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The influence of physical training on glucose tolerance, insulin sensitivity, and lipid and lipoprotein concentrations in middle-aged hypertriglyceridaemic, carbohydrate intolerant men

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Summary. The effects of 9 weeks of moderate intensity exercise training while on a weight-maintaining diet were studied in 19 untrained middle-aged, hypertriglyceridaemic, carbohydrate intolerant men. Initial mean maximum oxygen consumption was low (29.7 ± 1.0 ml · min^{-1} · kg^{-1}; mean ± SEM) and improved (34.2 ± 1.4 ml · min^{-1} · kg^{-1}, $p < 0.01$) with exercise training. Fasting glucose, insulin, lipid and lipoprotein concentrations did not change. While the abnormal glucose response to oral glucose did not change with training, insulin concentrations were significantly ($p < 0.05$) lower at 90 and 120 min during the final oral glucose tolerance test. Insulin mediated glucose uptake did not change, indicating that the degree of exercise training failed to improve in vivo insulin sensitivity. Significant associations were found between the following parameters measured: fasting concentrations of triglycerides and insulin, very low density lipoprotein-triglycerides and glucose, and measures of in vivo insulin resistance and fasting insulin levels, suggesting that insulin resistance in these glucose intolerant subjects may play a role in their hypertriglyceridaemia. These data indicate that moderate increases in physical training alone are not sufficient to improve the carbohydrate, insulin and lipid metabolism of hypertriglyceridaemic, glucose intolerant men.

Key words: Insulin sensitivity, hypertriglyceridaemia, exercise training, oxygen uptake, serum lipids, glycemic control.

Physical training has been reported to improve glucose metabolism in both non-diabetic and diabetic subjects [1, 2]. Since subjects with moderate impairment in glucose tolerance have insulin resistance [3], it has been suggested that the major effect of exercise on glucose tolerance is caused by an improvement in insulin sensitivity [1, 2]. Many subjects with abnormal glucose tolerance and insulin resistance also have lipid abnormalities [4] characterized by hypertriglyceridaemia, elevated very low density lipoprotein triglycerides (VLDL-TG) and low density lipoprotein cholesterol (LDL-C), and reduced high density lipoprotein cholesterol (HDL-C) levels. Consequently, these people are at increased risk for developing coronary artery disease [5].

Previous work from our laboratory indicated that moderate intensity aerobic physical training of middle-aged men with endogenous hypertriglyceridaemia and normal glucose tolerance significantly lowered plasma triglyceride concentrations ($p < 0.01$) [6]. We also demonstrated that this is effective in lowering fasting insulin levels, enhancing insulin sensitivity, and improving the ratio of HDL-C to total cholesterol [6].

The current study was undertaken to assess the effects of such a moderate exercise training programme upon glucose intolerance, insulin resistance, and elevated triglyceride and lipoprotein concentrations in hypertriglyceridaemic, middle-aged men with glucose intolerance.

Subjects and methods

Subjects

Nineteen untrained male subjects aged 29 to 63 years were selected for study from University of Michigan staff members known to have impaired glucose tolerance ($n = 14$) or Type 2 (non-insulin-dependent) diabetes mellitus, ($n = 5$), as defined by the World Health Organization Expert Committee [7]. All subjects gave written informed consent prior to participating in the study. None had evidence of cardiovascular, respiratory, hepatic, renal or infectious disease. A graded exercise tolerance test [6] was used during the initial evaluation to rule out clinical or electrocardiographic evidence of significant coronary artery disease. All denied taking any medication known to alter glucose or lipid metabolism in the weeks preceding or during the time of the study. Clinical characteristics and values for body weight and body mass index (BMI = kg/m^2) [8] before the 9 weeks of physical training were: age (years), 48.9 ± 2.2; height (cm), 175.9 ± 1.9; initial weight (kg), 81.0 ± 3.9; and BMI, 25.9 ± 0.8.

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Biochemical measurements. Blood for biochemical determination was obtained at baseline (initial), 3, 6 and 9 weeks (final). Blood was drawn into test tubes containing sodium EDTA, the plasma immediately separated, and aliquots obtained for determinations of glucose [9], insulin [10] and lipid [11] concentrations. Lipoproteins were separated by ultracentrifugation and plasma VLDL, total HDL+LDL, and HDL fractions were subsequently analyzed for cholesterol and triglyceride concentrations [11]. LDL fraction values were obtained by subtraction of HDL levels from those of the total fraction of HDL+LDL.

