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ORIGINAL ARTICLE

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The effects of 24 weeks of moderate- or high-intensity exercise on insulin resistance

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Abstract This study was designed to investigate the effect of exercise intensity on insulin resistance by comparing moderate- and high-intensity interventions of equal energy cost. Maximum oxygen consumption (VO_{2max}), insulin, glucose and triglycerides were measured in 64 sedentary men before random allocation to a non-exercise control group, a moderate-intensity exercise group (three 400-kcal sessions per week at 60% of VO_{2max}) or a high-intensity exercise group (three 400-kcal sessions per week at 80% of VO_{2max}). An insulin sensitivity score was derived from fasting concentrations of insulin and triglycerides, and insulin resistance was assessed using the homeostasis model assessment of insulin resistance (HOMA-IR). Data were available for 36 men who finished the study. After 24 weeks, insulin concentration decreased by 2.54 ± 4.09 and 2.37 ± 3.35 mU l^{-1}, insulin sensitivity score increased by 0.91 ± 1.52 and 0.79 ± 1.37, and HOMA-IR decreased by -0.6 ± 0.8 and -0.5 ± 0.8 in the moderate- and high-intensity exercise groups, respectively. When data from the exercise groups were combined, one-way analysis of variance with one-tailed post hoc comparisons indicated that these changes were significantly greater than those observed in the control group (all $P < 0.05$). Twenty-four week changes in insulin concentration, insulin sensitivity score and HOMA-IR were not significantly different between the exercise groups. These data suggest that exercise training is accompanied by a significant reduction in insulin resistance, as indicated by well-validated surrogate measures. These data also suggest that moderate-intensity exercise is as effective as high-intensity exercise when 400 kcal are expended per session.

Keywords Training · Dose–response · Insulin sensitivity · Diabetes

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Introduction

Insulin resistance, a reduction in insulin-mediated glucose uptake, is a risk factor for type 2 diabetes and coronary heart disease (DeFronzo and Ferrannini 1991). In the Diabetes Prevention Program, dietary modification, weight loss and moderate activity reduced the 3-year incidence of diabetes by 58% in 1,079 individuals with impaired glucose tolerance (Molitch et al. 2003). In light of the Diabetes Prevention Program, 30 min of moderate activity per day was recommended in the prevention and delay of type 2 diabetes (American Diabetes Association 2002). However, it is difficult to distinguish the protective effect of moderate activity from those of the co-interventions used in the Diabetes Prevention Program. It is also unclear whether moderate activity is as effective in preventing type 2 diabetes as vigorous activity. Indeed, large prospective studies have shown that vigorous activity is more effective in preventing type 2 diabetes than moderate activity (Helmrich et al. 1991; Manson et al. 1991).

In order to investigate the effect of exercise intensity, it is necessary to compare changes in insulin resistance

following moderate and vigorous interventions of equal energy cost. However, the comparison of isocaloric interventions is rare. Kang et al. (1996) reported that insulin sensitivity increased after 7 days of exercise at 70% of maximum oxygen consumption (VO_{2max}), but was unchanged after 7 days of exercise at 50% of VO_{2max}. In the Studies of Targeted Risk Reduction Interventions Through Defined Exercise (STRRIDE), insulin sensitivity increased after 6 months of moderate- or high-intensity exercise (Houmard et al. 2004). For this reason, it was concluded that improvement in insulin sensitivity was independent of exercise intensity. However, STRRIDE did not regularly re-prescribe exercise to accommodate improvements in cardiorespiratory fitness, which are rapid in previously sedentary individuals (Hickson et al. 1981).

To further elucidate the dose–response relationship, the present study tested the hypothesis that greater improvements in surrogate measures of insulin resistance are derived from 24 weeks of high-intensity exercise than from 24 weeks of moderate-intensity exercise of equal energy cost. Unlike previous randomised controlled trials, exercise was prescribed at baseline and after monthly fitness tests.

