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Clinical and Genetic Characteristics of Familial Hypercholesterolemia at Sultan Qaboos University Hospital in Oman

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ABSTRACT

Objectives: We sought to describe the clinical and genetic characteristics of patients with familial hypercholesterolemia (FH) that presented to the lipid clinic at Sultan Qaboos University Hospital, Muscat, Oman. ***Methods***: Patients who presented with high low-density lipoprotein cholesterol (LDL-C) levels (> 189.0 mg/dL or 4.9 mmol/L) were recruited to the study. FH was diagnosed according to the Dutch Lipid Clinic Network criteria. Analyses were performed using univariate statistics. ***Results:*** The study enrolled 450 patients with a mean age of 48.0±12.0 years, 56.0% (n = 252) were males and 11.3% (n = 51) were smokers. At admission, the proportion of 'probable/definite', 'possible', and 'unlikely' FH were 27.6% (n = 124), 70.0% (n = 315), and 2.4% (n = 11), respectively. Overall, 26.0% (n = 117) of patients had hypertension, 22.4% (n = 101) had a history of coronary artery disease, and 17.3% (n = 78) had diabetes mellitus. Those with 'probable/definite' FH were more likely to be prescribed high-intensity statin therapy (75.8% vs. 54.5%; $p < 0.001$) and statin ezetimibe combination (50.8% vs. 27.3%; $p < 0.001$) when compared to the 'unlikely' FH cohort. Additionally, those with very high atherosclerotic vascular disease (ASCVD) risk were also associated with high-intensity statin therapy (54.7% vs. 42.7%; $p = 0.006$) and statin ezetimibe combination (26.4% vs. 17.2%; $p = 0.023$). Patients with 'probable/definite' FH were less likely to achieve their LDL-C goal attainment compared to those with 'unlikely' FH (13.0% vs. 57.1%; $p < 0.001$). Furthermore, those with very high ASCVD risk were less likely to achieve their LDL-C goals compared to the high ASCVD risk cohort (9.6% vs. 32.0%; $p < 0.001$). ***Conclusions:*** FH patients are underdiagnosed, undertreated, and less likely to attain their LDL-C goals in Oman.

Familial hypercholesterolemia (FH) is a common genetic disorder and if not recognized early and treated appropriately can lead to severe atherosclerosis and premature coronary artery disease (CHD).[1,2]

The prevalence of FH varies greatly between different studies depending on clinical criteria used and/or genetic confirmation.[3,4] The most common clinical criteria used are the Dutch Lipid Clinic Network (DLCN)[5] and the Simon Broome Registry criteria.[2] These criteria are based on low-density lipoprotein cholesterol (LDL-C) levels of > 4.9 mmol/L (> 189.0 mg/dL), the presence of CHD in the patient or first-degree family member,

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and physical examination like tendon xanthoma or corneal arcus before the age of 40 years. FH is inherited as a monogenic mutation in the low-density lipoprotein receptor (LDLR), apolipoprotein-B (*Apo B*), or proprotein convertase subtilisin/kexin type 9 (*PCSK9*) genes.[6] However, FH can also be inherited as a polygenic form from the contribution of several common LDL-C raising single nucleotide variants.[7]

Our study aimed to describe the clinical and genetic characteristics of FH in patients presented to the lipid clinic at Sultan Qaboos University Hospital (SQUH), Muscat, Oman.

METHODS

SQUH is a tertiary hospital, and its lipid clinic is considered a referral center for FH patients across the country. In this study, a total of 450 patients who presented with high LDL-C (>189.0 mg/dL or 4.9 mmol/L) were recruited. The patients were stratified according to the DLCN criteria.[5] As per the DLCN criteria, the diagnosis of FH was derived from scores from several criteria, including clinical and family history, physical examination, baseline cholesterol levels, and molecular testing. A 'probable/definite' FH was considered when the DLCN score was 6 or higher, and a 'possible' FH was made when the DLCN score was 3 to 5. Those with DLCN scores of < 3 were classified as 'unlikely' FH. Data collection included patients' demographics, clinical history, physical examination, biochemical and radiological investigations as well as genetic analysis. The study was approved by the Sultan Qaboos University, College of Medicine and Health Science's ethics committee (Reference: SQU-EC/172/18). All patients were required to sign informed consent forms.

