Effects of high-cholesterol diet and parallel exercise training on the vascular function of rabbit aortas: a time course study

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Yang, Ai-Lun, Chauying J. Jen, and Hsiun-ing Chen. Effects of high-cholesterol diet and parallel exercise training on the vascular function of rabbit aortas: a time course study. J Appl Physiol 95: 1194–1200, 2003.—It is plausible to assume that exercise training, when applied early enough, can completely correct atherosclerotic defects. Using rabbit aortic specimens, we examined the effects of chronic exercise and high-cholesterol diet feeding on vascular function for different time periods. Male New Zealand White rabbits were divided into four groups: the normal diet groups with or without exercise training and the high-cholesterol diet groups with or without exercise training. Animals in high-cholesterol diet groups were fed 2% cholesterol rabbit chow for 2, 4, or 6 wk. Those in exercise training groups ran on a treadmill at 0.88 km/h for up to 40 min/day, 5 days/wk for the same period of time as the diet feeding. Thoracic aortas were isolated for functional and immunohistochemical analyses. We found that 1) although high-cholesterol diet feeding (≥2 wk) elevated serum cholesterol levels and impaired acetylcholine-evoked vasorelaxation, only the latter effect was reversed by exercise training; 2) the effects of diet and exercise on acetylcholine-evoked vasorelaxation were mainly due to altered release of nitric oxide and endothelium-derived hyperpolarizing factor; and 3) diet feeding for 4 or 6 wk caused significant lipid deposition and expression of P-selectin, VCAM-1, monocyte chemoattractant protein-1, and inducible nitric oxide synthase, which were largely reduced by exercise training. In conclusion, parallel exercise training almost completely reverses the early-stage endothelial dysfunction caused by high-cholesterol diet feeding.

atherogenesis is associated with vascular dysfunction, which is possibly caused by hypercholesterolemia, hypertension, smoking, diabetes mellitus, and genetic alterations. Moreover, endothelial dysfunction has been proposed to be the initial event during the progression of atherosclerosis (19, 25). Normally, the vascular endothelium releases various vasorelaxing factors, notably nitric oxide (NO) (24), which not only relaxes the vascular smooth muscle but also inhibits low-density lipoprotein (LDL) oxidation, platelet/monocyte adhesion, and smooth muscle proliferation/migration. Therefore, NO is widely accepted as an endogenous antiatherosclerotic factor (3). Previous studies have demonstrated that endothelial NO synthase expression and NO release are markedly reduced, whereas the expression of inducible NO synthase (iNOS) is increased in the vessels of high-cholesterol-fed animals or in human atherosclerotic lesions (2, 4, 22). In addition, the expression of vascular adhesion molecules, such as P-selectin and vascular cell adhesion molecule 1 (VCAM-1), is elevated in the early stage of atherogenesis (9, 15). Finally, monocyte chemoattractant protein-1 (MCP-1) in atherosclerotic lesions is believed to mediate the local monocyte infiltration (21).

Regular exercise reduces the incidence of atherosclerosis, causes the regression of atherosclerosis (10, 23, 25, 26), and even corrects the endothelial function in patients with coronary artery disease (12, 32). Our laboratory and others (5, 6, 8) have reported that exercise improves endothelial function by increasing the agonist-stimulated NO release and enhancing endothelium-dependent vasodilatation in vessels of normal or hypertensive animals. However, the underlying mechanisms of the exercise-induced protective effect against atherosclerosis remain to be answered.

Our recent study (34) demonstrated that 2% high-cholesterol diet feeding for 8 wk induced severe lipid deposits and impaired acetylcholine (ACH)-evoked vasorelaxation in the rabbit aortas and that parallel exercise training only partially corrected the vascular dysfunction in the aortas. In contrast, the same exercise training program almost completely reverses high-cholesterol diet-induced vascular functional changes in femoral arteries (16). Because this discrepancy is probably due to relatively milder vascular functional changes in femoral arteries than in aortas, it is interesting to know whether parallel exercise training protocols can completely correct early-stage atherosclerotic defects. This study was conducted to investigate the time course of high-cholesterol diet-induced vascular dysfunction (the formation of fatty streaks, expres-
tion of adhesion molecules, and vasodilating responses) in rabbit aortas, as well as the extent of improvements in these functional parameters by parallel exercise training protocols.

