Journal of Sports Sciences, 2002, **20**, 961–967

Taylor & Francis
healthsciences

Moderate exercise and post-prandial metabolism: issues of dose–response

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Accepted 21 August 2002

In this study, we examined the effects of 1 and 2 h of brisk walking on post-prandial metabolism. Eleven pre-menopausal women participated in three oral fat tolerance tests with different pre-conditions: control (no exercise), 1 h walk (1 h of walking at 50% maximal oxygen uptake, $\dot{V}O_{2max}$, on the day before) and 2 h walk (2 h walking at 50% $\dot{V}O_{2max}$ on the day before). Venous blood samples were taken in the fasted state and for 6 h after ingestion of a high-fat mixed meal. Compared with the control trial, the 1 h walk reduced post-prandial lipaemia by a mean of 9.3%, whereas the 2 h walk reduced it by 22.8% ($P < 0.01$ for trend). Similarly, the 2 h walk reduced the post-prandial insulin response to a greater extent than the 1 h walk (17.3 *vs* 7.6%; $P < 0.05$ for trend). The results demonstrate that the beneficial effects of exercise on post-prandial metabolism are related to the duration and, therefore, the energy expenditure of the exercise session.

Keywords: brisk walking, dose–response, exercise prescription, moderate exercise, post-prandial lipaemia, triglyceride.

Introduction

Exercise training has been consistently shown to increase high-density lipoprotein (HDL) cholesterol concentrations, a change associated with a reduction in cardiovascular risk (Durstine *et al.*, 2001; Leon and Sanchez, 2001). This, however, is likely to reflect enhanced triglyceride metabolism, because the HDL cholesterol concentration is determined largely by the rate of metabolism of triglyceride-rich lipoproteins, particularly in the post-prandial state (Miesenböck and Patsch, 1992; Cohn, 1998; Rashid *et al.*, 2002). Sluggish triglyceride metabolism facilitates neutral lipid exchange between triglyceride-rich particles (chylomicrons and very low-density lipoproteins) and cholesterol-rich particles (HDL and low-density lipoprotein, LDL). This depletes HDL of cholesterol and leads to a preponderance of atherogenic small-dense LDL particles (Miesenböck and Patsch, 1992; Cohn, 1998). Thus, HDL cholesterol concentration can be considered to be an integrative marker of triglyceride metabolism. Because plasma triglyceride concentration is highest during the post-prandial state, studying metabolism at this time is an excellent model to study influences on HDL cholesterol.

However, the importance of post-prandial triglyceride metabolism extends beyond its role in the re-modelling of other lipoprotein classes for at least two reasons. First, post-prandial lipoproteins and their remnants may be directly atherogenic (Zilversmit, 1979; Cohn, 1998); second, recent evidence suggests that endothelial dysfunction – an early marker of atherosclerosis – is evident during the hours after consumption of a fatty meal (Vogel *et al.*, 1997; Evans *et al.*, 2000). We spend most of our lives in this pro-atherogenic state and so it is important to study interventions that influence the post-prandial handling of circulating lipids.

There is convincing evidence that the effect of exercise in reducing post-prandial lipaemia is a consequence of acute metabolic responses to recent exercise, rather than of long-term adaptations to training (Tsetsonis *et al.*, 1997; Hardman *et al.*, 1998). The reduction has been reported to be greater after 90 min of exercise at 60% of maximal oxygen uptake ($\dot{V}O_{2max}$)

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than after 90 min of exercise at 30% $\dot{V}O_{2max}$ (Tsetsonis and Hardman, 1996a). Furthermore, 3 h of exercise at 30% $\dot{V}O_{2max}$ was shown to attenuate post-prandial triglyceride concentrations to the same extent as 90 min at 60% $\dot{V}O_{2max}$ (Tsetsonis and Hardman, 1996b). Collectively, these studies suggest that the influence of exercise on post-prandial triglyceride metabolism occurs in a dose-dependent manner determined by the energy expended in exercise rather than by exercise intensity *per se*.