Methods

Subjects

Participants in this study were men who volunteered to take part in an investigation of the effect of exercise training on coronary heart disease risk factors (O'Donovan et al. 2005). Sedentary, non-smoking men aged 30–45 years were recruited from large employers in the city of Canterbury, UK. Volunteers were examined by a cardiologist and were excluded if there was evidence of cardiovascular disease or if two or more of the following risk factors were present: family history of heart disease or sudden death; fasting cholesterol >6.2 mmol l^{-1}; fasting glucose >6.1 mmol l^{-1}; systolic blood pressure >140 mm Hg; or diastolic blood pressure >90 mm Hg. Daily energy expenditure was estimated using a 7-day physical activity recall questionnaire (Sallis et al. 1985) and volunteers were excluded if they revealed any participation in very hard activities or more than 2 h participation in hard activities. All participants signed a statement of informed consent as approved by the East Kent Hospitals Local Research Ethics Committee.

Interventions and randomisation

After screening, participants were randomly assigned to a non-exercise control group, a moderate-intensity exercise group or a high-intensity exercise group. All subjects were instructed not to change their dietary or lifestyle habits other than prescribed. In both exercise groups, cycling intensity and duration were gradually increased during the first 8 weeks of training (Fig. 1). Thereafter, the moderate-intensity group completed three 400-kcal sessions per week at 60% of VO_{2max} whilst the high-intensity group completed three 400-kcal sessions per week at 80% of VO_{2max}. Training heart rates were re-prescribed after monthly fitness tests, because improvements in fitness are rapid in previously sedentary men (Hickson et al. 1981). Exercise testing took place at the exercise physiology laboratory of Canterbury Christ Church University College and exercise training was undertaken ad libitum at the institution's supervised fitness centre during normal opening hours.

Participants were recruited by the principal investigator but were assigned to control or exercise groups by a third party using computer-generated sequences of random numbers. The principal investigator and the subjects were blinded to the randomisation process, and assignment was only divulged after baseline testing.

Outcomes

At baseline and after 24 weeks, venous blood was drawn following a 12-h overnight fast and 24-h abstinence from vigorous activity. Triglyceride and glucose concentrations were determined in fresh serum using standard enzymatic tests (Cobas Integra 800 analyser, Roche Diagnostics Ltd, Lewes, UK). Serum frozen at −70°C was later thawed, and baseline and post-intervention insulin concentrations were determined concurrently using a chemiluminescent immunoassay (ADVIA Centaur analyser, Bayer Corporation, Newbury, UK). The between-day coefficient of variation for all assays was $<3\%$. Insulin resistance was determined using the homeostasis model assessment of insulin resistance (HOMA-IR), which correlates well with the euglycaemic hyperinsulinaemic clamp technique (Matthews et al. 1985). Insulin sensitivity was assessed using the formula of McAuley and colleagues (2001) as the exponent of [2.63–0.28ln(insulin)–0.31ln(triglyceride)]. This score describes the glucose disposal rate (milligrams per kilogram of fat-free mass per minute) in relation to the average plasma insulin concentration during the final 60 min of a 120-min hyperinsulinaemic euglycaemic clamp. In 178 normoglycaemic individuals aged 25–68 years, this score was a better predictor of insulin sensitivity than fasting insulin, insulin-to-glucose ratio, HOMA-IR and other surrogate measures (McAuley et al. 2001).

Oxygen consumption was measured whilst cycling to exhaustion during an incremental test lasting around 8–16 min. Respiratory gases were measured by a mass spectrometer (model EX670, Morgan Medical Ltd, Gillingham, UK) that was validated periodically using a Gas Exchange System Validator (Medical Graphics Corporation, Minnesota, USA) first described by Huszczuk et al. (1990). Typically, high agreement was observed between expected and reported values. For

