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Effects of mild physical exercise on serum lipoproteins and metabolites of arachidonic acid: a controlled randomised trial in middle aged men

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Abstract

To study the effects of physical exercise on biochemical risk factors for ischaemic heart disease 31 healthy middle aged men undertook regular physical exercise for two months and 29 served as controls in a randomised trial. In the men taking regular exercise serum cholesterol concentrations increased 26% more in the high density lipoprotein subfraction two (HDL₂) and decreased 31% more in the subfraction three (HDL₃) and 9% more in the low density lipoprotein fraction than in the control group. A tendency towards increased plasma 6-keto-prostaglandin F_{1α} concentration and decreased serum thromboxane B₂ concentration was found during the period of regular exercise, but prostaglandin E₂ concentrations remained unchanged. The increase in plasma 6-keto-prostaglandin F_{1α} concentration was associated with an increase in serum HDL₂ cholesterol concentration in the group taking regular exercise.

Our data suggest that mild regular physical exercise favourably influences cholesterol distribution in serum lipoproteins in healthy middle aged men and may have beneficial effects on circulating metabolites of arachidonic acid.

Introduction

The relation of decreased serum high density lipoprotein cholesterol concentration and increased low density lipoprotein cholesterol concentration to ischaemic heart disease has been established epidemiologically.¹ Evidence suggests that it is the high density lipoprotein subfraction two (HDL₂) that protects against ischaemic heart disease.² Advanced atherosclerosis in man is also characterised by decreased production of prostacyclin in the vascular endothelium³ and increased production of thromboxane A₂ by the platelets.⁴ It has been suggested that regular physical activity prevents ischaemic heart disease,^{5,6} but the mechanisms are only partly known. The most convincing evidence for this effect of regular exercise is the increase in serum high density lipoprotein cholesterol concentrations^{7,8}; suggestions concerning the effects of exercise on high concentrations of low density lipoprotein cholesterol as well as on the antiaggregatory and proaggregatory metabolites of arachidonic acid—namely, prostacyclin and thromboxane—have been based on uncontrolled findings alone. We studied the effects of mild regular physical exercise on circulating lipoproteins and metabolites of arachidonic acid in healthy middle aged men in a controlled randomised clinical trial.

Subjects and methods

We recruited the subjects from a group of 82 clinically healthy male volunteers aged 32-44 who were contacted through an advertisement in a local newspaper and on the radio. The design of the study was explained to them, and they gave their spoken consent. They then underwent medical examination, chest x ray examination, exercise testing, and laboratory examinations. Twenty two men were excluded because they were overweight (body mass index (weight/(height)²) > 27 kg/m²), had a high maximal oxygen consumption (> 55 ml/kg × min), or had hypercholesterolaemia (serum cholesterol concentration > 7.5 mmol/l (290 mg/100 ml)) or hypertriglyceridaemia (serum triglyceride concentration > 2.0 mmol/l (175 mg/100 ml)). The mean (SD) age of the 60 men included in the study was 37 (2). They were all non-manual workers. The men were asked to keep their dietary and other living habits constant during the study.

After a lead in period of one month baseline laboratory tests were carried out. Blood samples for determining concentrations of lipoprotein and arachidonic acid metabolite were taken, after a 10 hour fast, from 0800 to 1000 with the subjects in a sitting position. The first 2 ml of blood obtained after the venous puncture was discarded; the sample for testing was then taken without a tourniquet. The men were advised not to drink alcohol or take physical exercise in their free

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time for three days before the samples were taken and not to use non-steroidal anti-inflammatory analgesics for seven days before.

A maximal exercise test was performed on an electrically braked bicycle ergometer (Siemens Elema 380B, Siemens Elema AB) on a different day from the blood sampling. The criterion for maximal loading was either a respiratory quotient of at least 1.0 or subjective exhaustion. The load was increased stepwise every three minutes. Analyses of respiratory gases were repeated every 30 seconds (Oxycon-4, Mijnhardt). Electrocardiography was performed continuously and the tracing recorded at the end of each three minute stage and every minute during recovery up to seven minutes. After the exercise test the subjects were randomly assigned either to undergo regular physical exercise (the exercise group; $n=31$) or to serve as sedentary controls ($n=29$). One man in the exercise group and two in the control group were regular smokers.