In practice, the easiest and safest way of increasing exercise energy expenditure – and thus enhancing its beneficial effect on triglyceride handling – is to increase the duration of exercise, particularly in previously sedentary people. The effects of altering exercise duration (at the same exercise intensity) on post-prandial lipaemia have not, however, been studied specifically. The aim of the present study was to test the hypothesis that the reduction in post-prandial lipaemia after 2 h of brisk walking is twice that observed after 1 h of brisk walking. These 'doses' of walking were chosen to represent achievable exercise targets for well-motivated, but not necessarily well-trained, healthy individuals who desire health gains beyond those associated with the minimal exercise prescription (Pate *et al.*, 1995).

Methods

Participants

Eleven apparently healthy, pre-menopausal women [age 24.3 (21.3–40.5) years, body mass index (BMI) 21.3 (18.9–30.1) $kg \cdot m^{-2}$, waist circumference 73.0 (61.1–88.4) cm, $\dot{V}O_{2max}$ 39.7 (31.5–50.9) $ml \cdot kg^{-1} \cdot min^{-1}$; median and range] volunteered to participate in the study. No participant was taking medication other than oral contraceptives (two women). The study was conducted with the approval of Loughborough University's Ethical Advisory Committee and the participants provided written informed consent.

Preliminary exercise tests

Maximal oxygen uptake was determined directly during uphill walking at a constant speed, using a modification of the Taylor treadmill test (Taylor *et al.*, 1955). In a separate test, the relationship between steady-state oxygen uptake and treadmill gradient was established. For both tests, expired air samples were collected using Douglas bags, with oxygen uptake and carbon dioxide production measured using a paramagnetic oxygen analyser (model 570A, Taylor-Servomex, Crowborough, UK), an infrared carbon dioxide analyser (Lira, Model 3250, Mines Safety Appliances Ltd, UK) and a dry gas meter (Harvard Apparatus, Edenbridge, UK). Heart rate was measured by short-range telemetry (Polar PE 3000 Sport Tester, Polar Electro Oy, Kempele, Finland). The gradient needed to elicit 50% $\dot{V}O_{2max}$ was then interpolated on an individual basis.

Study design

The participants completed three oral fat tolerance tests with different preceding interventions – that is, control (no exercise), 1 h of walking and 2 h of walking – at intervals of approximately 7 days and in a counterbalanced design.

For the walking trials, the participants walked on a motorized treadmill at an intensity of 50% $\dot{V}O_{2max}$ for either 1 or 2 h on the afternoon preceding the oral fat tolerance test. At 15 min intervals during the walk, expired air samples were collected using Douglas bags, heart rate was recorded and ratings of perceived exertion (Borg, 1973) were obtained. Capillary blood samples were taken at 30 min intervals for the determination of blood lactate concentration. In the control trial, the participants performed no exercise on the day before the oral fat tolerance test.

On the morning of the oral fat tolerance tests, the participants reported to the laboratory at 08:00 h after a 12 h fast (approximately 18 h after the end of exercise in the walking trials). A venous cannula was inserted and, after an interval of 20 min, a baseline blood sample was obtained. The participants then consumed a high-fat meal comprising whipping cream, fruit, cereal, nuts and chocolate (1.3 g fat, 1.2 g carbohydrate, 0.2 g protein and 73 $kJ \cdot kg^{-1}$ fat-free body mass). Further blood samples were obtained 30 min after the meal and then hourly for 6 h. The participants rested throughout this day and consumed only water. They were supine for at least 10 min before blood was sampled. The first 2 ml withdrawn was always discarded and the cannula was kept patent by flushing with non-heparinized saline (0.9%).

The participants refrained from all exercise (except for the supervised walks undertaken in the two exercise trials) during the 3 days leading up to each fat tolerance test; activities of daily living were kept to a minimum and walking or cycling for personal transportation was prohibited. The participants weighed and recorded the food and drink they consumed in the 2 days before their first fat tolerance test and replicated this consumption before their second test. No attempt was made to control for the phase of the menstrual cycle in this study, but it has been reported that there is no significant effect of menstrual phase on post-prandial lipaemia (Wendler *et al.*, 1992).

Analytical procedures

Capillary blood samples taken during the walks were immediately deproteinized, separated and the supernatant stored at −20°C for analysis of lactate (Maughan, 1982).