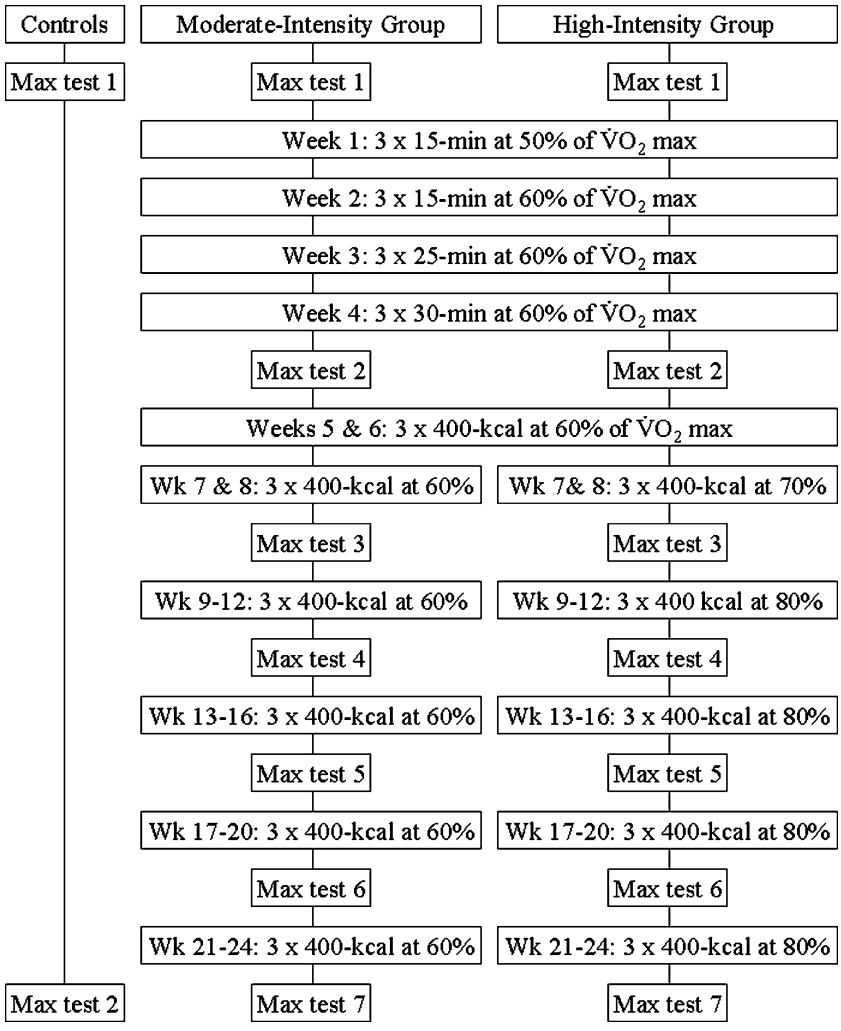

Fig. 1 Exercise interventions. Each exercise bout was accompanied by a 5-min warm-up and cool-down at 60 W. Cycling cadence was increased from 60 rpm to 70 rpm after week 8

example, in a recent validation test, VO_2 varied by −3.1%,−2.8% and −1.8% at low, medium and high metabolic rates, respectively. Heart rate was recorded periodically during each test using a Polar Accurex Plus heart rate monitor (Polar Electro, Kempele, Finland).

Fitness tests were also used to prescribe exercise. Training heart rate was determined from the regression of heart rate against VO_2. Energy expenditure was determined from oxygen consumption, assuming an energy cost of 5 kcal per litre of oxygen. For example, an individual with a VO_{2max} of 3.0 l min^{-1} uses 9.0 kcal per minute when exercising at 60% of VO_{2max} [(3.0×60%) ×5], and will expend 400 kcal in 44.4 min (400/9). At 80% of VO_{2max}, the same individual uses 12 kcal per minute and expends 400 kcal in 33.3 min.

The same trained investigator measured triceps, biceps, subscapular and suprailiac skinfolds at baseline and post-intervention, and percent body fat was estimated using a standard equation for men (Durnin and Womersley 1974). Waist girth was measured in a horizontal plane at the narrowest part of the torso. Body mass index (BMI) was expressed as the body weight in kg divided by the height in m^2. Socio-economic status was determined during an interview using the three-class version of the National Statistics Socio-Economic Classification: managerial and professional occupations; intermediate occupations; and, routine and manual occupations (Office for National Statistics 2002).