Dietary measures. Initially, a history of each subject's usual food intake was obtained by a dietitian using the dietary interview method. To exclude effects of dietary change and weight loss upon the study, the dietitian then instructed each subject to continue his typical eating patterns and to maintain weight by slightly increasing total calorie intake by 150–170 kcal/day to compensate for the additional caloric expenditure due to exercise training. Compliance with the diet protocol was monitored by having the subjects keep 3-day food diaries which were reviewed at 3-week intervals. Data from these records were subsequently analyzed to assess the subject's caloric consumption and food composition [12].

Progressive treadmill exercise test and exercise training prescription. The cardiovascular response during acute exercise of all subjects was measured on a treadmill as previously described [6]. Each subject was encouraged to walk to a termination point of subjective exhaustion. During the test, three leads of the 12-lead electrocardiogram were monitored, blood pressures were obtained by auscultation using Korotkoff I and IV sounds for systolic and diastolic blood pressure, respectively, and maximal oxygen uptake (Max $\dot{V}O_2$) was measured by indirect spirometry. The data from the initial test were used to prescribe the desired work intensity (effort needed to attain 85% of maximal heart rate for each subject). Three 30–40 min supervised exercise sessions were scheduled each week over the 9-week period as presiously described [6]. With this training protocol, the subjects averaged between 9 to 12 miles of jogging per week.

Oral glucose tolerance test (OGTT). Subjects received a 3-h oral glucose tolerance test (75-g oral glucose load) after an overnight fast and consumed an isocaloric diet containing 50% of calories as carbohydrate for three days preceding the OGTT. Subjects were classified as having abnormal glucose tolerance on the basis of criteria from the World Health Organization Expert Committee [7].

Insulin sensitivity test. Insulin sensitivity was measured in the first twelve subjects by the steady state plasma glucose (SSPG) technique [13]. The last seven subjects were studied using the euglycaemic clamp technique [14] to assess in vivo insulin resistance, since objections have been raised to measuring in vivo insulin sensitivity using pharmacological agents. These tests were performed 48 h after the OGTT and while still on the preparation diet.

Steady state plasma glucose (SSPG). As described by Shen et al. [13], this test consisted of a continuous intravenous infusion of epinephrine (6 μg/min), propranolol (0.08 mg/min), glucose (0.33 mmol/l), and insulin (80 mU/l) for a period of 150 min, using a constant infusion pump. The plasma concentrations of insulin and glucose were measured every 10 min from 90 to 150 min on samples obtained from an indwelling needle placed in the opposite forearm. Since this technique produces similar insulin concentrations in all subjects, the average level of glucose maintained in the final 90–150 min can be taken as an index of insulin sensitivity [13].

Euglycaemic clamp test (ECT). As described by De Fronzo et al. [14], an infusion of 20% glucose and insulin was administered through an indwelling needle in an antecubital vein. Insulin was infused at a rate of 40 mU/m^2 per min following a 10-min primed infusion. The glucose infusion was varied in order to maintain a serum glucose of approximately 4.72 mmol/l. Blood samples for glucose (glucose oxidase technique, Beckman Instruments, Fullerton, Calif, USA) and insulin [10], were obtained from the contralateral arm every 5 min and glucose concentrations maintained at the target level through a "feedback" algorithm. The total glucose disposal rate ("M" value) was calculated for baseline and final tests from values obtained at identical time periods for each subject at least 1 h after the onset of the glucose infusion.

