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ORIGINAL RESEARCH

CENIT (Impact of Cardiac Exercise Training on Lipid Content in Coronary Atheromatous Plaques Evaluated by Near-Infrared Spectroscopy): A Randomized Trial

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BACKGROUND: The effect of physical exercise on lipid content of coronary artery plaques is unknown. With near infrared spectroscopy we measured the effect of high intensity interval training (HIIT) on lipid content in coronary plaques in patients with stable coronary artery disease following percutaneous coronary intervention.

METHODS AND RESULTS: In CENIT (Impact of Cardiac Exercise Training on Lipid Content in Coronary Atheromatous Plaques Evaluated by Near-Infrared Spectroscopy) 60 patients were randomized to 6 months supervised HIIT or to a control group. The primary end point was change in lipid content measured as maximum lipid core burden index at 4 mm ($maxLCBI_{4mm}$). A predefined cutoff of $maxLCBI_{4mm}$ >100 was required for inclusion in the analysis. Forty-nine patients (HIIT=20, usual care=29) had $maxLCBI_{4mm}$ >100 at baseline. Change in $maxLCBI_{4mm}$ did not differ between groups (–1.2, 95% CI, –65.8 to 63.4, P=0.97). The estimated reduction in $maxLCBI_{4mm}$ was –47.7 (95% CI, –100.3 to 5.0, P=0.075) and –46.5 (95% CI, –87.5 to –5.4, P=0.027) after HIIT and in controls, respectively. A negative correlation was observed between change in peak oxygen uptake (VO_{2peak}) and change in lipid content (Spearman's correlation –0.44, P=0.009). With an increase in VO_{2peak} above 1 metabolic equivalent task, $maxLCBI_{4mm}$ was on average reduced by 142 (–8 to –262), whereas the change was –3.2 (154 to –255) with increased VO_{2peak} below 1 metabolic equivalent task.

CONCLUSIONS: Six months of HIIT following percutaneous coronary intervention did not reduce lipid content in coronary plaques compared with usual care. A moderate negative correlation between increase in VO_{2peak} and change in lipid content generates the hypothesis that exercise with a subsequent increase in fitness may reduce lipid content in coronary atheromatous plaques.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02494947.

Key Words: coronary atheromatous plaques ■ lipid core burden index ■ near infrared spectroscopy ■ physical exercise

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Physical exercise is highly recommended for secondary prevention of coronary artery disease (CAD),[1] and multiple beneficial biological effects are demonstrated with regular physical exercise.[2] Furthermore, several studies have demonstrated strong and positive associations between the level of physical exercise and life expectancy both in healthy subjects and in patients with CAD.[3,4] However, survival benefit from regular physical exercise has not been demonstrated in randomized clinical trials in CAD. There is a paucity of data on the effect of physical exercise on coronary artery atheromatous plaques. Studies on athletes with coronary computed tomography angiography indicate that strenuous physical exercise is associated with increased coronary artery calcium.[5,6] Data regarding the effect of physical

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CLINICAL PERSPECTIVE

What Is New?

- Physical exercise following percutaneous coronary intervention in patients with stable coronary artery disease may reduce lipid content in coronary atheromatous plaques assessed by near infrared spectroscopy with a potential positive correlation between increase in VO_{2peak} and reduction in lipid content.

What Are the Clinical Implications?

- A lipid-reducing effect of physical exercise in coronary atheromatous plaques reinforces the scientific evidence for recommending physical exercise in rehabilitation programs.

Nonstandard Abbreviations and Acronyms

HIIT	high intensity interval training
LCBI	lipid core burden index
NIRS	near infrared spectroscopy
PROSPECT	Providing Regional Observations to Study Predictors of Events in the Coronary Tree

exercise on plaque volume, plaque composition, and plaque vulnerability are modest. With radiofrequency intravascular ultrasound, we previously demonstrated a reduction in necrotic core following a period of exercise training in patients with CAD.[7] Furthermore, we demonstrated that plaque vulnerability following an exercise intervention could change in different directions within the same patient, indicating that local intracoronary factors affect plaque composition. Near infrared spectroscopy (NIRS) can be used to determine lipid content in coronary artery atheromatous plaques.[8] Previous studies have demonstrated that lipid-rich lesions are more vulnerable and together with plaque volume represent increased risk for future cardiac events,[9–13] recently also demonstrated in the PROSPECT 2 (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) trial.[14] With the use of NIRS, pharmacotherapy studies with lipid-lowering drugs have confirmed a favorable reduction in coronary artery lipid content.[15,16] No previous trial has investigated the effect of physical exercise on lipid content in coronary arteries. In this trial we hypothesized that lipid content in coronary atheromatous plaques assessed with NIRS would be reduced after a period of regular high intensity interval training (HIIT) when compared with usual care.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Design and Patient Population

This study was an investigator-initiated, single-center, open, parallel, randomized controlled trial undertaken at the Clinic of Cardiology, St. Olavs University Hospital in Trondheim, Norway. The study protocol was approved by the Regional Ethics Committee of Central Norway (2015/210), registered at clinicaltrials.gov (NCT02494947), and performed according to the Declaration of Helsinki. Written informed consent was obtained from all participants.