METHODS

Animals and diet. This study was conducted in conformity with the procedures described in the Guide for the Care and Use of Laboratory Animals of the National Institutes of Health, and the procedures were in accordance with institutional guidelines. Male New Zealand White rabbits (~1 kg at the beginning of the study) were randomly divided into four groups: the normal diet control (N), the high-cholesterol diet control (H), normal diet with exercise (NE), and high-cholesterol diet with exercise (HE). The control groups were fed normal rabbit chow, whereas the high-cholesterol diet groups were fed 2% high-cholesterol diet (PMI Feeds) for 2, 4, or 6 wk (100 g·day⁻¹·animal⁻¹). No statistical difference in the body weight among the four groups was found (data not shown). Animals were housed in an environmentally controlled room at National Cheng Kung University Animal Center.

Exercise training protocol. The exercise training protocol was similar to that described in our previous studies (6, 34). After 1 wk of familiarization, rabbits in exercise groups ran on a leveled treadmill (model Q55, Quinton Instrument) at a speed of 0.88 km/h for 5 days/wk for 2, 4, or 6 wk. During the training period, the running time was gradually increased to 30–40 min/day. In contrast, animals in sedentary groups were placed on the treadmill without running for 10 min each day.

At the end of experiments, rabbits were anesthetized by injecting ketamine (25 mg/kg iv) and pentobarbital sodium (20 mg/kg iv) via the marginal ear vein. To avoid the acute effects of exercise, animals were killed 1 h after training. Blood samples were withdrawn from the inferior vena cava to determine the lipid profile. Thoracic aortas were immediately isolated for various experiments described below.

Determination of serum lipid profile. Serum lipid profiles, including total cholesterol, triglyceride, and high-density lipoprotein (HDL) and LDL levels, were determined by enzymatic methods using an automatic analyzer (model 747, Hitachi).

Assay of citrate synthase activity. An increase in citrate synthase activity is commonly used to confirm the exercise training effect. In the present study, soleus muscle samples were isolated and homogenized in five volumes of 0.1 M of Tris buffer containing 0.1% Triton X-100. Citrate synthase activity in the muscle homogenate was measured by using the method described by Srere (28). The enzyme activity of citrate synthase was determined spectrophotometrically at 412 nm. It was expressed as micromoles of substrate utilized per minute per gram of wet tissue.

Evaluation of vasodilating responses. The isolated vessel rings (3 mm long) were mounted on force transducers and submerged in organ chambers containing Krebs-Ringer solution (in mM: 118 NaCl, 4.8 KCl, 2.5 CaCl₂, 1.2 MgSO₄, 1.2 KH₂PO₄, 24 NaHCO₃, 0.03 Na₂-EDTA, and 11 glucose) bubbling with 95% O₂-5% CO₂ at 37°C. They were stretched to the optimal passive tension (i.e., 8–9 g) at which the contraction evoked by phenylephrine was maximal. The vessel rings were equilibrated for at least 90 min, precontracted with phenylephrine (5 × 10⁻⁸ M), and exposed to various concentrations of ACh (10⁻⁶ to 10⁻⁸ M) to evoke endothelium-dependent vasorelaxation. The dilating responses were expressed as percentages of the precontractile force. In some vessels, possible roles of different endothelium-derived vasodilators in these responses were also examined by adding various inhibitors, such as 10⁻⁶ M Nω-nitro-l-arginine methyl ester (l-NAME; a relatively selective eNOS inhibitor) (14, 30) or 10⁻³ M tetroxyammonium chloride (TEA; an inhibitor of the endothelium-derived hyperpolarization factor (EDHF)) (14).

Vascular responses to either 3 × 10⁻⁸ M A 2+3187, a calcium ionophore that induces endothelium-dependent vasodilatation without receptor activation, or 3 × 10⁻⁸ M sodium nitroprusside (SNP), an endothelium-independent vasodilator, were also examined in some phenylephrine (5 × 10⁻⁸ M)-precontracted vessels to see whether these vascular responses were affected as well.

All chemicals for the solution preparation were purchased from Merck (Darmstadt, Germany). Other reagents were obtained from Sigma Chemical (St. Louis, MO).