The exercise programme lasted for eight weeks and consisted of walking and jogging for nine to 15 miles each week. For the first four weeks the exercise sessions took place four times a week and each lasted for 45 minutes, including periods for warming up and cooling down. During the subsequent four weeks exercise sessions were repeated five times a week for up to 60 minutes each time. The intensity of exercise was determined individually on the basis of the heart rate response in the exercise test. Heart rates during exercise were calculated with the following formula: resting heart rate $+((\text{from } 40 \text{ to } 60\%) \times (\text{maximal heart rate} - \text{resting heart rate}))$. Subjects were taught to measure their heart rate by palpating the carotid artery and to do this at least three times during each exercise session. The men in the exercise group kept a record of their physical activity during their free time. This was checked twice during the study at intervals of four weeks when the subjects visited the physician. The men in the control group were asked to abstain from physical exercise in their free time during the eight weeks of the study. None of the subjects dropped out of the study. Blood sampling and exercise testing were repeated within one week after the end of the physical exercise programme.

ANALYTICAL METHODS

For the analysis of lipoproteins serum was separated by centrifugation at 4°C for 10 minutes at 2000 g after coagulation at room temperature for one hour. Samples were stored at 4°C for not more than six days before analysis. All ultracentrifugations were done at 10°C with a Kontron TGA-65 ultracentrifuge. The main fractions (very low, low, and high density lipoproteins) were separated as described by Carlson.⁹ Serum was centrifuged for 16 hours at 115 000 g . Very low density lipoprotein was recovered as the top fraction and high density lipoprotein as the supernatant after precipitation of the bottom fraction with dextrane sulphate and magnesium chloride.¹⁰ The cholesterol concentration in low density lipoprotein was calculated as the difference between the bottom and high density lipoprotein fractions. To separate the main subfractions of high density lipoprotein, HDL₂ and HDL₃,¹¹ ultracentrifugation was carried out at a density of 1.125 g/cm^3 adjusted with sodium bromide. The serum samples were centrifuged for 48 hours at 115 000 g , and the top and bottom fractions were separated by the tube slicing technique. In this procedure the HDL₁ subfraction, a negligible component of the total high density lipoprotein,¹² is included in the HDL₂ subfraction. Thus the high density lipoprotein subfraction, calculated as the difference between total high density lipoprotein and HDL₃, consists mainly of HDL₂. Cholesterol was determined enzymatically with test kits (cholesterol CHOD-PAP method, Boehringer Mannheim).¹³ All tests were run in duplicate, and the method was controlled with commercial control serum (Seronorm, Nyegaard).

For the analysis of metabolites of arachidonic acid in plasma blood was placed in chilled tubes containing 10 mg disodium edetate and 0.18 mg acetylsalicylic acid/10 ml blood. The plasma was immediately separated by centrifugation at 500 g for 15 minutes at 4°C and then frozen at -20°C until assayed. For the processing of thromboxane B₂ in serum 1 ml blood was taken and allowed to clot at 37°C for 30 minutes. After centrifugation at 500 g for 15 minutes at 4°C the serum was frozen at -20°C until assayed. For the extraction of the metabolites of arachidonic acid tracer quantities (about 10 pg) of the corresponding metabolite labelled with tritium were added to the samples to monitor recovery. The samples were acidified to pH 4.0, and Amberlite XAD-2 (BDH Chemicals Ltd) was added. The resin was washed with distilled water until neutral, and the extracted solution and distilled water were discarded. The extraction was at first performed with isopropanol and then with a mixture of isopropanol ethyl acetate and distilled water. The organic phase was removed and stored. Remaining substances were extracted with ethyl acetate. The organic phases were pooled and evaporated under air, and the residue was reconstituted with assay phosphate buffer. The recovery was counted from the resolved extract. Radioimmunoassay of 6-keto-prostaglandin F_{1 α} , prostaglandin E₂, and thromboxane B₂ was performed by a modification of the double antibody procedure¹⁴ with commercial antisera (Immunoserums pour RIA, Pasteur Institute). All samples were tested in duplicate. To control for possible abuse of alcohol, γ -glutamyl-transferase activity in serum was determined during the study. It remained in the normal range and did not change in either of the groups during the eight weeks of the exercise programme.

