International Journal of Cardiology 201 (2015) 79–84

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Statins do not increase the risk of developing type 2 diabetes in familial hypercholesterolemia: The SAFEHEART study

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ARTICLE INFO

Article history:
Received 2 March 2015
Received in revised form 1 July 2015
Accepted 31 July 2015
Available online 5 August 2015

Keywords:
Type 2 diabetes
Statins
Familial hypercholesterolemia

ABSTRACT

Background: Familial Hypercholesterolemia (FH) is the most common monogenic disorder that causes premature coronary artery disease (CAD). Our objective was to examine the risk of new onset type 2 diabetes mellitus (T2DM) among FH patients and unaffected relatives in relation to treatment with different statins in the SAFEHEART cohort study.

Methods: This is a cross-sectional and prospective cohort study in 2558 FH and 1265 unaffected relatives with a mean follow-up of 5.9 years. Several pertinent data, such as age, gender, metabolic syndrome, lipid profile, body mass index (BMI), waist circumference, HOMA-IR, dose, duration and type of statins, were obtained and examined as predictors of incident diabetes.

Results: The new onset diabetes was 1.7% in FH and 0.2% in non FH patients ($p = 0.001$). In multivariate logistic regression, age (OR 1.02, CI 95%: 1.02–1.08), HOMA-IR (OR 1.17, CI 95%: 1.03–1.33), metabolic syndrome (OR 3.3, CI 95%: 1.32–8.28) and specifically plasma glucose, as a component of metabolic syndrome (OR 15.7, CI 95%: 4.70–52.53) were significant predictors of new onset T2DM in the FH group alone. In the adjusted Cox regression model in FH group, age (HR 1.03, CI 95% 1.00–1.06, $p = 0.031$) and metabolic syndrome (HR 4.16, CI 95% 1.58–10.92, $p = 0.004$) remained significant predictors of new onset T2DM.

Abbreviations: ACVD, Atherosclerotic cardiovascular disease; Apo AI, Apolipoprotein AI; Apo B, Apolipoprotein B; BMI, Body mass index; BP, Blood pressure; CAD, Coronary artery disease; CRP, C reactive protein; FH, Familial Hypercholesterolemia; HDL-C, HDL cholesterol; HMGCR, Hydroxy-3-methylglutaryl-CoA reductase; Lp (a), Lipoprotein (a); LDL-C, LDL cholesterol; LDL-R, Low density lipoprotein receptor; PCSK, Proproteinconvertase-subtilisin/kexin type 9; T2DM, Type 2 diabetes mellitus; TC, Total cholesterol.

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http://dx.doi.org/10.1016/j.ijcard.2015.07.107

Conclusions: Our data do not support the postulated diabetogenic effect associated with high-dose statins use in our cohort of FH patients.

1. Introduction

Familial Hypercholesterolemia (FH) is the most common monogenic disorder, affecting one in every 300–500 people in the general population. It is primarily due to mutations in the low density lipoprotein receptor (LDLR) gene and less frequently by mutations in the apolipoprotein B (apo B) and Proproteinconvertase-subtilisin/kexin type 9 (PCSK9) genes, resulting in an increase in plasma low density lipoprotein cholesterol (LDL-C) levels, which in turn leads to premature atherosclerotic cardiovascular disease (ACVD). Untreated patients with FH have an average reduction in life expectancy of 20–30 years in comparison with the general population [1].

The cardiovascular benefits of statins have been consistently demonstrated in a wide spectrum of at risk individuals [2,3]. Statins are the first line drugs for treating FH [4], with recent evidence suggesting that they effectively reduce coronary risk in such patients [5]. Because patients with FH are at very high cardiovascular risk, they generally require high potency statins with or without ezetimibe, or other drugs, to achieve targets of LDL-C as low as <70 mg/dL, but this is difficult to achieve in present day clinical practice [6–9]. Although statins are safe, recent studies have suggested that they can increase the risk of developing T2DM [10,11]. The risk for statin-related diabetes can depend on many factors including age, pre-existing diabetic risk, and type and potency of statin. Several mechanisms, mainly involving alteration in pancreatic islet ß-cell function, have been suggested for the diabetogenic effects of statins [12].