Table 1. Maximum heart rate, systolic blood pressure and aerobic capacity during treadmill exercise stress testing (mean ± SEM)

Measure	Baseline	Final (9 Weeks)
Maximum heart rate (beats/min)	181.8 ± 3.4	178.3 ± 3.9
Maximum systolic blood pressure (mmHg)	200.1 ± 6.2	204.1 ± 7.4
Maximum rate pressure product (heart rate × systolic blood pressure ÷ 100)	361.2 ± 12.7	363.2 ± 14.3
Maximum aerobic capacity ($ml \cdot min^{-1} \cdot kg^{-1}$)	29.7 ± 1.0	34.2 ± 1.4[a]
Total treadmill exercise stress Time (min)	18.4 ± 1.4	22.7 ± 1.7[a]

[a] Significantly ($p < 0.01$) different from baseline value

Intervention and final assessment. After initial assessment, subjects began their exercise program and returned to the hospital at three week intervals for interim and final assessments. At the three and six week visits, a blood sample was drawn (after a 12-h fast and 48 h after the last period of exercise) for determination of glucose, insulin and lipid concentrations. Stable body weight was maintained by the isocaloric diet program. At the end of the 9-week intervention period, the initial series of tests were repeated in the same sequence starting 48 h after the last exercise session.

Statistical analysis

Data from the two different insulin sensitivity tests (SSPG, $n = 12$ and ECT, $n = 7$) were analyzed separately. Since the same methods were used for treadmill testing and determinations of fasting glucose, insulin and lipid levels on all subjects tested, these data were pooled for statistical analysis. Student's paired t-tests were employed on data obtained from the treadmill exercise and insulin sensitivity tests; glucose and insulin values obtained during the oral glucose tolerance tests were analyzed using the Dunnett multiple comparison procedure [15]; fasting glucose, insulin, lipid and lipoprotein concentrations were analyzed using a one-way repeated measures analysis of variance (ANOVA); correlation matrices were calculated to investigate associations among variables. Data are reported as mean ± SEM.

Results

Effects of exercise training on maximum oxygen uptake

Results of treadmill testing to maximum exercise are shown in Table 1. Following 9 weeks of physical training, subjects increased their physical fitness level by 15.5 ± 3.2% ($p < 0.01$). Baseline aerobic capacity was 29.7 ± 1.0 $ml \cdot min^{-1} \cdot kg^{-1}$ and increased to 34.2 ± 1.4 $ml \cdot min^{-1} \cdot kg^{-1}$ ($p < 0.01$) following training. Mean duration of exercise during treadmill testing improved by 26.2 ± 6.9% ($p < 0.01$). Maximum heart rate, maxi-

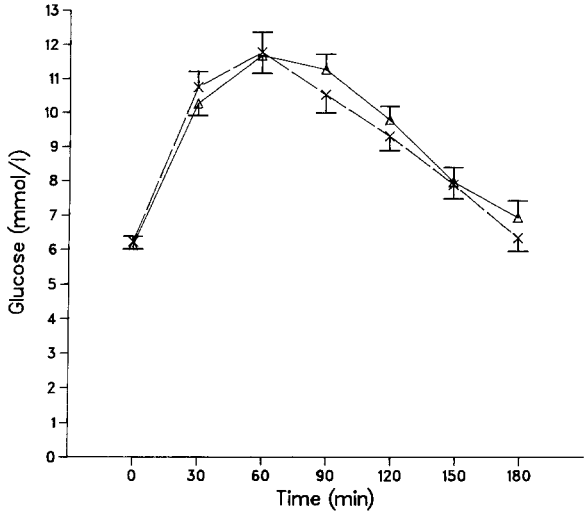

Fig. 1. Plasma glucose concentrations during oral glucose tolerance test at baseline (△) and after (final) (X) exercise ($n=19$)

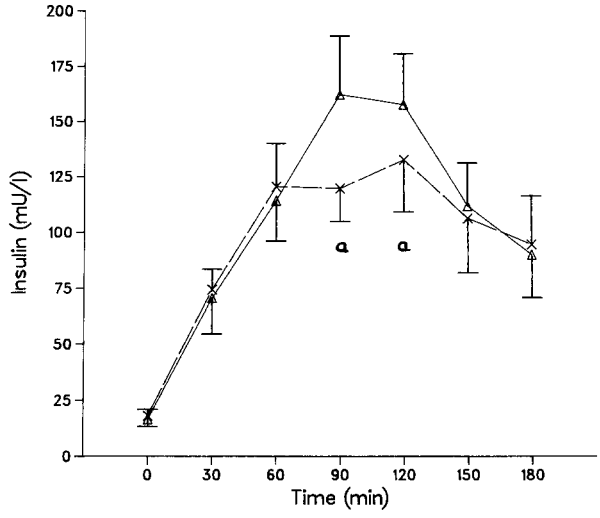

Fig. 2. Insulin concentrations during oral glucose tolerance test at baseline (△) and after (final) (X) exercise ($n=19$) [a] $p<0.05$

