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Original Article

Familial hypercholesterolemia in Mexico: Initial insights from the national registry

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KEYWORDS:
Familial hypercholesterolemia; Mexican registry

Abstract: **BACKGROUND:** Familial hypercholesterolemia (FH) remains underdiagnosed and undertreated.

OBJECTIVE: Report the results of the first years (2017-2019) of the Mexican FH registry.

METHODS: There are 60 investigators, representing 28 federal states, participating in the registry. The variables included are in accordance with the European Atherosclerosis Society (EAS) FH recommendations.

RESULTS: To date, 709 patients have been registered, only 336 patients with complete data fields are presented. The mean age is 50 (36-62) years and the average time since diagnosis is 4 (IQR: 2-16) years. Genetic testing is recorded in 26.9%. Tendon xanthomas are present in 43.2%. The prevalence of type 2 diabetes is 11.3% and that of premature CAD is 9.8%. Index cases, male gender, hypertension and smoking were associated with premature CAD. The median lipoprotein (a) level is 30.5 (IQR 10.8-80.7) mg/dl. Statins and co-administration with ezetimibe were recorded in 88.1% and 35.7% respectively. A combined treatment target (50% reduction in LDL-C and an LDL-C $<$100 mg/dl) was achieved by 13.7%. Associated factors were index case (OR 3.6, 95%CI 1.69-8.73, $P = .002$), combination therapy (OR 2.4, 95%CI 1.23-4.90, $P = .011$), type 2 diabetes (OR 2.8, 95%CI 1.03-7.59, $P = .036$) and age (OR 1.023, 95%CI 1.01-1.05, $P = .033$).

CONCLUSION: The results confirm late diagnosis, a lower than expected prevalence and risk of ASCVD, a higher than expected prevalence of type 2 diabetes and undertreatment, with relatively few patients reaching goals. Recommendations include, the use of combination lipid lowering therapy, control of comorbid conditions and more frequent genetic testing in the future.

Introduction

Familial hypercholesterolemia is a genetic lipid disorder, characterized by elevated LDL cholesterol (LDL-C) levels and the development of premature atherosclerosis.[1] Worldwide, it is the most common monogenic disorder. Despite this, the disease is often overlooked, resulting in underdiagnosis and consequently undertreatment. Autosomal dominant FH is associated with mutations in the LDL receptor (LDLR), apolipoprotein B (Apo B), or the proprotein convertase subtilin/kexin 9 (PCSK9) genes.[2] An autosomal recessive form has also been identified (alterations in the low-density lipoprotein receptor adaptor protein 1 (LDLRAP1) gene) but is exceedingly rare.[3] Mutations in the LDLR account for the majority of cases, however around 10-50% of patients may be mutation negative.[1,4] Homozygous (HoFH) FH is diagnosed in 1:160,000-300,000 persons, with LDL cholesterol levels between 460 - 1,160 mg/dl.[5–8] Heterozygous (HeFH) FH is more common, with a prevalence of up to 1:250, and LDL cholesterol levels ranging from 190-400 mg/dl. Diagnosis of FH is based on clinical criteria and/or mutational analysis with subsequent cascade screening in order to identify affected relatives.[9] Management of the disease aims to reduce the risk of cardiovascular mortality and involves timely initiation and lifelong therapy with one or more of the following: high intensity statins, ezetimibe, PCSK9 inhibitors and lipid apheresis.

The Mexican familial hypercholesterolemia (FH) registry was created in 2017, based on the recommendations of the global EAS Familial Hypercholesterolemia Studies Collaboration.[10] National registries can play an important role in improving patient management and long-term patient care.[11,12] They can provide population specific, real world information regarding the natural history, clinical management, and patient outcomes relating to a particular disease. In Mexico, there is an absence of healthcare policies specifically targeting FH and there is a general lack of awareness and education among healthcare professionals and policy-makers regarding this disease.[10] This registry aims to fill in knowledge gaps, assess the status of FH care, identify treatment barriers, and permit the recognition of this condition as an important health burden in our society. The observational data gathered also allows global collaboration, and may be hypothesis generating. In this report, a retrolective analysis of the first years (2017-2019) of this prospective follow-up registry are shown and discussed.