Blood samples taken during the fat tolerance tests were collected into pre-cooled potassium EDTA tubes and non-heparinized serum tubes (Sarstedt, Leicester, UK) and placed on ice. Plasma was separated within 15 min of collection, divided into portions and stored at −70°C. After samples for serum preparation were allowed to clot, they were separated and then stored at −70°C.

Plasma was analysed for triglyceride, cholesterol, HDL cholesterol, non-esterified fatty acids (NEFA) and glucose using enzymatic methods (Roche Diagnostics Corporation, Lewes, UK). The concentration of serum insulin was determined by radioimmunoassay (EURO/DPC Ltd, Caernarfon, UK).

Data analysis

Six-hour areas under plasma or serum concentration versus time curves were calculated using the trapezium rule and defined as the total post-prandial responses. The incremental areas under these curves were calculated in the same way after subtraction of the fasting concentration from each value and defined as the incremental post-prandial responses. The gross energy expenditure of the walks was calculated using indirect calorimetry, assuming no protein oxidation (Frayn and Macdonald, 1997). Dietary intake was analysed using a computerized version of food composition tables (CompEat 5, Carlson Bengston Consultants Ltd, Grantham, UK). Statistical analysis was performed using SPSS for Windows (SPSS Inc, Chicago, IL, USA). Means were compared using repeated-measures analysis of variance; linear trend analysis was used to determine whether variables changed in a dose-dependent manner with increasing exercise duration. Data whose distribution was significantly different from normal were logarithmically transformed before statistical analysis. Significance was set at $P < 0.05$ and the results are presented as the mean ± standard error of the mean ($s_{\bar{x}}$) unless otherwise stated. Data for triglyceride, total cholesterol and HDL cholesterol were obtained from all 11 participants, whereas those for insulin, glucose and NEFA were obtained from 9 participants.

Results

Cardiorespiratory and metabolic responses to brisk walking

Mean oxygen uptake was 20.3 ± 0.8 $ml \cdot kg^{-1} \cdot min^{-1}$ (50.0 ± 1.4% $\dot{V}O_{2max}$) during the 1 h walk and 20.9 ± 1.1 $ml \cdot kg^{-1} \cdot min^{-1}$ (51.3 ± 1.9% $\dot{V}O_{2max}$) during the 2 h walk, with average heart rates of 129 ± 2 and 135 ± 2 $beats \cdot min^{-1}$ and average blood lactate concentrations of 2.0 ± 0.6 and 1.8 ± 0.4 $mmol \cdot l^{-1}$ for the 1 and 2 h walks, respectively. The gross energy expenditure of exercise was 1.5 ± 0.1 MJ for the 1 h walk and 3.1 ± 0.2 MJ for the 2 h walk. The participants rated the intensity of both walks as 'fairly light': 10.5 ± 0.4 and 11.2 ± 0.5 on the Borg Scale (Borg, 1973) for the 1 and 2 h walks, respectively.

Dietary intake

Mean daily energy intake in the 2 days preceding the fat tolerance tests was 7.45 ± 0.75 MJ (57% energy from carbohydrate, 28% fat, 15% protein) for the control trial, 7.45 ± 0.69 MJ (58% energy from carbohydrate, 28% fat, 14% protein) for the 1 h walk trial and 7.62 ± 0.69 MJ (57% energy from carbohydrate, 28% fat, 15% protein) for the 2 h walk trial. Mean energy intake on the afternoon before the fat tolerance tests (i.e. after exercise in the two exercise trials) was 4.01 ± 0.49 MJ (56% energy from carbohydrate, 30% fat, 14% protein) for the control trial, 4.16 ± 0.49 MJ (57% energy from carbohydrate, 29% fat, 14% protein) for the 1 h walk trial and 4.42 ± 0.44 MJ (57% energy from carbohydrate, 29% fat, 14% protein) for the 2 h walk trial. None of these values differed significantly between trials.

Plasma and serum concentrations in the fasted state

Plasma concentrations of triglyceride, HDL cholesterol, total cholesterol, NEFA and glucose and serum concentrations of insulin in the fasted state during the three trials are shown in Table 1. Statistical analysis for fasting triglyceride was performed on log-transformed data. Fasting triglyceride concentrations decreased incrementally with increasing exercise, being 8.6% and 20.0% lower than the control trial after the 1 and 2 h walks, respectively ($P = 0.005$ for trend). There were no significant trends for changes in HDL cholesterol, glucose, NEFA or insulin with increasing exercise duration, but there was a tendency for total cholesterol to decrease with increasing exercise ($P = 0.06$ for trend).