Sixty patients with symptomatic stable CAD treated with percutaneous coronary intervention (PCI) were included. The inclusion criteria were use of statins for at least 6 weeks before undergoing PCI and being able to perform the prescribed exercise program. Exclusion criteria were previous coronary artery bypass surgery, known inflammatory disease other than atherosclerosis, planned surgery within the next 6 months, inclusion in another randomized trial or inability to comply with the study protocol due to any somatic disease, physical disability, mental problems, or already performing physical activity at a similar or higher level than the prescribed activity for the intervention group. Guideline-directed medical therapy was administered to all patients following PCI. However, no adjustments were made for lipid-lowering therapy throughout the study. After completion of baseline acquisitions, patients were randomly allocated to a supervised 6 months intervention with HIIT or advised to follow the current recommendations for secondary prevention in CAD with no protocol-based follow-up until the end of the study period. Randomization was performed by a web-based randomization system developed and administered by the Unit of Applied Clinical Research, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway.

Exercise Training

The intervention group joined supervised endurance training performed as walking or running on a treadmill or bicycling following the HIIT-principle 2 times weekly for 6 months. Each session started with a 10-minute warmup at moderate intensity (60% to 70% of peak heart rate), followed by 4×4 minute intervals with an intensity at 85% to 95% of peak heart rate with 3 minutes of active recovery at moderate intensity between intervals, ending with a 5-minute cooldown period.[17] In addition, patients were encouraged to perform

home-based endurance training with bouts of intervals, and any activity mode involving dynamic work with large muscle groups was recommended. To ensure adequate training intensity and increase adherence, the patients in the HIIT group were encouraged to use a wearable device for heart rate and activity tracking (Mio Global PAI, Toronto, Canada). The control group was encouraged to practice regular physical activity of moderate intensity according to contemporary guidelines[1] without receiving any further supervision.

Study Outcomes

The primary outcome was change in lipid content in matched coronary atheromatous plaques from baseline to follow-up measured by NIRS. Secondary outcomes were changes in cardiorespiratory fitness measured as peak oxygen uptake (VO_{2peak}), body mass index, waist circumference, blood lipids and glycosylated hemoglobin A1c.

Invasive Procedures

Coronary angiography and PCI were performed according to standard techniques, and a standard transthoracic echocardiography was performed at baseline following PCI. Drug-eluting stents were used in all cases. After successful treatment of all flow-limiting lesions, 3-vessel intravascular imaging of epicardial vessels was performed when feasible by a 3.2 Fr NIRS catheter using an automated pullback system (TVC-MC8 model system with a 3.2Fr 40 MHz catheter, Infraredx, Burlington, MA). Following administration of intracoronary nitroglycerine, the NIRS catheter was positioned as distally as possible in the coronary artery. The distal starting points of the pullbacks were recorded angiographically to assist in registration of the corresponding segments at follow-up. Untreated lesions were identified, and their plaque morphology was evaluated by NIRS. NIRS spectroscopic data generate a chemogram where data are illustrated by a color-coded distribution from red to yellow. Yellow pixels represent the highest probability of lipid deposition and allows for a calculation of lipid core burden index (LCBI) that ranges from 0 to 1000 equivalent to the percentage of yellow pixels in the segment of interest.[18]

Angiograms and intravascular ultrasound data were analyzed at an independent core laboratory, (KCRI, Krakow, Poland), without any knowledge of patient characteristics or randomization allocation. Intravascular data were analyzed using the commercial software (Pie Medical Imaging Software, CAAS Intravascular). Analyses were performed for every 0.5 mm of the arteries. Regions of interest were defined as a target segment lesion with an atherosclerotic plaque compromising the lumen by at least 30% by cross-sectional area, with the 5 mm segments proximal and distal to the target segment as reference. The corresponding regions of interest at baseline and follow-up were identified using fiduciary points such as side branches and the implanted stent, as well as comparison of angiographic records. LCBI was estimated for the analyzed segments and the change in maximal value of LCBI per 4 mm ($maxLCBI_{4\ mm}$) in matched coronary segments at baseline and follow-up was defined as the primary end point. The plaque with the highest $maxLCBI_{4\ mm}$ at baseline was used for further analysis irrespective of where in the coronary artery tree it was located.

Cardiovascular Risk Factors

Medical history uptake, physical examination, anthropometrics, fasting blood sampling, cardiopulmonary exercise testing, and echocardiography were performed at baseline and follow-up.