Methods

The design and rationale of the Mexican registry has been previously described.[4] Briefly, a web-based registry was created to capture information about persons with heterozygous/homozygous familial hypercholesterolemia (FH). This data is in accordance with the European Atherosclerosis Society (EAS) FH recommendations.[13,14] The variables included in the registry alongside data management are detailed in supplementary methods. Genetic testing is rarely carried out due to lack of resources. Where it was performed, standard methodology was used.[15]

Clinicians managing FH patients within public and private institutions were invited to participate in the Mexican FH national registry (Supplementary Table 2). A representative from each state was chosen in order to

Table 1 Baseline characteristics of subjects included in the FH registry.

Parameter	All-subjects (n = 336)	Index case (n = 170)	Relative (n = 166)	*P* value
Men (%)	222 (66.1)	117 (68.8)	61 (36.7)	0.281
Hispanic/Latino ethnicity (%)	330 (98.2)	165 (97.1)	165 (99.4)	0.217
Age (years) **n = 332**	50 (36-62)	54 (43-64)	44 (30-58)	<0.001
Time since diagnosis (years) **n = 319**	4 (2-16)	4 (1-18)	4 (2-14)	0.091
Time of follow-up visit (years) **n = 291**	2.05 (0.61)	1.96 (0.60)	2.14 (0.61)	0.009
Genetic study (%) **n = 327**	88 (26.2)	23 (13.5)	65 (41.6)	<0.001
Premature CAD (%) **n = 329**	33 (9.8)	24 (14.1)	9 (5.4)	0.004
Type 2 diabetes (%) **n = 333**	38 (11.3)	18 (10.6)	20 (12)	0.973
Arterial hypertension (%) **n = 331**	57 (17)	35 (20.6)	22 (13.3)	0.062
Smoking status (%) **n = 331**	56 (16.7)	31 (18.2)	25 (15.1)	0.366
Xanthomas (%) **n = 323**	145 (43.2)	86 (50.6)	59 (37.8)	0.019
Xanthelasma (%) **n = 322**	23 (6.8)	16 (9.4)	7 (4.5)	0.064
BMI (kg/m2) **n = 320**	25.28 (23.28-28.97)	26.23 (23.43-28.95)	25.3 (22.6-28.9)	0.401
Overweight (%)	118 (35.1)	69 (40.6)	49 (29.5)	0.111
Obesity (%)	65 (19.3)	29 (17.1)	36 (21.7)	
Glucose (mg/dl) **n = 170**	90 (84-99)	92 (84.5-100)	89 (83-97)	0.043
Hba1c (%) **n = 36**	5.6 (5.4-6.1)	5.6 (5.3-6.1)	5.6 (5.5-6.0)	0.417
High-dose statin (%) **n = 293**	173 (51.5)	86 (50.6)	87 (52.4)	0.110
LDL-C ≤100 mg/dl follow-up (%) **n = 291**	55 (16.4)	40 (23.5)	22 (13.3)	<0.001
LDL-C ≥50% reduction follow-up (%) **n = 291**	84 (25)	62 (36.5)	21 (13.5)	<0.001
Combined goal (%) **n = 291**	46 (13.7)	36 (21.2)	10 (6)	<0.001
LDL-C ≤70 mg/dl follow-up (%) **n = 291**	17 (5.8)	12 (7.8)	5 (3.6)	0.1997
LDL-C ≤55 mg/dl follow-up (%) **n = 291**	10 (3.4)	6 (3.9)	4 (2.9)	0.8759
Total cholesterol (mg/dl)	324 (291-373)	331 (301-377)	322 (277-368)	0.028
*At follow-up **n = 297***	245 (188-308)	218 (174-300)	270 (204-324)	0.001
Triglycerides (mg/dl)	138 (99-192)	147 (105-196)	126 (90-184)	0.028
*At follow-up **n = 297***	121 (90-178)	120 (90-176)	121 (85-178)	0.728
LDL-C (mg/dl)	237 (209-286)	243 (215-290)	231 (202-285)	0.107
*At follow-up **n = 297***	162 (113-221)	143 (99-211)	189 (135-239)	<0.001
HDL-C (mg/dl) *At follow-up **n = 297***	45.2 (39.5-55)	48 (40-59)	44 (38-53)	0.004
Low-HDL-C (% of population) ***n = 297***	46 (39-56)	48.9 (40-57.2)	38 (38-54)	0.016
Lp(a) mg/dl **n = 107**	30.5 (10.8-80.7)	24.50 (8.36-74)	37.8 (11.7-89.2)	0.155