Plasma and serum responses to the test meal

Figure 1 shows the plasma triglyceride, NEFA and glucose and serum insulin responses to the test meal in the three trials. Statistical analyses for the triglyceride responses were performed on log-transformed data. The total post-prandial triglyceride responses to the test meal decreased in a dose-dependent manner with increasing exercise duration with the total post-prandial

Table 1. Plasma and serum concentrations in the fasted state in the control, 1 h walk and 2 h walk trials (mean ± $s_{\bar{x}}$)

	Control	1 h walk	2 h walk	*P* for trend
TG ($mmol \cdot l^{-1}$)*	0.70 ± 0.06	0.64 ± 0.08	0.56 ± 0.09	0.005
HDL cholesterol ($mmol \cdot l^{-1}$)	1.49 ± 0.10	1.46 ± 0.10	1.50 ± 0.09	0.86
Total cholesterol ($mmol \cdot l^{-1}$)	3.84 ± 0.26	3.78 ± 0.27	3.68 ± 0.24	0.06
Insulin ($\mu U \cdot ml^{-1}$)	7.34 ± 0.63	7.44 ± 0.81	7.00 ± 0.72	0.60
NEFA ($mmol \cdot l^{-1}$)	0.42 ± 0.04	0.42 ± 0.03	0.53 ± 0.07	0.23
Glucose ($mmol \cdot l^{-1}$)	4.16 ± 0.08	4.36 ± 0.07	4.28 ± 0.04	0.18

Note: $n = 11$ for triglyceride (TG), HDL cholesterol and total cholesterol; $n = 9$ for insulin, non-esterified fatty acids (NEFA) and glucose.
* Statistical analysis performed on log-transformed data. *P*-value for linear trend in variable with increasing exercise duration [i.e. from control (no walk) to 1 h walk to 2 h walk].

