Atherosclerosis 256 (2017) 62–66

Contents lists available at ScienceDirect

Atherosclerosis

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

Carotid artery plaques and intima medial thickness in familial hypercholesteraemic patients on long-term statin therapy: A case control study

Sven Bos [a], Martijne H.C. Duvekot [a], Gert-Jan R. ten Kate [b], Adrie J.M. Verhoeven [a], Monique T. Mulder [a], Arend F.L. Schinkel [b], Koen Nieman [b, c], Gerald F. Watts [d], Eric J.G. Sijbrands [a], Jeanine E. Roeters van Lennep [a, *, 1]

[a] Department of Internal Medicine, Division Pharmacology, Vascular and Metabolic Diseases, Erasmus MC, Rotterdam, The Netherlands
[b] Department of Cardiology, Thorax Centre Rotterdam, Erasmus MC, Rotterdam, The Netherlands
[c] Department of Radiology, Erasmus MC, Rotterdam, The Netherlands
[d] Lipid Disorders Clinic, Cardiovascular Medicine, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, WA, Australia

ARTICLE INFO

Article history:
Received 9 August 2016
Received in revised form
23 November 2016
Accepted 1 December 2016
Available online 2 December 2016

Keywords:
Carotid plaque presence
Carotid intima media thickness
Familial hypercholesterolemia
Residual risk

ABSTRACT

Background and aims: Statins reduce subclinical atherosclerosis and premature atherosclerotic cardiovascular disease (ASCVD) in patients with familial hypercholesterolemia (FH). However, some FH patients still develop ASCVD despite statin therapy. We compared subclinical atherosclerosis assessed by carotid plaque presence and intima media thickness (C-IMT), in long-term statin-treated FH patients and healthy controls. Furthermore, we analysed whether carotid ultrasonography findings associated with subclinical coronary atherosclerosis.

Methods: We assessed the presence of carotid plaques and C-IMT in 221 asymptomatic heterozygous FH patients (48% men; 46 ± 15 years) on long-term (10.0 ± 7.8 years) statin treatment and 103 controls (32% men, 47 ± 16 years).

Results: The frequency of carotid plaques and C-IMT did not differ significantly between the FH patients and controls (69 (31%) *versus* 24 (23%), $p = 0.1$ and 0.58 ± 0.13 *versus* 0.58 ± 0.12 mm, $p = 0.9$, respectively). In a subgroup of 49 FH patients who underwent cardiac computed tomography, coronary artery calcification correlated with carotid plaque presence ($R = 0.47$; $p = 0.001$), but not with C-IMT ($R = 0.20$; $p = 0.2$).

Conclusions: Carotid plaques and C-IMT did not differ between long-term statin-treated heterozygous FH patients and healthy controls. This shows that long-term statin treatment in these FH patients reduces carotid atherosclerosis to a degree of a healthy population. These findings strongly suggests that sonography of the carotid arteries during follow-up of statin-treated FH patients has limited value.

1. Introduction

Familial hypercholesterolemia (FH) is the most common genetic disorder associated with premature atherosclerotic cardiovascular disease (ASCVD), and is caused by pathogenic mutations in the *LDLR*, *APOB* or *PCSK-9* gene [1–3]. The risk of premature ASCVD is increased due to high low-density lipoprotein cholesterol (LDL-C) levels [4], which can be lowered by statin treatment. Statin therapy can reduce ASCVD risk in heterozygous FH patients to the same risk as in the general population [5]. However, there are still FH patients who develop ASCVD despite statin treatment [5]. To identify these FH patients, imaging modalities that detect subclinical atherosclerosis may be useful. Carotid ultrasonography can be used to detect plaques and estimate carotid intima media thickness (C-IMT). Increased C-IMT and the presence of carotid artery plaques in particular, are significant predictors of ASCVD in the general population [6–9]. Previously, it was shown that treatment with a high

* Corresponding author. Gravendijkwal 230, 3015 CE, Rotterdam, The Netherlands.
E-mail address: j.roetersvanlennep@erasmusmc.nl (J.E. Roeters van Lennep).
[1] Postbus 2040, 3000 CA, Rotterdam, Room: D-425, The Netherlands.

http://dx.doi.org/10.1016/j.atherosclerosis.2016.12.005
0021-9150/

potency statin during 2 years inhibited progression of C-IMT in FH patients [10,11]. Sivapalaratnam et al. showed that the C-IMT of statin-treated FH patients is comparable to that of their healthy spouses [12], suggesting a normalization of risk of ASCVD in the former group. However, C-IMT is not as strongly associated with ASCVD as the presence of carotid plaques [9,13,14], which was not investigated in the aforementioned study. Whether the prevalence of carotid plaques is normalized in FH patients by long-term statin treatment, and whether normalized carotid parameters, indeed, reflect subclinical coronary atherosclerosis, remains unknown. We, therefore, compared carotid plaque prevalence and C-IMT between FH patients and healthy controls. Moreover, in a subgroup of FH patients, we correlated these parameters with coronary artery calcification.

