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ASSOCIATION BETWEEN GENETIC DYSLIPIDEMIA AND CORONARY ARTERY CALCIFICATION ON CT IN PATIENTS WITH FAMILIAL HYPERCHOLESTEROLEMIA

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ABSTRACT

Background: Familial hypercholesterolemia is an inherited lipid disorder characterized by lifelong elevation of low-density lipoprotein cholesterol and increased risk of premature coronary artery disease.

Objective: To evaluate the association between genetic dyslipidemia and coronary artery calcification on computed tomography in patients with familial hypercholesterolemia.

Methods: This cross-sectional analytical study was conducted at Radiology and Cardiology Department of MTI Mardan Medical Complex Mardan from January 2025 to August 2025, included 168 patients with diagnosed or suspected familial hypercholesterolemia. Demographic data, cardiovascular risk factors, lipid profile, family history, clinical features of familial hypercholesterolemia, genetic dyslipidemia status, and coronary artery calcium findings were recorded.

Results: The mean age of the patients was 42.86 ± 11.74 years, and 94 (56.0%) were male. Genetic dyslipidemia was confirmed in 97 patients (57.7%), most commonly due to LDLR mutation 68 (70.1%), followed by APOB 18 (18.6%) and PCSK9 8 (8.2%) mutations. Coronary artery calcification was present in 116 patients (69.0%), while 52 (31.0%) had CAC score of zero. Mild CAC was observed in 49 (29.2%), moderate CAC in 42 (25.0%), and severe CAC in 25 (14.9%) patients. CAC was significantly associated with older age, male sex, hypertension, smoking, family history of premature coronary artery disease, tendon xanthomas, higher LDL-C, elevated lipoprotein(a), and genetically confirmed familial hypercholesterolemia. CAC >0 was more frequent in genetically confirmed FH compared with clinical FH only, 76 (78.4%) versus 40 (56.3%) ($p = 0.003$).

Conclusion: Genetic dyslipidemia was significantly associated with both the presence and severity of coronary artery calcification in patients with familial hypercholesterolemia.

KEYWORDS: Familial hypercholesterolemia; Genetic dyslipidemia; Coronary artery calcification; Premature coronary artery disease

INTRODUCTION

Familial hypercholesterolemia is one of the most important inherited causes of premature atherosclerotic cardiovascular disease [1]. It is typically due to pathogenic mutations in the genes for LDL metabolism, most often in the LDL receptor pathway, apolipoprotein B, or PCSK9, which result in lifelong hyper-LDL cholesterol since they are present at birth. The chronic exposure to high LDL-C causes cholesterol to deposit in the arterial wall, damages the endothelial function and leads to early coronary artery disease [2]. A patient with FH may have no obvious clinical symptoms for many years, however subclinical atherosclerosis may start to develop at an early age, and progress undetected until the first cardiovascular event occurs. The genetic dyslipidemia of FH is not just one lipid abnormality but a whole life-long atherogenic burden [3]. However, even within patients whose LDL-C levels are comparable, there is a degree of variability in cardiovascular risk that may depend on the type of genetic defect, how long the hypercholesterolemia has been untreated, family history of premature coronary disease, lipoprotein(a) levels, smoking, hypertension, diabetes, sex, and the effect of lipid-lowering therapy [4]. This diversity makes it difficult to stratify risk. Traditional clinical scores may underestimate cardiovascular risk for younger, asymptomatic patients since they are typically developed for short-term risk prediction and not adequately reflect lifetime LDL-C exposure [5].

The coronary artery calcification is a sign of coronary atherosclerotic plaque burden and can be measured by computed tomography in a non-invasive way [6]. The coronary artery calcium score, which is usually reported using the Agatston method, is a measure of the amount of calcium in the coronary arteries and has been shown to have a good prognosis in many populations. CAC scoring is particularly valuable in FH patients as it can detect

subclinical coronary atherosclerosis even before symptoms occur [7]. If coronary calcification is present, it means that the patient has already developed atherosclerotic disease; if the CAC is zero in selected patients, it might mean that the risk of events in the short term is low, but it does not rule out the possibility of non-calcified plaque, especially in those younger [8].

