REVIEW

Exercise and Carotid Atherosclerosis

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Objectives. Both carotid atherosclerosis or increased carotid intima-media thickness (IMT) are common manifestations of generalized atherosclerosis, closely associated with increased risk of stroke and myocardial infarction. Despite the predominant involvement of physical activity in cardiovascular prevention and rehabilitation strategies, its role in carotid atherosclerosis progression is less evaluated. The aim of our study was to review the literature for the contribution of increased physical activity or structured exercise to the prevention and treatment of carotid atherosclerosis.

Materials/Methods. A systematic review was performed of all cross-sectional, interventional, prospective or retrospective, clinical studies. Using the following terms: carotid atherosclerosis, intima-media thickness, physical activity, exercise, lifestyle, stroke, cardiovascular risk factors, we searched MEDLINE and EMBASE databases from 1985 to 2007. Carotids ultrasonography and relevant quantitative indexes were prerequisites for our search.

Results. The majority of cross-sectional studies have demonstrated that physical inactivity is associated with increased carotid IMT, while structured lifestyle interventions have conferred inconsistent results on the progression of carotid thickening. The increment of cardiorespiratory fitness and the modification of numerous cardiovascular risk factors, such as hyperglycemia, insulin resistance, hyperlipidemia, hypertension and obesity provide plausible mechanisms by which exercise training may suppress the evolution of carotid atherosclerosis.

Conclusions. It remains questionable whether long-term exercise can decelerate the development of carotid atherosclerosis. Perhaps increased physical activity suppresses the overall cardiovascular risk and hence curtails the progression of carotid atherosclerosis. If carotid artery disease is regarded as a coronary artery disease equivalent, it is reasonable to recommend similar patterns of physical activity in patients with subclinical or manifest carotid atherosclerosis as for those with coronary atherosclerosis.

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Keywords: Carotid atherosclerosis; Intima-media thickness; Physical activity; Exercise; Life-style; Stroke; Cardiovascular risk factors.

Introduction

Carotid atherosclerosis is an easily detected, manifestation of cerebrovascular atherosclerosis and remains one of the leading causes of cerebral ischemic events.1 Carotid artery disease also indicates patients at increased risk for fatal and nonfatal myocardial infarction. In the Cardiovascular Health Study, the 6-year risk for myocardial infarction or stroke was increased 3.6-fold to ~40/1000 person-years in patients in the highest quintile of carotid intima-media thickness (IMT).1 The published prevalence of carotid narrowing in asymptomatic population ranges between 5.9% and 6.5% depending on the definition of significant carotid artery stenosis.2,3

To mitigate carotid artery disease progression and prevent cerebrovascular events, lifestyle modification and pharmaceutical therapy should be implemented. Accumulating evidence has demonstrated that structured exercise programs or even moderate levels of physical activity suppress cardiovascular morbidity and mortality in the whole population.4 Physical activity has been related inversely to the extent of atherosclerosis and the primary and secondary incidence of cardiovascular events.5,6 Physical activity is hypothesized to afford “pleiotropic” actions on cardiovascular system, which are merely explained by the modification of numerous cardiovascular risk factors.7
Despite the amount of data concerning the influence of exercise interventions, little consideration has been given to the effects of exercise alone on the development and evolution of carotid atherosclerosis. The scope of the present paper is to review the literature about the contribution of increased physical activity or structured exercise to the prevention and treatment of carotid atherosclerosis.

**Materials and Methods**

A search was conducted for English language publications on MEDLINE and EMBASE databases from 1985 to 2007. A similar search was done in Web of Science, Sports Discus and Cochrane Library, but no other papers were found. The following search terms, including Medical Subject Headings (MeSH) were used: carotid atherosclerosis, intima-media thickness, physical activity, exercise, life-style, stroke and cardiovascular risk factors. Two investigators (NK and FI) independently performed the literature research. From the potentially eligible studies, only cross-sectional, interventional, prospective or retrospective studies reporting quantitative indexes of carotids ultrasound were included. Studies without such imaging data were not enrolled. The reference list of the identified articles was checked and all additional relevant articles were included. Other relevant papers by the referred authors were retrieved and read. Finally, 20 possible articles were identified for inclusion in the review. The selected literature is reviewed below.