STATISTICAL METHODS

The significance of the mean changes in each subject during exercise was tested with the t test for paired samples. The effect of the exercise programme was estimated as the mean difference between values before and after the period of regular exercise in the exercise group less the corresponding difference in the control group (net difference) and tested for significance with the t test, comparing the means of the differences in values before and after the exercise programme between the two study groups. Additionally, estimates of the effect of exercise were tested with the analysis of covariance with an adjustment for the change in weight during exercise. The confidence intervals of the effects of regular exercise were estimated from the standard error of the difference between the values before and after regular exercise in each subject based on t distribution. The partial association of the change in plasma 6-keto-prostaglandin F_{1 α} concentration, the main metabolite of prostacyclin, with that in serum HDL₂ cholesterol concentration and one potential confounder (body weight) was estimated and tested with multiple least squares regression analysis of the statistical package for the social sciences.¹⁵ All statistical inferences were based on two tailed tests.

Results

Before the start of the exercise programme there was no difference in mean body weight, body mass index, maximal oxygen consumption, serum lipoprotein concentrations, or concentrations of any of the prostaglandins between the two groups (tables I and II). Over the eight week study period mean body weight decreased by 1.5 kg in the exercise group, the effect of exercise being 2%, and maximal oxygen consumption increased by 0.24 l/min (an effect of 7%) (or 4.2 ml/kg $\times$ min (9%)) in the exercise group.

TABLE I—Mean body weight, body mass index, and maximal oxygen consumption in exercise and control groups initially and after eight weeks, and net differences between means

	Group taking regular physical exercise (n = 31)		Control group (n = 29)		Net difference	
	Initially	After 8 weeks	Initially	After 8 weeks	Mean (95% confidence interval)	p
Body weight (kg)	76.0	74.5*	77.1	77.0	-1.4 (-2.1, -0.7)	<0.001
Body mass index (kg/m ²)	24.4	23.9*	24.3	24.3	-0.5 (-0.7, -0.3)	<0.001
Maximal oxygen consumption { (l/min) (ml/kg $\times$ min)	3.56	3.80*	3.51	3.61	0.13 (-0.06, -0.32)	0.159
	47.1	51.3*	45.6	47.1	2.8 (0, 5.6)	0.052

Significance of changes within groups: * $p < 0.001$.

TABLE II—Mean concentrations of cholesterol in total serum, very low density lipoprotein (VLDL), low density lipoprotein (LDL), and high density lipoprotein (HDL) fractions, and subfractions HDL₂ and HDL₃, and of plasma 6-keto-prostaglandin F_{1α} (6-Keto-PGF_{1α}) prostaglandin E₂ (PGE₂), and thromboxane B₂ produced by platelets (TxB₂) in the exercise and control groups initially and after eight weeks, and net differences between these concentrations

	Group taking regular exercise			Control group			Net difference	
	n	Initially	After 8 weeks	n	Initially	After 8 weeks	Mean (95%) confidence interval	p
Cholesterol (mmol/l) in:								
Total serum	31	5.34	5.15	29	5.76	6.31*	-0.74 (-1.04, -0.44)	<0.001
VLDL	31	0.64	0.70	29	0.55	0.91*	-0.30 (-0.51, -0.09)	0.007
LDL	31	3.59	3.19*	29	4.02	4.09	-0.47 (-0.76, -0.18)	0.002
HDL	31	1.11	1.26*	29	1.19	1.30*	0.03 (-0.05, 0.11)	0.498
HDL ₂	31	0.62	0.90*	29	0.66	0.76†	0.17 (0.09, -0.25)	<0.001
HDL ₃	31	0.49	0.36*	29	0.53	0.54	-0.14 (-0.15, -0.13)	<0.001
6-Keto-PGF _{1α} (pmol/l)	29	414.9	467.2†	25	422.4	444.6	30.2 (-33.0, 93.4)	0.338
PGE ₂ (pmol/l)	30	137.9	127.4	22	146.4	150.1	-14.2 (-34.6, 6.2)	0.168
TxB ₂ (nmol/l)	27	688.6	440.0*	22	614.6	493.4	-127.4 (-29.3, 43.5)	0.141

Changes within groups: *p < 0.001; †p = 0.001; ‡p = 0.025.

Conversion: SI to traditional units—Cholesterol: 1 mmol/l ≈ 38.7 mg/100 ml. 6-Keto-prostaglandin F_{1α}: 1 pmol/l ≈ 0.037 pg/100 ml. Prostaglandin E₂: 1 pmol/l ≈ 0.035 pg/100 ml. Thromboxane B₂: 1 nmol/l ≈ 0.037 ng/100 ml.