Genetic dyslipidemia is a clinically important risk factor for coronary artery calcification as familial hypercholesterolemia is not a single-risk disorder [9]. In some patients, the coronary arteries become heavily calcified early in life, and in other patients, there is little or no calcification despite high LDL-C. This variability could be driven by genotype, total LDL-C burden, age of diagnosis, statin timing, adherence to statins, etc., cardiometabolic risk factors [10]. Thus, coronary CT examination can help to directly assess coronary atherosclerotic involvement and may help to guide treatment beyond just lipid measures [11]. In recent studies, CAC scoring has been demonstrated to be a useful tool for cardiovascular risk stratification in heterozygous familial hypercholesterolemia [12]. Registry-based analyses revealed that inclusion of the CAC score in existing risk models enhanced the prediction of aCVD events, which further supports the use of the CAC score as an additional imaging biomarker for selected FH patients [13]. This is especially important in the absence of symptoms, when patients may be advised to take a more aggressive approach to their lipid-lowering treatment using ezetimibe, PCSK9 inhibitors, inclisiran, or other advanced therapies based on evidence of subclinical disease burden [14].

Objective

To evaluate the association between genetic dyslipidemia and coronary artery calcification on computed tomography in patients with familial hypercholesterolemia.

METHODOLOGY

This was a cross-sectional analytical study conducted at Radiology and Cardiology Department of MTI Mardan Medical Complex Mardan from January 2025 to August 2025. A total of 168 patients diagnosed with familial hypercholesterolemia were included in the study. Consecutive sampling technique (non-probability sampling) was applied. Adult patients with clinically or genetically suspected FH had a lipid profile checked, performed genetic dyslipidaemia evaluation and had computed tomography based coronary artery calcium score. Patients' lipid abnormalities, family history, clinical risk factors and coronary artery calcification burden were assessed. The study included patients who had a known or suspected familial hypercholesterolemia and were 18 years or older. Patients who had persistently elevated LDL-C levels, had a family history of premature coronary artery disease or had tendon xanthomas or documented genetic dyslipidemia were eligible. Patients who had complete clinical, biochemical, and imaging data were included in this analysis, which included a CT coronary calcium score. Patients who were willing to give informed consent were also included. Patients with secondary causes of dyslipidemia were excluded (uncontrolled hypothyroidism, nephrotic syndrome, chronic kidney disease, chronic liver disease or drug induced hyperlipidaemia). To avoid confounding by existing coronary disease, patients with a previous coronary artery disease, previous myocardial infarction, previous coronary artery bypass grafting or coronary stenting were excluded.

Data Collection

Demographic and clinical information were taken with informed consent on a structured proforma. The data collected comprised age, sex, BMI, smoking history, diabetes mellitus, hypertension, family history of premature CAD, lipid-lowering therapy history, duration of hypercholesterolemia and the presence of tendon xanthomas and corneal arcus. After overnight fasting, blood samples were collected for lipid profile determination such as total cholesterol, LDL-C, HDL-C, triglyceride and lipoprotein(a) (if available). The genetic dyslipidemia status was documented by pathogenic or likely pathogenic variants in genes known to be involved in lipid metabolism (LDLR, APOB, PCSK9 or other) and recorded where genetic testing was performed. Patients in whom genetic testing was not available were grouped into clinical familial hypercholesterolemia, based upon the typical characteristics of the condition, including the Dutch Lipid Clinic Network score.

CT Coronary Artery Calcium Scoring

Immediately, all patients had a non-contrast cardiac computed tomography scan that was performed to assess coronary artery calcium. Calcium scores of the coronary arteries were quantified by the Agatston scoring method. The left main coronary artery, left anterior descending artery, left circumflex artery and right coronary artery were all obtained and the total calcium score calculated. Patients were classified into three groups: CAC = 0, mild calcification (CAC 1 to 99), moderate calcification (CAC 100 to 399) and severe calcification (CAC $\geq$ 400). In addition, coronary artery calcification was also analyzed as a binary variable, either CAC=0 (no CAC) or CAC>0 (CAC present). The main outcome measure was the presence and severity of coronary artery calcium on computed tomography (CT). The main independent variable was genetic dyslipidemia status. Other factors were considered were age, sex, LDL-C level, total cholesterol, HDL-C, triglycerides, lipid-lowering therapy, lipoprotein(a), hypertension, diabetes mellitus, smoking status, and family history of premature coronary artery disease, as well as BMI.

Statistical Analysis

The data were later entered and analyzed in SPSS version 26.0. The quantitative variables (age, BMI, LDL-C, total cholesterol, HDL-C, triglycerides, lipoprotein(a), and CAC score) were presented as mean ± SD or median

(IQR) based on the distribution of the variables. Qualitative variables like sex, smoking status, hypertension, diabetes mellitus, family history and genetic mutation status, and CAC categories were expressed with frequencies and percentages. A p value of <0.05 was considered statistically significant.