**Exercise and prevention of carotid atherosclerosis**

**Cross-sectional studies.** Up to date few studies have examined the effects of regular physical activity on carotid IMT and most of them have been cross-sectional in design (Table 1). The Los Angeles Atherosclerosis Study demonstrated a protective association between leisure-time physical activity and the progression of carotid IMT in 500 cardiovascular disease-free, middle-aged subjects. Although the optimum effects were observed in the vigorous exercise group, the authors showed that there was a graded inverse relationship between self-reported physical activity and IMT progression, independent of other cardiovascular confounders (from 14.3 ± 1.7 microns/year in sedentary subjects, to 10.2 ± 1.0 microns/year in moderately active subjects, to 5.5 ± 1.5 microns/year in vigorously active subjects; p < 0.0001). Another large (N = 1632) population-based survey confirmed the independent association between lifestyle (leisure time physical activity plus optimal/or normal diet pattern) and common carotid IMT in non-smokers only. The Atherosclerosis Risk in Communities (ARIC) Study showed that only workplace activity was inversely associated with sub-clinical atherosclerosis, with leisure-time and sports activities having no effect on carotid IMT. Another community-based study of 3128 middle-aged individuals, the Tromso study, showed an independent relationship between regular activity and carotid IMT only among men. Authors attributed the findings to different activity levels between genders, which might have not been quantified with sufficient precision. Other investigators, studying small cohorts of healthy subjects, have argued that leisure-time physical activity or sporting activities do not attenuate the age-related carotid thickening.

We only identified one cross-sectional study evaluating the relationship between established carotid atherosclerosis and physical activity. The British Regional Heart Study did not demonstrate any relationship between carotid IMT or carotid plaque presence and sporting activities in 800 men and women from two British towns. However these results should be interpreted with caution regarding the high prevalence of carotid plaques, the observational design and the usage of self-administered lifestyle questionnaire.

**Interventional studies.** Based on a limited number of interventional studies, researchers have shown either positive or no effect of lifestyle modification on age-associated carotid IMT progression. Okada et al. demonstrated in a controlled, prospective study of 1390 individuals that lifestyle changes, involving dietary recommendations, smoking cessation, weight control and encouragement to exercise, regressed significantly (−6.8%) carotid IMT over a 2-year period in hypercholesterolemic men. Furthermore the combination of exercise and dietary intervention reduced slightly common carotid IMT in a small diabetic sample with inadequate glycemic control, while IMT increased in the control group (−0.040 ± 0.136 mm vs 0.083 ± 0.167 mm; p = 0.007). Other investigators examined the effects of a 4-year intervention program (diet plus physical activity) in 353 middle-aged women. They observed that the annual progression of average carotid IMT slowed down only in perimenopausal/postmenopausal women (intervention group: 0.004 mm/year vs control group: 0.008 mm/year; p = 0.02). Premenopausal women showed slower carotid thickening, which was almost unaffected by lifestyle intervention. In the DNASCOS study the prescription of low-to-moderate intensity activities did not curtail the progression of carotid IMT among Finnish men (p > 0.2). However subgroup analysis revealed that exercise-treated men, not
Table 1. Summarized list of studies concerning the effects of exercise/physical activity on carotid intima-media thickness