Statistical analyses

Baseline group scores for socio-economic status were compared using the chi-square test. All other baseline data were compared using general linear model analysis of variance (GLM ANOVA). The Shapiro–Wilk test was used to determine if the residuals were normally distributed. Analysis of variance (ANOVA) with one-tailed post hoc comparisons was used to test the hypothesis that high-intensity exercise is more effective in improving insulin resistance than moderate-intensity exercise. Using the methods described by Field (2000), two planned comparisons were conducted. Firstly, 24-week changes in the dependent variables were compared in the control group versus the two exercise groups. Secondly, 24-week changes were compared in the mod-

erate-intensity group versus the high-intensity group. Homogeneity of variance was determined using Levene's test. Relationships between dependent variables were tested with Pearson's correlation coefficient. Backward elimination was used in multiple linear regression models to determine whether changes in surrogate measures of insulin resistance were predicted by changes in body fat, waist girth, physical activity (kcal day^{-1}) or physical fitness (VO_{2max}). All data were analysed using SPSS for Windows, version 11.0 (SPSS Inc., Chicago, Illinois, USA).

Results

All data were normally distributed and the variances of the groups were not significantly different. The flow of participants through the study is shown in Fig. 2. Fifteen controls, 14 moderate-intensity exercisers and 13 high-intensity exercisers finished the study. However, insufficient serum was available in one control subject and four moderate-intensity exercisers. Similarly, data are not reported for a control subject who developed hyperinsulinaemia. Dropout was similar in both exercise groups, and the dependent variables were not significantly different in dropouts and men who finished the study.

The baseline physical and physiological characteristics of those who finished the study are shown in Table 1. Exercise and control groups did not differ significantly in age, height, weight, BMI, body composition, waist girth, energy expenditure or cardiorespiratory fitness. There were also no significant inter-group differences in fasting concentrations of triglycerides, insulin or glucose. Insulin sensitivity and insulin resistance were not significantly different between the groups. The groups were also of similar socio-economic status: 85% of controls, 80% of moderate-intensity exercisers and 85% of high-intensity exercisers were employed in managerial and professional occupations.

The efficacy of the interventions was demonstrated by a 0.40 ± 0.15 l min^{-1} increase in VO_{2max} in the moderate-intensity group and by a 0.55 ± 0.27 l min^{-1} increase in VO_{2max} in the high-intensity group (both $P < 0.001$ versus controls). Cardiorespiratory fitness did not change in the control group (-0.04 ± 0.17 l $min-^{1}$, $P = 0.38$ versus baseline). During the intervention, energy expenditure increased significantly in both exercise groups. However, the change in energy expenditure was not significantly different between the moderate- and high-intensity groups (78 ± 202 vs. 135 ± 83 kcal day^{-1}, $P = 0.37$). There was no evidence that either exercise group reduced its usual level of activity during the intervention.

When data from the exercise groups were compared with the control group, it was apparent that exercise training was accompanied by a significant reduction in insulin concentration, a significant increase in insulin sensitivity and a significant decrease in insulin resistance (Table 2). However, 24-week changes in insulin concentration, insulin sensitivity and insulin resistance were not significantly different between the moderate- and high-intensity exercise groups. Exercise training was not accompanied by a significant reduction in triglyceride concentration or by a significant reduction in glucose concentration.

Pooled data showed that the exercise-induced change in waist girth was associated with the 24-week change in insulin concentration and the 24-week change in insulin resistance (Table 3). Concurrently, change in physical activity was inversely related to change in insulin

