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Comparison of Coronary Artery Disease Involvement in Patients with or without Familial History

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Abstract: Introduction: It is demonstrated that both a familial history and genetic risk score are associated with subclinical atherosclerosis and most recently have been shown to each provide independent information for future cardiovascular events that seems additive when both are present. The exact mechanism that is responsible for higher risk of patients with positive familial history is yet unknown. In order to find this relationship in Iranian population because of lack of data, we assessed pattern of CAD involvement in patients with positive familial history and without. **Methods:** This was a cross sectional study that was performed between April 2019 and April 2020 in Imam Rezan and Ghaem Hospitals, Mashhad, Iran. We enrolled all patients with typical chest pain and markedly CAD such as STEMI, non-STEMI, unstable angina, chronic stable angina or sudden cardiac death. Patients' age were between 18 to 65 years of old. They were divided into 2 groups: patient with familial history of CAD and those without and evaluated for potential risk factors of CAD. **Results:** This study was performed on 300 patients with CAD who underwent coronary angiography. Of these patients, 180 of them had positive familial history and 120 of them were without familial history. One hundred seventy five of participants were male (58.3%) with mean age of 54.2 years old. Multivariate regression analysis of risk factors showed that age (OR: 1.04, P=0.014), gender (OR: 0.564, P=0.035) and hypertension (OR: 1.99, P= 0.008) are significantly different in two groups. Vessel involvement in both groups showed that multi-vessel involvement in patients with positive familial history (49.2%) was higher than in patients without (36.1%). Three vessel disease (OR: 2.55, P=0.013) was significantly higher in patients with previous familial history rather than patients without after adjusting for other risk factors. **Conclusion:** In conclusion, we found that a positive familial history of CAD is associated with the severity, morphology (non-calcified and mixed) and extent of coronary atherosclerosis.

Keywords: familial history; coronary artery disease; atherosclerosis

Introduction

Hereditary nature of coronary artery disease (CAD) is established before and it is probably came out a combination of risk factors like environmental and conventional risk factors with precipitating genetic mechanisms [1]. In developing countries, the age of CAD is diminishing with respect to social and economic factors [2]. CAD is not common among young adults and considered an imperative problem for such patients because of its distressing consequences on their active lifestyle. It is

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reported that risk factors, angiographic profiles and clinical presentations could be different comparing young and old patients, having different prognostic effects in each group [3]. There are different evidences indicated that positive familial history for CAD is strongly correlated with cardiovascular disorders, which is independent from traditional risk factors [4–6].

A positive familial history and a high genetic risk score can predispose to acute coronary syndrome (ACS) via accelerated atherosclerosis, a propensity to thrombosis or other, as of yet, undetermined mechanisms [7]. It is demonstrated that both a familial history and genetic risk score are associated with subclinical atherosclerosis and most recently have been shown to each provide independent information for future cardiovascular events that seems additive when both are present [7]. Whether this relationship may be mediated by more advanced angiographic burden of CAD, as opposed to a higher propensity for thrombosis or other mechanism, has not been established [8–10].

The exact mechanism that is responsible for higher risk of patients with positive familial history is yet unknown. In order to find this relationship in Iranian population because of lack of data, we assessed pattern of CAD involvement in patients with positive familial history and without.

Methods

This was a cross sectional study that was performed between April 2019 and April 2020 in Imam Rezan and Ghaem Hospitals, Mashhad, Iran.

Subjects

We enrolled all patients with typical chest pain and markedly CAD such as STEMI, non-STEMI, unstable angina, chronic stable angina or sudden cardiac death. Patients' age were between 18 to 65 years of old. A checklist consisting demographic, clinical, laboratory data obtained for each patients.

Definitions

We defined the stenosis of 50 percent or more in at least 1 major epicardial coronary artery as CAD. A positive family history of coronary disease was determined as a first-degree relative of a person less than 55 years old in men and less than 45 years old in women. Abnormal triglyceride (TG) and low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were defined as > 150 mg/dL and > 130 mg/dL, <50 mg/dL, respectively. Angiographic diagnosis of patients were defined as: none (less than 50% stenosis of the vessels), left main disease (LMD), 3Vessel Diseases (3VD), 2 Vessel Disease (2VD) and single vessel disease (SVD). Multi-vessel disease was defined as ≥2vessels involvement.

