Genotyping Kit, AppliedBiosystems, USA). The kit contains the sense (Forward) and antisense (Reverse) sequences of the primer oligonucleotides that amplify the polymorphic sequence of interest and a TaqMan® Probe. Genotyping was performed by analyzing the fluorescence pattern of each sample in the StepOnePlus™ systems thermal cycler (ApplieBioystems, EUA).

qPCR reactions were performed following the manufacturer's recommendation. For a final volume of 10 µL, 1 µL of genomic DNA at a concentration of 20 ng, 4.5 µL of TaqMan® Universal Master Mix (2X concentration), 1 µL of Custom TaqMan® Assay SNP Genotyping (20X concentration) containing both primers and probes, and 3.5 µL of H2Omq were used. The amplification protocol: 60°C girdling for 30 sec, followed by 95°C for 10 min enzymatic activation and then 40 cycles containing 95°C denaturation for 15s and 60°C girdling for 1 min (AppliedBiosystems, EUA).

To determine the diagnosis of FH, we used the partial criteria and scores established by the Dutch Lipid Clinic Network - DUTCH MEDPED (12.13), as shown in the score table below.

Table 1.

Diagnostic criteria for heterozygous and modified homozygous FH.

Heterozygous FH

Parameters	
Levels of LDL-c (mg/dL)	**Points**
≥330	8
250 – 329	5
190 – 249	3
155 – 189	1
DNA analysis	
Presence of functional mutation in the LDLR gene	8
Diagnosis of FH	
Sure if	>8
Likely to be	6 to 8
Possible if	3 to 5
Homozygous HF	
1. Genetic confirmation of two mutant alleles in the LDLR gene.	

Source: Williams et al., 1993; Izar et al., 2021.

Descriptive statistics were used to determine the absolute and relative frequencies (percentage) of the variables under study (presence or absence of polymorphic nucleotide alteration). Pearson's chi-square test, G test, and Mann-Whitney test adopted a 95% confidence interval for the outcome and a significance level of 5% ($p<0.05$). The software used to perform the statistical tests and the boxplot graph was BioEstat® 5.3.

Results

Of 200 military police officers sampled for the study, 93% (186/200) were male and 7% (14/200) were female. In the classification related to the lipid profile, 58% (116/200) belonged to the group with the presence of some degree/class of dyslipidemia, categorized as the case group and 42% (84/200) as the control group, presenting normolipidemia (Table 2). The mean age of the case group was 43.4 years with a standard deviation (SD) of ± 5.5 years, while the

mean age of the control group was 39.8 years and a mean SD of ± 8.4 years. Age had no statistically significant influence on the determination of dyslipidemia (Data not shown).

In the genetic analysis of the individuals in the case group, the LDLR gene polymorphism showed 68.1% (79/116) with Cytosine/Cytosine (CC) genotype, 19.8% (23/116) Cytosine/Thymine (CT) and 12.1% (14/116) Thymine/Thymine (TT). In the control group, the CC genotype was detected in 82.1% (69/84) of the police officers, TC in 14.3% (12/84) and TT in 3.6% (3/84) (Table 2).

Significant differences were identified between the case and control groups, considering BMI, TC, TG, LDL-c, HDL-c and N-HDL influence the development of dyslipidemia. A chi-square test was performed to compare the CC, TC and TT genotypes between the case and control groups, resulting in a p=0.0430. Thus, it is suggested that patients with homozygous wild-type CC and heterozygous CT genotypes may be more likely to develop dyslipidemia (Table 2).

Table 2.
General characteristics, lipid parameters and allelic distribution of the LDLR gene in military police officers in the state of Goiás, Brazil.