Immunohistochemical studies of adhesion molecules, MCP-1, and iNOS in aortas. Vessel frozen sections (6 μm thick) were placed on glass slides and fixed in cold acetone (−20°C) for 5 min. Sectioned specimens incubated in PBS containing 10% normal goat serum for 1.5 h at room temperature to block nonspecific binding were subsequently treated with 3% hydrogen peroxide for 5 min at room temperature to block the endogenous peroxidase activity. The primary mouse monoclonal antibodies against P-selectin (clone 1E3, DAKO; 1:200 dilution) or iNOS (clone 54, Transduction Laboratories; 1:200 dilution) were applied for 1 h at room temperature. In some specimens, normal mouse IgG was used as the negative control. To label the bound primary antibody, sections were incubated with the polymeric conjugate consisting of a large number of peroxidase and secondary goat anti-mouse antibodies (EnVision system, DAKO). Polyclonal goat anti-human MCP-1 antibody (R&D Systems; 1:50 dilution) and biotinylated horse anti-goat IgG (Vector Laboratories; 1:200 dilution) were used for the detection of MCP-1. The mouse monoclonal antibody against VCAM-1 (Clone 1.4C3, DAKO; 1:50 dilution) and biotinylated goat anti-mouse IgG (Vector Laboratories; 1:200 dilution) were used for the detection of VCAM-1. These slides were incubated with avidin-biotinylated enzyme complex solution (Vector Laboratories) and exposed to nickel-free diaminobenzidine tetrahydrochloride (DAB) solution for positive staining (brown color). The specimens were not counterstained with hematoxylin to avoid the confounding effects during quantification. By using an image analysis system (Image-Pro Plus, Media Cybernetics, the stained regions on the endothelium were analyzed blindly by a technician unaware of group treatments. The results were expressed as the ratio of DAB-positive endothelial boundary length to the total endothelial boundary length of the same specimen.

Statistical analysis. Data were expressed as means ± SE. Sample sizes (animal numbers) were indicated by n (n = 6–9 rabbits for each group in our experiments). Results among the four groups were analyzed by ANOVA and further by multiple range tests. Dose responses were analyzed by ANOVA with a repeated-measures design. If only two groups were compared, unpaired Student’s t-test was applied. Differences were considered at P < 0.05.
RESULTS

Serum lipid profile and citrate synthase activity. High-cholesterol diet feeding significantly increased serum concentrations of total cholesterol and LDL as early as 2 wk (Fig. 1). Six, but not two or four, weeks of concomitant exercise training significantly reduced diet-increased serum levels of total cholesterol and HDL (Fig. 1, A and C). Although exercise tended to reduce LDL, the effect was not statistically significant (Fig. 1B). There was no significant difference in the serum level of triglyceride among four groups at different time periods (data not shown).

Exercise training (≥2 wk) significantly increased citrate synthase activities of soleus muscles in both normal diet groups and high-cholesterol diet groups (Table 1), indicating that our training protocol was effective.

Fig. 1. Comparison of serum lipid profiles, including total cholesterol (A), low-density lipoprotein (LDL; B) cholesterol, and high-density lipoprotein (HDL; C) cholesterol, among 4 groups at different time periods. N, normal diet control; NE, normal diet with exercise; H, high-cholesterol diet control; HE, high-cholesterol diet with exercise. The results indicate that high-cholesterol diet feeding for ≥2 wk drastically elevated serum levels of total cholesterol and LDL (*P < 0.05), whereas only 6 wk of exercise training reduced the total cholesterol levels significantly (#P < 0.05; HE vs. H; n = 6–8).

Oil red O staining. High-cholesterol diet feeding for 2 wk induced small lipid deposits on the downstream of the aortic branch site (visible in all animals of the H group, but in only half of the HE animals). In comparison, the diet intervention for 4 or 6 wk induced obvious lipid deposition in the aortas of the H and HE groups (Table 2). Moreover, exercise intervention for 4 or 6 wk significantly reduced lipid deposition in the aortas when the HE group was compared with the H group (Table 2). There were no fat deposits in vessels from normal diet groups.