Data is presented in frequency (percentage), mean (standard deviation) or median (interquartile range) wherever appropriate.
Abbreviations: CVD = cardiovascular disease; BMI = body mass index. All percentages are calculated according to the available data for each variable.

achieve greater coverage of the country. To date, 28 of 32 states are participating in this project, with 60 investigators registered on the website. The representative is required to stay in contact with other participants from their state and encourage active completion of registry data fields. The majority of these are board certified endocrinologists, all of which are members of the Sociedad Mexican de Nutrición y Endocrinología.

Each institution (public or private) and/or researcher received the approved study protocol and informed patient consent form. The registry is conducted in accordance with the principles of the Declaration of Helsinki and approval by the corresponding Ethics Committees has been obtained.

Patients considered for the registry include both children (6-18 years) and adults with an elevated LDL cholesterol level (>160 mg/dl and > 190 mg/dl respectively), and a clinical diagnosis of FH according to Dutch Lipid Clinic Diagnostic criteria.[16] All subjects are asked to give informed consent. The principal exclusion criteria were persons with other primary lipid disorders and secondary causes of severe hypercholesterolemia.

Statistical analysis

The distribution of categorical variables is reported as frequencies and percentages. Continuous data is described as mean and standard deviation or with median and interquartile range depending on the parametric or non-parametric distribution of variables. Categorical variables are compared using the chi-square test or Fisher's test as appropriate. Repeated data measurements are compared with a paired t-test for normally distributed variables, the Wilcoxon test for non-normally distributed variables, and the McNemar test for binary variables.

Stepwise logistic regression models have been constructed to identify factors associated with likelihood of achieving the LDL-C goal. The model was adjusted for gender and baseline LDL-C levels. Another model was constructed to explore factors associated with the presence of premature coronary artery disease. A *P*-value ≤.05 was considered as statistically significant. Statistical analyses was performed using Statistical Package for Social Science (SPSS Inc, Chicago, IL, and Version 21.0) and GraphPad Prism, version 7.0.

Results

General characteristics

At the time of analysis, 709 patients (238 probands and 471 family members) have been registered in the Mexican FH registry (2017-2019); however, 336 patients had complete data and follow-up, and were included in this analysis. The characteristics of this population are shown in Table 1. There is a male predominance (66.1%) with almost all cases being of Hispanic/Mestizo origin (98.2%). The mean age is 50 (36-62) years and the average time since diagnosis is 4 (IQR: 2-16) years. Almost all the patients are heterozygous (98.8%) with four cases registered as homozygous FH (Supplementary Table 3). There are 170 (50.6%) index cases; the remaining 166 (49.4%) are affected family members. The probands are significantly older than the relatives. In the vast majority of patients, the diagnosis of FH is based on clinical criteria. Using the Dutch Lipid Clinic Network criteria (65.9% are definitive cases, 21.5% probable and 12.5% possible cases [Supplementary Table 4]).