Table 2. Fasting glucose, insulin, lipid and lipoprotein concentrations (mean ± SEM)

Measure	Time period			
	Initial	3 Weeks	6 Weeks	Final (9 Weeks)
Glucose (mmol/l)	6.47 ± 0.21	6.49 ± 0.29	6.41 ± 0.29	6.31 ± 0.19
Insulin (mU/l)	17.0 ± 2.4	15.2 ± 2.6	14.5 ± 2.4	17.5 ± 2.4
Cholesterol (mmol/l)	5.54 ± 0.21	5.18 ± 0.22	5.32 ± 0.31	5.42 ± 0.31
HDL-Cholesterol (mmol/l)	0.89 ± 0.06	0.86 ± 0.07	0.88 ± 0.06	0.87 ± 0.07
LDL-Cholesterol (mmol/l)	3.26 ± 0.24	3.06 ± 0.29	3.24 ± 0.31	3.23 ± 0.32
Triglycerides (mmol/l)	3.30 ± 0.68	2.67 ± 0.48	2.90 ± 0.67	3.23 ± 0.70
VLDL-Triglycerides (mmol/l)	2.28 ± 0.49	2.08 ± 0.46	2.32 ± 0.64	1.90 ± 0.37

HDL = high density lipoprotein; LDL = low density lipoprotein; VLDL = very low density lipoprotein

mum systolic blood pressure and maximum pressure rate products were similar between baseline and final tests, indicating that equal cardiovascular demands were imposed during both stress tests.

Effects of exercise training on glucose and insulin levels fasting and on 3-h oral glucose tolerance test

Subjects demonstrated high glucose (6.5 ± 0.2 mmol/l) and insulin (17.0 ± 2.4 mU/l) concentrations at baseline which remained constant following training (Table 2). Plasma glucose and insulin responses, both before and after physical training, are shown in Figures 1 and 2. Following exercise training, no significant change was observed in glucose levels during the 3-h oral glucose test. While similar overall insulin response patterns to the oral glucose challenge were noted on both tests, final insulin concentrations at 90 and 120 min were lower ($p<0.05$) as compared to initial values. Baseline and final individual values for fasting glucose and insulin levels and for glucose and insulin levels at 2 h during the oral glucose tolerance test are shown in Table 3.

Effects of exercise training on serum lipids

During the initial period of exercise training (3 weeks), slight reductions were observed in most values (Table 2). No significant changes were found after 9 weeks of training.

Effects of exercise training on in vivo insulin sensitivity SSPG test. Only a minor change was observed in in vivo insulin sensitivity (Fig. 3) as measured by the steady state glucose concentrations during the 90–150 min period of the insulin sensitivity test (baseline SSPG value, 9.2 ± 1.2 mmol/l; final SSPG value, 8.8 ± 1.3 mmol/l, NS). Slightly higher, but not significantly different, plasma insulin values were observed during the test following training (baseline, 88 ± 12 mU/l; final, 107 ± 18 mU/l).

Euglycaemic clamp test. Plasma glucose values were maintained during the baseline and final testing procedures at 4.7 ± 0.05 mmol/l and 4.7 ± 0.07 mmol/l, respectively. The insulin infusion induced slightly lower mean plasma insulin levels during the steady state period following exercise training (baseline, 96 ± 13 mU/l; and final, 75 ± 13 mU/l, NS). The glucose utilization rate (M) measured at baseline was 3.1 ± 0.8 $mg \cdot kg^{-1} \cdot min^{-1}$ and remained at 2.9 ± 1.2 $mg \cdot kg^{-1} \cdot min^{-1}$ after the physical training program (Fig. 4).