Exercise Testing

Two weeks following PCI, and after the study period, an individualized cardiopulmonary exercise testing was performed to determine exercise tolerance, VO_{2peak}, and peak heart rate in order to tailor exercise prescription and evaluate training effects. Data from the 12-lead ECG, blood pressure, and respiratory gases (Jaeger Vyntus CPX, Hoechber, Germany) were recorded continuously. The individualized steady-state test protocol started at a speed and inclination set during the 15 minutes warmup guided by the Borg scale. Thereafter workload was increased either by 1 km/h in speed or by 2% every minute until the participant stopped the test due to exertion or VO_{2max} was achieved. The protocol lasts 8 to 12 minutes. VO_{2max} was defined as a flattening of the oxygen uptake curve despite an increased workload combined with a respiratory exchange ratio above 1.05.

Statistical Analysis

In the planning of this study, we had no data on the effect of physical exercise on $maxLCBI_{4mm}$. In a previous study using radiofrequency intravascular ultrasound (IVUS) of 36 patients undergoing PCI, we demonstrated a reduction in necrotic core both for patients undertaking 12 weeks of HIIT and those exercising at moderate intensity with no in-between group difference.[7] Based on this experience, we designed the present study with a sample size of 60 and prolonged the intervention from 3 to 6 months.

Statistical analyses were performed using the SPSS version 26.0 (IBM Corporation) and Microsoft Office Excel 2016. Baseline clinical characteristics are presented as means with SDs or as frequencies and percentages. Normally distributed continuous variables

were compared using the Student *t*-test and categorical variables were compared by the chi-square test or Fisher's exact test. For the comparison of the primary end point, change in maxLCBI$_{4mm}$ (ΔmaxLCBI$_{4mm}$) between groups, we specified a linear mixed model with time and group as fixed effects variables. Dependence of observations within individuals was handled by including individual-specific random intercepts. Owing to randomization, mean outcomes at baseline were in the models constrained to be equal between the groups.[19] Similar models were used for the secondary end points. To study the relationship between the change in VO_{2peak} (ΔVO_{2peak}) and ΔmaxLCBI$_{4mm}$ from baseline to follow-up, the Spearman's correlation coefficient was calculated. *P* values <0.05 were considered statistically significant and CIs are presented at the 95% level. Normality of residuals was checked by visual inspection of normal QQ-plots.

RESULTS

Study Patients and Lesion Characteristics

From February 2016 to April 2019, 60 patients with stable CAD on statin treatment for at least 6 weeks before undergoing PCI were found eligible and enrolled in the study. In patients with no atheromatous plaque with maxLCBI$_{4mm}$ >100 at baseline, lipid content was considered too low to predict alterations in plaque composition with certainty. Accordingly, 11 patients were excluded. Thus, 49 patients (20 in the HIIT group and 29 in the control group) with a total of 142 imaged coronary arteries at baseline (mean 2.9 per patient) were included and analyzed for the primary end point (Figure 1). During the intervention period, 1 patient in the HIIT group developed severe angina pectoris and underwent coronary artery bypass grafting and another patient in the HIIT group emigrated. Also, 1 patient in the HIIT group had unsuccessful NIRS-IVUS imaging at follow-up. Thus, there were no follow-up NIRS-IVUS data from these 3 patients. One patient in the control group suffered a minor stroke at the end of the follow-up period; otherwise there were no adverse events during the study. There were no complications related to the invasive procedures. Baseline patient characteristics were similar between the 2 groups (Table 1). The patients were middle aged and cardiovascular risk factors were prevalent. All patients were on dual antiplatelet therapy and stable statin treatment.

Primary End Point: Changes in maxLCBI$_{4mm}$

At baseline, the maxLCBI$_{4\ mm}$ was well balanced between the 2 groups (Table 2). The artery with the highest maxLCBI$_{4\ mm}$ was the left anterior descending artery (including the first diagonal branch) in 21 patients, the right coronary artery in 13 patients, the circumflex artery in 14 patients, and the intermediate artery in 1 patient. There was no significant difference in the change of maxLCBI$_{4\ mm}$ from baseline to follow-up between the HIIT and the control group (–1.2; 95% CI, −65.8 to 63.4; *P*=0.97), and a similar mean reduction in maxLCBI$_{4mm}$ was observed in both groups (Table 3). Figure 2 demonstrates an imaged vessel with coronary angiography and NIRS-IVUS. When comparing maxLCBI$_{4mm}$ between different arteries in the same patient, we observed that lipid content in atheromatous plaques changed in both directions in 16 patients at follow-up. No consistent pattern with respect to changes in maxLCBI$_{4mm}$ based on the anatomical origin of the coronary artery was observed.

Changes in maxLCBI$_{4mm}$ Relative to VO_{2peak}

When analyzing patients with increased peak oxygen uptake at follow-up, a moderate negative correlation (Spearman's correlation −0.44, *P*=0.009) between ΔVO_{2peak} and ΔmaxLCBI$_{4mm}$ was found (Figure 3). Among those with an increase in VO_{2peak} above 1 MET (3.5 mL·kg^{-1}·min^{-1}) maxLCBI$_{4mm}$ were on average reduced by 142 (range –8 to –262), whereas the change was –3.2 (range 154 to –255) among those with an increased VO_{2peak} below 1 MET. Among the 17 patients with an increased VO_{2peak} below 1 MET, 9 had increased and 8 decreased LCBI$_{4mm}$ (Figure 3).