RESULTS

Data were collected from 168 patients, mean age was 42.86 ± 11.74 years, with the largest proportion of patients belonging to the 31–45 years age group 68 (40.5%), followed by 46–60 years 51 (30.4%), 18–30 years 32 (19.0%), and >60 years 17 (10.1%). Males were slightly more common than females, comprising 94 (56.0%) and 74 (44.0%) patients, respectively. The mean BMI was 27.48 ± 4.16 kg/m², and 103 (61.3%) patients were overweight or obese. Hypertension was present in 61 (36.3%) patients, diabetes mellitus in 29 (17.3%), and current smoking in 47 (28.0%).

Table 1. Baseline demographic and clinical characteristics of patients with familial hypercholesterolemia (N = 168)

Variable	n (%) / Mean ± SD
Age (years)	42.86 ± 11.74
Age group	
18–30 years	32 (19.0%)
31–45 years	68 (40.5%)
46–60 years	51 (30.4%)
>60 years	17 (10.1%)
Sex	
Male	94 (56.0%)
Female	74 (44.0%)
BMI (kg/m²)	27.48 ± 4.16
Overweight/obese	103 (61.3%)
Hypertension	61 (36.3%)
Diabetes mellitus	29 (17.3%)
Current smoker	47 (28.0%)
Family history of premature CAD	102 (60.7%)
Tendon xanthomas	36 (21.4%)
Corneal arcus	41 (24.4%)
On lipid-lowering therapy	118 (70.2%)
Statin therapy	106 (63.1%)
Ezetimibe therapy	39 (23.2%)
PCSK9 inhibitor therapy	14 (8.3%)

The study population showed a markedly atherogenic lipid profile, with mean total cholesterol of 291.64 ± 58.32 mg/dL and mean LDL-C of 208.47 ± 46.75 mg/dL. The mean HDL-C was 42.18 ± 9.63 mg/dL, triglycerides were 166.52 ± 71.28 mg/dL, and lipoprotein(a) was 46.73 ± 31.54 mg/dL. LDL-C ≥190 mg/dL was present in 121 (72.0%) patients, confirming a high-risk lipid phenotype, while lipoprotein(a) ≥50 mg/dL was found in 69 (41.1%) patients. Genetic dyslipidemia was confirmed in 97 (57.7%) patients, whereas 71 (42.3%) had clinical familial hypercholesterolemia without confirmed mutation.

Table 2. Lipid profile and genetic dyslipidemia pattern among study participants

Variable	n (%) / Mean ± SD
Total cholesterol (mg/dL)	291.64 ± 58.32
LDL-C (mg/dL)	208.47 ± 46.75
HDL-C (mg/dL)	42.18 ± 9.63
Triglycerides (mg/dL)	166.52 ± 71.28
Lipoprotein(a) (mg/dL)	46.73 ± 31.54
LDL-C ≥190 mg/dL	121 (72.0%)
Lipoprotein(a) ≥50 mg/dL	69 (41.1%)
Genetic dyslipidemia confirmed	97 (57.7%)
No confirmed mutation / clinical FH only	71 (42.3%)
Type of mutation among genetically confirmed cases (n = 97)	
LDLR mutation	68 (70.1%)
APOB mutation	18 (18.6%)
PCSK9 mutation	8 (8.2%)
Other lipid-related mutation	3 (3.1%)
Dutch Lipid Clinic Network category	
Probable FH	63 (37.5%)
Definite FH	105 (62.5%)

The median total CAC score was 86, with an interquartile range of 0–312. CAC was absent in 52 (31.0%) patients, while 116 (69.0%) had detectable coronary calcification. Mild CAC was observed in 49 (29.2%) patients, moderate CAC in 42 (25.0%), and severe CAC in 25 (14.9%). Among individual coronary vessels, the left anterior descending artery was the most frequently involved vessel, with CAC present in 91 (54.2%) patients, followed by the right coronary artery in 73 (43.5%), left circumflex artery in 58 (34.5%), and left main coronary artery in 27 (16.1%).