Regulatory agencies have accordingly changed the labeling of all statins warning of the risk of emergent diabetes [13]. Although the cardiovascular benefits of statin therapy clearly outweigh the risk of developing diabetes, current data suggest that physicians need to be aware of this potential adverse effect and should therefore monitor the potential risk of developing diabetes, especially in patients who are treated with high doses of statins. Nevertheless, statins remain the cornerstone of treatment for patients at high or very high cardiovascular risk, including those with diabetes and FH [14].

Patients with FH are usually treated with high doses of potent statins, often for the major part of a lifetime, and accordingly may be at particular risk of developing diabetes, which could further compound their risk of ACVD [15]. We therefore aimed to investigate the incidence and predictors of diabetes in a large prospective cohort of FH patients treated with statins.

2. Methods

2.1. Study design and population

A cross-sectional and prospective analysis was carried out in index cases and relatives enrolled into the Spanish Familial Hypercholesterolemia Cohort Study (SAFEHEART), an open, multicenter, prospective, long-term study in a population diagnosed genetically as having FH [16]. Selection criteria were described previously [16] and in essence included patients aged ≥18 years with a molecular diagnosis of FH and their non-affected relatives (DNA negative) as controls. Follow-up of this population is performed every year through a standardized phone-call by trained personnel (mean follow-up 5.9 years).

Patients with homozygous FH and patients with established diabetes before entry into the cohort were excluded from the present analysis. The study was approved by the ethics and clinical research committee and complies with the Declaration of Helsinki. A written informed consent was obtained from all participants.

2.2. Study variables

The following variables were collected at entry and follow-up: age, gender, cardiovascular history, cardiovascular risk factors: smoking (current smoker, ex-smoker > 1 year, non-smoker), diagnosis of hypertension (BP > 140/90 mm Hg or receiving antihypertensive treatment), diagnosis of T2DM, type and years of any lipid-lowering treatment and current treatment, anthropometric measures (weight, height, body mass index (BMI), waist circumference), systolic and diastolic blood pressure, plasma lipid, lipoprotein and apolipoprotein concentrations (total cholesterol [TC], HDL-cholesterol [HDL-C], triglycerides, lipoprotein (a) [Lp (a)], apolipoprotein AI [apo AI], apolipoprotein B [apo B], calculated LDL-C), glucose, insulin, C-reactive protein [CRP], TSH, HOMA-IR, LDLR mutation, and type of LDLR mutation (negative allele and defective allele). Metabolic syndrome was defined according to ATP-III criteria [17].

Diagnosis of T2DM was considered at inclusion and in the follow-up if one of the following criteria was present: fasting glycemia > 126 mg/dL at least in two separately occasions, glycosylated hemoglobin ≥ 6.5%, and/or patient receiving antidiabetic drugs. In all cases, the diagnosis of T2DM is confirmed by patient's physician or general practitioner [18].

The following statin dose regimens were considered as high intensity: rosuvastatin 20 mg and 40 mg/day, atorvastatin 40 mg and 80 mg/day, simvastatin 80 mg; the following were considered as low-to-moderate intensity: rosuvastatin 5 mg/day, atorvastatin 10 mg and 20 mg/day, simvastatin 10 mg, 20 mg and 40 mg/day, pitavastatin 1, 2 and 4 mg/day, pravastatin 10, 20 and 40 mg/day, fluvastatin 10, 20, 40 and 80 mg/day and lovastatin 10, 20 and 40 mg/day. Years on statin therapy were grouped as <5 years, 5–10 years and >10 years and the mean of years in treatment with statins was 10 years.

Venous blood samples were collected after 12 h of fasting. All the samples were processed and after separation of plasma were frozen at −80 °C, with all analyses carried out using standard laboratory methods in the central laboratory. Molecular testing for a pathogenic mutation causative of FH was performed using a DNA microarray [19]. Glucose levels, total cholesterol, triglycerides and HDL cholesterol were measured using standardized enzymatic methods. LDL cholesterol concentration was calculated using the Friedewald formula if triglycerides were <350 mg/dL. Lipoprotein (a) levels were measured using a turbidimetric method (QuantiaLp(a) 7K00-01) in an Architect autoanalyzer C16000 (Abbott Diagnostics, Lake Forest, Illinois) [20]. Insulin was measured by standardized radioimmunoassay and CRP was measured by quantitative immunoturbidimetry using the Architect c Systems (Abbott Diagnostics, Lake Forest, Illinois). HOMA-IR was calculated through the formula (fasting serum insulin (μU/mL) × fasting plasma glucose (mmol/L) / 22.5) [21].