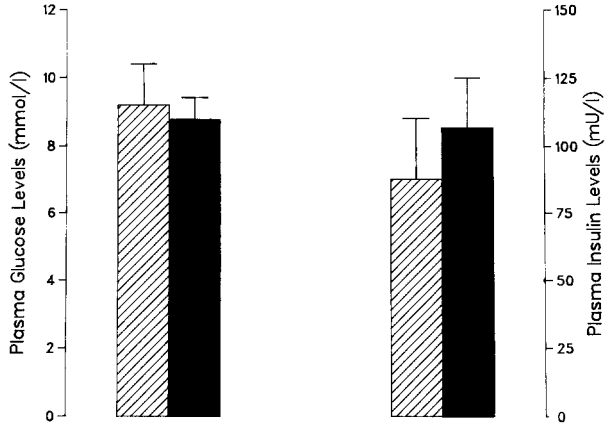

Fig. 3. Steady state plasma glucose (left) and insulin levels (right) at baseline (▨) and after final (■) physical training ($n=12$)

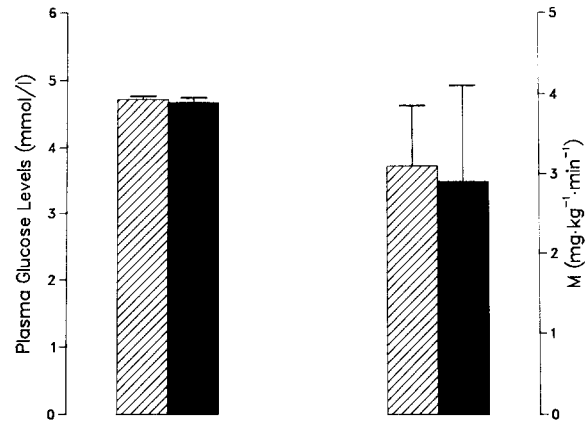

Fig. 4. Plasma glucose levels (left) and insulin-mediated glucose utilization rate (M) (right) at baseline (▨) and after final (■) physical training ($n=7$)

Table 3. Baseline and final data for body mass index (BMI), fasting glucose and insulin levels and glucose and insulin levels at 2 h during the oral glucose tolerance test

Subject	Baseline measures					Final measures				
	Fasting			2 h		Fasting			2 h	
	BMI (kg/m^2)	Glucose (mmol/l)	Insulin (mU/l)	Glucose (mmol/l)	Insulin (mU/l)	BMI (kg/m^2)	Glucose (mmol/l)	Insulin (mU/l)	Glucose (mmol/l)	Insulin (mU/l)
1	25.2	7.0	16.0	11.3	109.0	25.3	6.8	17.0	11.1	57.0
2	25.2	6.1	11.0	8.8	30.0	24.4	5.7	6.0	6.5	18.0
3	28.6	9.0	17.0	11.4	99.0	28.6	8.4	26.0	10.2	151.0
4	28.0	6.7	15.0	12.9	73.0	27.7	6.7	13.0	9.8	73.0
5	19.4	6.1	12.0	8.3	105.0	19.8	6.6	7.0	7.9	62.0
6	24.3	5.6	9.0	10.4	330.0	22.2	5.3	19.0	8.9	322.0
7	27.8	6.9	27.0	10.3	243.0	27.6	6.9	27.0	13.8	227.0
8	24.4	6.8	14.0	9.0	334.0	24.3	5.6	12.0	7.5	290.0
9	27.1	6.3	18.0	13.7	303.0	27.4	6.1	28.0	10.9	369.0
10	23.4	6.3	5.0	8.6	142.0	23.5	6.3	8.0	9.8	128.0
11	22.2	6.3	12.0	7.9	109.0	22.2	6.3	11.0	8.0	54.0
12	24.4	6.3	10.0	9.0	184.0	23.9	6.2	17.0	7.9	149.0
13	24.7	5.4	6.0	7.9	44.0	23.7	5.3	3.0	7.8	50.0
14	29.1	8.1	21.0	9.2	108.0	29.5	6.6	21.0	11.5	129.0
15	30.9	6.5	20.0	9.4	111.0	30.6	6.8	13.0	6.9	58.0
16	28.0	5.8	18.0	10.7	107.0	28.4	5.4	21.0	8.7	52.0
17	32.3	6.0	37.0	10.4	332.0	32.3	5.6	42.0	11.1	167.0
18	19.7	5.3	7.0	7.9	76.0	19.7	5.6	7.0	8.1	60.0
19	28.3	6.6	47.0	9.2	156.0	29.6	7.7	34.0	10.7	103.0
Mean ± SEM	25.9 ± 0.8	6.5 ± 0.2	17.0 ± 2.4	9.8 ± 0.4	157.5 ± 23.1	25.8 ± 0.8	6.3 ± 0.2	17.5 ± 2.4	9.3 ± 0.4	132.6 ± 23.3