Cardiovascular Risk Factors

Cardiovascular risk factors at baseline and follow-up are presented in Table 2. There was a larger increase in VO_{2peak} in the HIIT group compared with the control group (*P*=0.034). VO_{2peak} increased significantly after HIIT (*P*<0.001) but not in the control group (*P*=0.113, Table 3). The reduction in body mass index and waist circumference was also significantly larger after HIIT compared with the control group. In both groups a modest although significant increase was observed for both high-density lipoprotein cholesterol and apolipoprotein A1 during the intervention period. There were no changes in glycosylated hemoglobin A1c levels.

DISCUSSION

The CENIT (Coronary Disease and the Effect of High-Intensity Interval Training) study is the first study to assess potential effects from exercise training on lipid content in coronary artery atheromatous plaques by NIRS. Main findings were (1) we did not observe any effect of HIIT compared with usual care on maxLCBI$_{4mm}$; lipid content was reduced by similar amounts in both groups, with a slightly stronger evidence of a difference

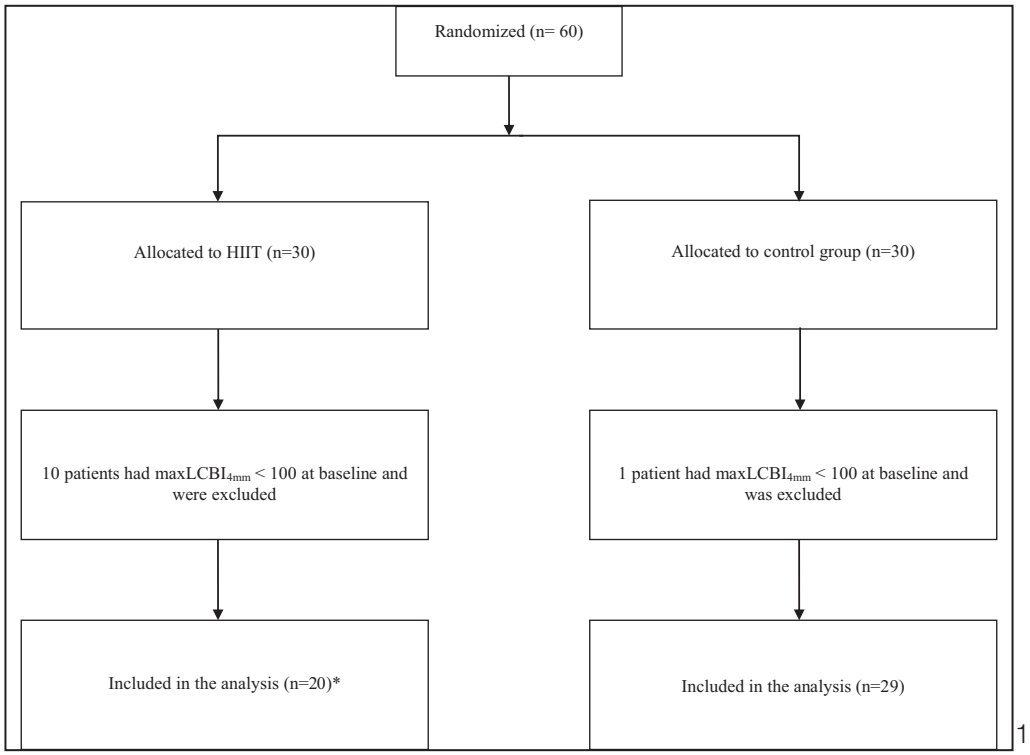

Figure 1. Flow diagram of randomization, allocation and analysis of study data.
Flow chart illustrating enrolment, randomization, allocation, and follow-up throughout the study. *At 6 months follow-up 1 patient had emigrated, 1 patient underwent coronary artery bypass grafting, and in 1 patient the near-infrared spectroscopy chemogram was not interpretable. HIIT indicates high intensity interval training; and maxLCBI$_{4mm}$, maximum lipid core burden index within any 4 mm segment across the entire lesion.

in the control group; (2) we observed a moderate positive correlation between increase in VO_{2peak} and reduction in lipid content; and (3) when analyzing patients with increased VO_{2peak} at follow-up, a larger reduction in maxLCBI$_{4mm}$ was observed in patients with an increase in VO_{2peak} above 1 MET compared with patients with an increased VO_{2peak} below 1 MET.