Descriptive statistics were used to describe the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analyzed using Pearson's chi-squared tests (or Fisher's exact tests for expected cells < 5). For continuous variables, mean and standard deviation were used to summarize the data while analysis was performed using ordinary least squares regression. An a priori two-tailed level of significance was set at the 0.05 level. Statistical analyses were conducted using STATA version 13.1 (STATA Corporation, College Station, TX, USA).

RESULTS

The overall mean age of the cohort was 48.0±12.0 years, 56.0% (n = 252) were males and 11.3% (n = 51) were smokers. The proportion of patients with premature CHD, family history of FH, hypertension, and diabetes mellitus were 22.4% (n = 101), 99.6% (n = 448), 26.0% (n = 117), and 17.3% (n = 78), respectively. A total of 17.3% (n = 78) of the patients had percutaneous coronary intervention, 46.7% (n = 210) had high statin intensity therapy while 20.2% (n = 91) had statin and ezetimibe combination.

Table 1 shows demographic, clinical, and statin characteristics of the patients according to DLCN criteria. The proportion of 'probable/definite', 'possible', and 'unlikely' FH were 27.6% (n = 124), 70.0% (n = 315), and 2.4% (n = 11), respectively. Compared to the 'unlikely' FH cohort, the 'probable/definite' FH group more likely to be associated with confirmed mutations (33.9% vs. 0.0; $p < 0.001$), tendon xanthomas (25.0% vs 0.0; $p < 0.001$), arcus corneal (36.3% vs 9.1%; $p < 0.001$), coronary artery bypass graft (10.5% vs. 0.0; $p = 0.008$), high-intensity statin therapy (75.8% vs. 54.5%; $p < 0.001$), and statin ezetimibe combination (50.8% vs. 27.3%; $p < 0.001$). Furthermore, those with very high atherosclerotic vascular disease (ASCVD) risk were also associated with high-intensity statin therapy (55% vs. 43%; $p = 0.006$) and statin ezetimibe combination (26% vs. 17%; $p = 0.023$) [Table 2].

Lipid profiles of Omani FH patients stratified by the DLCN criteria are outlined in Table 3. All lipid fractions (total cholesterol (TC) and LDL-C) at baseline and post-index were significantly higher in the 'probable/definite' FH group compared to the 'unlikely' FH cohort (all *p*-values < 0.001). When compared to the baseline period [Table 4], post-index lipid levels that included TC (5.4 vs. 8.1 mmol/L; $p < 0.001$), LDL-C (3.5 vs. 6.2 mmol/L; $p < 0.001$), and non high-density lipoprotein cholesterol (non HDL-C) (4.1 vs. 6.9 mmol/L; $p < 0.001$) were significantly lower in not only the high ASCVD risk but also very high ASCVD risk TC (5.3 vs. 8.2 mmol/L; $p < 0.001$), LDL-C (3.3 vs. 6.3 mmol/L; $p < 0.001$), and non HDL-C (4.2 vs. 7.0 mmol/L; $p < 0.001$).

Figure 1 represents LDL-C goal attainment at admission stratified by the DLCN and ASCVD criteria, respectively. Patients with 'probable/

Table 1: Demographic and clinical characteristics of Oman familial hypercholesterolemia (FH) cohort stratified by the Dutch Lipid Clinic Network (DLCN) criteria.

