Long-term changes in serum cholesterol level does not influence the progression of coronary calcification

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ABSTRACT

Background: A number of reports controversially describe the influence of cholesterol level and lipid-lowering treatment (LLT) on the progression of coronary calcium (CC). We tested the hypothesis that long-term changes in serum cholesterol (CL) would affect the progression of CC.
Methods: The study population comprised 510 patients with stable angina pectoris, mean age of 63 ± 9 years. At baseline 372 patients received statin and/or fibrate (LLT group) while 138 patients did not (No-LLT at baseline group). Spiral CT every 24 months was used to track the progression of CC over a median 5.6 year follow-up.
Results: CL decreased during follow-up in both groups, but more pronouncedly in patients with LLT. The changes in total calcium score (TCS) were similar in both groups ($p = 0.3$). Changes in CL during follow-up were not associated with CC: TCS increased by 501 ± 63 from baseline in the 1st (upper) quartile, and by 350 ± 44, 403 ± 41 and 480 ± 56 in the 2nd, 3rd, and 4th quartiles of CL longitudinal changes ($p = 0.2$), respectively. Baseline TCS and its changes were not correlated with baseline CL and its changes. New calcified lesions were diagnosed in 132 (28.2%) out of the 467 patients available for this analysis, without significant difference between groups ($p = 0.4$). Multivariate analysis demonstrated that only baseline TCS ($p < 0.001$), body mass index ($p = 0.007$) and age ($p = 0.006$) were independent predictors for the TCS changes.
Conclusions: Longitudinal CL changes do not seem to have a measurable effect on the rate of progression of CC.

1. Introduction

Coronary calcification (CC) measured by different computed tomography (CT) techniques closely correlates with the extent of atherosclerosis, predicts clinical outcome and has therefore been suggested as a reliable surrogate marker of coronary plaque burden [1–6]. Based on the same rationale, serial CC scanning has been proposed as a good tool for tracking the longitudinal progression of coronary atherosclerosis and for evaluating the effects of a lipid-lowering therapy (LLT) [7–10].

However, a number of reports controversially describe the influence of cholesterol level and LLT on the rate of change of CC. Some studies observed an important influence of cholesterol level and statin therapy on the serial CC measurements [7,10,11] and emphasized that LLT reduces the progression of CC. In sharp contrast, a number of groups have reported that LLT has no effect on CC changes

[12–16] or even was associated with a significantly more CC progression [17,18]. Most of these studies reported only relatively short one- or two-year median follow-up period whereas long-term relationships between longitudinal cholesterol changes and the rate of progression of CC are still elusive.

In light of the pointed out controversies and the unresolved questions, we decided to test the hypothesis that long-term changes in serum cholesterol level would affect the progression of CC.

2. Materials and methods

2.1. Study design

We used the database of the ACTION (A Coronary disease Trial Investigating Outcomes with Nifedipine GITS) study: a multi-center, randomized, placebo–controlled double-blind trial which compared the effect on clinical outcomes and safety of nifedipine GITS or placebo in treated patients with stable angina pectoris attributable to coronary artery disease. A detailed description of the ACTION design and results has been published previously [19–21]. LLT was either continued or started according to local guidelines. The following drugs could not be used in combination with study medication: calcium antagonists (2-week washout needed), cardiac glycosides (unless given for supraventricular arrhythmias), other positive

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inotropic agents, class I or III antiarrhythmics other than amiodarone or sotalol, cimetidine, rifampicin, antipsychotic and antiepileptic drugs. Blood pressure was recorded with a standard sphygmomanometer in the sitting position after 5 min of rest. Functional class was rated according to the New York Heart Association (NYHA) scale.

The CC side-arm study of the ACTION trial was designed to assess the changes (from baseline) in calcium score and in the number of new calcific atherosclerotic lesions in the coronary arteries over a 4.5–6.2 (median 5.6) year period. It was conducted in Israel. Between June 1997 and October 1998, 510 patients with data regarding LLT (372 received LLT and 138 did not) were included from 16 sites. All patients were sent to the single referral center that performed the baseline dual slice spiral CT (DSCT) of the coronary arteries and signed the CC informed consent. A follow-up DSCT scan was performed every 2 years thereafter. The maximum number of follow-up DSCT scans for any one patient was three.