Although physical exercise is considered a cornerstone in cardiac rehabilitation, only a few randomized trials using intracoronary imaging for assessing the effects of physical exercise on atherosclerosis progression have been conducted, typically with a limited number of patients included.[20–22] This reflects the complexity, resource demands and patient safety aspects of such studies. The rationale for our study has gained increased importance as the recently published PROSPECT 2 trial demonstrated maxLCBI4$_{mm}$ in coronary plaques to be a risk factor for subsequent acute coronary events.[14] In an earlier study from our group,[7] exercise-induced changes on coronary plaque geometry and composition following 3 months of exercise were evaluated by greyscale- and radiofrequency IVUS. In that study, aerobic exercise for 12 weeks following PCI induced a reduction in necrotic core, a marker of plaque vulnerability. Based upon this study, we expected that 6 months of HIIT would reduce lipid content more than usual care in the present study applying a novel technology like NIRS. However, change in maxLCBI$_{4mm}$ did not differ between groups in our study. A challenge in trials comparing exercise protocols with different intensity is that the control group tends to increase their physical activity level, thus masking the effect of the intervention, as observed in a previous exercise trial.[23] In our study 15 out of 29 controls with a maxLCBI$_{4mm}$ >100 at baseline increased their VO_{2peak} more than 1 mL·kg^{-1}·min^{-1} in the study period, an increase that has been considered clinically relevant in previous studies.[24] We found an increase in VO_{2peak} of more than 3.5 mL·kg^{-1}·min^{-1} (1 MET) increased the probability of reduced lipid content in coronary plaques (Figure 3). However, this was a secondary post hoc analysis and as such only hypothesis generating.

Table 1. Baseline Characteristics

	Exercise group HIIT (n=20)	Control group (n=29)
Characteristics		
Age, y	57.6±6.2	58.4±7.4
No. of men/women	19/1	26/3
Body mass index, kg/m^2	29.1±4.4	29.2±3.6
Medical history, n (%)		
Hypertension, medically treated	9 (45)	15 (52)
Hyperlipidemia	6 (30)	15 (52)
Diabetes	1 (5)	5 (17)
Smoking currently	1 (5)	4 (14)
Smoked previously	11 (55)	15 (52)
Heredity for premature cardiovascular disease	18 (90)	22 (76)
Prior history of coronary artery disease	11 (55)	15 (52)
Congestive heart failure	1 (5)	2 (7)
Left ventricular ejection fraction, %	53±3	52±3
Medication at baseline, n (%)		
Dual antiplatelet therapy	20 (100)	29 (100)
Statins	20 (100)	29 (100)
Combined therapy with ezetimib	1 (5)	3 (10.3)
β-blockers	8 (40)	10 (34.5)
Angiotensin-converting enzyme inhibitors/ angiotensin II receptor antagonists	9 (45)	14 (48.3)

Values are presented as mean±SDs for continuous variables and as frequencies (%) for categorical variables. HIIT indicates high intensity interval training.

There are no previous exercise trials to compare these data with. However, it has been documented that lipid content measured by NIRS decreases during intensive pharmacological cholesterol lowering therapy. Changes in plaque lipid content after short-term intensive statin therapy versus standard statin therapy were described in the YELLOW (Reduction in Yellow Plaque by Aggressive Lipid-Lowering Therapy) trial.[15] Comparing with the YELLOW trial, patients in our study increasing their VO_{2peak} with more than 1 MET

Table 2. Outcomes

	Exercise group HIIT (n=20)		Control group (n=29)	
Outcome	Baseline	Follow-up	Baseline	Follow-up
Maximum lipid core burden index within any 4 mm segment	357±136	306±150	336±157	292±186
Exercise testing				
VO_{2peak}, mL·kg^{-1}·min^{-1}	32.3±5.9	36.2±7.0	29.1±6.2	30.6±7.0
$VO_{2peak,}$ mL·min^{-1}	2917±557	3099±656	2635±523	2732±539
Body mass index, kg/m^2	29.1±4.4	28.5±4.7	29.2±3.6	29.0±4.1
Waist, cm	107.0±9.6	100.1±6.7	107.7±11.1	106.9±11.9
Glycosylated hemoglobin A1c, %	5.4±1.5	5.6±0.4	5.8±1.0	5.8±0.8
Lipid profile				
Total cholesterol, mmol/L	3.6±0.9	3.6±0.7	3.8±0.9	3.9±0.9
Low-density lipoprotein cholesterol, mmol/L	2.1±0.8	1.9±0.6	2.2±0.8	2.2±0.6
High-density lipoprotein cholesterol, mmol/L	1.1±0.3	1.2±0.4	1.0±0.2	1.1±0.2
Triglycerides, mmol/L	1.3±0.6	1.1±0.3	1.7±0.8	1.8±1.9
ApoA1, g/L	1.3±0.2	1.4±0.2	1.2±0.2	1.4±0.2
ApoB, g/L	0.7±0.2	0.7±0.2	0.8±0.2	0.8±0.2

Values are mean±SDs. Apo indicates apolipoprotein; and VO_{2peak}, peak oxygen uptake. HIIT indicates high intensity interval training.