Characteristics	All (n = 450) n (%)	DLCN criteria			*p*-value
		Unlikely, n(%) (n = 11)	Possible, n(%) (n = 315)	Probable/definite, n(%) (n = 124)	
Demographic					
Age, years, mean ± SD	48.0 ± 12.0	41.0 ± 15.0	49.0 ± 12.0	44.0±13.0	< 0.001
Male gender	252 (56.0)	7 (63.6)	177 (56.2)	68 (54.8)	0.847
Smoking	51 (11.3)	0 (0.0)	45 (14.3)	6 (4.8)	0.039
Medical history					
History of FH	448 (99.6)	11 (100)	314 (99.7)	123 (99.2)	0.510
Genetic testing	72 (16.0)	0 (0.0)	15 (4.8)	57 (46.0)	< 0.001
Confirmed mutation*	42 (58.3)	0 (0.0)	0 (0.0)	42 (33.9)	< 0.001
Tendon xanthomas	31 (6.9)	0 (0.0)	0 (0.0)	31 (25.0)	< 0.001
Arcus corneal	65 (14.4)	1 (9.1)	19 (6.0)	45 (36.3)	< 0.001
Diabetes mellitus	78 (17.3)	0 (0.0)	57 (18.1)	21 (16.9)	0.432
Hypertension	117 (26.0)	1 (9.1)	89 (28.3)	27 (21.8)	0.228
Hx of premature CAD	101 (22.4)	3 (27.3)	59 (18.7)	39 (31.5)	0.041
Angina	54 (12.0)	1 (9.1)	36 (11.4)	17 (13.7)	0.628
Myocardial infarction	55 (12.2)	2 (18.2)	35 (11.1)	18 (14.5)	0.650
Hx of premature CBVD	14 (3.1)	1 (9.1)	8 (2.5)	5 (4.0)	0.428
Hx of premature PAD	3 (0.7)	0 (0.0)	2 (0.6)	1 (0.8)	0.479
Procedures and investigations					
PCI	78 (17.3)	2 (18.2)	48 (15.2)	28 (22.6)	0.229
CABG	21 (4.7)	0 (.0.)	8 (2.5)	13 (10.5)	0.008
Hx of CT angiogram	30 (6.7)	1 (9.1)	13 (4.1)	16 (12.9)	0.012
Hx of CT coronary calcium score	35 (7.8)	0 (0.0)	16 (5.1)	19 (15.3)	0.007
Hx of echocardiography,	91 (20.2)	1 (9.1)	66 (21.0)	24 (19.4)	0.881
Hx of carotid doppler	3 (0.7)	0 (0.0)	0 (0.0)	3 (2.4)	0.086
Statin therapy**					
Low-intensity statin therapy	56 (12.4)	3 (27.3)	49 (15.6)	4 (3.2)	
Medium-intensity statin therapy	184 (40.9)	2 (18.2)	156 (49.5)	26 (21.0)	< 0.001
High-intensity statin therapy	210 (46.7)	6 (54.5)	110 (34.9)	94 (75.8)	
Statin+ezitimibe combination	91 (20.2)	3 (27.3)	25 (7.9)	63 (50.8)	< 0.001

SD: standard deviation; Hx: history; CAD: coronary artery disease; CBVD: cerebrovascular disease; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; CT: computed tomography.
Percentages might not add to 100% due to rounding off.
**Out of the 16.0% (72/450) that had genetic testing, 58.3% (42/72) had low-density lipoprotein receptor mutation.*
***High-intensity statin therapy was defined as those on atorvastatin 40–80 mg and rosuvastatin 20–40 mg, while medium-intensity statin therapy was defined as those on atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg, and pravastatin 40–80 mg. There were no patients on fluvastatin or lovastatin.*

Table 2: Statin therapy stratified by atherosclerotic vascular disease (ASCVD) risk.