2.2. DSCT protocol: dual-slice CT-image acquisition

We used a CT-Twin double helical scanner and spiral scanning mode (Twin, Marconi Ltd., Cleveland, Ohio) without contrast material. Scanning time was 1 s for two contiguous 2.5-mm slices and 15–22 s for the entire zone of interest. Examination was performed during a single unforced withheld inspiration. During helical scanning with the tube rotating at 1 rps and the table moving at 5 mm/s with a 1:1 scanning pitch, images were obtained with an effective slice thickness of 3.2 mm (a nominal slice width of 2.5 mm) and a reconstruction increment of 1.5 mm (overlapping section method). Scanning was performed with 120 kVp and 210 mAs as standard resolution and a 43-cm field of view. The total duration of the procedure was 10 min. For calcium scoring the 40 most cephalic contiguous slices were selected, starting at the level of the first visible coronary artery — left main or left anterior descending. This provided 6 cm coverage of the proximal portion of the coronary tree as measured along the longitudinal axis of the patient.

2.3. Quantification of coronary calcium

A calcific lesion was defined as an area within a coronary artery whose tomographic density was above a threshold of 90 Hounsfield (HU)>8 SD above blood density, covering an area of 0.5 mm^2 (more than 2 pixels).

Regions of interest were placed around all lesions and an experienced physician categorized the lesion as either left anterior descending, circumflex, or right coronary artery. Calcifications in the location of the left main as well as diagonal branches were grouped with the left anterior descending artery, and those in the location of the obtuse marginal branches were grouped with the left circumflex artery. The software (Heart Beat — CS Marconi Ltd., Cleveland, Ohio) calculated and recorded the area of each lesion in square millimeters as well as its average and peak density value. A score for each region of interest was calculated automatically by multiplying the density factor by the area. The density factor was derived from the CT density as follows: For CT values of 9–199 HU the factor was 1, for 200–299 HU the factor was 2, for 300–399 HU the factor was 3 and for CT values of 400 HU the factor was 4. The total coronary calcification score (TCS) was the combined sum of the lesion scores for all 40 slices. All 40 slices, which included traced regions of interest, were filmed. This facilitated the adjustment of the starting level to the one of the baseline scan, as well as the accurate identification of all baseline calcium lesions in each follow-up scan. All films were systematically reviewed by a single experienced physician blinded to the clinical data (JS). Intra-observer variation of this reader was evaluated upon a random sample of 30 consecutive measurements blinded to previous results. No significant difference was found between the two measurements. Wherever significant mitral annulus calcification prevented accurate separation from the left circumflex artery calcification, the entire left circumflex artery score was subtracted from the total calcium score.

DSCT was repeated every 2 years and at the conclusion of the patient's participation in ACTION, which occurred between 4.5 and 6 years after the baseline scan was performed. These assessments were carried out in conjunction with the main ACTION study visits, allowing a time window of ± 2 months for each visit.

2.4. Statistical analysis

Continuous variables at baseline were presented as mean values ± standard deviation (SD) and a comparison between the two groups was analyzed using independent t-test. Categorical variables were presented by frequencies and percentage. Comparisons between groups were made using chi-square tests.

Spearman's correlation coefficients were calculated to examine the relationships between TCS and cholesterol level at baseline and changes during follow-up for the study population as a whole.

For the assessment of differences of TCS and cholesterol during follow-up an analysis-of-variance (ANOVA) was used. Repeated measures analysis was used for the evaluation differences between the groups in cholesterol and TCS during follow-up. Logistic regression was performed to identify the independent predictors for TCS change above the median. A p value of less than 0.05 (two-side) was considered as statistically significant.

3. Results

3.1. Baseline data

Our population included 2 groups: 1) LLT group — 372 patients; 2) No-LLT at baseline group — 138 patients.

In the LLT group patients were somewhat younger; their total cholesterol level was higher (Table 1). Patients of both groups were similar in regard to gender and the prevalence of the most relevant cardiovascular diseases and risk factors (body mass index, TCS, MI in the past, smoking, heart failure, diabetes, heart rate and blood pressure).