Physical examination

Physical examination reveals a median BMI of 25.3 (IRQ: 23.28-28.97) kg/m2 with 19.3% (n = 65) of the population fulfilling obesity criteria. Tendon xanthomas are present in 43.2% (n = 145), corneal arcus in 17.9% (n = 60) and xanthelasma in 6.8% (n = 23). Index cases have a significantly higher prevalence of xanthomas than family members. Cases with xanthomas are significantly older and with a greater number of years since diagnosis compared to persons without xanthomas. Additionally, these patients have a higher prevalence of arterial hypertension and premature coronary artery disease (Supplementary Table 5).

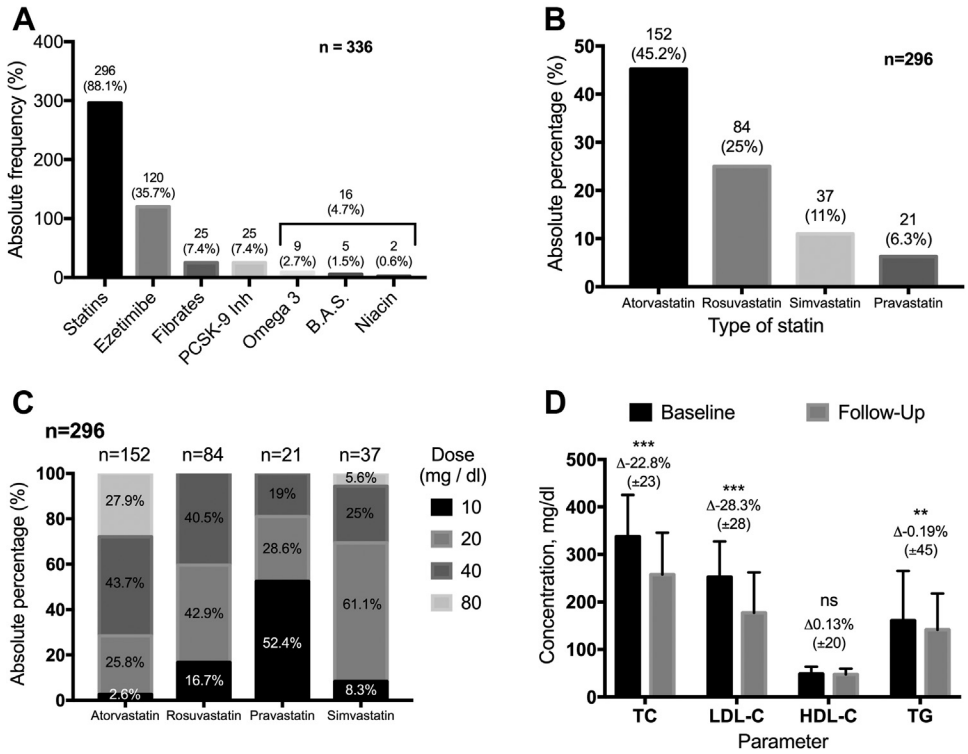

Fig. 1 Prescription therapy of lipid-lowering agents (A), type of statins prescribed (B) alongside with their respective dosage (C) and lipid levels changes (D) at baseline and follow-up with their respective percentage of change (Δ) in the FH registry. Abbreviations: AICE: Angiotensin-converting-enzyme inhibitors; ARBs: Angiotensin II receptor blockers; CCB: Calcium channel blockers. (B)A.S. = Bile Acid Sequestrant; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides. Mean values are shown for TC, LDL-C, LDL- C and TG. *** = $P < .001$; **$P < .01$. Annotation: 2 patients were receiving Lovastatin and Fluvastatin.