Statin therapy*	All, n(%) (n = 450)	Very high ASCVD risk, n(%) (n = 148)	High ASCVD risk, n(%) (n = 302)	*p*-value
Low-intensity statin therapy	56 (12.4)	9 (6.1)	47 (15.6)	
Medium-intensity statin therapy	184 (40.9)	58 (39.2)	126 (41.7)	0.006
High-intensity statin therapy	210 (46.7)	81 (54.7)	129 (42.7)	
Statin+ezitimibe combination	91 (20.2)	39 (26.4)	52 (17.2)	0.023

**High-intensity statin therapy was defined as those patients on atorvastatin 40–80 mg and rosuvastatin 20–40 mg. Medium-intensity statin therapy was defined as those on atorvastatin 10–20 mg, rosuvastatin 5–10 mg, simvastatin 20–40 mg and pravastatin 40–80 mg. There were no patients on fluvastatin or lovastatin.*

Table 3: Lipid profiles of Omani familial hypercholesterolemia cohort stratified by the Dutch Lipid Clinic Network (DLCN) criteria.

Characteristic	All (N = 450)	DLCN			*p*-value
		Unlikely (n = 11)	Possible (n = 315)	Probable/Definite (n = 124)	
Total cholesterol					
Baseline	8.0 ± 1.4	6.8 ± 0.1	7.6 ± 0.8	9.2 ± 1.9	< 0.001
Post-index	5.3 ± 1.4	4.2 ± 1.0	5.1 ± 1.2	5.8 ± 1.8	< 0.001
LDL-cholesterol					
Baseline	6.1 ± 1.3	4.9 ± 0.0	5.7 ± 0.7	7.4 ± 1.8	< 0.001
Post-index	3.4 ± 1.3	2.3 ± 0.7	3.2 ± 1.1	3.4 ± 1.3	< 0.001

Data are given as mean ± standard deviation.
LDL: low-density lipoprotein.

definite' FH were less likely to achieve their LDL-C goal attainment compared to those with 'unlikely' FH (13.0% vs. 57.1%; $p < 0.001$). Those with very high ASCVD risk were less likely to their LDL-C goals compared to the high ASCVD risk cohort (9.6% vs. 32.0%; $p < 0.001$).

DISCUSSION

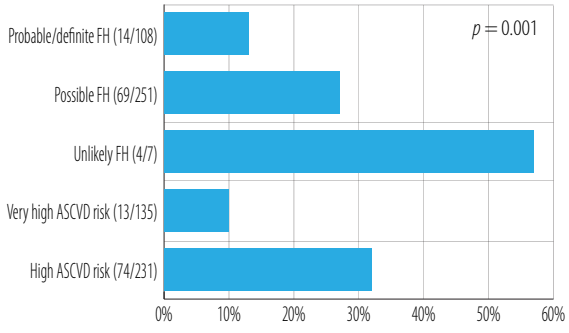
This paper describes the clinical and the genetic characteristics of patients referred to the lipid clinic at SQUH as a suspected case of FH. Patients were stratified according to the DLCN, with 27.6% patients diagnosed as 'probable/definite' FH, 70.0% as 'possible' FH, and 2.4% as the 'unlikely' FH group. There are few case reports about FH and its genetic characteristics in Oman.[8–13] Currently, most suspected FH cases are referred to SQUH lipid clinic for genetic confirmation and advanced management.

FH remains underdiagnosed worldwide.[14] There are no wide national registries for FH in Oman. The "Oman cascade screening to prevent early onset risk of cardiovascular diseases in FH Young children and adult index cases and their families (OMANORYX) study"[15] is an ongoing study aimed to initiate early detection and treatment of FH in Oman through detection of index cases and cascade screening of first- and second-degree relatives to prevent CVD outcomes. The Gulf Familial Hypercholesterolemia Registry (Gulf FH)[8] was a cross-sectional and prospective study to determine the FH prevalence, genetic characteristics, and current management in the adult patients living in the Arabian Gulf region. The prevalence of FH (based on both probable and possible FH) was 0.96%, 1/104 (332/34366). In Oman, the expected number of FH patients

Table 4: Lipid profiles of Omani familial hypercholesterolemia patients stratified by the atherosclerotic vascular disease risk status.