Data regarding treatment with cardiovascular drugs among the study groups are presented in Table 2. Nitrates, calcium antagonists, beta blockers, antiplatelet drugs (mainly aspirin), diuretics and angiotensin converting enzyme inhibitors were the most commonly used medications. In patients from the No-LLT at baseline group the use of antiplatelet drugs was somewhat lower whereas the use of diuretics was somewhat higher. There were no significant differences in the proportion of patients receiving the other cardiovascular drugs.

3.2. LLT on baseline and during follow-up

At baseline 331 (89%) of patients from the LLT group received HMG-CoA reductase inhibitors (statins), 32 (8.6%) received fibric acid derivative bezafibrate and 9 (2.4%) of patients received combination of statin and bezafibrate. The most commonly used statins were simvastatin — 174 (46.8%) of patients, pravastatin — 88 (23.7%) of patients and atorvastatin — 56 (15.0%) of patients, while 13 (3.5%) of patients used other statins. During follow-up we observed that in the LLT group, 33 (8.6%) of patients discontinued LLT whereas in the No-LLT at baseline group 83 (62.9%) of patients have started statins (mainly after the first 2 years of follow-up).

3.3. Correlation analyses between TCS and total cholesterol when pooling both groups together

TCS did not correlate with total cholesterol at baseline ($r = -0.085$, $p = 0.55$). On the contrary, weak albeit significant negative correlations were found at the end of the study between TCS and both baseline and last measured total cholesterol ($r = -0.105$, $p = 0.017$ and $r = -0.101$, $p = 0.035$ respectively). TCS changes did not correlate with changes in total cholesterol levels during the follow-up.

3.4. TCS and total cholesterol changes during follow-up

TCS and total cholesterol changes during follow-up are shown in Tables 3, 4 and Fig. 1 (Panels A and B). Total cholesterol decreased in the LLT group throughout the entire follow-up period. In the No-LLT at baseline group total cholesterol did not change during the first 2 years of follow-up, but thereafter it began to decrease significantly — probably as a result of initiation of statin therapy.

The increase of TCS values was similar in both groups ($p = 0.3$). Changes in total cholesterol during follow-up were not associated with CC: TCS increased during follow-up by 501 ± 63 from baseline in the 1st (upper) quartile, and by 350 ± 44, 403 ± 41 and 480 ± 56 in the 2nd, 3 rd, and 4th quartiles of total cholesterol longitudinal changes ($p = 0.16$), respectively.

New calcified lesions were diagnosed in 132 (28.2%) out of the 467 patients available for this analysis, without significant difference between groups: in 93 out of the 343 patients (27.3%) in the LLT group and in 39 out of the 124 patients (31.5%) in the No-LLT at baseline group ($p = 0.4$).

Table 1
Baseline characteristics of the study population.

Characteristics	No LLT ($n = 138$)	LLT ($n = 372$)	p value
Age (years)	65 ± 8.2	62 ± 9.3	0.001
Body mass index (kg/m2)	28.0 ± 4.1	27.8 ± 3.7	0.577
Men (%)	123 (89)	316 (84)	0.168
Diabetes (%)	31 (22)	93 (25)	0.587
Past myocardial infarction (%)	65 (47)	185 (49)	0.660
NYHA class ≥2 (%)	73 (52)	201 (53)	0.238
Smokers (%)	14 (10)	62 (17)	0.072
Systolic blood pressure (mm Hg)	137 ± 18	135 ± 18	0.272
Diastolic blood pressure (mm Hg)	79 ± 9.1	80 ± 8.5	0.507
Heart rate (beats/min)	65.7 ± 10.4	65.3 ± 10.2	0.642
Glucose (mg/dl)	112 ± 44	115 ± 46	0.533
Total cholesterol (mg/dl)	192 ± 25	215 ± 38	<0.001
TCS	539 ± 820	479 ± 732	0.420

NYHA — the New York Heart Association.
TCS — the total coronary calcification score.
LLT — lipid-lowering therapy at baseline.
No LLT — No-LLT at baseline.

Table 2
Distribution of cardiovascular drugs among the study patients on baseline.

Drugs — baseline	No LLT ($n = 138$)	LLT ($n = 372$)	p value
Beta blockers (%)	106 (76)	287 (76)	0.937
Nitrates (%)	100 (72)	262 (69)	0.563
Calcium antagonists (%)	58 (42)	129 (34)	0.111
Diuretics (%)	17 (12)	18 (5)	0.003
Antiplatelets (%)	121 (88)	353 (95)	0.001
Angiotensin converting enzyme inhibitors (%)	42 (30)	109 (29)	0.760

LLT — lipid-lowering therapy at baseline.
No LLT — No-LLT at baseline.