2.3. Statistical analysis

A descriptive analysis was carried out of the clinical characteristics of the patients with FH and their non-affected relatives. Numerical summaries were made for quantitative variables (mean and standard deviation for all variables with a normal distribution and for non-normal data described used log transformation) and frequency tables for qualitative variables (number of cases and percentages).

A bivariate analysis was carried out to described the relationship between the dependent variable (new onset diabetes as a diabetes event) in FH patients and the control group, and a set of predictor variables, including age, gender, type of LDL receptor mutation (negative allele vs defective allele), BMI, metabolic syndrome, hypertension, smoking

habits, plasma lipid and lipoprotein levels, CRP, TSH, glucose, HOMA-IR and anthropometric parameters.

Comparisons between FH patients and the control group were performed using Chi-square tests with qualitative variables and, Student's t-tests and ANOVA with quantitative variables. Statistical significant was defined at the 5% level.

A multivariate analysis of binary logistic regression was used to assess the predictors of new onset diabetes, with statistical significance also defined at the 5% level. All significant variables from the bivariate analysis and those considered predictive of diabetes were included in the model: age, gender, presence or absence of LDLR mutation, type of LDLR mutation, BMI, years of statin therapy, dose and potency of statins (we use for analysis: rosuvastatin, atorvastatin and simvastatin — other statins were excluded because few patients took them: fluvastatin 15 patients, lovastatin 12 patients, pravastatin 22 patients, and pitavastatin 8 patients), smoking habits, hypertension, metabolic syndrome and insulin resistance defined as HOMA-IR > 3. The strength of the association was estimated as odds ratio with 95% confidence interval. A Cox regression analysis was also performed to estimate the relationship between statin use and new onset diabetes. To achieve this, we assumed the log–log survival curve model and adjustments were made for age, gender, LDLR mutation and type of LDLR mutation. We used adjusted Kaplan–Meier curves to compare the time to new T2DM in relation to the duration and the product of dose and duration of treatment with statins. All statistical analyses were carried out using SPSS (v 18.0, Chicago, IL, USA).

3. Results

SAFEHEART is a prospective study of patients who have undergone genetic testing to confirm or exclude FH, with a lengthy follow-up; 76.3% of the patients with FH are receiving treatment with statins at entry into cohort, 59% in high doses. The number and percentage of patients on the different type of statins in the pooled cohort were: rosuvastatin 326 (8.5%), atorvastatin 1323 (34.6%), and simvastatin 577 (15%); the different types of statins in the FH patients were: rosuvastatin 281 (10.9%), atorvastatin 1168 (45.6%), and simvastatin 467 (18.2%). In addition, 12.6% of the patients not taking statins are only receiving treatment with ezetimibe and/or resins.

A total of 3823 people (18–80 years) were included in the analyses: 2558 patients with a genetic diagnosis of FH (66.9%) and 1265 unaffected relatives (33.1%). There were no differences in gender, triglycerides, TSH, glucose, CRP, HOMA-IR, metabolic syndrome, insulin resistance, and hypertension between the FH and non-FH subjects (Table 1). The groups were on average of early middle age, but the FH patients were significantly older ($p < 0.05$) than the controls. There were statistically significant differences in total cholesterol, HDL-C, LDL-C, Apo AI, Apo B and Lp (a) levels, BMI, waist circumference, prevalence of type 2 diabetes at inclusion, smoking, years of treatment with statins, and statin dose.