TABLE III—Partial regression of increase in plasma 6-keto-prostaglandin F_{1α} concentration on increase in serum HDL₂ cholesterol concentration and reduction in body weight in group taking regular exercise and controls

	Group taking regular physical exercise (n = 29)			Control group (n = 25)		
	Partial coefficient	Increase in R ²	F value	Partial coefficient	Increase in R ²	F value
Increase in HDL ₂ cholesterol	330.6	0.27	7.88*	214.0	0.06	2.08
Reduction in weight	17.0	0.05	1.87	23.8	0.08	1.95
Whole model		0.32	6.07*		0.16	1.75

There were two missing observations in the exercise group and four missing observations in the control group in any of the three variables.

Significance of regression coefficients: *p < 0.01.

The low density lipoprotein cholesterol concentration decreased by 0.4 mmol/l (15 mg/100 ml) (11%) in the group taking exercise, the crude effect of the exercise programme being 13% and, after allowing for the weight change, 9% (p = 0.05). The HDL₂ cholesterol concentration rose by 0.28 mmol/l (11 mg/100 ml) (49%) in the exercise group but also by 0.1 mmol/l (3.9 mg/100 ml) (19%) in the control group; the effect of exercise was 27%. When the change in weight over the study was allowed for the effect of exercise still reached 26% (p = 0.001). The HDL₃ cholesterol concentration decreased by 0.13 mmol/l (5 mg/100 ml) (25%) in the test group, the effect of exercise being 29%, and 31% (p < 0.001) when the change in weight was allowed for.

The plasma 6-keto-prostaglandin F_{1α} concentration increased by 52 pmol/l (19.2 pg/ml) and serum thromboxane B₂ concentration (produced by platelets) decreased by 249 nmol/l (92.1 ng/ml) in the exercise group during the exercise programme. The estimated effect of regular exercise was 1% for 6-keto-prostaglandin F_{1α}, 14% for prostaglandin E₂, and 12% for serum thromboxane B₂ when the weight change was allowed for. None of these estimates was significant.

The increase in plasma 6-keto-prostaglandin F_{1α} concentration had a significant positive partial regression on the increase in serum HDL₂ cholesterol concentration in the group taking regular exercise (table III). Thus plasma 6-keto-prostaglandin F_{1α} concentration increased more in the subjects taking regular exercise whose serum HDL₂ cholesterol concentration also increased. After the change in weight was controlled for, the change in HDL₂ cholesterol concentration accounted for 27% of the change in 6-keto-prostaglandin F_{1α} concentration in the multiple regression model in the exercise group. The change in body weight did not have any significant independent association with the change in 6-keto-prostaglandin F_{1α} concentration.

Discussion

Our study shows that mild but regular physical activity influences serum concentrations of high density lipoprotein cholesterol by increasing the HDL₂ and reducing the HDL₃ subfractions in healthy middle aged men. In addition, the increases in 6-keto-prostaglandin F_{1α} concentration, the main metabolite of prostacyclin, and HDL₂ cholesterol concentration appear to be parallel during exercise. These and the decreased low density lipoprotein cholesterol concentration suggest that aerobic exercise has a beneficial effect.

The considerable increase in HDL₂ cholesterol concentration in our study agrees with a previous finding of an increase in HDL₂ mass concentration associated with jogging for at least eight miles each week.⁸ Our study shows that physical exercise does not necessarily have to be strenuous to modify the distribution of serum lipoproteins; the changes in serum lipoprotein concentrations in our exercise group were probably a consequence of increased physical activity. Only a small part of the increase in HDL₂ cholesterol concentrations and reduction in HDL₃ and low density lipoprotein cholesterol concentrations may be explained by the decrease in body weight. Furthermore, the changes in serum lipoprotein concentrations in the exercise group cannot to any appreciable degree be attributed to dietary changes. To reduce the high serum concentration of low density lipoprotein cholesterol typical in eastern Finland by dietary means a considerable reduction in saturated fat intake is required, but such a reduction leads to a decrease in high density lipoprotein cholesterol concentration as well.¹⁶ In addition, it has been found that after a one year programme of moderately intensive jogging there was no change in food intake, even though body weight had decreased slightly.⁸

Prostacyclin and thromboxane are two important prostaglandins that have counteracting effects on the vascular bed. Prostacyclin has a vasodilatory effect and is a potent inhibitor of platelet aggregation, and thromboxane A₂ is a proaggregatory agent.^{3,4} Aerobic exercise seems to be associated with increases in vasodilatory prostaglandins in the circulation,¹⁷ but anaerobic and exhaustive physical exercise promote the dominance of the proaggregatory thromboxane.¹⁸⁻²⁰ During a short treadmill running exercise thromboxane B₂ concentrations increased and stayed raised transiently after exercise but 6-keto-prostaglandin F_{1α} concentrations did not change.²¹ The long term importance of such acute effects of exercise on metabolites of arachidonic acid is not known.