Study Design

The enrolled patients were divided into 2 groups: patient with familial history of CAD and those without. We evaluated risk factors for CAD including gender, diabetes mellitus, smoking, hypertension, abnormal lipid profile and family history of CAD in each group. Positive history of opium and smoking was also obtained through a self-report assessment. All patients underwent angiography and the pattern of coronary artery disease was compared between the two groups.

Ethics

Ethical committee of Mashhad University of Medical Sciences approved this study. We obtained informed written consent for each patient to participate in the study.

Statistics

We used descriptive statistical analyses to present mean and standard deviation of quantitative variables. Independent T-Test or Mann Whitney Test were used for comparison of quantitative variables between two groups. We compared qualitative data with Chi square or Fisher' Exact Test. For all analyses, we used SPSS (SPSS 19.0 for Windows; SPSS Inc. Chicago, Illinois).

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Results

This study was performed on 300 patients with CAD who underwent coronary angiography. Of these patients, 180 of them had positive familial history and 120 of them had without familial history. One hundred seventy five of participants were male (58.3%) and 125 of them (41.7%) were female with mean age of 54.2 years old (range: 33-65). Baseline characteristics of both groups are shown in Table 1.

Table 1. Baseline characteristics of CAD patients with or without familial history.

Characteristics	All Patients (n=300)	Positive FH n= 180	Negative FH n=120	P Value
Age (mean ±SD), year	54.20 ± 7.0	52.6	55.3	**0.002 ***
Female (n, %)	125 (41.7%)	83 (46.1%)	42 (35.0%)	**0.056****
Male (n, %)	175 (58.3%)	97 (53.9%)	78 (65.0%)	
Diabetes mellitus (n, %)	89 (29%)	49 (27.2%)	40 (33.3%)	**0.256****
Hyperlipidemia (n, %)	62 (20.6%)	37 (20.6%)	25 (20.8%)	**0.954****
Hypertension (n, %)	140 (46%)	74 (41.1%)	66 (55.0%)	**0.018****
IHD (n, %)	44 (14.6%)	29 (16.1%)	15 (12.5%)	**0.386****
Cigarette smoking (n, %)	115 (38%)	71 (39.4%)	44 (36.7%)	**0.628****
Unstable angina (n, %)	168 (56.0%)	107 (59.4%)	61 (50.8%)	
STEMI (n, %)	83 (27.7%)	46 (25.6%)	37 (30.8%)	**0.338****
Non-STEMI (n, %)	49 (16.3%)	27 (15.0%)	22 (18.3%)	
Abnormal HDL (n, %)	79 (26%)	50 (28%)	29 (24%)	**0.408**
Abnormal TG (n, %)	109 (37%)	66 (20%)	43 (36%)	**0.755**
Abnormal LDL (n, %)	66 (29%)	37(21%)	29 (24%)	**0.532**

FH= familial history, STEMI= ST segment elevation myocardial infarction, IHD= ischemic heart disease, TG= triglyceride, LDL= low-density lipoprotein, HDL= high-density lipoprotein.

Multivariate regression analysis of risk factors showed that age (OR: 1.04, P=0.014), gender (OR: 0.564, P=0.035) and hypertension (OR: 1.99, P= 0.008) are significantly different in two groups (Table 2).

Table 2. Multivariate analysis of risk factors in CAD patients with or without positive familial history.

Risk factor	P value	OR	95% CI for OR	
			Lower	Upper
Gender	0.035	0.564	0.332	0.960
Diabetes Mellitus	0.426	1.249	0.723	2.158
Hypertension	0.008	1.995	1.200	3.317
IHD	0.174	0.601	0.289	1.251
HLP	0.820	0.921	0.455	1.866
Smoking	0.097	0.639	0.376	1.084
Abnormal HDL	0.354	1.308	0.742	2.305
Abnormal TG	0.507	1.204	0.696	2.081
Abnormal LDL	0.452	1.280	0.673	2.436
Age	0.014	1.042	1.008	1.077

FH= familial history, STEMI= ST segment elevation myocardial infarction, IHD= ischemic heart disease, TG= triglyceride, LDL= low-density lipoprotein, HDL= high-density lipoprotein.