Variables	Case (n= 116) (Dyslipidemic)	Control (n= 84) (Normolipidemics)	*p-value
Years	43.4 ± 5.5	39.8 ± 8.4	0.0056
Gender			
M	109 (94.0)	77 (91.7)	1.0000
F	7 (6.0)	7 (8.3)	1.0000
BMI (kg/m²)	28.7 ± 3.3	26.0 ± 2.6	<0.0001
CT (mg/dL)	217.5 (173.7 - 247)	172.5 (150.7 - 190)	<0.0001
TG (mg/dL)	216 (165.7 - 306,2)	78.5 (59 - 116)	<0.0001
LDL-c (mg/dL)	121.2 (88.2 - 155,8)	101.2 (82.7 - 121)	0.0003
HDL-c (mg/dL)	41.5 (36 - 46.2)	50 (44 – 55.2)	<0.0001
N-HDL (mg/dL)	177.5 (135.7 - 199.2)	119.5 (97.5 - 139)	<0.0001
Genotypes			
CC	79 (68.1%)	69 (82.1)	
CT	23 (19.8)	12 (14.3)	0.0430‡
TT	14 (12.1)	3 (3.6)	

*Mann-Whitney test. ‡Chi-square test. **Mean and standard deviation were calculated for age and BMI. For the other variables, median and interquartiles (25% and 75%) were calculated. For the calculation of mean and standard deviation of BMI, 11 patients in the case group and 2 patients in the control group were excluded, because they did not present weight and height data for the BMI calculation. 4 patients were excluded from the case group for the LDL-c parameter, as they had indeterminate values. M= Male gender; f= female; BMI = Body mass index; TC= Total cholesterol; TG- Triglycerides; LDC-c = low-density lipoprotein; HDL-c=High-density lipoprotein; N-HDL = Non-HDL cholesterol; CC= Cytosine/Cytosine; TC= Cytosine/thymine; TT= Thymine/Thymine.

Table 3 shows the association between TC (mg/dL) and LDL-c (mg/dL) values associated with heterozygous (TC) and homozygous dominant and recessive (CC and TT) genotypes in the diagnosis of FH. Based on the genetic+biochemical criterion (genotype + TC (mg/dL), 2.5% of the police officers had homozygous dominant genotype with TC ≥ 310 mg/dL and 97.5% had homozygous dominant genotype with TC < 310 mg/dL, representing certainty of FH diagnosis.

For the dominant heterozygous TC genotype, 4.4% of the police officers exhibited TC ≥ 310 mg/dL with a positive diagnosis of FH and 95.6% had TC < 310 mg/dL, representing a probable diagnosis of FH. For the TT genotype, 100.0% of the police officers had TC < 310 mg/dL, with a negative diagnosis for FH.

Regarding the genetic evaluation associated with LDL-c, of the 116 patients, only 31 presented classification values according to the Update of the Brazilian Guideline on Familial Hypercholesterolemia. For the CC genotype, 19.4% had LDL-c in the range between 190 - 249 mg/dL and 58.1% in the range of 155 - 189 mg/dL, concluding the diagnosis with certainty of FH according to the homozygous criterion of the FH guideline. For the CT genotype, 6.4% had LDL-c in the range between 190 - 249 mg/dL and 9.7% in the range of 155 - 189 mg/dL, concluding a certain diagnosis of FH by the score >8. For the TT genotype, 6.4% had LDL-c in the range of 155 - 189 mg/dL, corresponding to a negative diagnosis of FH.

Table 3.
Stratification of the LDLR rs2228671 polymorphism associated with TC and LDL-c levels, according to the diagnosis of familial hypercholesterolemia based on the partial criteria of the Update of the Brazilian Guideline on Familial Hypercholesterolemia (Izar et al., 2021) and Update of the V Brazilian Guideline on Dyslipidemia (Mion et al., 2004)

Case (dyslipidemia)	CT (mg/dL) n=116		LDL-c (mg/dL) n=31			
	≥ 310	< 310	≥ 330	250 - 329	190 - 249	155 - 189
CC (n=79) n (f%)	2 (2.5)	77 (97.5)	0	0	6 (19.4)	18 (58.1)
HF Diagnosis	Certainty	Certainty	-	-	Certainty	Certainty
CT (n=23) n (f%)	1 (4.4)	22 (95.6)	0	0	2 (6.4)	3 (9.7)
HF Score	-	-	0	0	11	9
Diagnosis	Certainty	Probable	-	-	Certainty	Certainty
TT (n=14) n (f%)	0 (0,0)	14 (100.0)	0	0	0	2 (6.4)
HF Diagnosis	Probable	Negative	-	-	-	Negative

Source: own authorship.