Multivariate analysis demonstrated that only baseline TCS (ln transformed, $p < 0.001$), body mass index ($p = 0.007$) and age ($p = 0.006$) were independent predictors for the 5.6-year TCS changes above the median.

4. Discussion

Our data demonstrate that the progression of CC in patients with CAD is not related to long-term lowering of the serum cholesterol or use of LLT. To the authors' knowledge, our multicenter study represents the longest reported follow-up which explores the relationship between cholesterol changes and the rate of progression of CC, as measured by serial spiral CT. These data are in line with some previous short-term studies, which have shown that longitudinal cholesterol changes and LLT does not influence progression of CC [12–18,22].

On average, the baseline parameters of our patients were very similar to those from the main ACTION study [20]. In our study 73% of patients received LLT at baseline (89% of them received statins and 11% of them received bezafibrate or bezafibrate/statin combination). In the LLT group cholesterol level declined consistently throughout follow-up while in the group without LLT at baseline, values of total cholesterol remained stable for 2 years; thereafter, they significantly declined. Of note, the protocol of the ACTION study encouraged start of the open-label LLT during follow-up according to the permanently updated local guidelines and most of the patients from the No-LLT at baseline group (62.9%) have started statins after the first 2 years of follow-up. Nevertheless, the increases of TCS values as well as appearance of the new calcified lesions were similar in both groups and, most important, irrespective of the longitudinal cholesterol changes. Moreover, even weak negative correlations were observed between the TCS at the end of the study vs. both baseline and last measured total cholesterol.

Obviously, we should differentiate between the proven and useful ability of vascular calcium assessment by different CT techniques (spiral dual slice, spiral gated multi-detector and electron-beam) to contribute to patient's risk-stratification [1–6,23–25] and the contro-

Table 3
Total cholesterol (mg/dl) and total coronary calcium score TCS) levels at baseline and during follow-up.

Variable	No LLT ($n = 138$)	LLT ($n = 372$)	p value
Total cholesterol			
Baseline	192 ± 25	215 ± 38	<0.001
2 years	193 ± 28	200 ± 34	0.035
4 years	183 ± 29	193 ± 34	0.007
Last visit (4.5–6 years)	170 ± 30	183 ± 36	<0.001
TCS			
Baseline	539 ± 820	479 ± 732	0.420
2 years	687 ± 917	665 ± 882	0.814
4 years	894 ± 1101	825 ± 1077	0.562
Last visit (4.5–6 years)	922 ± 689	916 ± 1087	0.951

LLT — lipid-lowering therapy at baseline.
No LLT — No-LLT at baseline.

Table 4
Differences in total cholesterol (mg/dl) and total coronary calcium score (TCS) levels during follow-up among the study patients.

Variable	No LLT ($n = 138$)	LLT ($n = 372$)	***p*** value
Differences in total cholesterol			
From baseline to 2 years	−0.44 ± 28.6	−13 ± 38	<0.001
From baseline to 4 years	−8.5 ± 32	−20.5 ± 40	0.002
From baseline to last visit (4.5–6 years)	−23.1 ± 36	−30.5 ± 45	0.081
Differences in TCS			
From baseline to 2 years	182 ± 324	179 ± 366	0.955
From baseline to 4 years	392 ± 467	364 ± 477	0.607
From baseline to last visit (4.5–6 years)	452 ± 515	495 ± 588	0.512

LLT — lipid-lowering therapy at baseline.
No LLT — No-LLT at baseline.