Outcomes and comorbid conditions

A history of coronary artery disease (CAD) is present in 13.7% (n = 46), of which premature myocardial infarction is confirmed in 9.8% (n = 33). Stroke, peripheral artery disease and aortic valve disease have been recorded in 3.0% (n = 10), 3.9% (n = 13) and 1.2% (n = 4) respectively. Active smoking is present in 16.7% (n = 56). Other prevalent comorbid conditions include, arterial hypertension in 17% (n = 57) and type 2 diabetes in 11.3% (n = 38). Index cases have a higher prevalence of arterial hypertension and premature coronary artery disease compared to affected family members. In the regression models,the presence of premature CAD is associated with index cases (OR: 2.79, 95%CI 1.07-8.08; $P = .043$), male gender (OR: 4.90, 95%CI 1.99-12.83; $P = .001$) arterial hypertension (OR: 2.53, 95%CI 1.31-9.76; $P = .011$) and positive smoking status (OR: 2.87, 95%CI 1.06-7.45; $P = .032$). Furthermore, an increasing number of comorbid conditions (eg, type 2 diabetes, arterial hypertension, hypertriglyceridemia, smoking status, alcohol consumption and hepatic steatosis) is associated with the presence of premature CAD (OR: 1.71, 95%CI 1.13-2.60; $P = .01$).

Molecular analysis

Molecular analysis has been undertaken in 26.9% of cases (88 patients) (13.5% of index cases and 41.6% of affected family members). Of these, a mutation in the LDL receptor is most common (73 cases); only 3 cases have an alteration in the ApoB gene and in 1 case, a mutation in the LDLR adaptor gene. To date, family trees for cascade screening have been generated for 107 probands and include 241 family members. The specific site mutation in our FH registry is presented in Supplementary Table 6.

Lipid levels and treatment

Baseline diagnostic lipid levels show a mean total cholesterol of 324 (291-373) mg/dl with a median LDL-C of 237 (IQR: 209-286) mg/dl (Table 1). Index cases have a significantly higher concentration of total cholesterol, triglycerides and HDL cholesterol, compared with their relatives. The median fasting glucose level is 90 (84-99) mg/dl and the median glycated hemoglobin is 5.6% (5.4-6.1). The median concentration of lipoprotein (a) (Lp(a)) is 30.5 (10.8-80.7) mg/dl; only 37.4% of these patients (n = 107) have levels over 50 mg/dl. There was no significant association between elevated Lp(a) and premature coronary artery disease.

Current use of statins has been recorded in 88.1% of patients (n = 296). Other lipid lowering therapy includes treatment with ezetimibe (35.7%, n = 120), fibrates (7.4%, n = 25), and PCSK9 inhibitors (7.4%, n = 25) (Fig. 1-A). The most frequently prescribed statin is atorvastatin (45.2%), followed by rosuvastatin (25%), pravastatin

Table 2 Characteristics of patients with FH who achieved a combined endpoint (50% LDL-C reduction + LDL-C <100 mg/dl) at follow-up.

Parameter	Combined Goals (n = 46)	Non-Combined goals (n = 245)	*P* value
Women (%)	28 (60.9)	168 (68.6)	0.307
Age (years)	59 (47-66)	48 (34-60)	0.003
Time since diagnosis (years)	4 (2-19.5)	4 (2-17)	0.612
High-school education or higher (%)	33 (71.7)	155 (63.3)	0.280
Index cases (%)	36 (71.7)	117 (47.8)	<0.001
Premature CAD (%)	4 (8.7)	29 (11.8)	0.538
Type 2 diabetes (%)	9 (19.6)	19 (7.8)	0.013
Arterial hypertension (%)	12 (26.1)	37 (15.1)	0.068
Smoking status (%)	10 (21.7)	43 (17.6)	0.499
Glucose (mg/dl)	94 (89-99)	89 (83-99)	0.006
HbA1c (%)	5.7 (5.4-11.2)	5.6 (5.4-6.1)	0.078
BMI (kg/m^2)	25.8 (22.4-27.7)	25.5 (22.8-28.9)	0.461
Total cholesterol (mg/dl)	153 (127-166)	265 (209-323)	<0.001
At baseline	320 (292-401)	327 (289-371)	0.824
LDL (mg/dl)	81 (61-90)	189 (136-235)	<0.001
At baseline	232 (198-268)	236 (207-285)	0.323
High-dose statin (%)	29 (63)	133 (54.3)	0.213
Triglycerides (mg/dl)	95 (72.5-153)	123 (94-180)	0.006
At baseline	150 (83-194)	135 (99-191)	0.117
HDL-C (mg/dl)	49 (38-58)	46 (39-55)	0.361
At baseline	47 (35-61)	46 (40-55)	0.784