Table 1. Comparison of citrate synthase activity between control and exercise groups after 2, 4, or 6 wk of exercise training

<table>
<thead>
<tr>
<th>Group</th>
<th>Citrate Synthase Activity, μmol · min⁻¹ · g wet wt⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 wk</td>
</tr>
<tr>
<td>N</td>
<td>1.33 ± 0.01(7)</td>
</tr>
<tr>
<td>NE</td>
<td>1.45 ± 0.01(6)*</td>
</tr>
<tr>
<td>H</td>
<td>1.35 ± 0.01(6)</td>
</tr>
<tr>
<td>HE</td>
<td>1.40 ± 0.01(6)*</td>
</tr>
</tbody>
</table>

Values are means ± SE. Numbers in parentheses indicate the number of animals used in each group. N, normal diet control; NE, normal diet with exercise; H, high-cholesterol diet control; HE, high-cholesterol diet with exercise. *P < 0.01 (NE vs. N, or HE vs. H).

Table 2. Comparison of the areas of lipid deposit in the thoracic aortas between HE and H groups after high-cholesterol diet feeding for 2, 4, or 6 wk

<table>
<thead>
<tr>
<th>Group</th>
<th>Lipid Deposit, % surface area</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 wk</td>
</tr>
<tr>
<td>H</td>
<td>1.5 ± 0.3(6)</td>
</tr>
<tr>
<td>HE</td>
<td>1.5 ± 1.0(6)</td>
</tr>
</tbody>
</table>

Values are means ± SE. Numbers in parentheses indicate the number of animals used in each group. *P < 0.05 (HE vs. H).
The vascular responses to SNP (3 × 10⁻⁸ M) or A-23187 (3 × 10⁻⁸ M) were the same among four groups (data not shown), indicating that neither high-cholesterol diet nor exercise intervention for ≥6 wk affected vascular responses to endothelium-independent or receptor-independent vasodilators in rabbit aortas.

Roles of endothelium-derived relaxing factors in diet or exercise-altered ACh responses. Before the administration of L-NAME, the vascular response to 3 × 10⁻⁸ M of ACh in the H group was significantly lower than that in the N group (2 wk: 29 ± 3 vs. 48 ± 5%; 4 wk: 26 ± 4 vs. 45 ± 4%; 6 wk: 21 ± 7 vs. 51 ± 7% for H vs. N groups, respectively; n = 6–7 rabbits, P < 0.05). The pretreatment of L-NAME partially inhibited ACh-evoked vasorelaxation in both N and H groups with results in the N group being more pronounced than in the H group (Table 3). Furthermore, the diet-induced group difference disappeared after L-NAME treatment (P > 0.05). Similar results were observed when the vessels were pretreated with TEA alone (Table 3). The pretreatment of TEA also eliminated the group difference (Table 3). The pretreatment of L-NAME partially inhibited ACh-evoked vasorelaxation in both groups and blunted the group difference (Table 3). The pretreatment of TEA also inhibited ACh responses and eliminated the group difference between the HE and H groups (Table 3). These results imply that both NO and EDHF play important roles in exercise-enhanced vascular responses to ACh in hypercholesterolemia.

Table 3. Inhibitory effects of L-NAME or TEA on ACh (3 × 10⁻⁸ M)-induced vasorelaxation in the thoracic aortas

<table>
<thead>
<tr>
<th>Group</th>
<th>Inhibitory Effect, %precontraction</th>
<th>2 wk</th>
<th>4 wk</th>
<th>6 wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-NAME</td>
<td>N</td>
<td>28 ± 4(6)</td>
<td>31 ± 3(7)</td>
<td>29 ± 5(6)</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>18 ± 2(6)*</td>
<td>14 ± 3(7)*</td>
<td>13 ± 5(5)*</td>
</tr>
<tr>
<td></td>
<td>HE</td>
<td>31 ± 5(6)†</td>
<td>32 ± 5(8)†</td>
<td>30 ± 3(6)†</td>
</tr>
<tr>
<td>TEA</td>
<td>N</td>
<td>41 ± 4(6)</td>
<td>42 ± 2(3)</td>
<td>39 ± 5(5)</td>
</tr>
<tr>
<td></td>
<td>H</td>
<td>28 ± 4(6)*</td>
<td>18 ± 3(3)*</td>
<td>15 ± 5(5)*</td>
</tr>
<tr>
<td></td>
<td>HE</td>
<td>38 ± 5(6)†</td>
<td>40 ± 4(3)†</td>
<td>38 ± 7(5)†</td>
</tr>
</tbody>
</table>