The presence of high levels of TC associated with the presence of the CC+CT allele evidences 3.0%, i.e., low dominance in the population studied. When LDL-c data were cross-referenced with the genetic component, the prevalence of LDL-c was 7.8% for CC+CT. The statistical analysis showed a p>0.05 showing that there is no difference between police officers with normal and altered TC and LDL-c values for the CC+CT and TT genotypes in the case group.

Table 4.

Allele frequencies of the polymorphism of the LDLR gene rs2228671 associated with TC and LDL-c levels.

Variable	Case (dyslipidemia)				
	CC+CT (n=102)		TT (n=14)		
	N	f(%)	n	f(%)	*p-value
****CT (mg/dL)**					
≥310	3	3.0	0	0	
<310	99	97.0	14	100	0.4654
****LDL-c (mg/dL)**					
≥190	8	7.8	0	0	
<190	90	88.2	14	100	0.1682
Indeterminate	4	4.0	0	0	

*G test (comparing TC and LDL-c values for CC+CT and TT genotypes). F= Frequency. TC= Total cholesterol; LDL-c= Low-density lipoprotein.

In the genetic analysis associated with body mass index (BMI), higher concentrations of police officers were observed for the classification of overweight or pre-obesity and obesity grade I. The CC genotype stands out with frequencies of 33.6% and 19.8% and TC with 10.3% and 2.6% for the group with the presence of dyslipidemia. The control group exhibited a WC frequency of 27.4% for the eutrophic nutritional classification, but a higher prevalence of individuals in the pre-obesity condition, a rate of 47.6%. Statistical analysis using the G test showed that police officers who have the CC genotype of the case group are more likely to develop obesity when compared to the control group. Similarly, police officers with CC+CT genotype are more likely to develop obesity than the control group.

Table 5.

Association of LDLR gene alleles with nutritional diagnosis of obesity made by BMI (14).

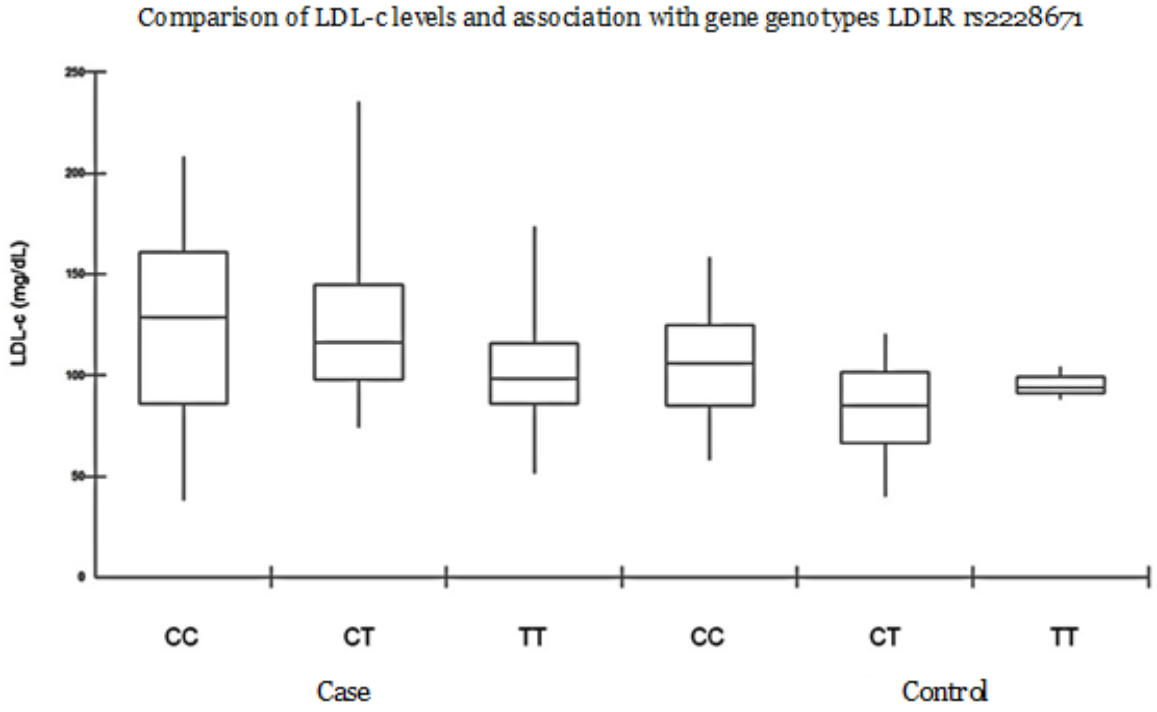
BMI	***rs2228671***						Diagnosis Nutritional
	Case (n=116)			Control (n=84)			
	CC	CT	TT	CC	CT	TT	
<18.5	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	Slim or
18.5 - 24.9	5 (4.3)	5 (4.3)	1 (0.9)	23 (27.4)	4 (4.8)	2 (2.4)	Low Weight
25.0 - 29.9	39 (33.6)	12 (10.3)	9 (7.8)	40 (47.6)	6 (7.1)	1 (1.2)	Normal or
30.0 - 34.9	23 (19.8)	3 (2.6)	3 (2.6)	4 (4.8)	2 (2.4)	0 (0.0)	Eutrophic
35.0 - 39.9	4 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	Overweight or
≥40.0	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	Pre-Obese
Not determined	7 (6.0)	3 (2.6)	1 (0.9)	2 (2.4)	0 (0.0)	0 (0.0)	----------