<table>
<thead>
<tr>
<th>Source</th>
<th>Number of subjects (age)/Study design</th>
<th>Exercise prescription</th>
<th>Results on carotid ultrasound indexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nordstrom et al.(^8)</td>
<td>500 (40–60 yr)/Observational.</td>
<td>1.5–3 yr follow-up. Self-reported leisure time physical activity index.</td>
<td>↓Carotid IMT progression from 14.3 ± 1.7 microns/year in sedentary subjects, to 10.2 ± 1.0 microns/year in moderately active subjects, to 5.5 ± 1.5 microns/year in vigorously active subjects (p &lt; 0.001).</td>
</tr>
<tr>
<td>Luedemann et al.(^9)</td>
<td>1632 (45–70 yr)/Cross-sectional survey in German population.</td>
<td>Lifestyle (physical activity + dietary pattern): a) optimal, b) moderate, c) unfavorable.</td>
<td>↓Carotid IMT and carotid plaque prevalence only in never smokers with optimal lifestyle pattern vs those with unfavorable pattern.</td>
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<td>Folsom et al.(^10)</td>
<td>14430 (45–64 yr)/Cross-sectional.</td>
<td>Questionnaire for workplace, leisure-time and sports activities.</td>
<td>Inverse association of workplace activity with carotid thickness.</td>
</tr>
<tr>
<td>Schmidt-Trucksass et al.(^12)</td>
<td>51 male (16–78 yr male subjects)/Cross-sectional.</td>
<td>Questionnaire for physical activity (recreational activities).</td>
<td>No effect of leisure-time physical activity on carotid IMT. ↓Arterial stiffness.</td>
</tr>
<tr>
<td>Tanaka et al.(^13)</td>
<td>137 healthy subjects (18–77 yr)/Cross-sectional.</td>
<td>Questionnaire: sedentary (not regular physical activity), endurance trained (vigorous endurance exercise ≥ 5 times/week and active in local road running races).</td>
<td>No difference of carotid IMT between sedentary and endurance-trained subjects.</td>
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<td>Tanaka et al.(^13)</td>
<td>18 healthy sedentary subjects (54 ± 2 yr)/Interventional.</td>
<td>3-month aerobic exercise training (40–45 min/day, 4–6 days/week, at 70–75% of maximal heart rate). Supervised orientation and thereafter self-controlled exercise.</td>
<td>No change of carotid IMT after intervention (from 6.9 ± 0.2 mm to 7.0 ± 0.2 mm).</td>
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<tr>
<td>Ebrahim et al.(^14)</td>
<td>425 men and 375 women (56–77 yr)/Cross-sectional.</td>
<td>Self-administered questionnaire. Sporting activity was classified as none, occasional, or frequent</td>
<td>No difference of carotid IMT and prevalence of carotid plaques between groups.</td>
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<tr>
<td>Markus et al.(^15)</td>
<td>94 subjects randomly assigned to the placebo group of MARS study/Interventional.</td>
<td>Lifestyle modification (targets: diet, alcohol, smoking, and weight).</td>
<td>Modifications reducing body mass index (5 kg/m²), quitting smoking habit (10 cigarette/day), and reducing dietary cholesterol intake (~100 mg/day) on average reduced annual rate of carotid artery IMT progression.</td>
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<tr>
<td>Okada et al.(^16)</td>
<td>1390 male and female residents of a suburban Japanese town/Prospective, interventional.</td>
<td>2-yr follow-up: a) lifestyle modification alone group (TC ≥ 220 mg/dl, n = 437), b) lifestyle modification with lipid-lowering drug group (TC ≥220 mg/dl, n = 159), c) control group (TC &lt; 220 mg/dl, n = 794).</td>
<td>↓Carotid IMT in both lifestyle groups. Higher reduction in the group of combined treatment with lifestyle and lipid-lowering drug.</td>
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<td>Kim et al.(^17)</td>
<td>58 subjects with type 2 diabetes mellitus (mean age 54.4 yr)/Interventional.</td>
<td>6-month study. 16-lesson (1/week) curriculum covering diet, exercise, and behaviour modification. The aim was individualized to 3–12 hours of brisk walking, hiking, or swimming per week (40%–60% of maximum exercise capacity).</td>
<td>Mean CCA IMT showed no significant change in the interventional group, but increased in the control group. The difference of changes of mean CCA IMT was significant between groups (–0.040 ± 0.136 mm vs +0.083 ± 0.167 mm; p = 0.007).</td>
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<td>Source</td>
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<td>Wildman et al.²⁸</td>
<td>355 women (44–50 yr)/Interventional.</td>