Table 3. Results for the Main Outcome ΔmaxLCBI$_{4mm}$ and Secondary Outcomes

	Baseline to follow-up Exercise group HIIT(n=20)	Baseline to follow-up Control group (n=29)	Group difference at follow-up HIIT vs control group
ΔMaxLCBI$_{4mm}$	−47.7 (−100.3 to 5.0) *P*=0.075	−46.5 (−87.5 to −5.4) *P*=0.027	−1.2 (−65.8 to 63.4) *P*=0.970
VO_{2peak}, mL·kg^{-1}·min^{-1}	3.1 (1.5 to 4.7) *P*<0.001	1.0 (−0.2 to 2.2) *P*=0.113	2.2 (0.2 to 4.1) *P*=0.034
Body mass index, kg/m^2	−0.8 (−1.3 to −0.3) *P*=0.004	0.0 (−0.4 to 0.4) *P*=0.887	−0.7 (−1.4 to −0.1) *P*=0.027
Waist, cm	−3.5 (−5.1 to −2.0) *P*<0.001	−0.9 (−2.0 to 0.1) *P*=0.083	−2.6 (−4.4 to −0.7) *P*=0.008
Glycosylated hemoglobin A1c, %	0.1 (−0.3 to 0.5) *P*=0.578	0.1 (−0.2 to 0.5) *P*=0.485	0.0 (−0.5 to 0.5) *P*=0.993
Total cholesterol, mmol/L	−0.1 (−0.4 to 0.3) *P*=0.725	0.1 (−0.2 to 0.3) *P*=0.639	−0.1 (−0.5 to 0.3) *P*=0.555
Low-density lipoprotein cholesterol, mmol/L	−0.1 (−0.4 to 0.2) *P*=0.412	0.0 (−0.2 to 0.20) *P*=0.981	−0.1 (−0.4 to 0.2) *P*=0.516
High-density lipoprotein cholesterol, mmol/L	0.2 (0.1 to 0.2) *P*<0.001	0.1 (0.0 to 0.1) *P*=0.010	0.1 (0.0 to 0.2) *P*=0.040
Triglycerides, mmol/L	−0.3 (−0.8 to 0.2) *P*=0.223	0.2 (−0.2 to 0.6) *P*=0.265	−0.5 (−1.1 to 0.1) *P*=0.081
ApoA1, g/L	0.1 (0.1 to 0.2) *P*<0.001	0.1 (0.0 to 0.1) *P*<0.002	0.0 (0.0 to 0.1) *P*=0.230
ApoB, g/L	0.0 (−0.1 to 0.0) *P*=0.336	0.0 (−0.1 to 0.1) *P*=0.846	0.0 (−0.1 to 0.1) *P*=0.368

Results for the main outcome maxLCBI$_{4mm}$ and secondary outcomes showing treatment effect as time×group interaction with 95% confidence intervals and *P* value for high intensity interval training compared with control. Apo indicates apolipoprotein; HIIT, high intensity interval training; maxLCBI$_{4mm}$, the maximum lipid core burden index within any 4 mm segment across the entire lesion; and VO_{2peak}, peak oxygen uptake.

had similar reduction in maxLCBI$_{4mm}$ as observed in the group receiving intensive statin therapy (40 mg rosuvastatin), and somewhat lower than seen after treatment with proprotein convertase subtilisin/kexin type 9 inhibitors.[16] To reduce the risk of confounding, only patients on stable lipid lowering therapy for more than 6 weeks were included in the CENIT trial. Furthermore, there were no changes in lipid-lowering therapy for any patients during the study period, and none of the patients used other anti-inflammatory therapies that potentially could influence results. It seems that this strategy was successful as during the study period neither low-density lipoprotein cholesterol nor apolipoprotein B changed in either group.

Although it is difficult to isolate the effect of exercise in our study, we argue that our results provide evidence that physical exercise may reduce lipid content in coronary atheromatous plaques and contribute to plaque stabilization. The results in this study support our previous findings with radiofrequency IVUS demonstrating reduced necrotic core in coronary plaques following aerobic exercise with different intensity.[7] However, future studies are needed to confirm our results and to understand why some individuals respond in a way that is highly beneficial in terms of reduced lipid content as a function of a modest increase in VO_{2peak} whereas others do not. Understanding this may lead to a more precise prediction of treatment outcomes, treatment goals and improved individual patient care.