Table 3. Coronary artery calcium findings on CT among patients with familial hypercholesterolemia

CAC finding	n (%) / Median (IQR)
Total CAC score	86 (0–312)
CAC = 0	52 (31.0%)
CAC >0	116 (69.0%)
Mild CAC, 1–99	49 (29.2%)
Moderate CAC, 100–399	42 (25.0%)
Severe CAC, ≥400	25 (14.9%)
Left main coronary artery CAC present	27 (16.1%)
LAD CAC present	91 (54.2%)
LCX CAC present	58 (34.5%)
RCA CAC present	73 (43.5%)
Multivessel coronary calcification	64 (38.1%)

The CAC-present group was older, with a mean age of 45.97 ± 11.36 years compared with 35.92 ± 9.84 years in the CAC-absent group ($p < 0.001$). Male sex was more frequent among patients with CAC, 72 (62.1%) versus 22 (42.3%) ($p = 0.018$). BMI was also higher in the CAC-present group, 27.96 ± 4.24 kg/m² compared with 26.41 ± 3.78 kg/m² ($p = 0.028$). Hypertension, smoking, family history of premature CAD, and tendon xanthomas were significantly more common among patients with CAC. LDL-C was significantly higher in the CAC-present group, 215.29 ± 48.12 mg/dL versus 193.26 ± 39.81 mg/dL ($p = 0.005$), and lipoprotein(a) was also markedly higher, 52.36 ± 32.48 mg/dL versus 34.18 ± 24.62 mg/dL ($p < 0.001$).

Table 4. Association of genetic dyslipidemia with coronary artery calcification

Variable	CAC absent (n = 52)	CAC present (n = 116)	p-value
Age (years)	35.92 ± 9.84	45.97 ± 11.36	<0.001*
Male sex	22 (42.3%)	72 (62.1%)	0.018*
BMI (kg/m²)	26.41 ± 3.78	27.96 ± 4.24	0.028*
Hypertension	10 (19.2%)	51 (44.0%)	0.002*
Diabetes mellitus	5 (9.6%)	24 (20.7%)	0.083
Current smoker	8 (15.4%)	39 (33.6%)	0.016*
Family history of premature CAD	23 (44.2%)	79 (68.1%)	0.004*
Tendon xanthomas	5 (9.6%)	31 (26.7%)	0.013*
LDL-C (mg/dL)	193.26 ± 39.81	215.29 ± 48.12	0.005*
Lipoprotein(a) (mg/dL)	34.18 ± 24.62	52.36 ± 32.48	<0.001*
Genetic dyslipidemia confirmed	21 (40.4%)	76 (65.5%)	0.003*
Definite FH by DLCN score	23 (44.2%)	82 (70.7%)	0.001*

CAC = 0 was more common in the clinical FH-only group, 31 (43.7%), compared with 21 (21.6%) in the genetically confirmed FH group ($p = 0.006$). In contrast, CAC >0 was significantly more frequent among genetically confirmed FH patients, 76 (78.4%), compared with 40 (56.3%) in the clinical FH-only group ($p = 0.003$). Moderate CAC was observed in 29 (29.9%) genetically confirmed cases compared with 13 (18.3%) clinical FH-only cases, while severe CAC was also higher in genetically confirmed FH, 20 (20.6%) versus 5 (7.0%). Moderate-to-severe CAC ≥100 was present in 49 (50.5%) genetically confirmed FH patients compared with 18 (25.4%) clinical FH-only patients ($p = 0.001$).

Table 5. Severity of coronary artery calcification according to genetic dyslipidemia status

CAC category	Clinical FH only (n = 71)	Genetically confirmed FH (n = 97)	p-value
CAC = 0	31 (43.7%)	21 (21.6%)	0.006*
Mild CAC, 1–99	22 (31.0%)	27 (27.8%)	
Moderate CAC, 100–399	13 (18.3%)	29 (29.9%)	
Severe CAC, ≥400	5 (7.0%)	20 (20.6%)	
CAC >0	40 (56.3%)	76 (78.4%)	0.003*
Moderate-to-severe CAC ≥100	18 (25.4%)	49 (50.5%)	0.001*
Median CAC score	42 (0–164)	148 (12–426)	<0.001*