*The statistical test applied was for the overweight, obesity I, II, severe and undetermined age groups. Test G = p<0.0043 (comparing patients with CC genotype between case and control groups); p=1.0000 (comparing patients with CT genotype between case and control group and TT between case and control group); p=0.0077 (comparing CC+CT patients between case and control groups); p=1,000 (comparing patients with TT genotype between case and control group).

In the comparative analysis between the CC, CT and TT genotypes of the case and control groups, the chi-square test showed a statistically significant difference between all groups, indicating that the dominant homozygous CC genotype has higher serum levels of LDL-c when compared to the control group.

Figure 1.

Comparative Boxplot of Serum LDL-c Values Associated with LDLR Gene Genotypes.



We excluded 4 patients from the case group in this analysis because they had indeterminate LDL-c values. *Chi-square test comparing CC genotype of the case and control group (p<0.0001), CT genotype (p<0.0001) and TT genotic (p<0.0001).

Discussion

Dyslipidemia is prevalent in the police force, since the work of this officer involves high levels of work stress, and may develop important comorbidities, such as diabetes mellitus, systemic arterial hypertension, hypertriglyceridemia, hyperinsulinemia, atherosclerosis, irritation and insomnia, being conditions strongly linked to the development of obesity and CVD's, presenting a higher frequency in this population group, compared to other professions (Frighetto, 2020; Do Nascimento et al., 2021; Rughi et al., 2021).

According to the latest dyslipidemia guideline published in 2013, the classification of lipid-metabolic alterations has a hereditary nature involving genetic factors and the second way being lipid alterations of a secondary nature, which may be associated with environmental conditions, such as lifestyle (Xavier et al., 2013).

Among the dyslipidemias, FH stands out, which can be diagnosed through molecular criteria (genotypical) in addition to biochemical criteria (phenotypics). FH is autosomal dominant with a significant increase in LDL-c levels in addition to the presence of clinical alterations, such as tendon xanthomas, corneal arch and cardiovascular atherosclerotic disease. From a genetic point of view, FH is diagnosed through genetic tests that identify mutations in specific genes, such as the LDLR protein rs2228671. More than 2,251 mutations have been described for this gene, exhibiting a clinical phenotype in more than 84% of cases evaluated through single nucleotide genetic polymorphisms (Izar et al., 2021).