Values are means ± SE. Numbers in parentheses indicate the numbers of animals used in each group. Inhibitory effect = (ACh response before inhibitor treatment) – (ACh response after inhibitor treatment). L-NAME, N-nitro-l-arginine methyl ester; TEA, tetraethylammonium. *P < 0.05 (H vs. N). †P < 0.05 (HE vs. H).
lipid deposition, it caused significant impairment in ACh-evoked vasodilating response. Prolonged high-cholesterol diet feeding for ≥4 wk caused widespread lipid deposition and impaired ACh-evoked endothelium-dependent vasorelaxation in a duration-dependent manner. Moreover, our results also revealed that a parallel exercise-training program for as short as 2 wk could recover the diet-impaired vasodilating responses to nearly normal level. As a comparison, the areas of lipid deposition on aortas were significantly reduced after only 4 wk of chronic exercise. It has been established that the thoracic aorta is more susceptible to atherosclerosis than the abdominal aorta in the rabbit animal model (36). Our laboratory’s recent studies (16, 34) demonstrated that 8-wk feeding of a high-cholesterol diet caused extensive fatty streak formation in rabbit aortas, with only small and scattered lipid deposits in femoral arteries. Furthermore, exercise training for the same time period completely recovered diet-impaired ACh responses in femoral arteries, whereas it only partially reversed the functional defects in aortas (16, 34). Taken together, these results imply that aortas are more susceptible to hypercholesterolemia than femoral arteries and that exercise can completely correct the endothelial dysfunction only when the vascular endothelium is not severely damaged.

Exercise training is known to exert beneficial effects on blood vessels of both normal and atherosclerotic animals (6, 34). However, this study is the first to report that this beneficial effect appears to be more pronounced in the diseased animals than in the normal controls. Chronic exercise for 8 wk enhances ACh-evoked vascular responses in normal rabbit aortas (6, 34), whereas exercise training that lasted ≤6 wk was ineffective (Fig. 2). As mentioned before, exercise for as short as 2 wk was effective in rescuing the impaired ACh-evoked vasorelaxation in hypercholesterolemic rabbit aortas (Fig. 2).

Both high-cholesterol diet and exercise training appeared to exert their vascular effects through modulating the endothelial function. To determine whether diet or exercise also affects endothelium-independent vascular responses, the vasodilating response to SNP was examined in this study. Our results showed that

### Table 4. Comparison of the protein expression between control and exercise groups after 4 or 6 wk of exercise training

<table>
<thead>
<tr>
<th>Group</th>
<th>P-selectin</th>
<th>VCAM-1</th>
<th>MCP-1</th>
<th>iNOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>1.67 ± 0.40</td>
<td>1.85 ± 0.45</td>
<td>1.27 ± 0.45</td>
<td>1.22 ± 0.37</td>
</tr>
<tr>
<td>HE</td>
<td>0.38 ± 0.15*</td>
<td>0.32 ± 0.15*</td>
<td>0.36 ± 0.18*</td>
<td>0.28 ± 0.14*</td>
</tr>
<tr>
<td>6 wk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>2.22 ± 0.35</td>
<td>1.63 ± 0.21</td>
<td>1.76 ± 0.28</td>
<td>2.42 ± 0.23</td>
</tr>
<tr>
<td>HE</td>
<td>0.87 ± 0.35*</td>
<td>0.43 ± 0.14*</td>
<td>0.55 ± 0.18*</td>
<td>0.93 ± 0.36*</td>
</tr>
</tbody>
</table>

Values are in arbitrary units and are means ± SE (n = 6 for each group). VCAM-1, vascular cell adhesion molecule 1; MCP-1, monocyte chemotactic protein-1; iNOS, inducible nitric oxide synthase. *P < 0.05 (HE vs. H).
there were no significant differences among four groups. The vascular responses to A-23187, an endothelium-dependent vasodilator that was uncoupled to surface receptors, did not vary among four groups either. Furthermore, the pretreatment of L-NAME or TEA abolished the influence of high-cholesterol diet or exercise intervention for 2–6 wk, indicating that NO and EDHF were involved. These data are consistent with our previous study with rabbits fed high-cholesterol diet for 8 wk (34). Therefore, only receptor-mediated endothelium-dependent release of vasodilating factors in rabbit aortas are affected by high cholesterol diet or exercise intervention.