Data is presented in frequency (percentage), mean (standard deviation) or median (interquartile range) wherever appropriate.
Abbreviations: CVD = cardiovascular disease; BMI = body mass index; HDL-C = high-density lipoprotein cholesterol.

Table 3 Logistic regression models exploring factors associated with a 50% reduction in C-LDL at follow-up and a combined endpoint (50% reduction in LDL-C + LDL-C< 100 mg/dl).

Model	Parameter	B	SE	Wald	OR	95% CI	*P* value
50% LDL-C reduction at follow-up	Intercept	-3.132	0.579	-5.404	0.02	0.01-0.07	<0.001
	Index case	1.254	0.300	4.175	3.51	1.97-6.42	<0.001
	Combination of Statin and Ezetimibe	1.063	0.292	3.640	2.89	1.64-5.17	<0.001
Combined goals (50% LDL-C reduction + LDL ≤100 mg/dl at follow-up)	Intercept	-4.172	0.700	-5.958	0.015	0.00-0.05	<0.001
	Age	0.023	0.010	2.124	1.023	1.01-1.05	0.033
	Index Case	1.299	0.414	3.133	3.667	1.69-8.73	0.002
	T2D	1.053	0.502	2.094	2.866	1.03-7.59	0.036
	Combination of Statin and Ezetimibe	0.889	0.350	2.535	2.433	1.23-4.90	0.011

Variables included in the model were sociodemographic factors (age, time since FH diagnosis and education) clinical findings (index case or relative, premature CAD and presence of xanthomas), associated comorbidities (arterial hypertension, type 2 diabetes) and pharmacological treatment (use of high dose statins, use of combination therapy with statin and ezetimibe). The model was adjusted for gender and baseline LDL-C.

Abbreviations: SE = Standard error; OR= Odds ratio; CI= Confidence interval.

(21%), and simvastatin (11%) (Fig. 1-B). Overall, 109 cases are taking ≥40 mg atorvastatin and 70 are taking ≥20 mg of rosuvastatin (Fig. 1-C).

Lipid levels at follow-up visit show a significant lowering in total cholesterol, LDL-C and triglycerides concentrations compared with baseline (Fig. 1-D). The attainment of treatment goals is assessed using several definitions; a 50% reduction of LDL-C compared with baseline levels, an LDL-C level <100 mg/dl and a combined endpoint (a 50% reduction in C-LDL from baseline and an LDL-C <100 mg/dl). On follow-up, 13.7% (n = 46) achieved the combined endpoint, 30.3% (n = 84) achieved a 50% reduction in LDL-C and 18.5% (n = 55) an LDL-C <100 mg/dl (Table 2, and Supplementary Tables 7 and 8). Index cases are significantly more likely to achieve these goals than family members. Patients who achieve these goals are older compared to those who do not.