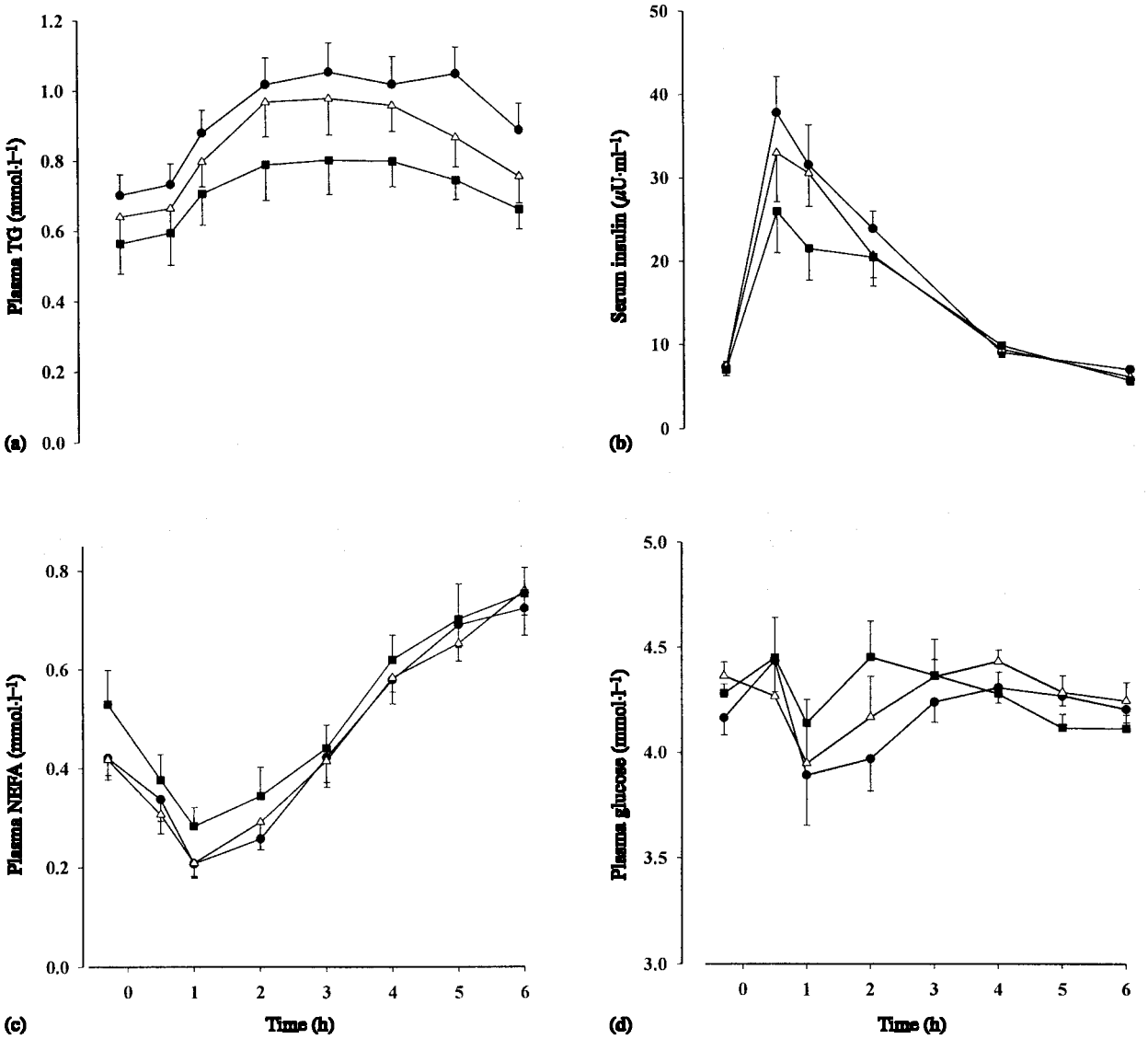

Fig. 1. (a) Plasma triglyceride, (b) serum insulin, (c) plasma non-esterified fatty acids and (d) plasma glucose concentrations in the fasted state and for 6 h after the consumption of a high-fat mixed test meal consumed ~ 18 h after three protocols: a 1 h walk (△), a 2 h walk (■) and a day of no exercise (control, ●) (mean ± $s_{\bar{x}}$). $n = 11$ for triglyceride, $n = 9$ for the other responses.

triglyceride response being 9.3% lower and 22.8% lower than the control trial after the 1 and 2 h walks, respectively ($P = 0.001$ for trend) (see Fig. 2a). The same pattern of change with exercise was evident for the incremental post-prandial triglyceride response (10.6% and 31.8% lower than control after the 1 and 2 h walks, respectively), but the trend for changes in this parameter with increasing exercise duration was not significant ($P = 0.10$) (Fig. 2a).

Both the total and incremental insulin responses to the test meal decreased with increasing exercise duration in a dose-dependent manner. The total insulin response was 7.6% and 17.3% lower than the control and the incremental response was 14.1% and 26.5% lower than the control after the 1 and 2 h walks, respectively (for both responses, $P = 0.02$ for trend) (Fig. 2b). There were no significant trends for changes in the total post-prandial glucose response (control 25.1 ± 0.4 mmol·l^{-1}·h, 1 h walk 25.6 ± 0.6 mmol·l^{-1}·h, 2 h walk 25.7 ± 0.4 mmol·l^{-1}·h; $P = 0.27$ for trend) or the total post-prandial NEFA response (control 2.74 ± 0.18 mmol·l^{-1}·h, 1 h walk 2.74 ± 0.14 mmol·l^{-1}·h, 2 h walk 3.02 ± 0.20 mmol·l^{-1}·h; $P = 0.29$ for trend) with increasing exercise duration.

Discussion

The nature of the dose–response relationship between exercise and health benefits is important for exercise prescription (Haskell, 2001). The results of this study show that increasing exercise duration induces changes to post-prandial metabolism in a dose-dependent manner, with 2 h of brisk walking approximately doubling the hypotriglyceridaemic and hypoinsulinaemic effect observed after a 1 h walk. These findings are in line with those of other studies, suggesting that exercise effects on post-prandial triglyceride metabolism are related to energy expenditure (Tsetsonis and Hardman, 1996a,b; Gill *et al.*, 1998; Malkova *et al.*, 2000).

