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Angiographic progression of coronary atherosclerosis in patients with familial hypercholesterolaemia treated with non-statin therapy: Impact of a fat-modified diet and a resin

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ABSTRACT

Background and aims: Familial hypercholesterolaemia (FH) profoundly increases the risk of coronary artery disease (CAD). We investigated whether diet and a bile-acid sequestrant decrease coronary atherosclerosis in patients with FH.

Methods: We identified 26 men with FH and CAD, participating in the St Thomas' Atherosclerosis Regression Study, who had been randomized to receive a fat-modified diet plus cholestyramine (8 g twice daily) (DC, n = 12) or usual care (UC, n = 14), and investigated the relative effects of these treatments on the angiographic progression of coronary atherosclerosis over 39 months. FH was defined as probable/definite according to Dutch Lipid Clinic Network criteria; mean FH score was 8.7 (range 6 −15) and mean baseline low-density lipoprotein cholesterol (LDL-Ch) concentration was 5.4 (SD 1.4) mmol/L. Coronary atherosclerosis was assessed by serial quantitative angiography as the global changes in mean and minimum absolute width of segments (MAWS and MinAWS, respectively).

Results: Mean plasma LDL-Ch concentration fell by 35% with DC and remained significantly ($p < 0.001$) lower during the trial at 3.78 (SD 0.98) mmol/L compared with UC at 4.89 (1.04). MAWS decreased by 0.252 (SEM 0.072) mm in the UC group and by 0.001 (0.065) mm in the DC group ($p = 0.007$), with corresponding reductions in MinAWS of 0.290 (0.087) mm and 0.013 (0.058) mm ($p = 0.009$); these changes were significant after adjusting for baseline variables, including coronary luminal dimensions and lipoprotein(a). Progression was observed in 7 patients (50%) on UC and 3 (25%) on DC ($p = 0.19$), with regression in no patients (0%) and 3 patients (25%) ($p < 0.05$), respectively.

Conclusions: This investigation, carried out in the pre-statin era, demonstrates that a prudent diet and cholestyramine could improve the course of coronary atherosclerosis in men with phenotypic FH through sustained reductions in LDL-Ch.

1. Introduction

Familial hypercholesterolaemia (FH) is a common, monogenic disorder that causes sustained elevation in plasma low-density lipoprotein cholesterol (LDL-Ch) from birth and premature atherosclerotic coronary artery disease (CAD) [1,2]. Despite its importance, most cases of FH remain undetected or inadequately treated worldwide. Although high intensity statin based therapy is widely recommended for FH [1–3], no controlled studies have specifically demonstrated that reduction in LDL-Ch decreases CAD events in such patients [4]. The evidence for LDL-Ch lowering with statins in FH is primarily derived from cohort or registry studies [5–8] and surrogate endpoint trials based on estimates of endothelial function [9] and carotid intima-medial thickness [10].

Statin associated muscle symptoms (SAMs) are relatively common [11] and higher doses can increase the risk of type 2 diabetes [12], both of which are particularly relevant to the long-term management of FH [1,2]. With complete intolerance to statins due to SAMs, lowering LDL-Ch requires use of a strict fat-modified diet and non-statin medications, such as ezetimibe and/or bile-acid

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binding resins (BABRs, e.g. cholestyramine) [11,13], and in the future PCSK9 inhibitors [14], although these new agents are at present expensive [15]. A heart, healthy diet is central to the management of FH [1,2,16], but its importance has tended to be overshadowed by focus on high-potency drugs.

In hypercholesterolaemic patients, cholestyramine monotherapy can decrease the incidence of CAD events [17,18] and in combination with other agents, including statins, can inhibit progression of coronary atherosclerosis [19–23]. By contrast to statins [12], BABRs can also have a specific anti-diabetic effect [24]. The value of BABR monotherapy in combination with a diet in decreasing risk of CAD has not yet been specifically demonstrated in FH.

2. Materials and methods

We investigated the effect of a fat-modified diet plus cholestyramine (8 g twice daily) on angiographic progression of CAD over 39 months in male patients with FH participating in the St Thomas' Atherosclerosis Regression Study (STARS) [25,26], a trial carried out in the United Kingdom (UK) between 1985 and 1990 at a time when statins were not clinically available and the drug therapy of patients with CAD was less intensive and evidence-based.

STARS selected non-diabetic men aged less than 66 years of age with a plasma cholesterol between 6.1 and 10 mmol/L on usual diet and who were referred for coronary angiography for suspected CAD; patients with Type III hyperlipidaemia were excluded [25]. The present opportunistic investigation constituted a post-hoc, non-prespecified analysis with a non-probability sample group.