Factors associated with a 50% reduction in LDL-C and the combined endpoint at follow up were explored (Table 3). Variables included in the model were sociodemographic factors (age, time since FH diagnosis and education) clinical findings (index case or relative, premature CAD and presence of xanthomas), associated comorbidities (arterial hypertension, type 2 diabetes) and pharmacological treatment (use of high intensity statins, use of combination therapy with statin and ezetimibe). The models were adjusted for gender and baseline LDL-C. Index cases and those on combination therapy are 3.5 times (95% CI: 1.97-6.42, $P < .001$) and 2.9 times (95% CI: 1.64-5.17, $P < .001$) more likely to achieve the 50% reduction in LDL-C, respectively. Index cases (OR 3.6, 95%CI 1.69-8.73, $P = .002$), those on combination therapy (OR 2.4, 95%CI 1.23-4.90, $P = .011$), persons with type 2 diabetes (OR 2.8, 95%CI 1.03-7.59, $P = .036$) and older patients (OR 1.023, 95%CI 1.01-1.05, $P = .033$), were more likely to achieve the combined endpoint. Finally, we found that male patients (OR: 3.74, 95% CI 1.51-9.85, $P < .01$), index cases (OR: 2.72, 95% CI 1.03-7.90, $P < .01$), history of arterial hypertension (OR: 4.49, 95% CI 1.65-12.36, $P < .01$) and smoking status (OR: 2.66, 95% CI 1.00-7.16, $P = .05$) were factors associated with premature CAD (Supplementary Table 9).

Discussion

This is the first detailed analysis of the Mexican familial hypercholesterolemia (FH) registry since its availability online in December 2017. The variables included are in accordance with the European Atherosclerosis Society (EAS) FH recommendations and common to many FH registries.[10,13,14,17,18] In this article, the results of patients with the most complete data, including follow up results are discussed (n = 336). The principal findings confirm late diagnosis, a lower than expected prevalence and risk of ASCVD, a higher than expected prevalence of type 2 diabetes and, undertreatment, as shown by the low number of patients reaching treatment goals.

Clinical characteristics of the cases are similar to that reported in other surveys.[19] The mean age of probands is greater than family members, with most cases discovered in adulthood. Moreover, tendon xanthomas are present in a higher proportion than habitually reported in the literature.[20–22] The late age of diagnosis and late treatment initiation permits the development and persistence of such lesions. In addition, tendon xanthomas, as a diagnostic criterion, probably contributed to diagnosis more often than in other populations.[23] Patients with xanthomas had a significantly higher prevalence of premature coronary artery disease. This supports the idea that a greater proportion of patients without xanthomas have a milder polygenic form of the disease.

Genetic testing is uncommon, illustrating the lack of resources for molecular analysis in the majority of centers. In centers where genetic testing is carried out, cascade screening with genetic confirmation in affected family members appears to be the strategy.[24,25]

In this population, the prevalence of smoking is surprisingly high (16.7%); however, this figure is still lower than in the majority of other registries.[20,26–28] Arterial hypertension is less prevalent than in other registries; however, the prevalence of type 2 diabetes is higher than expected (generally 2.1-11%).[21,23,26–29] In Mexico, the prevalence of type 2 diabetes is high, estimated to be between 13.5-15.2%.[30] Besseling et al. reported that the prevalence of diabetes was significantly lower in patients with familial hypercholesterolemia; there was an inverse dose-response relationship between the severity of the disease-causing mutation and the prevalence of type 2 diabetes.[31] They hypothesize that this is because of a decreased cholesterol uptake in the pancreatic beta cell, resulting in improved function and survival.

In general, heterozygous FH patients, have an increased risk of premature CAD, by at least 30% in women and 50% in men.[32,33] In this registry, the prevalence of CAD and peripheral arterial disease is low, with probands showing a significantly greater risk than affected family members. The association of heterozygous FH with an increased risk of stroke is debatable. In our registry, the prevalence of stroke is low compared with that reported in other studies.[34] Our results may reflect survival bias due to the effects of longstanding statin therapy, but may also suggest a lack of reliable documentation, resulting in an underestimation of events.