The mechanisms for reduced maxLCBI$_{4mm}$ following improved VO_{2peak} remain unclear. Beneficial effects on established cardiovascular risk factors may be of importance. In our study, high-density lipoprotein cholesterol and apolipoprotein A1 increased significantly in both groups at follow-up and could represent a link between physical exercise and reduced maxLCBI$_{4mm}$. Furthermore, there is strong evidence that coronary plaque progression and characteristics are influenced by local factors in the coronary artery tree.[25] Studies using computational fluid dynamics modeling have linked low wall shear stress to plaque volume progression and high wall shear stress to a more vulnerable plaque phenotype.[26] In our previous study using HIIT as a model of bouts of "systemic" high wall shear stress, we demonstrated that plaque vulnerability could change in either direction when comparing separate lesions in the same coronary artery.[7] This observation supports that local circulatory factors are important for plaque development and that assessing plaque biology following exercise is complex as the potential effect from exercise may influence different coronary segments divergently. In the CENIT trial, which allowed for multivessel NIRS imaging, we compared changes in maxLCBI$_{4mm}$ between different coronary arteries within the same patient and observed a similar phenomenon

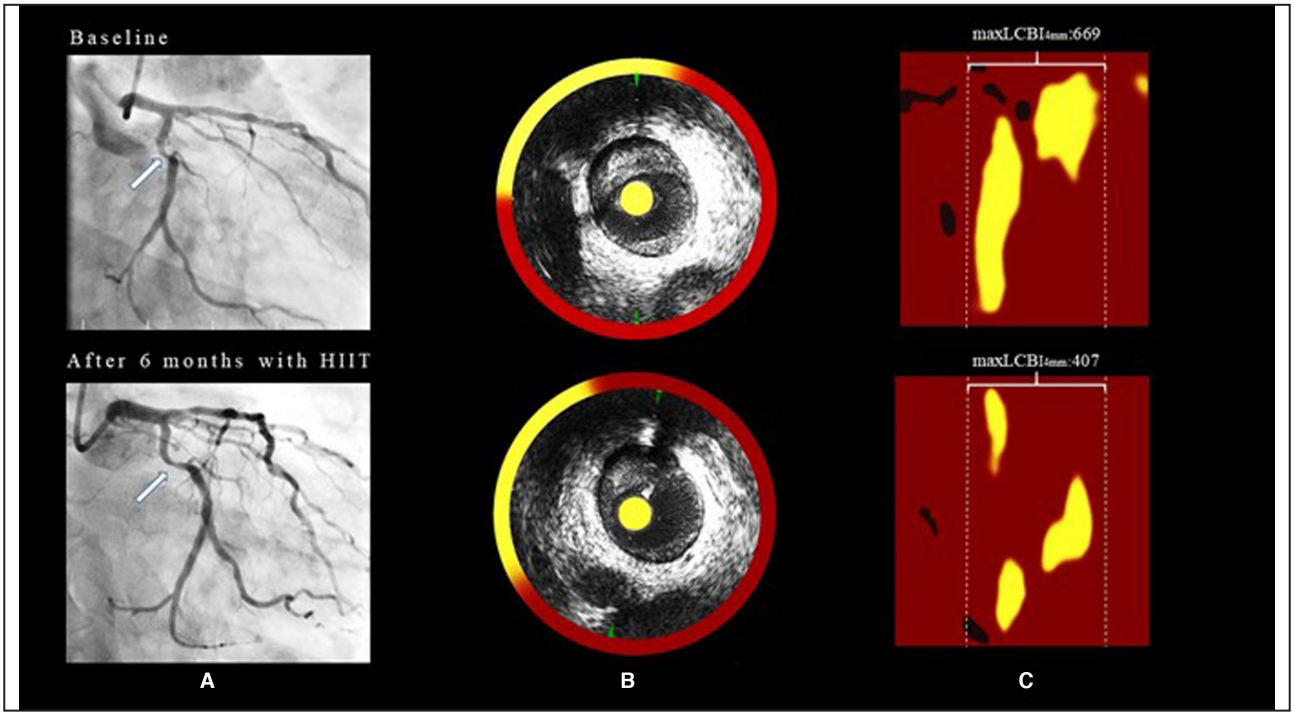

Figure 2. Case demonstrating findings from an imaged vessel with coronary angiography and near-infrared spectroscopy combined with intravascular ultrasound (NIRS-IVUS) in a patient in the high intensity interval training-group at baseline (upper panel) and at follow-up (lower panel).
A, Coronary angiogram with arrow showing a plaque in the proximal segment of the circumflex artery. **B**, Cross-section of NIRS-IVUS image where the yellow circumferential rings represent lipid accumulation within the plaque. **C**, NIRS chemogram demonstrating $maxLCBI_{4mm}$ at baseline and at follow-up with a reduction in $maxLCBI_{4mm}$ from 669 to 407 during the intervention period. Yellow represents high probability of lipid and red denotes no lipid. HIIT indicates high intensity interval training; and $maxLCBI_{4mm}$, maximum lipid core burden index within any 4 mm segment across the entire lesion.

as one third of the patients had plaques where $maxLCBI_{4mm}$ changed in both directions. However, in the majority of plaques with increased $maxLCBI_{4mm}$ during the study period, the baseline $maxLCBI_{4mm}$ was low and the increase modest. Nevertheless, this observation indicates that even for lipid content in coronary atheromatous plaques local circulatory factors may be of significance. Interestingly, studies using coronary computed tomography angiography have demonstrated a higher prevalence of coronary artery calcification and fewer mixed plaques in athletes compared with less active controls.[5,6] Thus, it is suggested that high-volume aerobic endurance exercise may induce a more stable, less inflamed and therefore more benign plaque phenotype compared with sedentary counterparts.[5]