Vessel involvement in both groups showed that multi-vessel involvement in patients with positive familial history (49.2%) was higher than in patients without positive familial history (36.1%). Multinomial regression analysis showed that 3VD (OR: 2.55, P=0.013) was significantly different in

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patients with previous familial history rather than patients without after adjusting for other risk factors like age, hyperlipidemia, hypertension, gender, diabetes and smoking (Table 3).

Table 3. Multinomial logistic regression for major epicardial vessel stenosis in patients with or without familial history.

No. of major epicardial coronary artery	All Patients n=300	Negative FH n= 180	Positive FH n= 120	Unadjusted OR (95% CI); P Value	Adjusted* OR (95% CI); P Value
0	100 (33.3%)	71 (39.4%)	29 (24.2%)	Reference	Reference
1	77 (25.7%)	44 (24.4%)	33 (27.5%)	1.83 (0.98-3.43); P=0.057	1.72 (0.88- 3.33) 0.109
2	66 (22.0%)	36 (20.0%)	30 (25.0%)	2.04 (1.06-3.90); P=0.001	1.85 (0.92- 3.72) 0.082
3	57 (19.0%)	29 (16.1%)	28 (23.3%)	2.36 (1.20-4.64); P=0.013	2.55 (1.22- 5.33) 0.013

CI: confidence interval, FH: family history, OR: odds ratio. *Adjusted for age, sex, history of hypercholesterolemia, history of diabetes mellitus, history of hypertension, current cigarette smoking.

Therapeutic recommendations after angiography were categorized in three groups: MFU, PCI and CABG in two groups, which was significantly different (P=0.014). Patients without FH was more in MFU (44.4%) and patients with positive FH were underwent more invasive and non-pharmacologic treatments (Table 4).

Table 4. Comparison of therapeutic approaches based on angiography in CAD patients with or without positive familial history.

No. of major epicardial coronary artery	All Patients n=300	Negative FH n= 180	Positive FH n= 120	Unadjusted OR (95% CI); P Value	Adjusted* OR (95% CI); P Value
MFU	114 (38.0%)	80 (44.4%)	34 (28.3%)	Reference	Reference
CABG	43 (14.3%)	21 (11.7%)	22 (27.5%)	2.46 (1.20-5.06); P=0.014	2.41 (1.12-5.18) P= 0.024
PCI	143 (47.7%	79 (43.9%)	64 (53.3%)	1.90 (1.134-3.20); P=0.015	1.75 (1.01-3.05) P= 0.046

MFU: Medical follow-up, CABG: Coronary Artery Bypass Grafting, PCI: Percutaneous coronary artery intervention, CI: confidence interval, FH: family history, OR: odds ratio. *Adjusted for age, sex, history of hypercholesterolemia, history of diabetes mellitus, history of hypertension, current cigarette smoking.

Our findings showed that there was significant difference between severity of stenosis (P<0.001) and location of stenosis (P=0.046) in left coronary artery in two groups. There was no significant difference between length of stenosis in left coronary artery system and severity, location and length of stenosis in right coronary artery systems (P>0.05). In overall right and left arteries, there was significant difference between severity of stenosis in patients with or without positive familial history (P<0.001).

Comparison of severity of calcification in left coronary artery system was significantly higher in patients with positive FH (P<0.001) and both right and left systems (P<0.001) but not right system (P>0.05) (Table 5).

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Table 5. Pattern of right and left coronary systems in severity, location and length of stenosis in CAD patients with or without positive familial history.