1.1. Patients and methods

1.1.1. Study population

Between May 2012 and May 2015, asymptomatic heterozygous FH patients were recruited from the outpatient cardiogenetics clinic at the Erasmus Medical Centre in Rotterdam. FH was defined as a score ≥6 on 'The Dutch Lipid Clinic Network criteria' (addendum 1) [15]. All patients were on statin treatment. All patients were screened for mutations in the *LDLR*, *APOB* and *PCSK-9* genes. Patients with two mutations, compound heterozygous FH and homozygous FH, were excluded as were patients with symptoms of ASCVD or a history of ASCVD.

Controls were recruited through public advertisements, and were included between April 2014 and May 2015. Inclusion criteria for the controls were: no major illness, no statin or any other lipid-lowering medication use, and no history of ASCVD.

A total of 221 FH patients were included in our study. Expecting 15% ± 7% difference in carotid plaque presence (primary endpoint) between FH patients and controls, at least 96 controls were required for a power of 80% and α of 5%. For C-IMT (secondary end point), we considered 0.05 mm to be a clinically significant difference and previously, we observed standard deviation of ±0.12 mm; to obtain a power of 80%, α of 5%, at least 69 controls were required.

All subjects were over 18 years of age. Written informed consent was obtained from all participants and healthy volunteers. This study is in accordance with the declaration of Helsinki and was approved by the local ethical committee (MEC-2012-309); (MEC-2013-556).

1.1.2. Blood analyses

Fasting blood was collected in EDTA, processed the same day, and plasma samples were stored at −80 °C. Lipid levels were measured using standard laboratory techniques.

1.1.3. Carotid ultrasonography

All carotid ultrasound scans and measurements were performed using a Panasonic CardioHealthStation (Yokohama, Japan) that uses a validated automated C-IMT capturing method [16]. The scanning protocol is based on the ASE consensus [17], and has been previously published [18]. In short, plaque scans were performed bilaterally in the internal carotid artery, external carotid artery and common carotid artery. Plaques were defined as a local enlargement of the C-IMT of more than 50% of the surrounding C-IMT, or if the C-IMT was above 1.5 mm, and were scored as present or absent [19]. C-IMT was measured over 1-cm length, at least 0.5 cm proximal of the bifurcation in the common carotid artery, and measured in the end-diastolic phase, which was identified by the vessel motion detector system based on the change in arterial diameter during the cardiac cycle [16]. The C-IMT was measured twice on each side, in a 45° angle determined by positioning the patients head against a 45° wedged pillow, and the mean of these four orientations was used in our study.

1.1.4. CT calcium imaging

A subgroup (n = 49, 22%) of the asymptomatic FH patients in this cohort underwent a non-enhanced cardiac computed tomography (CT) scan (Somatom Definition, Siemens Medical Solutions, Forchheim, Germany) in the same period, to quantify the coronary calcium burden, not on indication but for another research study. The calcium score was measured as described previously [20], and expressed as the Agatson score [21]. The FH patients who had their calcium score determined were divided in three subgroups. The first group were patients without detectable calcification [n = 14). Patients with a positive calcium scan were split in two comparable sized groups (n = 17; n = 18) based on the calcium score, by using the median calcium score of the FH patients with coronary calcification (Agatston score cut-off of 136).

1.1.5. Statistical analyses

Data with a normal distribution were expressed as mean (±SD), and data with a skewed distribution as median (IQR). Differences between the groups at baseline were compared by a Chi-square test for binary variables and by ANOVA for continuous variables.

Factors associated with C-IMT and plaques were tested in linear and logistic regression analyses. Regression analyses were repeated separately in the FH patients and the controls to see if there were different predicting variables in the groups.

To test the association of carotid plaques and C-IMT with coronary artery calcification, univariable ordinal regression analyses were performed. Finally, multiple ordinal regression analyses were performed to determine the predictive values of the carotid plaques presence and C-IMT for coronary calcification.

Statistical analyses were performed using SPSS, version 20 (SPSS, Chicago, Illinois).

2. Results

2.1. Clinical characteristics

Data were collected from 221 FH patients, and 103 healthy controls. DNA analysis confirmed FH in 170 patients (77%), with mutations in the *LDLR* and *APOB* gene in 151 and 19 patients, respectively. *PCSK-9* gene mutations were not present in our patients.

Characteristics of FH patients and controls are depicted in Table 1. FH patients were of similar age and had similar LDL-C levels as controls. All FH patients used statins on average for 10.0 ± 7.8 years. At inclusion, 74% of patients used rosuvastatin or atorvastatin, 23% used simvastatin and the remainder used fluvastatin or pravastatin. The FH group contained more men than the healthy control group. The main differences between the groups were a higher BMI and lower blood pressure, total cholesterol and HDL cholesterol in the FH group.

2.2. Carotid ultrasonography findings

The frequency of plaques in 69 out of 221 FH patients was not significantly different from 24 out of 103 controls (31% *versus* 23%; $p = 0.09$). The mean C-IMT was similar in the FH patients compared to the healthy controls (0.58 ± 0.13 mm and 0.58 ± 0.12 mm, respectively; $p = 0.90$). Adjustment for age, male sex, body mass index, systolic and diastolic blood pressure, total cholesterol, and HDL-cholesterol did not materially change these results (data not shown).

In the FH group, plaque presence was associated with age, male