Body weights and diet

Body weights were 81.0 ± 3.9 kg at baseline and 80.7 ± 3.9 kg at final; (NS). The subjects reported no change in dietary constituents during the study. Their typical diet showed a caloric intake of 2371 ± 120 and a dietary composition as follows: protein (%), 18 ± 1; fat (%), 42 ± 3; carbohydrates (%), 37 ± 2; ethanol (%), 3 ± 1; ratio of polyunsaturated fat to saturated fat, 1.2 ± 2.2; sugar as % of carbohydrates, 46 ± 3; cholesterol (mg), 451 ± 107; and caffeine (mg), 470 ± 85.

Relationship among variables before and following exercise training

At baseline, significant ($p<0.05$) associations were found between the following variables: insulin and body weight, HDL-C and insulin, LDL-C and fasting insulin, TG and fasting insulin, VLDL-TG and glucose, VLDL-TG and TG, insulin resistance (SSPG) and fasting insulin, and insulin mediated glucose uptake (M value) and fasting insulin (Table 4). In general, the magnitude of associations for variables at baseline remained similar when assessed following exercise training.

Table 4. Relationship among variables at baseline and following 9 weeks of physical training[a]

	Weight (kg)	Aerobic capacity ($ml \cdot kg^{-1} \cdot min^{-1}$)	Glucose (mmol/l)	Insulin (mU/l)	Cholesterol (mmol/l)	HDL-Chol (mmol/l)	LDL-Chol (mmol/l)	TG (mmol/l)	VLDL-TG (mmol/l)	SSPG ($n=12$)	Euglycaemic clamp ($n=7$)
Weight (kg)											
Aerobic capacity ($ml \cdot kg^{-1} \cdot min^{-1}$)	0.13 (0.05)										
Glucose (mmol/l)	0.28 (0.24)	0.03 (0.10)									
Insulin (mU/l)	0.73[d] (0.68[d])	0.06 (0.10)	0.24 (0.30)								
Cholesterol (mmol/l)	0.04 (0.10)	0.20 (0.10)	0.09 (0.27)	0.09 (0.30)							
HDL-Chol (mmol/l)	0.24 (0.20)	0.13 (0.31)	0.17 (0.35)	0.52[g] (0.37)	0.11 (0.02)						
LDL-Chol (mmol/l)	0.43 (0.42)	0.42 (0.18)	0.35 (0.11)	0.54 (0.54[c])	0.45 (0.72)	0.30 (0.23)					
TG (mmol/l)	0.40 (0.44)	0.13 (0.22)	0.44 (0.49[c])	0.57[d] (0.57[d])	0.03 (0.04)	0.55[c] (0.57[c])	0.73[d] (0.57[c])				
VLDL-TG (mmol/l)	0.18 (0.04)	0.11 (0.07)	0.53[c] (0.48[c])	0.17 (0.15)	0.12 (0.09)	0.25 (0.50[c])	0.44 (0.42)	0.76[d] (0.60[d])			
SSPG ($n=12$)	0.55 (0.69[c])	0.25 (0.34)	0.55 (0.43)	0.89[d] (0.73[h])	0.23 (0.41)	0.21 (0.46)	0.01 (0.38)	0.25 (0.18)	0.25 (0.19)		
Euglycaemic[b] Clamp ($n=7$)	0.52 (0.83[c])	0.34 (0.14)	0.66 (0.46)	0.81[c] (0.83)	0.59 (0.08)	0.66 (0.29)	0.62 (0.21)	0.66 (0.53)	0.28 (0.86[c])		

HDL-Chol = high density lipoprotein cholesterol; LDL-Chol = low density lipoprotein cholesterol; TG = triglycerides; VLDL-TG = very low density lipoprotein triglycerides; SSPH = steady state plasma glucose levels (mmol/l) during insulin sensitivity test [13].