In bivariate analysis of the pooled cohort, the prevalence of diabetes was 2.3% in FH vs 3.6% in non FH patients at entry into cohort ($p = 0.025$). The use of high doses compared with low doses of statins was significantly associated with more cases of new onset T2DM (2.5% for high doses vs 0.6% for low doses, $p < 0.0001$) in pooled cohort alone. However, there were no significant differences among type of statins and the development of diabetes in that analysis. The new onset diabetes was 1.7% in FH and 0.2% in non FH patients ($p = 0.001$). In the FH cohort alone there was no significant difference in the prevalence of T2DM at entry into the study (2.1% vs 2.2%, $p = 0.795$) nor in the incidence of T2DM at follow-up (2% vs 1.6%, $p = 0.458$) between FH patients with LDL receptor negative mutations compared with those with LDL receptor defective mutations. On the other hand, in this subgroup of patients, there were no differences regarding incidence of new onset T2DM and the use of different statins and doses (data not shown). Although in bivariate analysis we found differences but this difference was not statistically significant after adjustment for age, metabolic syndrome, BMI, component of metabolic syndrome nor in logistic regression. In multivariate logistic regression, age (OR 1.02, CI 95%: 1.02–1.08), HOMA-IR (OR 1.17, CI 95%: 1.03–1.33), metabolic syndrome (OR 3.3, CI 95%: 1.32–8.28) and plasma glucose, as a component of metabolic syndrome, (OR 15.7, CI 95%: 4.70–52.53) were significant predictors of new onset diabetes in the FH group alone (Table 2).

In the adjusted Cox regression model in the FH group, age (HR 1.03, CI 95% 1.00–1.06, $p = 0.031$) and metabolic syndrome (HR 4.16, CI 95% 1.58–10.92, $p = 0.004$) were significant predictors of new onset diabetes. The ROC curve showed an area under the curve of 0.791 (CI 95% 0.71–0.86, $p = 0.0001$) (Fig. 1). There were no significant differences among statins in relation to risk of new onset T2DM. Finally in the adjusted Kaplan–Meier curve, we did not find differences between FH group vs control group in the incidence of T2DM according the duration of treatment with statins (Fig. 2).

4. Discussion

This cohort study shows that in patients with FH, long-term treatment with high doses of statins does not increase the risk of developing T2DM. In the analysis of the entire cohort and in the subgroup of FH patients, we did not find a higher incidence of T2DM in patients who had taken statins for more than 5 or 10 years. The best predictors for the development of T2DM in FH patients were increasing age (range 50–75 years) and the presence of metabolic syndrome at entry. Plasma glucose levels were, however, the only component of metabolic syndrome that predicted increased risk of T2DM in FH. Age and metabolic syndrome are well known risk factors that are also predictors of type 2 diabetes in the general population [22].

In the last 5 years, different meta-analyses have shown an increased risk of diabetes with medium- to long-term statin treatments [10,11]. In most of these studies, the association was greater with the use of high

Table 1
Clinical and biochemical characteristics of the FH patients and control subjects without FH.

	HF patients (N = 2558)	Control group (N = 1265)	p value for difference
Male gender, % (N)	47.3 (1214)	46.2 (585)	0.48
Age, mean (SD), years	47.6 (17.3)	44 (17.4)	**0.001**
Total cholesterol, mean (SD), mg/dL	250.4 (66.4)	205.5 (45.4)	**0.001**
LDL-c, mean (SD), mg/dL	181.2 (61.8)	131.2 (41)	**0.001**
HDL-c, mean (SD), mg/dL	49.5 (12.5)	54.4 (13.2)	**0.001**
Triglycerides, mean (SD), mg/dL	96.6 (55.3)	97.2 (57.1)	0.75
Lp (a), median (IQR), mg/dL	37.4 (39.3)	31.4 (33.2)	**0.001**
CRP, mean (SD), mg/L	2.2 (4.8)	2.2 (3.7)	0.75
TSH, mean (SD), UI/L	2 (5.7)	1.8 (3)	0.25
Glucose, mean (SD), mg/dL	86.1 (15.2)	86.4 (16.8)	0.64
BMI, mean (SD), Kg/m^2	26 (4.7)	25.3 (4.9)	**0.001**
Waist, mean (SD), cms	86.3 (24.2)	84 (15.2)	**0.001**
HOMA-IR, mean (SD)	2 (5)	1.9 (2.1)	0.57
BMI, % (N)			
Normal (<25 kg/m^2)	45.7 (1167)	52.5 (663)	**0.001**
Overweight (25–29.9 kg/m^2)	35.2 (901)	31.2 (395)	
Obesity (≥30 kg/m^2)	19.1 (490)	16.3 (207)	
Metabolic syndrome, % (N)	16.4 (281)	13.6 (114)	0.06
Type 2 diabetes, % (N)	2.3 (59)	3.6 (45)	**0.02**
Hypertension, % (N)	13.7 (352)	11.8 (150)	0.10
Smoking, % (N)			
Habitual smoker	25.1 (644)	30.4 (385)	**0.001**
Ex smoker > 1 year	22.8 (584)	16 (202)	
No smoker	52.1 (1336)	53.6 (679)	
Years of statins therapy, % (N)			
<5 years	5.7 (147)	18.4 (53)	**0.001**
5–10 years	21.3 (430)	27.8 (80)	
>10 years	71.4 (1442)	53.8 (155)	
Statin doses, % (N)			
No take	23.7 (610)	77.3 (979)	**0.001**
Low doses	16.9 (434)	12.2 (155)	
High doses	59.3 (1520)	10.4 (132)	