Coronary artery system		Severity of stenosis			Length of stenosis			Location of stenosis		
		Non significant	> 50% stenosis	total	1 cm >	> 1 cm	total	Ostio proximal	distal	total
Left (n, %)	FH+	47(23.7)	151(76.3)	198	117(59)	81(41)	198	148(74.7)	50(25.3)	198
	FH-	107(40.2)	159 (59.8)	266	157(59)	109(41)	266	176(66.1)	90(33.9)	266
	p value		<0.001			0.988			0.046	
Right (n, %)	FH+	23(29.4)	55(70.6)	78	56(71.7)	22(28.3)	78	44(56.4)	34(43.6)	78
	FH-	40(35)	74(65)	114	67(58.7)	47(41.3)	114	69(60.5)	45(39.5)	114
	p value		0.417			0.065			0.569	
Right + Left (n, %)	FH+	70(25.4)	206(74.6)	276	173(62.7)	103(37.3)	276	192(44.4)	84(47.4)	276
	FH-	147(38.6)	233(61.4)	380	224(59)	156(41)	380	245(64.5)	135(35.5)	380
	p value		<0.001			0.334			0.172	

FH: family history.

Discussion

Coronary atherosclerosis is affected by different environmental and genetic factors. Family history of premature CAD is a well-established risk factor for cardiovascular diseases [11,12]. In patients with a history of premature CAD, genetic susceptibility and possible novel cardiovascular risk factors causing premature atherosclerosis may play role in the progression of early atherosclerotic process. Furthermore, common environmental risk factors shared by the same family members may be the causative trigger in premature atherosclerosis. However, there has been a controversy regarding the magnitude of the risk conferred by FH of premature CAD over traditional cardiovascular risk factors. Additionally many cardiovascular risk assessment scores, do not include the FH of premature CAD as a cardiovascular risk factor in their charts [13].

Our findings showed that vessel involvement in both groups showed that multi-vessel involvement in patients with positive familial history (49.2%) was higher than in patients without positive familial history (36.1%). Multinomial regression analysis showed that 3VD (OR: 2.55, P=0.013) was significantly different in patients with previous familial history rather than patients without after adjusting for other risk factors. Therapeutic recommendations after angiography was significantly different (P=0.014) and patients without FH was more in MFU (44.4%) and patients with positive FH were underwent more invasive and non-pharmacologic treatments. We showed that there was significant difference between severity of stenosis (P<0.001) and location of stenosis (P=0.046) in left coronary artery in two groups.

Parikh et al. showed that a family history of CAD was associated with increased subclinical coronary disease as measured by coronary artery calcification in the Framingham Offspring Study, which has also been confirmed in the MultiEthnic Study of Atherosclerosis [14]. Otaki et al. [15] prospectively evaluated a subset of young patients (n=6308, men aged <55 years and women aged <65 years) from the CONFIRM registry who underwent CCTA for suspected CAD. They found that compared with patients without a positive FHx, patients with a positive FHx had a higher prevalence of any CAD (40% versus 30%; P<0.001) and obstructive CAD (11% versus 7%; P<0.001) on CCTA. Similarly, Sunman et al [16] investigated patients (n=349; mean age, 57.8±10.8 years) who underwent CCTA for suspected CAD and reported that a positive FHx was associated with a higher presence of CAD, with a predilection for stenosis in left anterior descending (79.8% versus 58.0%; P=0.013) and left circumflex arteries (42.3% versus 30.4%; P=0.021). Fischer et al [1] retrospectively studied the coronary angiograms of 882 siblings with CAD from 401 families. These families were ascertained through index patients defined by MI before the age of 60 years and at least 1 sibling with MI or coronary revascularization procedures. They investigated the hypothesis that various morphological characteristics of CAD have a genetic component.they demonstated that a highly heritable component was observed for hazardous manifestations of coronary atherosclerosis, namely, ostial

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lesions and left main CAD.in their observation they found that stenoses are particularly heritable at proximal localizations. Hindieh et al [16] (n=763; mean age, 50 years) on premature CAD (<55 yaers) , they demonstrate that FHx of premature MI is strongly associated with CAD severity at angiography as quantified by the number of epicardial vessels with >50% stenosis. They observed that an FHx is associated with a nearly 60% higher odds of multi-vessel disease and a 2 times greater likelihood of 3-vessel disease at ACS presentation, independent of traditional risk factors. Having both a positive family history and a high genetic risk score is associated with a higher prevalence of multi-vessel disease than having either of these factors alone, which suggests that accelerated atherosclerosis rather than thrombosis may explain the higher event rate reported in young patients with acute coronary syndrome.