[a] Values without parentheses represent pre-training correlation coefficients and those with parentheses represent post-training correlation coefficients; [b] euglycaemic clamp, total glucose disposal rate ($mg \cdot kg^{-1} \cdot min^{-1}$) determining insulin sensitivity according to the euglycaemic clamp technique [14]; [c] significant ($p<0.05$) association between variables; [d] Highly significant ($p<0.01$) association between variables

Discussion

The exercise training program employed in this study resembled one used previously [6], and produced a $16 \pm 3\%$ increase in aerobic capacity. Nevertheless, oral glucose tolerance, insulin resistance and lipid concentrations changed little. These findings contrast with our recent report showing improvements in glucose and lipid metabolism as well as insulin sensitivity in a similar, but normoglycaemic, hypertriglyceridaemic group of middle-aged men [6].

The initial aerobic capacities found among subjects in this study were approximately 4–5 $ml \cdot min^{-1} \cdot kg^{-1}$ lower than those we found in similarly aged subjects with normal glucose intolerance [6]. Lower than normal aerobic capacities in diabetic patients have been noted by others [16]. Since maximum heart rate and blood pressure responses to stress testing were comparable to those found in subjects without glucose intolerance [6], reduced aerobic capacities were not due to the failure of these subjects to adequately stress their cardiovascular systems. The improvement in oxygen consumption with exercise in these patients was similar to that reported in subjects without glucose intolerance [6]. But because of the lower initial values observed, they never exceeded the initial values which we have reported for hypertriglyceridaemic middle-aged men without glucose intolerance [6]. It is possible that untrained glucose intolerant subjects have greater body fatness, which whould tend to reduce maximum oxygen uptake. Since these subjects showed reduced aerobic capacities, both initially and after training, there may be a minimal fitness level at which the metabolic effects of exercise training are likely to occur. The work of Trovati et al. [17] supports this contention; more frequent and stressful exercise led to beneficial effects in young subjects not observed in this study.

As reported by others [16] glucose tolerance in our subjects did not change following a moderate exercise training program. If weight loss is added to an exercise program, however, glucose intolerant subjects improve their oral glucose tolerance [18]. The insulin response patterns to the oral glucose challenge also failed to change with physical training except for lower insulin concentrations observed at 90 and 120 min in the OGTT performed after training.

Fasting insulin levels, a simple measurement that correlates with in vivo insulin sensitivity [19], remained stable. These results agree with the minimal change observed in in vivo insulin resistance, measured directly by either the SSPG or ECT method. Several recent studies have reported conflicting effects of physical training on insulin mediated glucose disposal. We found earlier that exercise training improved insulin sensitivity in non-diabetic, hypertriglyceridaemic, middle-aged men [6]. Trovati et al. [17] reported improvements in insulin sensitivity in five non-insulin-dependent diabetic patients participating in a very strenuous exercise program. Reitman et al. [20] found no change in insulin mediated glucose uptake in six obese Indians after training, yet Bogardus et al. [45] showed improvements in insulin sensitivity on a weight reducing diet for obese subjects only if exercise training was involved. None of these other studies has assessed both carbohydrate and lipid metabolism as well as in vivo insulin sensitivity, so that the discrepant results may be due to concurrent abnormalities in lipid metabolism, the severity of alteration in glucose tolerance, obesity or levels of training employed.

Our data concurs with those of Reaven et al. [21], showing that mild endogenous hypertriglyceridaemia and insulin resistance can occur even in non-obese subjects. This supports the contention of Ruderman et al. [22] that normal-weight individuals can display many obesity-related metabolic disorders. Our results also substantiate the theory that a link exists between impaired glucose tolerance, hyperinsulinaemia and insulin resistance to abnormalities in lipoproteins [23].

Development of improved strategies to reduce insulin resistance and to correct associated metabolic abnormalities is important for controlling hyperglycaemia and the risk associated with its presence. Exercise programs are being promoted as a means to achieve these changes. Our study was designed to assess the effects of moderate exercise in the absence of weight loss. Despite clear evidence of improved aerobic capacity, we failed to find the desired benefits upon insulin sensitivity, lipid and glucose metabolism.

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