Our study shows the effect of physical exercise on the main metabolites of arachidonic acid, but this effect seems mostly to be mediated by a reduction in weight. There was, on the other hand, a positive association between the increases in 6-keto-prostaglandin F_{1α} and HDL₂ cholesterol concentrations in the group taking regular physical exercise. This indicates that HDL₂

cholesterol contributes to the metabolism of prostacyclin. These changes together could partly mediate the preventive potential of regular physical exercise against ischaemic heart disease. It has been shown that high density lipoprotein stimulates and low density lipoprotein inhibits synthesis of prostacyclin *in vitro*.²²⁻²⁵ The association between the main metabolite of prostacyclin and HDL₂ cholesterol in the present study also accords with the suggested stimulatory effect of high density lipoprotein production of prostacyclin. We conclude that regular aerobic exercise of only mild intensity has favourable effects, at least for a short time, on some of the biochemical risk factors for ischaemic heart disease in healthy middle aged men. Exercise has its most pronounced effect on serum lipoproteins, especially as an increase in serum HDL₂ concentration and a decrease in HDL₃ and low density lipoprotein cholesterol concentration.

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SHORT REPORTS

Paranoid psychosis induced by tocainide

Tocainide is a primary amine analogue of lignocaine which has a high level of bioavailability after oral administration.¹ Its use is indicated for the control of ventricular tachyarrhythmias after myocardial infarction. Although psychoses occurring in association with lignocaine toxicity are well recognised,² there are no reports of psychosis induced solely by tocainide. We describe two such cases.

Case reports

Case 1—A 58 year old man with an acute myocardial infarction developed recurrent symptomatic ventricular tachycardia the day after admission to hospital. The arrhythmia was initially suppressed by intravenous lignocaine (4 mg/min) followed by oral tocainide 400 mg three times daily. Recurrence of ventricular tachycardia on the fifth and sixth days was treated by increasing tocainide to 400 mg and 600 mg four times daily, respectively. On the eighth day, one hour after administration of tocainide, the patient suddenly became garrulous, irrational, suspicious, agitated, and irritable. He suffered recurrent visual hallucinations including visions of animals. His delusions of persecution concerned fellow patients, nurses, and medical staff, and he was aggressive to anyone who approached him. The symptoms subsided over the subsequent two hours, only to recur again within one hour

after the next dose of tocainide. The serum tocainide concentration was estimated to be 6.7 mg/l. The psychological disturbance disappeared after withdrawing tocainide, and the arrhythmia was successfully controlled by oral disopyramide.

Case 2—A 48 year old man began to suffer recurrent syncope due to ventricular tachycardia five months after myocardial infarction. The arrhythmia was initially suppressed by intravenous lignocaine (4 mg/min), and oral tocainide (400 mg three times daily) was started on the second day. Recurrent ventricular tachycardia the next day necessitated increasing the tocainide to 600 mg three times daily. Two hours after tocainide on the fifth day he suffered sudden dysarthria, nausea, incoordination, paraesthesia, confusion, agitation, and flight of ideas. He became frightened and thought that the nursing staff were persecuting him and trying to harm him. The symptoms disappeared spontaneously over the next hour and he apologised for his behaviour. The serum tocainide concentration was 10.2 mg/l during the psychosis. Withdrawal of tocainide led to further ventricular tachycardia necessitating DC cardioversion and intravenous lignocaine (4 mg/min). The lignocaine induced a similar psychotic behaviour pattern and was therefore replaced by intravenous and oral amiodarone with good effect.

Comment

Adverse effects of tocainide include tremor, dysarthria, nausea, blurred vision, night sweats, and paraesthesia.^{1,3,4} Our two patients developed an acute short lived confusional state with paranoid features after receiving tocainide. Paranoid delusions and mental impairment