<td>Average follow-up 3.9 yr. Goals of lifestyle intervention: reduction of dietary fat (to 25% of total fat, 7% of saturated fat, and 100 mg of cholesterol); reduction in caloric intake (to 1300 kcal/day); increase of leisure-time physical activity (to 1000–1500 kcal/week of energy expenditure).</td>
<td>Lower annual progression of average carotid IMT in the interventional group than control group of peri-/post-menopausal women sub-population (0.004 mm/year vs 0.008 mm/year; p = 0.02).</td>
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<td>Rauramaa et al.¹⁹</td>
<td>140 middle-aged Finnish men/Randomized, controlled trial.</td>
<td>6-yr study. Low-to-moderate intensity aerobic exercise.</td>
<td>↓40% less progression of carotid IMT only in the exercise subgroup of men not receiving statins compared to control group: (0.12 mm [CI, −0.01–0.26 mm]) vs (0.20 mm [CI, 0.05–0.35 mm]) over 6-year period (p = 0.02).</td>
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<tr>
<td>Meyer et al.²⁰</td>
<td>67 obese and 35 lean children (11–16 yr)/Randomized, interventional.</td>
<td>6-month study. Randomization into exercise group: supervised sports activities (1 hour/session, progressively intensified 3 times/week) or control group.</td>
<td>↓Progression of maximum CCA and carotid bifurcation IMT in the exercise group. The relative differences between exercise and control group were for maximum IMT of A) CCA: −8.4 ± 15.8% vs +0.5 ± 12.8%; p = 0.01 and B) carotid bulb: −10.9 ± 17.1% vs +1.5 ± 20.9%; p = 0.015.</td>
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<tr>
<td>Anderssen et al.²¹</td>
<td>568 drug-treated hypertensive men (40–74 yr)/Randomized, interventional.</td>
<td>4-yr study. Patients randomized to receive either fluvastatin (40 mg/day) or placebo, and either intensive lifestyle intervention (physical activity initially supervised and diet) or usual care.</td>
<td>Fluvastatin reduced the progression of CCA and carotid bulb IMT. No effect of lifestyle on CCA and carotid bulb IMT.</td>
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<tr>
<td>Hagg et al.²²</td>
<td>29 healthy volunteers (16 men, 13 women, 20–40 yr)/Cross-sectional.</td>
<td>Total self-reported physical activity was calculated as the sum of time spent weekly on high-intensity aerobic training and daily activity. Cardiorespiratory fitness assessment.</td>
<td>Inverse correlation between VO2max and CCA IMT.</td>
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<tr>
<td>Lakka et al.²⁸</td>
<td>854 subjects (42–60 yr)/Population-based observational.</td>
<td>4-yr follow-up study. KIHD 12-Month Leisure-Time Physical Activity History.</td>
<td>Inverse association between initial VO2max and progression of maximal carotid IMT, mean IMT, plaque height, surface roughness.</td>
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<tr>
<td>Ruaramaa et al.²⁹</td>
<td>163 Finnish men (50–60 yr)/Cross-sectional.</td>
<td>Cardiorespiratory fitness assessment.</td>
<td>Inverse correlation between VO2max and IMT of carotid bifurcation.</td>
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<td>Ferreira et al.³⁰</td>
<td>154 subjects (75 men and 79 women, 36 yr old)/Observational</td>
<td>Changes in cardiorespiratory capacity from adolescence to 36 yr old age.</td>
<td>Longitudinal changes in VO2max were not significantly associated with carotid IMT.</td>
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<tr>
<td>Chan et al.³⁵</td>
<td>156 patients with CAD (55.9 ± 6.2 yr)/Interventional.</td>
<td>2-yr study. Minnesota Physical Activity Questionnaire (leisure time energy expenditure). Multifactorial modification (e.g., leisure time physical exercise: &gt;2000 kcal/week).</td>
<td>No effect of physical activity on carotid IMT ↑Plaque area.</td>
</tr>
<tr>
<td>Watarai et al.³⁷</td>
<td>53 type 2 diabetic patients (mean age: 53 ± 10 yr)/Cross-sectional.</td>
<td>Questionnaire of habitual exercise (low, moderate, and high active group).</td>
<td>Inverse relationship of carotid IMT along the degrees of activity. Relationship with peripheral insulin resistance.</td>
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yr, years; IMT, intima-media thickness; CCA, common carotid artery; CAD, coronary artery disease; VO2max, maximal oxygen uptake.
receiving statins, experienced a 40% slower progression of IMT (0.12 mm [CI, −0.01−0.26 mm]) than the control group (0.20 mm [CI, 0.05−0.35 mm]) over a 6-year period (p = 0.02).