Details of the trial design and ethics clearance, clinical and biochemical methods, quantitative image analysis and principal results of STARS were published elsewhere [25,26]. The diet employed was designed to be readily complied with, included all usual food groups and comprised 27% energy fat (8–10% saturates), a P:S ratio of 0.8–1.0, reduced cholesterol (100mg/1000 kcal/day) and increased soluble fibre; provision of lean meats and health food was provided to promote dietary compliance. Detailed advice and counselling was intermittently given on how to consume cholestyramine to prevent gastrointestinal side-effects and concurrent medications were taken to minimise interference in absorption, drug compliance was defined as >80% ingestion of cholestyramine, as assessed by sachet count. From edge-detection endpoints relating to a maximum of 10 paired coronary segments, luminal dimensions were computed as the mean absolute width of segments (MAWS) and minimum absolute width of segments (MinAWS), as well as the relative measure of coronary luminal change [26]; baseline and global (ie. mean for all paired segments) changes in luminal dimensions were estimated. Regression and progression were defined as a global change in MAWS of +0.17 mm and - 0.17 mm [25,26].

We employed the Dutch Lipid Clinic Network Criteria (DLCNC) [27] to identify a subset of patients from the parent study who had a probable or definite diagnosis of FH and who had been randomised to receive diet plus cholestyramine (DC) or usual care (UC); we did not report the effect of diet alone because its effect on LDL-Ch was modest and our aim here was to assess the impact of diet plus a BABR on progression of CAD in FH patients treated with this regimen. According to our exclusion criteria, the FH patients would have had heterozygous FH with moderately high LDL-Ch concentrations.

Baseline characteristics of the study groups (FH vs non-FH patients from the parent study; DC vs UC groups of FH patients alone) were compared by unpaired t-tests and chi-square tests. Between-group changes in outcome variables with interventions were analysed by general linear modelling, including adjustments for individual baseline co-variates, including the absolute and relative estimates of coronary luminal dimensions and lipoprotein(a) [Lp(a)]. Associations were examined by linear regression methods.

3. Results

Of 48 eligible participants in the parent trial, we identified 26 who had FH and of whom 12 and 14 had been randomized to DC and UC, respectively; all were known to have hypercholesterolaemia and CAD, but none had a total cholesterol above 10 mmo/L. Clinical and biochemical characteristics were comparable between the groups (Table 1), the overall DLCN score being 8.7 (range 6–15) and there being no significant group differences in the proportion of patients with elevated plasma Lp(a) (>0.4 g/L) in each group, 30% used beta-blocker and calcium antagonists and 20% aspirin, nitrates and diuretics. In the main STARS study, the only significant differences in baseline clinical characteristics between patients with and without FH were a greater frequency of a family history of premature CHD and a higher plasma LDL-Ch in the former group ($p < 0.001$ for both).

Good compliance with diet was confirmed by weighed dietary food records and with cholestyramine by returned sachet counts. Mean plasma LDL-Ch concentration fell over 3 years (mean of at least 7 in-trial measurements) with DC by 35% and was significantly ($p < 0.001$) lower at 3.78 (SD 0.98) mmol/L than with UC at 4.89 (1.04); plasma triglyceride and HDL-Ch did not alter significantly in either group (Table 2).

The average baseline and global changes in MAWS, MinAWS and percentage diameter stenosis (%DS) within the UC and DC groups are shown in Table 3. There were no significant differences in coronary luminal dimensions between the groups at baseline.

It can be seen that MAWS decreased by 0.252 (SEM 0.072) mm in the UC group and by 0.001 (0.065) mm in the DC group ($p = 0.007$, adjusted for baseline MAWS), with corresponding reductions in MinAWS of 0.290 (0.087) mm and 0.013 (0.058) mm ($p = 0.009$, adjusted for baseline MinAWS) and increases in %DS by 7.5 (2.74) % and 0.68(0.68) % ($p = 0.043$, adjusted for baseline %DS), respectively. The changes in absolute of coronary luminal width (MAWS and MinAWS) in individual patients in the UC and DC groups are shown in Fig. 1. The changes in MAWS and MinAWS with DC relative to UC remained statistically significant after adjusting individually for age, BMI, family and personal history of CAD, DLCN score, and baseline plasma lipid and lipoprotein concentrations, including Lp(a).

There were 3 new occlusions of coronary segments in UC compared with none in DC. Progression (global change in MAWS of - 0.17 mm) was observed in 7 patients (50%) in UC and 3 (25%) in DC ($p = 0.19$ for difference) and regression (global change in MAWS of +0.17 mm) in no patients (0%) in UC and 3 patients (25%) in DC ($p < 0.05$ for difference).

The changes in MAWS, MinAWs and %DS were also statistically significant with DC compared with UC in the non-FH patients (n = 22) not included in the present report; however, the relative changes in MAWS, MinAWs and %DS in the non-FH patients were statistically significantly greater ($p = 0.037$, $p = 0.0.18$ and $p = 0.016$, respectively, adjusting for baseline variables) than in the FH group (data not shown).

After pooling data from the UC and DC groups of FH patients, there was an inverse correlation between both the in-trial LDL-Ch and the % reduction in LDL-Ch and the changes in MAWS ($r = -0.372$, $p = 0.067$ and $r = -0.469$, $p = 0.018$, respectively, adjusting for baseline variables) and MinAWS ($r = -0.514$, $p = 0.009$ and $r = -0.497$, $p = 0.011$, respectively, adjusting for baseline variables). The in-trial plasma apolipoprotein B concentration was also inversely and significantly associated with the