The association between clinical and subclinical atherosclerosis and the FH of premature CAD was investigated in previous studies. In a large study including 8549 asymptomatic subjects, Nasir et al. [8] examined the association of a family history of CAD with coronary artery calcification (CAC) in asymptomatic individuals and demonstrated a highly significant association between FH of premature CHD and the presence and extent of CAC. In a large study consisted of 1662 subjects, Wang et al. [17] found that mean internal carotid intima media thickness was higher in subjects who had a parental history of premature CAD than in those without a validated parental history of premature CHD. Additionally, Michos et al. [18] examined the extent of subclinical atherosclerosis in asymptomatic women with a FH of CAD and low risk according to the Framingham risk score and found that one third of the patients had significant coronary atherosclerosis shown by MDCT for CAC scoring.

The results of several studies investigating the association between FH of premature CAD and MDCT variables are conflicting. In a study by Bamberg et al. [19] FH of CAD was statistically significantly associated with the extent of CAP, as analyzed using a multivariate linear regression model. However, in the study by Rivera et al. [20] FH of CAD was not a significant predictor of the extent of non-calcified CAP in a large cohort of asymptomatic subjects without any cardiovascular disease. Furthermore, in a study by Faletra et al. [21], FH of CAD was not associated with the presence of CAP in a group of patients with suspected CAD.

In a study, evaluating the prognostic role of a FH for CAD, Harpaz et al. [22] reported that patients with a positive FH of premature CAD developed their first acute myocardial infarction more than one decade earlier in comparison to those without such a history indicating a higher vulnerability of CAPs in patients with a positive FH of premature CAD. Therefore, as in line with those previous studies, our findings may have clinical importance when the more vulnerable nature of mixed and noncalcified plaques was considered compared to calcified plaques in patients with a FH of premature CAD.

The results of our study should be interpreted in the context of several limitations. First, the FH of CAD was obtained from the subject's interview. The optimal method for premature history of CAD should be obtained from the medical records or direct examination of the affected person, however medical records are often not available. Second, this study was performed in a selected group of patients with suspected CAD; therefore our findings cannot be extrapolated to a general population.

Conclusion

In conclusion, we found that a positive familial history of CAD is associated with the severity and extent of coronary atherosclerosis. On the basis of our data, we believe it is reasonable to consider coronary angiography in patients with suspected CAD and a FH of premature CAD. Besides, from the diagnostic data relevant to lesion severity, coronary angiography can provide valuable data regarding pattern of vascular involvement of coronary atherosclerosis, which may guide for more intensive therapy at an early period to reduce cardiovascular risk. Further investigation is needed to clarify the exact diagnostic and prognostic role of coronary angiography in subjects with a positive FH and suspected CAD.

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Authors' Contributions: R.Kh,B and A.E analyzed and interpreted the patient data regarding the cardiovascular disease and managed patient. H.H.M helped in management of patients, data gathering and diagnosis patient in echocardiographic evaluation. M.E helped in data analysis. F.K was major contributor in writing the first draft of manuscript. All authors read and approved the final manuscript.

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Availability of Data and Material: The data that support the findings of this study are available from Qaem Hospital, Mashhad University of Medical Sciences, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the corresponding author.

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Competing Interests: The authors declare that they have no competing interests.

Ethics Approval and Consent to Participate: A written informed consent was obtained from all patients in both case and control groups prior to participation in the study. The study steps were performed in line with Helsinki declaration. The study protocol was approved by the Ethical Committee of Mashhad University of Medical Sciences.

Consent for Publication: Written consent to publish this information was obtained from study participant.

List of Abbreviations

CAD= coronary artery disease
ACS= acute coronary syndrome
TG= triglyceride
LDL= low-density lipoprotein
HDL= high-density lipoprotein
LMD= left main disease
3D= 3Vessel Diseases
2D= 2 Vessel Disease
SVD= single vessel disease
FH= familial history
STEMI= ST segment elevation myocardial infarction
IHD= ischemic heart disease
MFU= Medical follow-up
CABG= Coronary Artery Bypass Grafting
PCI= Percutaneous coronary artery intervention
CI= confidence interval
FH= family history
OR= odds ratio
CAC= coronary artery calcification

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