On the other hand, HYRIM trial reported that 4-year fluvastatin treatment decelerated common and bulb carotid thickening in drug-treated hypertensive and sedentary individuals. The addition of an individualized physical activity program did not affect carotid IMT progression in the same study population over the same time-period. Similarly Tanaka et al. failed to demonstrate positive changes of carotid IMT after 3 months of endurance training in 18 sedentary healthy men (from 6.9 ± 0.2 mm before to 7.0 ± 0.2 mm after).13

It is possible that the early implementation of an exercise program can prevent atherosclerosis development in young, high-risk subjects. In obese children, who are predisposed to cardiovascular complications, the performance of supervised exercise training ameliorated cardiovascular risk profile, improved endothelial function and carotid IMT.21

The relative differences between exercise-treated and control obese children were for maximum IMT of common carotid artery: −8.4 ± 15.8% vs +0.5 ± 12.8%; p = 0.01 and for carotid bifurcation: −10.9 ± 17.1% vs +1.5 ± 20.9%; p = 0.015. Thus as earlier the intervention begins, the more effective will be.

Explanation of discordant results

One possible explanation for the differing results derives from the wide variability of studies’ populations. The influence of physical activity on carotid IMT is inconsistent among healthy subjects.10,14,22 Lifelong exercise could have beneficial effects on IMT progression in certain subpopulations, including older and atherosclerotic-prone subjects, postmenopausal women or in those with manifest atherosclerotic lesions.19 The Framingham Heart Study supports the notion that physical activity elicits higher stroke-protective effects in older than younger subgroups.23 From another point of view most researches have been cross-sectional in design, which might be subject to a publication bias of reporting positive results only. Interventional and randomised studies usually provide better evidence and their results carry greater weight than those from observational studies. However, only limited numbers of interventional studies have examined the influence of lifestyle changes on carotid IMT. Interestingly, interventional studies included a wide variety of lifestyle changes where exercise was just one of several components. To our knowledge only 3 studies reported the net effects of structured exercise on carotid atherosclerosis, none of which have reported a beneficial effect of exercise on carotid atherosclerosis.13,19,21

The combined data from these studies may be too few to draw firm conclusions. Moreover, the studies have some drawbacks, such as the imprecise assessment of physical activity by self-directed questionnaires, the almost arbitrary criteria of physical activity stratification, the relatively small sample sizes and the quantitative measurement of IMT in different segments of carotid arteries (common, internal, bifurcation). Differences in sensitivity and specificity of the ultrasound methods could contribute to inconsistent findings. In most, but not all studies, two blinded sonographers participated, although intra-observer variability was not reported always. Since all ultrasound machines were not equivalent (linear array probes 5 MHz–10 MHz), we must regard the comparative evaluation of IMT changes between studies with caution.

Another possible explanation is that structural changes of arterial wall in physically active subjects were not evident in the relatively short term follow-up of the published studies. Galeta et al. observed that elderly athletes showed higher carotid wall compliance in comparison to age-matched sedentary healthy controls.24 However 3 months of endurance training was inadequate to reduce the age-related increment of IMT.13 Thus future studies should designate the length of time required to produce sustained changes in vasculature. Finally we cannot rule-out the possibility that regular exercise may favorably change the composition of artery wall (e.g. matrix metalloproteinases activity) which cannot be observed ultrasonographically. Previous studies have demonstrated femoral IMT as a valid surrogate marker of coronary and peripheral artery disease.25 Growing evidence suggests more pronounced effects of exercise on muscular (e.g. femoral) than elastic arteries (e.g. carotid).26 Perhaps femoral IMT monitoring could more precisely and straightforwardly reflect the effects of exercise on vascular structure and function.

Cardiorespiratory fitness and carotid atherosclerosis

Cardiorespiratory capacity is a highly objective index of cardiovascular function and an independent predictor of cardiovascular and overall mortality.27 Previous studies have demonstrated that exercise capacity is strongly influenced by age, gender, physical activity
level and genetic background. In previous cross-sectional studies low exercise capacity correlated independently with increased carotid IMT in both genders, which is of clinical importance. However single time-point data do not reflect habitual physical activity. Cardiorespiratory capacity level also may be attributed to genetic background, subclinical disease or continuous structural and functional changes of the myocardium and vasculature. It would be more valuable to examine prospectively the relationship between carotid IMT progression and maximum oxygen consumption changes. Ferreira et al. found that age-related alterations of cardiorespiratory fitness were not associated with carotid IMT in 154 healthy, 36-year old men and women. In contrast a population study of middle-aged men demonstrated that VO2max was the strongest independent predictor of maximal and mean carotid IMT, plaque height and surface roughness over a 4-year period. Although the reasons for this discrepancy are not evident, the different characteristics of recruited subjects and the wide inter-individual variability of VO2max response to physical training may provide an explanation.