As the participants consumed virtually the same diet during the days leading up to each of their fat tolerance tests, but expended 1.5 ± 0.1 MJ and 3.1 ± 0.2 MJ of energy during the 1 h and 2 h walks, respectively, they would have been in energy deficit (relative to the control trial) during the two exercise trials. However, it is unlikely that energy deficit *per se* was a major mediator of the exercise-induced hypotriglyceridaemic effect, as we have previously demonstrated that exercise reduces post-prandial lipaemia to a much greater extent than an equivalent energy deficit induced by a restriction on energy intake (Gill and Hardman, 2000). Hence, the reductions in post-prandial lipaemia observed in the present study are likely to be predominantly an exercise-specific effect. Although the mechanisms underpinning the relationship between exercise energy expenditure and triglyceride-lowering are yet to be firmly established, it is possible that specific exercise-induced substrate deficits in skeletal muscle or the liver, which differ from the substrate changes induced by dietary energy deficit, contribute to these processes (Gill and Hardman, 2000).

The results of this study clearly demonstrate that 2 h of walking had more potent effects on post-prandial metabolism than a 1 h walk; however, it is not clear

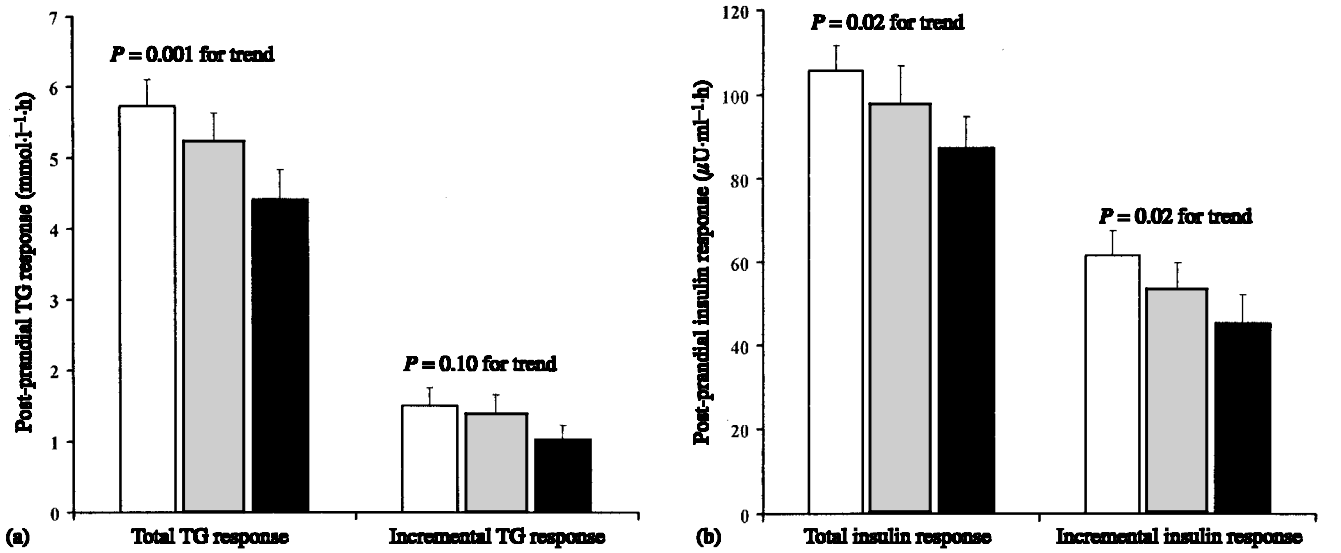

Fig. 2. Total and incremental post-prandial triglyceride (a) and insulin (b) responses to the high-fat mixed test meal in the three trials: a day of no exercise (control, □), a 1 h walk (▒) and a 2 h walk (■) (mean ± $s_{\bar{x}}$). $n = 11$ for triglyceride, $n = 9$ for insulin.