Lp(a) levels are low in our population, this is in line with previously reported ethnicity based differences.[35] There was no association between elevated Lp(a) levels and premature CAD; this result lacks statistical power, as only a third of the population currently have measurements. Cardiovascular risk in FH is heterogeneous; some individuals will suffer premature ASCVD, whereas others will remain event free. This is due to differences in genetics, the presence or absence of cardiovascular risk factors and the duration and intensity of treatment.[36]

The majority of patients are on statin therapy and at least a third are taking ezetimibe. In other registries, the use of statins is variable (43%-99%), possibly reflecting differences in healthcare systems, more newly diagnosed patients, and the degree of awareness of the disease.[21,23,26–29] With respect to LDL-C targets, the combined endpoint was present in only 13.7% of cases: in addition, less than a third achieved a 50% reduction in LDL-C compared to baseline, and less than a fifth an LDL-C $<$100 mg/dl. Index cases are more likely to achieve LDL-C objectives. This is probably because probands receive more medical attention initially compared with family members who are discovered latter with cascade screening. In addition, this group had a higher prevalence of CHD and thus stricter LDL-C targets may have been applied. Another significant factor associated with achieving LDL targets was the use of combination treatment (statin and ezetimibe). Persons with type 2 diabetes were also more likely to achieve goals. This reflects physicians being more aware of the cardiovascular risk associated with this disease and following LDL-C targets.

In the preliminary report of the EAS FH registry only 59% of patients are on lipid lowering therapy.[37] The latest EAS/ESC guidelines recommend an LDL-C goal of less than 70 mg/dl in FH patients without known atherosclerotic cardiovascular disease or other risk factors.[38] Yet, in their analysis less than 3% achieve this threshold. In our registry 5.8% have an LDL-C $<$70 mg/dl on follow up. The SAFEHEART registry showed that despite 71.8% of cases being on high intensity statins, an LDL-C goal $<$100 mg/dl was achieved by only 11.2%. This could be attributable to the type of LDL receptor mutation, which is consistent with previous reported studies.[39,40]

The challenges involved in establishing and sustaining a registry include factors that are common to all registries, but also aspects unique to a particular population.[41] Shared factors include difficulties in obtaining long term infrastructural support; often there are insufficient resources available on a local and national level.[23] Investigators involved in the registry may have time constraints; registering patients and cascade screening is labor intensive and time consuming.

The Mexican population faces some unique challenges. A fragmented public healthcare system means there is an inefficient provision of care.[42] One system may provide a certain treatment, but if the patient changes systems, a different statin or dose may be prescribed, with continuity of care being lost. Furthermore, the lack of awareness of the disease means that severe hypercholesterolemia continues to be managed with low intensity statin therapy.The public health care sector predominantly supplies low intensity statins; The use of high intensity statins and ezetimibe remains an out of pocket expense.[43]

We acknowledge there are strengths and limitations of this study. The principal limitation of the registry is the lack of genetic confirmation at many sites. This is not systematically carried out due to economic reasons. Follow-up data is not available for all patients; a more proactive planning of follow-up visits is needed. In addition, registry data suffers from the same drawbacks as all observational studies, variability in the quality of the data and the potential for patient selection and ascertainment bias.[44] The strengths of this registry include the involvement of representatives of almost all the federal states, the data is representative on a population level and permits analysis of national tendencies in the care of FH.

Conclusions

This study clearly shows that there is room for improvement in FH care in Mexico. This disease continues to be underdiagnosed and undertreated. The use of combination lipid lowering therapy must be promoted in all FH patients.

Affected family members should receive the same level of attention and follow up as probands. Furthermore, the implementation of genetic testing in more sites would allow us to explore mutations unique to this Mestizo population.

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Authors' contributions

Research idea and study design RM, AJM, CAAS; data acquisition: RM, AJM, GAGR, AVV, DEL, GGR, BR; data analysis/interpretation: RM, AJM, NEAV; statistical analysis: NEAV, RM; manuscript drafting: RM, AJM, GAGR, NEAV; supervision or mentorship: CAAS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

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Supplementary data

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