Mechanisms

It is well-known that structured exercise improves glucose regulation, lipid profile, blood rheology and endothelial function. It also promotes weight loss, fat reduction and redistribution, and attenuates insulin resistance, hypertension and inflammatory milieu (Table 2). These effects may slow the progression of carotid atherosclerosis.

Weight loss - body composition. Diet and physical exercise have a dominant role in the mediation of healthier body weight. Recent reports have outlined the primacy of weight loss in the prevention and treatment of cardiovascular diseases. Body weight and body fat seem to be associated with carotid IMT and carotid plaque presence. Insulin resistance and adipose-derived substances (e.g. adipocytokines) link excessive body weight and atherosclerosis. Unfortunately the majority of overweight/obese patients do not achieve therapeutic goals of weight loss, despite weight-lowering medications (orlistat, sibutramine). Indisputably, physical activity affects favorably fat storage (lipogenesis and fat distribution), nutrient metabolism (free fatty acids) and adipocytokines involved in metabolic processes and inflammation. Thus the combination of exercise and dietary recommendations has the potential to suppress the progression of carotid subclinical atherosclerosis.

Glucose regulation. Compared to healthy individuals, patients with type 2 diabetes have a 2-fold greater rate of carotid IMT progression. Among diabetic populations better glycemic control has been found to be associated with slower progression of carotid IMT. Recently, a lifestyle intervention attenuated the progression of IMT in the diabetic cohort through the regulation of glucose levels underscoring a possible beneficial mechanism on carotid atherosclerosis.

Insulin resistance. Reduced insulin sensitivity has been documented as an independent determinant of carotid IMT. It is well known that exercise training augments insulin sensitivity via modulation of insulin signaling pathway and fatty acid availability. Taking all together the exercise-induced improvement of insulin sensitivity could offer a valuable atheroprotective mechanism in patients at high risk of carotid atherosclerosis. Up to date there is only one study suggesting that exercise attenuates carotid atherosclerosis through insulin sensitivity improvement in the setting of type 2 diabetes mellitus. Future studies will shed light on the interplay between insulin resistance, exercise and carotid atherosclerosis evolution.

Lipid profile. National Cholesterol Education Program Adult Treatment Panel III defined carotid artery disease as coronary artery disease (CAD) equivalent, associated with high risk of cardiovascular events. In parallel, low HDL and high LDL levels have been identified as strong predictors of carotid IMT in healthy population, outlining the clinical importance of their modification. Up to now, randomized and non-randomized studies using long-term exercise training have conferred inconsistent results on lipid profile. Baseline levels of lipid parameters and characteristics of exercise interventions may explain the controversial response of lipids to exercise. Nevertheless the majority of those studies showed a prominent increase of HDL indicating a strong atheroprotective effect. In a recent study, lifestyle therapy regressed carotid thickening significantly in a large cohort of healthy individuals despite the elevated

<table>
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<tr>
<th>Established mechanisms</th>
<th>Potential mechanisms</th>
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<td>1. Glucose regulation</td>
<td>Lipid lowering</td>
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<tr>
<td>2. Weight loss</td>
<td>Anti-thrombotic/fibrinolytic effects</td>
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<td>3. Fat redistribution/loss</td>
<td>Suppression of elevated blood pressure levels</td>
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<td>4. Amelioration of endothelial dysfunction</td>
<td>Modification of novel cardiovascular risk factors (e.g. inflammatory cytokines)</td>
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<tr>
<td>5. Improvement of insulin sensitivity</td>
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<td>6. Increment of cardiorespiratory fitness</td>
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levels of total cholesterol (>220 mg/dl) at the endpoint. The contribution of exercise-induced modification of lipid profile to carotid artery disease needs further investigation.

**Blood rheology.** Disturbed balance between procoagulant and fibrinolytic activity in blood is clearly associated with atherosclerosis development. Lee et al. found significant associations between carotid IMT and blood viscosity, plasma fibrinogen and hematocrit in men. Factor V Leiden mutation, platelet count, fibrinogen, and anti-thrombin were found as independent haemostatic predictors associated with advanced carotid atherosclerosis. There is no study reporting the effects of exercise on hemorheologic parameters in patients with early or established carotid atherosclerosis. However evidence from patients with cardiovascular diseases points toward suppressed coagulation and enhanced fibrinolysis after chronic exercise intervention. Prospective studies will clarify the underlying mechanism and the clinical outcomes.