whether increasing exercise duration beyond 2 h would result in further lowering of triglyceride. To the authors' knowledge, no study has established whether exercise continues to reduce post-prandial lipaemia in a dose-dependent manner at higher energy expenditures. However, a study of the fasted state suggests that, when the energy expenditure of an exercise session is increased beyond 3.3 MJ (approximately the same energy expenditure as the 2 h walk in the present study), the triglyceride-lowering effect of exercise begins to plateau (Ferguson *et al.*, 1998). This energy expenditure equates to approximately 12–15 km of running on level ground. Interestingly, if this amount of exercise was undertaken on most days of the week, it would place someone at the upper end of the dose–response relationship for exercise and HDL cholesterol described in a large observational study. This report showed that HDL cholesterol concentrations increased with increasing weekly running distance up to, but not beyond, a training volume of 80 $km \cdot week^{-1}$ (Williams, 1997). Thus, it is conceivable that exercising for 2 h at 50% $\dot{V}O_{2max}$ could maximize the reduction in post-prandial triglyceride concentrations (and subsequent increases in HDL cholesterol concentrations) and increasing exercise duration beyond 2 h may not induce further benefits. In any case, performing more than 2 h exercise per day – even at a moderate level – is unlikely to be an achievable goal for individuals exercising for health benefits.

Although 2 h is a long time to exercise, the moderate nature of this exercise intervention meant that all participants completed the walk without difficulty. The participants rated the 2 h walk as 'fairly light' on the Borg scale (Borg, 1973) and mean blood lactate concentration during the walk was less than 2 $mmol \cdot l^{-1}$; thus, while the walk was long, the participants felt comfortable throughout. Previous results suggest that the triglyceride-lowering effects of exercise are the same when an equivalent amount of exercise is performed in single or multiple sessions (Gill *et al.*, 1998); thus, in practice, 1 h of walking in the morning and 1 h in the evening would impart substantial benefits to lipid metabolism.

Insulin is an important regulator of triglyceride metabolism, controlling both the uptake and release of lipid in adipose tissue (Frayn *et al.*, 1996), the uptake of triglyceride into skeletal muscle (Pollare *et al.*, 1991) and the hepatic production of very low-density lipoproteins (Steiner and Lewis, 1996). Thus, insulin resistance is an important cause of hypertriglyceridaemia and improving insulin sensitivity can improve the metabolism of triglyceride-rich lipoproteins (Jeppesen *et al.*, 1994; Grosskopf *et al.*, 1997). In line with this, the present results show that, as for triglyceride, 2 h of walking reduced post-prandial insulin concentrations to a greater extent than 1 h of walking. It is, however, unclear whether these changes to insulin would have contributed directly to the observed reductions in triglyceride, as we have previously demonstrated that the effects of exercise on triglyceride metabolism may be dissociated from its effects on insulin sensitivity (Gill *et al.*, 2002).

Although the HDL cholesterol concentration is governed, in large part, by the efficacy of triglyceride metabolism, no significant differences in HDL cholesterol concentration were observed between trials in the present study. This is not surprising, however, as the turnover rate for HDL particles is slow – in the order of days to weeks (Herbert *et al.*, 1984; Brinton *et al.*, 1991) – and thus a remodelling of the HDL profile is unlikely to be observed within hours of a triglyceride-lowering intervention. It is likely that a low triglyceride-rich lipoprotein environment would be required for several weeks before a measurable effect on HDL cholesterol concentrations would be observed. Thus, while single exercise sessions have an acute benefit for triglyceride metabolism, the associated increase in HDL cholesterol concentrations would be expected to take some weeks.

In conclusion, we have shown that the effects of moderate exercise on post-prandial lipaemia – a risk marker for cardiovascular disease (Cohn, 1998) and implicated in the atherosclerotic disease process by several mechanisms (Miesenböck and Patsch, 1992; Vogel *et al.*, 1997; Zilversmit, 1979; Cohn, 1998) – are related to the duration, and thus the energy expenditure, of the exercise session. Thus, although exercise guidelines recommend that relatively modest exercise volumes can elicit measurable health benefits (Pate *et al.*, 1995), these should be viewed as minimum rather than optimal exercise volumes and, at least with respect to triglyceride metabolism, increasing exercise volume will enhance the potentially cardioprotective effects.

Acknowledgement

This work was supported by the British Heart Foundation.

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