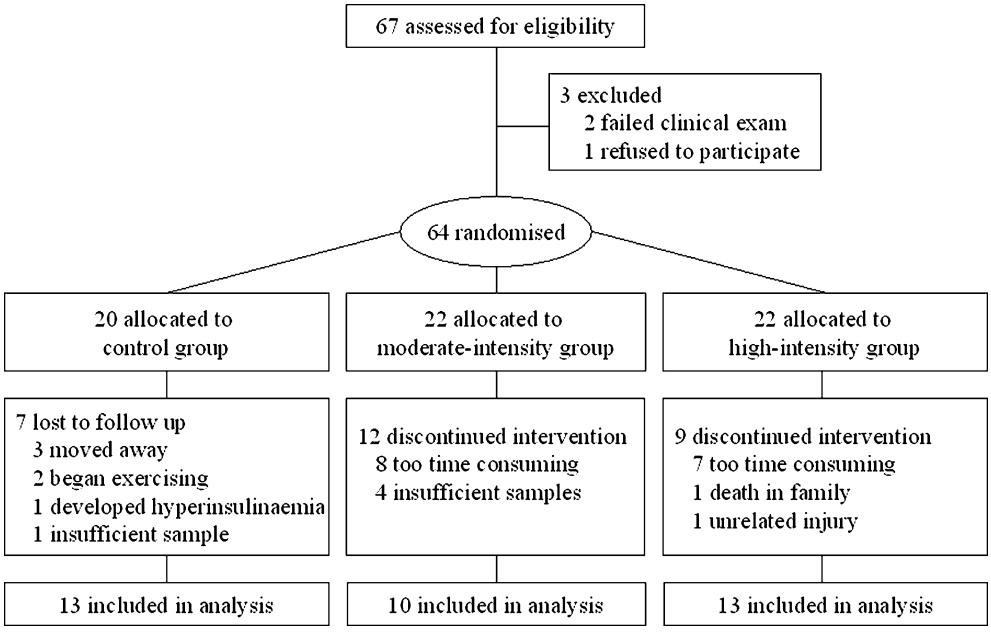

Fig. 2 Flow of participants through the study

Table 1 Baseline physical and physiological characteristics of each group

	Control group ($n = 13$)	Moderate-intensity group ($n = 10$)	High-intensity group ($n = 13$)
Age (years)	40.7 ± 2.9	41.5 ± 1.5	40.6 ± 3.5
Height (m)	1.84 ± 0.05	1.80 ± 0.05	1.79 ± 0.06
Weight (kg)	97.1 ± 18.2	89.4 ± 21.8	83.6 ± 10.1
Body mass index (kg m^2)	28.7 ± 4.9	27.5 ± 6.0	26.2 ± 2.6
Body fat (%)	24.4 ± 5.8	22.6 ± 4.7	23.4 ± 3.9
Waist girth (cm)	100.42 ± 12.2	96.67 ± 17.52	94.22 ± 9.19
Energy expenditure (kcal day^{-1})	3485 ± 710	3314 ± 838	2953 ± 480
VO_{2max} (l min^{-1})	2.89 ± 0.31	2.67 ± 0.47	2.62 ± 0.43
VO_{2max} (ml kg^{-1} min^{-1})	30.5 ± 5.8	30.6 ± 5.8	31.8 ± 6.0
Triglycerides (mmol l^{-1})	1.55 ± 0.59	1.92 ± 1.09	1.20 ± 0.38
Insulin (mU l^{-1})	9.89 ± 5.25	8.30 ± 4.46	9.03 ± 4.00
Glucose (mmol l^{-1})	5.11 ± 0.42	5.08 ± 0.39	5.02 ± 0.35
Insulin sensitivity	7.0 ± 1.9	7.1 ± 2.2	7.5 ± 1.4
HOMA-IR	2.3 ± 1.2	1.8 ± 0.9	2.1 ± 1.0

Groups compared using GLM ANOVA. All values are mean ± standard deviation. VO_{2max}, maximum oxygen consumption. HOMA-IR, homeostasis model assessment for insulin resistance

Table 2 Twenty-four-week changes in insulin concentration, glucose concentration and surrogate measures of insulin sensitivity