**Endothelial function.** Vascular endothelium plays a vital role in vascular homeostasis by synthesizing and releasing numerous biologically active factors involved in the regulation of vascular tone, platelet aggregation, cells adhesion, thrombosis and smooth muscle cells function. Endothelial dysfunction occurs early in the atherosclerotic process. Rundek et al. demonstrated that impairment of endothelial function is associated with carotid plaque presence in a multi-ethnic community based population. It is well-documented that exercise ameliorates endothelial derangement in patients with CAD and chronic heart failure. Moreover a 6-month exercise program improved endothelial function in parallel with carotid IMT in obese children. It is argued that exercise modifies endothelial-related nitric oxide (NO) production and degradation. This endothelial response may be not localized to the exercised limb. The repetitive elevation of shear stress during exercise increases NO bioavailability and thereby attenuates endothelial dysfunction in the whole vascular system.

**Hypertension.** Hypertension is one of the strongest predictors of carotid atherosclerosis. It is well-known that an aerobic conditioning program decreases elevated blood pressure and thereby constitutes an essential component of preventive strategies in patients at high risk of cardiovascular events. The underlying mechanism is the subject of controversy. The influence of exercise on vascular wall properties, arterial distensibility and cardiovascular risk factors have been proposed as candidate mechanisms, but they do not exclusively explain how physical activity alleviates hypertension and atherosclerosis.

**Novel cardiovascular risk factors.** Numerous biochemical factors have emerged as independent determinants of carotid atherosclerosis. The impact of inflammation has been recognized at several points in the carotid atherosclerotic process. Regular exercise exerts anti-inflammatory effects, which are of clinical relevance in terms of cardiovascular morbidity and mortality. Prospective studies are still needed to evaluate whether the anti-inflammatory protection of exercise mediates carotid atherosclerosis mitigation. Based on experimental data, it is postulated that exercise not only regresses atherosclerotic plaque, but it can augment plaque stability, but these promising findings require clinical confirmation.

Concerning the underlying mechanisms it is obvious that exercise modulates the whole cardiovascular environment and alters vascular homeostasis and atherosclerosis development via systemic metabolic and hemodynamic effects. Perhaps increased physical activity may suppress the overall cardiovascular risk and thereby may curtail the progression of carotid atherosclerosis. Patients with carotid atherosclerosis require multifactorial interventions leaving it difficult to control other risk factors in order to investigate the net effects of exercise training on carotid atherosclerosis progression.

**Recommendations**

Until now there have been no exercise guidelines for patients with subclinical or manifest carotid atherosclerosis. If carotid artery disease is regarded as a CAD equivalent, conservative treatment should incorporate specific recommendations for physical activity. According to the American Heart Association most patients with other manifestations of cardiovascular diseases should be assisted to perform at least 150 minutes of moderate-intensity (40–60% of maximal capacity) exercise per week, with no more than two consecutive days without physical activity. Patients should be encouraged to adopt brisk walking and energetic daily activities like household work; leisure time sports activities; in their daily program. Vigorous activity which increases cardiorespiratory fitness may provide additional benefits. However in this case the amount, the duration, the intensity and the type of intensive exercise should be determined. Since patients with carotid atherosclerosis often have concomitant clinical or occult CAD, hypertension, diabetes or dyslipidemia, adverse cardiovascular and metabolic responses during exercise training are possible. It is prudent to perform routine cardiac and metabolic examination (e.g. treadmill exercise testing with 12-lead electrocardiographic monitoring, glucose
and renal function measurements) before an exercise program is initiated. Resistance exercise, when appropriately prescribed, is generally recommended by the American Heart Association for most patients with other manifestations of cardiovascular disease. It is important to underline that a scientific statement about exercise recommendations for patients with carotid atherosclerosis is vital.

Conclusions

An expanding body of evidence has implicated several aspects of physical activity in the progression of carotid atherosclerosis. Despite the disparity of data, physical activity can effectively control cardiovascular risk parameters which are strongly associated with carotid IMT, vascular function and structure. Perhaps the vascular-protective effects may not be always visible in carotid ultrasound examination. Moreover lifestyle encouragement must be always combined with optimal medical or interventional treatment. For carotid atherosclerosis the characteristics of exercise intervention (type, intensity, frequency) require definition. Prospective, interventional studies are required to establish whether there is a physical activity-related influence on carotid IMT and long-term risk for cerebrovascular events.

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