BMI: body mass index.

doses of the most potent statins compared with the use of the same statins in moderate doses [11].

However, the meta-analysis from Sattar et al. should be interpreted with caution, because it was based on a post-hoc analysis, and incident T2DM was not a predefined objective in most of the studies [10]. In our study, we have found no association of risk of diabetes with the duration of statin treatment nor with the use of higher doses of statins.

Preiss et al. [11] reported an increased risk of developing T2DM when high doses of statins were used compared with moderate doses, but did not study subjects with FH. Our finding of a non-diabetogenic effect of higher dose nor longer duration of statins may relate to the prevalence of T2DM in our FH patients is lower (3.7%) than the corresponding prevalence in the general population in Spain (13.8%) [23]. The lower average age of our cohort compared with a previous meta-analysis might have also influenced both the low prevalence and low incidence of T2DM, noting that age is a major risk factors for the development of type 2 diabetes. Similar results have been reported in a recent work [24] which found no association between the use of high doses of statins in HF patients and the risk of diabetes, although the sample size of the study is very small compared to ours. A recent cross sectional study of 63,320 patients from the Netherlands reported a prevalence of type 2 diabetes in FH of 1.75% and 2.93% in unaffected relatives [25]; the mean of age of the FH and non-FH group was 38 and 43 years, respectively. The younger age of the Dutch sample may explain why the prevalence of diabetes was lower than in our population.

Very recent data from 43 observational genetic studies analyzing more than 220,000 patients showed that inhibition of 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) seems to be causally related to risk for diabetes [26,27].

The alleles for two single-nucleotide polymorphisms (SNPs) within or near the gene that encodes HMGCR, were associated with excess incidence and prevalence of T2DM, as well as with higher body weight, BMI, and plasma glucose and insulin levels. These modifiable risk factors were the main predictors of diabetes, consistent with our findings in FH subjects. We cannot exclude a small, contributory effect of variation in HMGCR activity to the risk of diabetes in our cohort. We propose that this is minor compared with the effects of age and insulin resistance, but would have been underpowered to compare these relative effects.

Also, a recent population-based study from Canada [28] showed an association between treatment with statins and the development of T2DM. However, subjects were over 66 years old and accordingly had a markedly increased risk of developing diabetes of between 10% and 22% compared with the much lower rates of 1.7% in our sample