Study Limitations

Several limitations should be taken into consideration when interpreting the CENIT trial. The sample size was small. However, the study protocol with invasive procedures means obvious limitations and the number of included patients is higher than in most other exercise studies with a similar design. The number of lipid-rich plaques was lower than expected in baseline acquisitions and the power problem was reinforced as 11 participants had a $maxLCBI_{4mm}$ <100 at baseline and thus were excluded from further analyses. Furthermore, this phenomenon appeared imbalanced between the 2 groups.

Like other exercise trials with equivalent design, we experienced a challenge with respect to the level of exercise and activity in the control group, as these patients were given advice to follow recommendation in guidelines including principles for cardiac rehabilitation following PCI. Thus, the intended difference in exercise level between patients randomized to HIIT and the control group may have been diminished. The plaque with the highest $maxLCBI_{4mm}$ at baseline was located in stented artery in 16 of 49 patients, but only 6 plaques located distally to an implanted stent were included in the analyses. Thus, it is unlikely that altered flow dynamics following stent implantation has influenced our results significantly. The positive correlation demonstrated between increase in VO_{2peak} and reduction in lipid contents and the larger reduction in $maxLCBI_{4mm}$ observed in patients with an increase in VO_{2peak} above 1 MET were results of a secondary post hoc

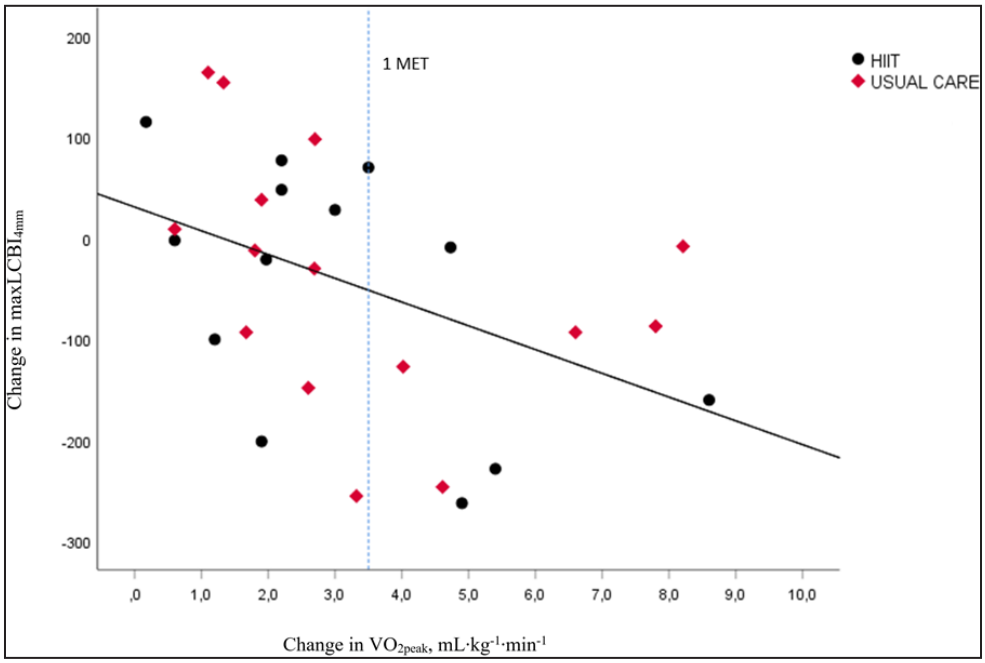

Figure 3. Scatterplot between ΔVO_{2peak} and Δ during the intervention period in patients with increased VO_{2peak} (Spearman's correlation −0.44, *P*=0.009).
HIIT indicates high intensity interval training; $maxLCBI_{4mm}$, the maximum lipid core burden index within any 4 mm segment across the entire lesion; and VO_{2peak}, peak oxygen uptake.

analysis and accordingly only hypothesis generating. A strength of our study is that patients were on stable lipid lowering drugs for at least 6 weeks before inclusion with no change in this medication throughout the study. Furthermore, NIRS data were analyzed at an independent core laboratory and validated exercise protocols in line with contemporary guidelines were used.

CONCLUSIONS

In the CENIT trial, we did not demonstrate a significant difference in $maxLCBI_{4mm}$ between 6 months of supervised HIIT versus usual care following PCI for stable CAD. Lipid content was numerically reduced in both groups with a slightly stronger evidence of a difference in the control group. A significant, moderate positive correlation was demonstrated between increase in VO_{2peak} and reduction in lipid content suggesting that exercise with a subsequent increase in fitness may reduce lipid content in coronary atheromatous plaques.

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Disclosures

None.

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