LDL-c levels above 190 mg/dL show a three-fold increased risk of developing coronary artery disease in individuals with a genetic mutation, when compared to individuals without the mutation, since these patients have developed LDL-c alterations since childhood and progressing throughout life (Xavier et al., 20213; Izar et al., 2021;).

Our study showed that the CC genotype of the LDLR gene has a higher risk of developing lipid alterations associated with FH and obesity. However, these data are contrary to the study by Jha et al. (2020) conducted in India, which showed that the rs2228671 gene showed the TT genotic as the most prevalent in increasing the risk of developing conorarian artery disease.

On the other hand, Pourzargham et al. (2020), in a study conducted with 248 patients in Iran, evaluated the genotypic frequency of the rs2228671 gene, showing the prevalence of the CC and CT genes in determining the risk for cardiac alterations and acute myocardial infarction, corroborating the findings of this study. These mutations that occur in the LDLR gene can decrease the expression of LDL receptors and, consequently, defect in LDL-c uptake

(Leigh et al., 2017). In addition, it is seen that LDLR expression is regulated differently in the liver and gut by dietary cholesterol and dietary saturated fat. Therefore, the disturbed catabolism of LDL-c can lead to an increase in its content and the association with a higher risk of atherosclerosis has already been demonstrated, but there seem to be differences between populations studied (Ference et al., 2017).

Sandhu et al., (2008) in a large genome-wide association study (GWAS) demonstrated that in the same serum of an individual, lipid concentrations may occur inter-individual variations regarding several SNPs in the LDLR. These variations show around 10% in plasma levels. In addition, in the study by Jah et al. (2018) demonstrated that the association of LDL-c and SNP rs688 is associated with the gender of the population studied. In British and German populations, the T allele in SNP rs2228671, which is located in exon 2, is associated with decreased LDL-c levels and risk of coronary heart disease (Linsel-Nitschke et al., 2008). On the other hand, no association between this SNP and cardiovascular diseases in the Chinese population is seen (Ye et al., 2014). It is also suggested that the T allele of rs2228671 is associated with LDL-c levels, but no association has been found with the risk of coronary heart disease (Martinelli et al., 2010).

In the comparative analysis of LDL-c indices, Linsel-Nitsckel et al. (2008) demonstrated in a randomized study that the T allele is protective, which decreases LDL-c rates, corroborating our study, which evidences lower LDL-c rates for case and control patients.

Final considerations

It was concluded that the C allele of the LDLR rs2228671 gene in CC-dominant homozygosity and CT-dominant heterozygosity presents a high risk for the development of FH and obesity in relation to the T allele in military police officers. The T allele, on the other hand, is protective in reducing LDL cholesterol levels, showing benefit to carriers of the TT genotype. The study had some limitations, such as the lack of in-depth clinical evaluation for accurate diagnosis of FH, and further studies were needed in this group to elucidate the genetic investigations.

REFERENCES

ABESO. Associação Brasileira para o Estudo da Obesidade e da Sindrome Metabólica. (2016). Diretrizes brasileiras de obesidade. https:abeso.org.br/wp-content/uploads/2019/12/diretrizes-downloaddiretrizes-brasileiras-de-obesidade-2016.pdf.

BRASIL. Ministério da Saúde. (2021). Secretaria de Vigilância em Saúde. Departamento de Análise em Saúde e Vigilância de Doenças Não Transmissíveis. Plano de Ações Estratégicas para o Enfrentamento das Doenças Crônicas e Agravos não Transmissíveis no Brasil 2021-2030. – Brasília: Ministério da Saúde.

BAYNES, J. W.; DOMINICZAK, M.H. (2011). Bioquímica Médica. [Elsevier]. (3th ed.)

DA SAÚDE. (2008). Diretrizes e Recomendações para o Cuidado Integral de Doenças Crônicas Não-Transmissíveis. https://bvsms.saude.gov.br/bvs/publicacoes/diretrizes_recomendacoes_cuidado_doencas_cronicas.pdf.