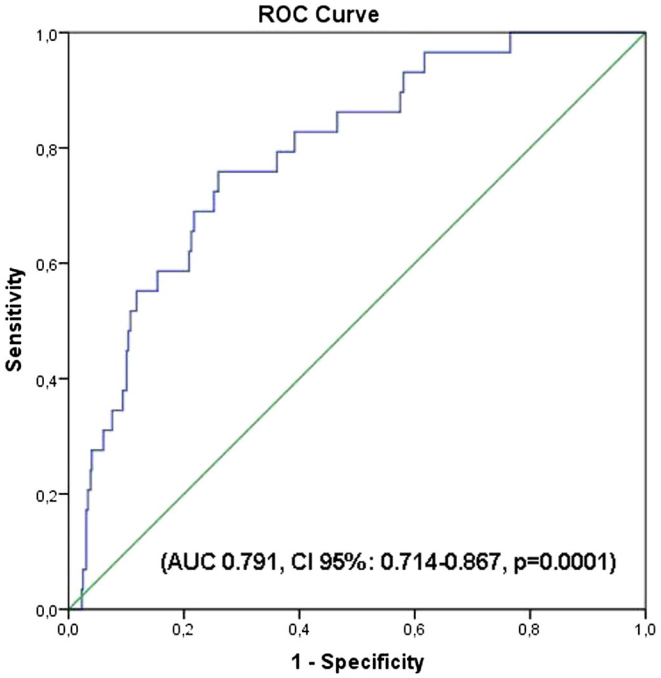

Fig. 1. Receiver Operator Characteristic curve showing the sensitivity and specificity of the statistical model (including age, doses and types of statins, doses/duration of statins, BMI, HOMA-ir, metabolic syndrome, and Tgs/HDL-C) in predictive new onset diabetes mellitus (AUC 0.791, CI 95% 0.71-0.86, p = 0.0001).

Table 2
Binary logistic regression: variables associated with the development of diabetes, adjusted for potential confounding factors, in FH group.

	OR adjusted diabetes event (no/yes)	95% CI	p value
Age	1.02	(1.02–1.08)	**0.001**
Grouped age			
<25 years	1 (ref.)*		
25–50 years	17.69	(0.40–77.10)	0.13
50–75 years	5.96	(1.49–23.83)	**0.01**
>75 years	0.69	(0.03–12.66)	0.80
Triglycerides	1.00	(0.99–1.01)	0.50
Tgs/HDL-c	1.32	(0.97–1.80)	0.06
HOMA-IR	1.17	(1.03–1.33)	**0.01**
BMI	1.06	(0.97–1.16)	0.17
Dose/duration statins	1.00	(0.99–1.02)	0.08
Years of treatment with statins	0.97	(0.90–1.04)	0.40
Doses of statins			
Low doses	1 (ref.)*		
High doses	0.97	(0.95–1.08)	0.31
Smoking			
No smoking	1 (ref.)*		
Ever smoked	2.35	(0.99–5.59)	0.06
Metabolic syndrome (MS)			
No	1 (ref.)*		
Yes	3.30	(1.32–8.28)	**0.01**
Components of MS			
No components	1 (ref.)*		
Tgs	0.41	(0.08–2.05)	0.27
HDL-c	0.40	(0.13–1.15)	0.09
BP	0.49	(0.16–1.47)	0.20
WC	0.43	(0.13–1.40)	0.16
Glucose	15.71	(4.70–52.53)	**0.001**
Type LDL receptor allele			
Defective allele	1 (ref.)*		
Null allele	1.21	(0.62–2.36)	0.56

BMI: body mass index.

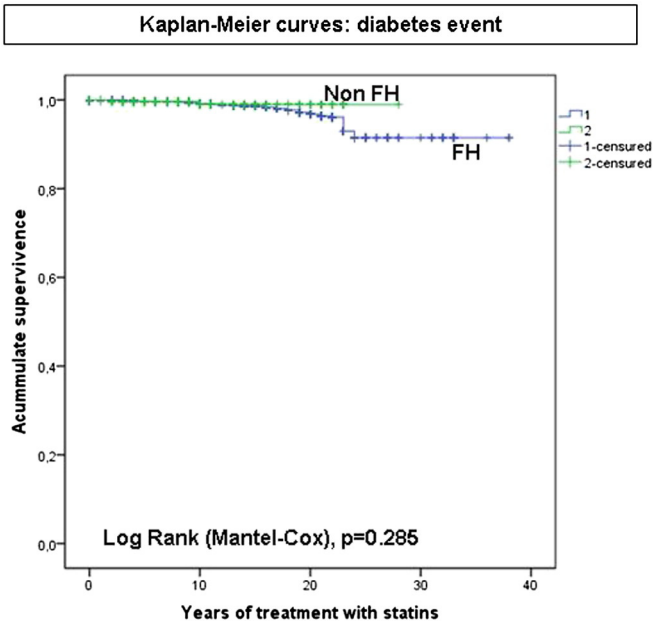

Fig. 2. Kaplan-Meier survival curves in relation to the development of new onset diabetes in patients with FH and subjects without FH.