Variable	Control group ($n = 13$)	Moderate-intensity group ($n = 10$)	High-intensity group ($n = 13$)	One-tailed P for planned comparisons	
				Control group versus both exercise groups	Moderate-intensity versus high-intensity group
Triglycerides (mmol l^{-1})	0.10 ± 0.50	−0.36 ± 0.68	−0.04 ± 0.39	0.053	0.08
Insulin (mU l^{-1})	0.13 ± 5.29	−2.54 ± 4.09	−2.37 ± 3.35	0.048	0.46
Glucose (mmol l^{-1})	0.19 ± 0.62	−0.02 ± 0.35	Nil ± 0.32	0.11	0.46
Insulin sensitivity	−0.12 ± 1.13	0.91 ± 1.52	0.79 ± 1.37	0.02	0.42
HOMA-IR	0.2 ± 1.5	−0.6 ± 0.8	−0.5 ± 0.8	0.03	0.49

Groups compared using one-way ANOVA with one-tailed post hoc comparisons. All values are mean ± standard deviation. HOMA-IR, homeostasis model assessment for insulin resistance

Table 3 Correlates of change in insulin concentration and changes in surrogate measures of insulin resistance

	Δ insulin concentration	Δ insulin sensitivity	Δ HOMA-IR
Δ Body fat (%)	0.002	0.02	−0.002
Δ Weight (kg)	0.17	−0.17	0.17
Δ Waist girth (cm)	0.48*	−0.39	0.48*
Δ Energy expenditure (kcal day^{-1})	−0.49*	0.33	−0.39
Δ Physical fitness (l min^{-1})	−0.10	0.03	−0.04

Data derived from both exercise groups, $n = 23$. Δ, change in
*Two-tailed correlation is significant, $P < 0.05$. HOMA-IR, homeostasis model assessment for insulin resistance

concentration. Changes in weight, body fat and VO_{2max} were not associated with changes in insulin concentration, insulin sensitivity or insulin resistance. In multiple linear regression models, 38% of the variance in the exercise-induced change in insulin concentration was explained by changes in waist girth and energy expenditure. Change in waist girth was the sole predictor of change in insulin sensitivity and change in insulin resistance, predicting 15% and 23% of the variance, respectively.

Discussion

There were two main findings in this study of the effect of exercise intensity on insulin resistance. Firstly, 24 weeks of exercise is accompanied by a significant reduction in insulin resistance, as indicated by well-validated surrogate measures (Matthews et al. 1985; McAuley et al. 2001). Secondly, training at 60% of VO_{2max} is as effective as training at 80% of VO_{2max} when 400 kcal are expended per session.

It is well-documented that exercise training decreases insulin resistance (Ivy 1997). Less certain is the effect of exercise intensity on insulin resistance. In a recent review, Carroll and Dudfield (2004) identified randomised controlled trials in which insulin resistance was improved in overweight men following 3–10 months of exercise without weight loss at 50–80% of heart rate reserve [approximately 55–82% of VO_{2max} (Swain and Leutholtz 1997)]. In the Studies of Targeted Risk Reduction Interventions Through Defined Exer-

cise (STRRIDE), insulin sensitivity increased in 111 overweight, dyslipidaemic adults allocated to one of three groups for 6 months: low-volume/moderate-intensity exercise (1,200 kcal week^{-1} at 40–55% of VO_{2max}); low-volume/high-intensity exercise (1,200 kcal week^{-1} at 65–80% of VO_{2max}); or, high-volume/high-intensity exercise (2,000 kcal week^{-1} at 65–80% of VO_{2max}) (Houmard et al. 2004). Collectively, these findings suggest that improvement in insulin resistance is independent of exercise intensity. However, the effect of low-intensity exercise is unclear.