Characteristics, mean ± SD, mmol/L	Baseline	Post-index	*p*-value
Total cholesterol			
All (n = 329)	8.1 ± 1.4	5.4 ± 1.5	< 0.001
High risk (n = 216)	8.1 ± 1.3	5.4 ± 1.3	< 0.001
Very high risk (n = 113)	8.2 ± 1.6	5.3 ± 1.7	< 0.001
LDL-cholesterol			
All (n = 331)	6.3 ± 1.4	3.4 ± 1.3	< 0.001
High risk (n = 217)	6.2 ± 1.3	3.5 ± 1.3	< 0.001
Very high risk (n = 114)	6.3 ± 1.6	3.3 ± 1.3	< 0.001
Non-HDL-cholesterol			
All (n = 320)	6.9 ± 1.4	4.1 ± 1.5	< 0.001
High risk (n = 213)	6.9 ± 1.4	4.1 ± 1.4	< 0.001
Very high risk (n = 107)	7.0 ± 1.6	4.2 ± 1.7	< 0.001

SD: standard deviation; LDL: low-density lipoprotein; HDL: high-density lipoprotein.
At baseline, 415 patients had populated lipid profiles while at follow-up 366 patients had their lipid levels documented.



DLCN: Dutch Lipid Clinic Network; ASCVD: atherosclerotic vascular disease; FH: familial hypercholesterolemia.

Figure 1: Low-density lipoprotein cholesterol goal attainment of the cohort stratified by DLNC and ASCVD risk.

according to the Gulf FH registry[9] prevalence of 1/104 and the Omani population of 2 994 601 (based on the 2019 census[16]) is around 28 794 patients. This indicates a significant gap in the diagnosis of FH in Oman, and the OMANORYX study may help to decrease this gap. Nonetheless, there is a definite need to engage local health care authorities to establish quality improvement programs, policies, and centers like lipid clinics for FH screening, diagnosis, and management.[15]

FH remains undertreated worldwide.[9,14,17] In the SAFEHEART Registry,[17] only 11% of the FH patients reached their target goal of < 2.6 mmol/L despite being on maximum lipid-lowering treatments. In our study, the overall goal attainment of LDL-C < 2.6 mmol/L was achieved in 24.0% (data is not shown) of patients while only 10.0% of FH patients with very high risk and LDL-C goal of < 1.8 mmol/L was achieved. High-intensity statins were prescribed in only 46.7% of patients, and 20.2% of patients were on both statins and ezetimibe.

Lipoprotein apheresis[10] is only available at SQUH in Oman, and patients across the country are being referred to our center for the treatment of homozygous and severe heterozygous FH patients who do not respond to the maximum tolerated lipid-lowering treatments.

The Oman Society for Lipid and Atherosclerosis with support from the International Atherosclerosis Society has established an educational program like the 'Lipid Metabolism and Cardiovascular Risk' and 'Severe FH' courses[18] to improve the knowledge and the management of various lipid disorders and FH in the Middle East and North Africa (MENA) region. Moreover, there are consensus clinical recommendations for the management of FH in the region.[19,20]

Although molecular testing of FH is considered as a confirmatory step in the diagnosis and important to screen the family members of the index cases, it is still not widely available worldwide, and few centers perform them in the MENA region.[21] In Oman, molecular testing for FH is performed in the biochemistry laboratory at SQUH.[11–13] The genetic test is only performed in 16.0% of suspected cases due to limited resources. As expected, the mutation was confirmed in the 'probable/definitive' FH group (33.9%), and the most common type of mutation was the LDLR mutation. A total of 58.3% of the suspected cases were reported to have causative FH mutation. The rest of the cases were more likely to have a polygenic form of hypercholesterolemia.

CONCLUSION

FH in Oman is still underdiagnosed and undertreated. Despite the use of high-intensity statin and combination therapies, a significant number of high and very ASCVD FH patients did not reach the LDL-C therapeutic goals. This implies the high need to engage the local health care authorities to set recommendations and quality improvement programs and policies for FH screening, diagnosis, and aggressive management.

Disclosure

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