Exercise training can ameliorate the proinflammatory changes in the aortas of hypercholesterolemic rabbits. Our recent study (34) has demonstrated that high-cholesterol diet feeding for 8 wk induces the expression of adhesion molecules, MCP-1, and iNOS, whereas exercise training significantly reduced these changes. Consistently, this study showed that 4–6 wk of high-cholesterol diet feeding also induced the expression of these molecules and that concomitant exercise significantly eliminated the expression of these molecules. Epidemiological evidence also shows that leisure-time physical activity can reduce the concentration of C-reactive protein (11), a cytokine-stimulated acute-phase protein that is associated with infection. Existing evidence supports the notion that chronic inflammation plays a key role in atherogenesis. For example, the expression of adhesion molecules (such as P-selectin and VCAM-1) and other inflammation-related factors (such as MCP-1) are elevated in the early stage of atherosclerotic progression (9, 15, 21). Therefore, exercise training can be an effective intervention to mitigate the inflammatory changes, such as the adhesion of leukocytes or platelets on the endothelium, and to retard atherosclerosis at an early stage.

Several possible mechanisms of exercise-induced atheroprotective effect have been proposed, such as an increase in HDL cholesterol level (13), decreases in total cholesterol levels or oxidation of LDL cholesterol (18, 31), a decrease in the production of atherogenic cytokines, and an increase in the production of atheroprotective cytokines (27). In this study, it took 6 wk of chronic exercise to significantly reduce total serum cholesterol levels. Based on our results, we propose two other possibilities for the exercise-induced protective effect against atherosclerosis. First, exercise may ameliorate the defect of EDHF and NO release in hypercholesterolemia to improve the endothelium-dependent vasodilating responses. Second, exercise may eliminate inflammatory changes in the vessels of atherosclerosis. Because NO inhibits the expression of various proinflammatory proteins (3), it is plausible to assume that the second possibility is actually the consequence of the first one.

Although exactly how exercise improves vascular function is still unclear, we favor the exercise-associated blood flow elevation as being one of the major responsible factors. Consistent with our laboratory’s (6) previous observation in normal animals, exercise training in this study significantly improved vasorelaxation in thoracic aortas of hypercholesterolemic rabbits but not in the carotid arteries of the same animals (data not shown). It is well known that the blood flow in aortas increases severalfold during exercise, whereas the flow in carotid arteries remains relatively constant due to efficient cerebral autoregulation. In addition, the blood chemical composition at any moment is presumably identical within the major arterial system. Therefore, the exercise-induced changes are likely due to local increases in blood flow or shear stress instead of to systemic changes in the plasma hormone levels. Our laboratory’s previous studies with rat aortic specimens (7, 17) have shown that chronic exercise or flow pretreatment of vascular segments increases ACh-induced intracellular calcium elevation in endothelium, which is one of the major upstream signals in endothelium-derived NO production. As the promoter region of eNOS gene contains a shear stress-responsive element (20), exercise training may upregulate eNOS gene expression by an increase in shear stress, and then facilitate NO release. Indeed, several studies have demonstrated that chronic exercise upregulates gene expression of eNOS (33, 35). Furthermore, previous exposure to fluid flow or shear stress decreases VCAM-1 gene expression on the endothelial cells and suppresses endothelial adhesiveness (1, 29), possibly due to flow-mediated NO production.

In conclusion, high-cholesterol diet feeding causes vascular structural changes and impairs ACh-induced vasorelaxation of rabbit aortas in a time-dependent manner. The concomitant exercise intervention can ameliorate endothelium-dependent vascular dysfunction as early as 2 wk and reduce proinflammatory changes after 4 wk of intervention. We suggest that exercise is an effective lifestyle modification to prevent and retard atherosclerotic progression in the early stage.

DISCLOSURES

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