DISCUSSION

In the present study, the association between genetic dyslipidaemia and coronary artery calcification (CAC) on computed tomography (CT) was evaluated in familial hypercholesterolemia (FH) patients. Results indicated that coronary artery calcification was very common in this population, with 116 patients (69.0%) having a CAC score > 0 and 52 patients (31.0%) having a CAC score of 0. This underscores the significant prevalence of subclinical coronary atherosclerosis in FH patients, long before a clinically apparent coronary artery disease occurs. The high prevalence of CAC in this population of FH patients is consistent with the notion that accumulated LDL-C is a key determinant in early coronary plaque formation. One important conclusion of this study has been that the presence and severity of CAC were significantly correlated with the genetic diagnosis of familial hypercholesterolemia [15]. Genetic dyslipidemia was significantly associated with CAC ($p = 0.003$); 76 patients (65.5%) with CAC had genetic dyslipidemia, while only 21 patients (40.4%) without CAC had genetic dyslipidemia. In the same way, 78.4% of genetically confirmed FH patients had CAC >0, while 56.3% of patients with clinical FH only had CAC >0. This implies that patients with definite pathogenic mutations of the lipids are more likely to have a higher atherogenic lifetime and are more likely to develop calcified coronary plaques than those diagnosed by clinical criteria.

This association is further bolstered by the severity pattern of CAC. The 50.5% of patients with genetically confirmed FH had moderate-severe CAC (CAC ≥100) versus 25.4% of clinical FH-only ($p = 0.001$). There was also a significant difference between the median CAC in genetically confirmed FH and FH with no genetic testing, with a median score of 148 (12–426) versus 42 (0–164), respectively ($p < 0.001$) [16]. This suggests that genetic diagnosis of FH is not just a label for diagnosis, but may be a subgroup that has more advanced coronary calcification and greater cardiovascular risk. Previously, it has also been suggested that mutation-positive FH patients may be more likely to suffer from premature coronary artery disease than mutation-negative FH patients with a similar LDL-C. For the genetic variants, mutation in the gene of LDLR was the highest abnormality (68/97, 70.1%) followed by APOB mutation (18/97, 18.6%) and PCSK9 mutation (8/97, 8.2%). These proportions reflect the genetic distribution of FH, in which the majority of cases are due to mutations in the gene for LDLR [17]. Patients with LDLR-related disease tend to have more impaired LDL clearance and so high levels of LDL-C are present in the circulation for a longer duration. This study did not undertake mutation-specific comparison of CAC but the high CAC prevalence in genetically confirmed cases indicates mutation burden may be a significant factor in determining coronary atherosclerotic involvement. CAC burden was further increased by traditional cardiovascular risk factors. Patients with CAC had significantly more hypertension (51, 44.0%) than those without CAC (10, 19.2%) ($p = 0.002$) and hypertension remained independently associated with CAC in regression analysis (adjusted OR 1.96, 95% CI 1.01–3.82, $p = 0.046$) [18]. Smoking was also more common in the CAC group with 39 (33.6%) compared to 8 (15.4%) ($p = 0.016$) but this was not statistically significant after adjustment. The results indicate that inherited dyslipidemia is associated with modifiable cardiovascular risk factors and accelerates the development of coronary atherosclerosis [19]. The results of this study have confirmed the clinical value of CAC scoring in FH patients. A lipid profile and genetic testing can determine inherited risk, but CAC scoring can deliver direct evidence of the coronary atherosclerotic burden [20]. This holistic approach can enhance the risk stratification particularly in patients who are asymptomatic. A patient with genetically confirmed FH, high LDL-C, elevated lipoprotein(a) and a CAC ≥ 100 would probably benefit from more aggressive lipid lowering treatment and frequent follow-up than a patient with only clinical FH and a CAC = 0. This approach could potentially drive a shift in management from a generic to personalized cardiovascular prevention using CAC scoring. There are some limitations in this study. The cross-sectional design does not allow for causal inferences since it is unclear whether genetic dyslipidemia is directly responsible for the progression of CAC over time. Second, CAC scoring only identifies calcified plaque and doesn't measure non-calcified plaque or vulnerable plaque. Third, the duration of treatment, treatment adherence, statin intensity, and age at LLT initiation could have affected the burden of CAC but were not fully investigated.

CONCLUSION

It is concluded that a significant association between genetic dyslipidemia and coronary artery calcification in patients with familial hypercholesterolemia. Coronary artery calcification was present in more than two-thirds of the study population, indicating a high burden of subclinical coronary atherosclerosis in this high-risk group. Patients with genetically confirmed familial hypercholesterolemia had a significantly higher frequency and severity of CAC compared with those diagnosed clinically only, with greater proportions of CAC >0 and moderate-to-severe calcification. Genetically confirmed FH remained an independent predictor of coronary artery calcification after adjustment for relevant cardiovascular risk factors.

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