population of FH subjects. While the Canadian study is notable owing to its very large sample size (over 450,000 subjects), the study has important limitations, including the absence of statistical adjustment for the effect of risk factors for diabetes such as weight, race, dyslipidemia and family history. There are possible mechanisms that could explain the increased risk of new onset diabetes in patient receiving statins: the increased production of LDL-C as a compensatory response to the novo cholesterol synthesis inhibition that might result in direct inflammation and oxidation within the Beta cell, and that statins can also inhibit calcium mediated pancreatic insulin release and decrease expression of the Beta cell glucose transporters GLUT-2 and GLUT-4 [12]. Other evidence highlights a role of adiponectin and ubiquinone [29–31]. Statins inhibit HMGCR and increase the expression of LDL receptors in several tissues, chiefly the liver, and thereby promote the transmembrane uptake and plasma clearance of LDL-cholesterol. This is opposite to the genetically impaired cellular uptake of LDL-cholesterol uptake in FH. Perturbation in cellular cholesterol transport might be implicated in the pathogenesis of type 2 diabetes [32]. It is possible that the prevalence of type 2 diabetes is decreased in patients with FH because their pancreatic beta cells have decreased cholesterol uptake and therefore improved function reserve in insulin secretion [25].

4.1. Limitations and strengths

A major limitation may be the statistical power of our study so that a true population effect of statins might have been missed, given the very large sample sizes of other studies in which the diabetogenic effect of statins were demonstrated [11,27]. Our work was also limited in its observational design, noting that the associations between predictor variables and T2DM could subject to confounding factors. Although we adjusted our analysis for all available known risk factors, not all sources of variation of risk of diabetes were accounted for e.g., family history of T2DM.

By contrast to other reports [10,27] we focused on molecularly defined patients at very high risk of CAD who would be at special risk of developing diabetes according to the use of higher potency statins over a prolonged period; we also adopted a prospective design to test our study hypothesis. In addition unlike other works in our study the diagnosis of diabetes is consistent. Although we employed self-reported diabetes by the patient as our primary outcome variable, the diagnosis of T2DM was confirmed independently by the patient's primary care physician and by the measurement of a plasma glucose concentration.

5. Conclusions

In conclusion, our data suggest that in a molecularly characterized FH population at high cardiovascular risk who need life-long treatment with high dose drug therapy, statins do not increase the risk of T2DM. The main predictors of new onset T2DM in this FH population are age and features of the metabolic syndrome. FH patients on high dose statins may be reasonably reassured that they are not at increased risk of developing diabetes, especially if they avoid obesity and metabolic syndrome through preventive measures, such as a prudent diet and regular exercise. In FH population a protection against diabetes could result from the earlier use if lifestyle, including diet, and a protective genetic mechanism has not yet been demonstrated. Future studies are required, however, to explore the potential diabetogenic effects of statins in other population samples of FH patients.

6. Perspectives

Competency in medical knowledge. Familial Hypercholesterolemia (FH) is the most common monogenic disorder that causes premature coronary artery disease (CAD). High-dose statins are the cornerstone of treatment of FH. The diabetogenic effect of statins remains controversial and has not been enough studied in FH patients.

Translational outlook. FH population needs life-long treatment with high dose of statins that do not increase the risk of T2DM. They are not at increased risk of developing diabetes, especially if they avoid obesity and metabolic syndrome through preventive measures.

Conflicts of interest

The authors report no relationships that could be construed as a conflict of interest.

Financial support

This study was supported by the Fundación Hipercolesterolemia Familiar; Grant G03/181 and ISCIII-Subdirección General de Evaluación y Fomento de la Investigación PI12/01289, Grant 08-2008 Centro Nacional de Investigación Cardiovascular (CNIC). Juan F. Alcala-Diaz is supported by a public research contract of ISCIII (Programa Rio-Hortega).

Acknowledgments

We are most grateful to all the FH families for their valuable contribution and willingness to participate. We also thank the Spanish Familial Hypercholesterolemia Foundation for assistance in the recruitment of participants. Francisco Fuentes and Pedro Mata had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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