DO NASCIMENTO, V. M.S.; SOARES, N.M.M.; OLIVEIRA, D.P.M.; TELE, L.L.; OLIVEIRA, L.A.S.; SILVA, J.S. (2021). NÍVEL DE ATIVIDADE FÍSICA E SAÚDE MENTAL EM POLICIAIS MILITARES DE SERGIPE, BRASIL. In: Congresso Internacional em Saúde.

GARBARINO, S. (2014). Police and military. *Sleepiness and human impact assessment*, 4(2), 159-168.

FALUD, A.A.; IZAR, M.C.O.; SARAIVA, J.F.K.; CHACRA, A.P.M.; BIANCO, H.T.; AFIUNE, N.A.; BERTOLAMIM, A.P.; SPOSITO, A.C.; CHAGAS, A.C.P.; CASELLA-FILHO, A.; SIMAO, A.F.; ALENCAR, F.A.C. (2017). Atualização da diretriz brasileira de dislipidemias e prevenção da aterosclerose–2017. *Arquivos brasileiros de cardiologia*, 109, 1-76.

FERENCE, B.A; GINSBERG, H.N., GRAHAM, I., RAY, K.K., PACKARD, C.J., BRUCEKT, E., HEGELE, R.A., KRAUSS, R.M., RAAL, F.J., SCHUNKERT, H., et al. (2017). Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinicalstudies. A consensus statement from the European Atherosclerosis Society Consensus Panel. *Eur Heart J*. 38(2), 2459-2472.

FRIGHETTO, M. (2020). AVALIAÇÃO DE SAÚDE EM POLICIAIS MILITARES DE UM MUNICÍPIO DO MEIO OESTE CATARINESE. *Anuário Pesquisa e Extensão Unoesc Videira*, 5(2), e24695-e24695.

IZAR, M.C.O.; BERTOLAMI, A.; FILHO, R.D.S.; LOTTENBERG, A.M.; ASSAD, M.H.V.; SARAIVA, J.F.K.; CHACRA, A.P.M.; MARTINEZ, T. L.R.; BAHIA, L.R.; FONSECA, F.A.H.; FALUDI, A.A.; SPOSITO, A.C.; COUTINHO, E.R.; NETO, J.R.F. KATO, J.T. (2021). Atualização da Diretriz Brasileira de Hipercolesterolemia Familiar–2021. *Arquivos Brasileiros de Cardiologia*, 117, 782-844.

JHA, C.K. MIR, R.; BANU, S.; ELFAKI, I.; CHAHAL, S.M.S. (2020). Heterozygosity in LDLR rs2228671 and rs72658855 Gene is Associated with Increased Risk of Developing Coronary Artery Disease in India–A Case-Control Study. *Endocrine, Metabolic & Immune Disorders-Drug Targets (Formerly Current Drug Targets-Immune, Endocrine & Metabolic Disorders*), 20(3), 388-399.

LEIGH, S.; FUTEMA, M., WHITTALL, R., TAYLOR-BEADLING, A., WILLIAMS, M., DEN DUNNEN, J.T., HUMPHRIES, S.E., (2017). The UCL low-density lipoprotein receptor gene variant database: Pthogenicity update. *J Med Genet*. 54(1), 217-223.

LINSEL-NITSCHKE, P.; GOTZ, A. ERDMANN, J.; BRAENNE, I.; BRAUND, P.; HENGTENBERG, C.; STARK, K.; FISCHER, M.; SCHREIBER, S.; NOUR, ED.; MOKHARI, E.; SCHAEFER A.; MANGINO, M.; LIEB, W.; LAMINA, C.; ZIEGLER I.; KRONENBERG, F. (2008). Lifelong reduction of LDL-cholesterol related to a common variant in the LDL-receptor gene decreases the risk of coronary artery disease—a Mendelian randomisation study. *Plos One*, 3(8), .e2986.

LIUINSEL- X.Q.; XIE, Y.N.; BAI, Z. J.; WANG, W. (2006). Mental stress and its related factors in armed police soldiers at high altitude. *Chinese Journal of Clinical Rehabilitation*, 10(30), 60-62.