versial suggestion that serial CT scanning could be a suitable tool for evaluation of anti-atherosclerotic therapy by tracking the progression of CC as a "surrogate marker" for atherosclerosis. Calcific plaques (in contrast to "soft" plaques) are resistant to undergoing changes in size in response to systemic anti-atherosclerotic therapy [26]. Furthermore, the process of vascular calcification may spread out in a different manner than the overall development of atherosclerosis [27]. HMG-CoA reductase inhibitors (statins) may differentially regulate calcification within vascular tissue. For example, bone cell calcification, which is also observed in vascular tissues, appeared to be paradoxically stimulated by HMG-CoA reductase inhibitor therapy [28]. Coronary calcification is composed of both hydroxyapatite and organic matrix, including type I collagen and non-collagenous bone-associated proteins [29]. Collagen-associated crystal deposition initiates mineralization within matrix vesicles, leading to the hypothesis that dystrophic calcification is an active, regulated process rather than passive accumulation of mineral. The most relevant non-
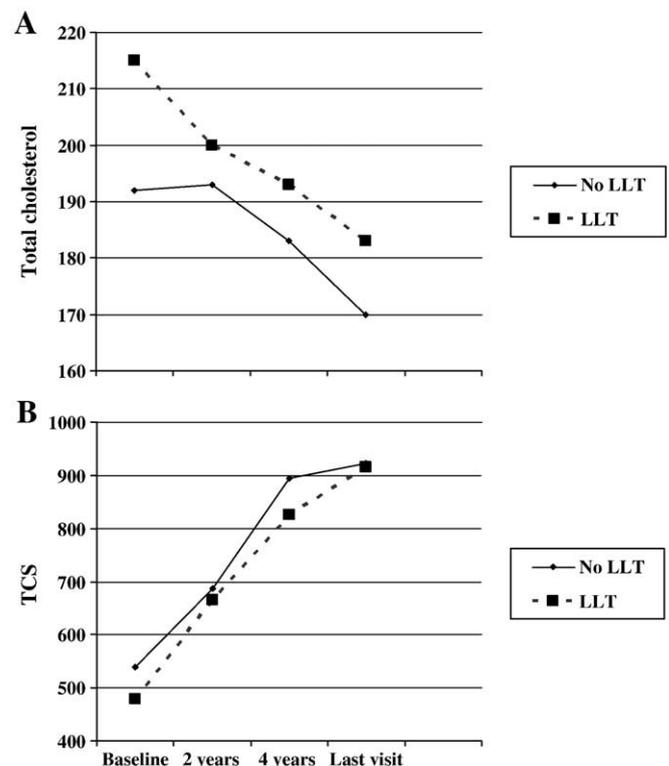

Fig. 1. Changes of mean total cholesterol level (mg/dl, Panel A) and mean total coronary calcium score (TCS, Panel B) in the study groups during follow-up. LLT — lipid-lowering treatment on baseline.

collagenous bone-associated proteins associated with vascular calcification include osteopontin, osteonectin, osteoprotegerin, and matrix Gla protein [30]. In some cases calcification may probably stabilize atherosclerotic lesions, making them less likely to undergo fibrous cap rupture (which leads to an acute cardiac event) and therefore supposedly represent a kind of a "healing" process. Therefore, the identification of vascular calcification does not necessarily imply growing atheroma. This is summarized in five phases, from early lesions to plaque rupture, thrombosis and plaque healing, followed by fibrocalcification [30].

On the other hand, the extent, location, and morphologic appearance of calcification should be taken into consideration. For example, micro-calcification deposits in the region of atheroma which prone to a shear stress could be associated with an increased risk of fibrous cap rupture and subsequent ischemic events [26,31–33]. Lesions associated with unstable angina or infarction tend to have multiple, small calcium deposits, in "spotty" or "speckled" patterns, whereas those in stable angina are associated with few, large calcium deposits [31–34]. These clinical findings are in agreement with analyses showing that large deposits reduce circumferential stress in adjacent plaque and that small deposits increase stress at their edges [35–37].

Therefore, such widespread parameter as TCS does not have the capability of assessing the distribution of various morphologic patterns of calcium and their relation to other "soft" plaque components [38].

Technical study limitations. Since the electrocardiographic gating technique was not available at the time we began this long-term study (1997), we used a nongated dual-detector technique which was state of the art at the time. This technique has since been replaced by the use of faster electrocardiographically gated multi-detector row spiral techniques with higher reproducibility and accuracy. However, the clinical accuracy of the nongated procedure, its reproducibility, and its usefulness in tracking the progression of calcific coronary atherosclerosis has been shown to be adequate [8,21,39–42].

We conclude that both cholesterol changes over time and LLT do not seem to have any measurable effect on the rate of progression of CC.

Acknowledgement

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