It has been shown that insulin sensitivity is increased following exercise of sufficient magnitude to deplete muscle glycogen (Perseghin et al. 1996). It has also been shown that muscle glycogen makes no discernible contribution to the energy demands of exercise at 25% of VO_{2max} (Romijn et al. 1993). However, muscle glycogen is utilised at 50%, 65% and 85% of VO_{2max} (Kang et al. 1996; Romijn et al. 1993). Whilst the rate of utilisation at 85% is twice that at 65% of VO_{2max} (Romijn et al. 1993), it is reasonable to suggest that meaningful glycogen depletion can be achieved during moderate-intensity exercise of longer duration. Such a mechanism would explain the increases in insulin sensitivity observed in the present study and in STRRIDE. The effect of lower intensity exercise on insulin sensitivity is not well documented. Seals et al. (1984) found no change in insulin sensitivity in 11 adults who walked for 30 min, three-to-four times per week for 6 months. Walking reduced the incidence of type 2 diabetes in the Diabetes Prevention Program (Molitch et al. 2003), but its influence cannot be distinguished from that of co-interventions.

Perhaps the most compelling endorsement of moderate-intensity exercise is provided by the HERITAGE Family Study (Boule et al. 2005). In that 20-week intervention, mean insulin concentration fell by 8% and mean insulin sensitivity increased by 10% in 596 healthy adults who exercised three times per week, progressing from 30 min per session at 55% of VO_{2max} to 50 min per session at 75% of VO_{2max}. Because of its large sample size, the HERITAGE Family Study was able to demonstrate (1) the variability of the exercise-induced change in glucose metabolism, and (2) the tendency for normal weight individuals to demonstrate a lower mean increase in insulin sensitivity (6%) than overweight (14%) or obese (15%) individuals. The findings of the HERITAGE Family Study are only limited by the absence of a non-exercise control group. In the present study, mean insulin concentration fell by 19% and mean insulin sensitivity increased by 15% in overweight men who exercised for 24 weeks. During the same period, insulin concentration increased by 12% and insulin sensitivity was unchanged in overweight men who did not exercise.

Moderate activity is recommended on the basis that vigorous activity is accompanied by increased risk of injury and dropout (American Diabetes Association 2002). Although, moderate interventions are often more successful (Dishman and Buckworth 1996), the present study is in agreement with others finding no difference in injury or dropout rates between moderate- and high-intensity interventions (Crouse et al. 1997; Gossard et al. 1986; Houmard et al. 2004). In the present study, the high-intensity group was able to expend 1,200 kcal per week with three 30–40 min visits to the gym. To achieve the same energy expenditure whilst walking briskly, these men would have to walk for around 30 min per day, 7 days a week (Ainsworth et al. 2000).

It might be argued that the results of the present study are explained by an acute response to recent exercise, given that insulin sensitivity is increased from 12 up to 24 h postexercise (Albright et al. 2000). Indeed, participants were instructed to observe a 24-h abstinence from vigorous activity before providing blood. However, as blood was drawn early in the morning, it is more likely that subjects avoided exercise for around 36 h. Diet was not standardised before blood was drawn. Thus, we cannot exclude the possibility that changes in nutrient intake might have contributed to the changes in glucose and insulin concentrations observed in the present study. However, blood was drawn after a 12-h fast and subjects were instructed to maintain their usual dietary practices.

Insulin sensitivity can be increased by exercise, weight loss, or exercise in conjunction with weight loss (Dengel et al. 1996; Houmard et al. 2004; Lamarche et al. 1992). In the present study, exercise-induced changes in weight were minimal and did not predict changes in surrogate measures of insulin resistance. Instead, changes in waist girth and changes in energy expenditure explained much of the variance in insulin concentration and insulin resistance. These findings are not surprising, given the metabolic complications of visceral obesity (Despres et al. 2001) and the inverse relationship between energy expenditure and the development of type 2 diabetes (Helmrich et al. 1991; Hu et al. 1999).

Conclusion

The recommendation that exercise be performed frequently (Albright et al. 2000; American Diabetes Association 2002) is logical, given that insulin sensitivity is transiently increased following a single bout of exercise (Albright et al. 2000; Thompson et al. 2001). Data from the present study and a larger randomised controlled trial (Houmard et al. 2004) suggest it is also possible to improve glucose metabolism by exercising three times per week whilst leading an otherwise inactive lifestyle. Busy individuals may find such a commitment more realistic than the lifestyle approach, even with the caveat that one should expend 400 kcal per session at 60% or 80% of maximum capacity.

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