MAGNAVITA, N.; GARBARINO, S. (2017). Sleep, health and wellness at work: a scoping review. *International journal of envi ronmental research and public health*, 14(11), 1347-1368.

MARTINELI, N., GIRELLI, D., LUNGHI, B., PINOTTI, M., MARCHETTI, G., MALERBA, G., PIGNATTII, P.F., CORROCHER, R., OLIVIERI, O., BERNARDI, F. (2010). Polymorphisms at LDLR locus may be associated with coronary artery disease through modulation of coagulation factor VIII activity and independently from lipid profile. *Blood*. 116, 5688-5697.

MION, J.R.; NOBRE, F. G.; AMODEO, C.; JUNIOR, O. A.; PRAXEDES, J. N.; MACHADO, C.A.; PASCOAL, I.; MAGALHÃES, LC. (2004). IV Diretrizes brasileiras de hipertensão arterial. *Arquivos Brasileiros de cardiologia*, 82, 1-57.

OLIVEIRA, K.L.S.; SANTOS, L.M. (2010). Luana Minharo dos. Percepção da saúde mental em policiais militares da força tática e de rua. *Sociologias*, 12(2), 224-250.

PAULINO, F.R.; LOURINHO, L.A. (2014). O adoecimento psicológico do policial militar do Ceará. *Revista trabalho e sociedade, Fortaleza*, 2(2), 58-77.

POURZARGHAM, P.; ATAOLAHI M.; FOULADSERESHT, S.; KHOSROPANAH, M.; DOROUDCHI, M. (200). Association of anteroseptal hypokinesia after myocardial infarction with LDLR variation: A cross-sectional case-control study. *Journal of Experimental and Clinical Medicine,* 37(3), 87-95.

SANDHU, M.S., WATERWORTH, D.M., DEBENHAM, S.L., WHEELER, E., PAPAPDAKIS, K., ZHAO, J.H., SONG, K., YUAN, X., JOHNSON, T., ASHFORD, S., INOUYE, M., LUBEN, R., SIMS, M., HADLEY, D., MCARDLE, W., BARTER, P. (2008). LDL-cholesterol concentrations: A genome-wide association study. *Lancet*. 371, 483-491.

RUGHI, A.L.; BASSO, C.; SCHUCH, N. J. (2021). Síndrome Metabólica e Fatores de Risco Cardiovascular em Policiais Militares: uma revisão da literatura. *Disciplinarum Scientia| Saúde*, 22(1), 123-133.

TAYLOR, Y.; MERAT, N.; JAMSON, S. (2019). The Effects of Fatigue on Cognitive Performance in Police Officers and Staff During a Forward Rotating Shift Pattern. *Saf Health Work*, 10(1), 67-74.

YE, H., ZHAO, Q., HUANG, Y., WANG, L., LIU, H., WANG, C., DAI, D., XU, L., YE, M., DUAN, S., 2014. Meta-analysis of low density lipoprotein receptor (LDLR) rs2228671 polymorphism and coronary heart disease. Biomed. Res. Int. 2014,

564940.

WILLIAMS, R.R.; HUNT, S.C.; SCHUMACHER, M.C.; HEGELE, R.A.; LEPPERT, M.F.; LUDWIG, E.H.; HOPKINS, P.N. (1993). Diagnosing heterozygous familial hypercholesterolemia using new practical criteria validated by molecular genetics. *Am J Cardio*l, 72(2), 171-176.

XAVIR, H.T.; IZAR, M.C.; NETO, F.J.R.; ASSAD, M.H.; ROCHA, V.Z.; SPOSITO, A.C.; FONSECA, F.A.; SANTOS, J.E.; SANTOS, R.D.; BERTOLAMI, M.C.; FALUDI, A.A.; MARTINES, T.L.R.; DIAMENT, J.; GUIMARAES, A.; FORTI, N.A.; MORIGUCHI, E.; CHAGAS, A.C.P.; COELHO, O.R.; RAMIRES, J.A.F. (2013). V Diretriz brasileira de dislipidemias e prevenção da aterosclerose. *Arquivos brasileiros de cardiologia*, 101(3), 1-20.