A comparison of the effects of fluvastatin and bezafibrate on exercise metabolism: a placebo-controlled study in healthy normolipidaemic subjects

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- 1 We have examined the interaction between aerobic exercise and lipid-lowering drugs in a crossover study of 16 healthy normolipidaemic volunteers who each received 21 days' treatment with bezafibrate (400 mg), fluvastatin (40 mg), and placebo, in random order.
- 2 Fluvastatin treatment reduced pre-exercise total cholesterol (TC) by 23% ($P < 0.0001$), low-density lipoprotein cholesterol (LDL-C) by 33% ($P < 0.0001$), and plasma triglycerides by 11%, compared with pre-treatment values. Bezafibrate reduced TC by 11% ($P < 0.01$); LDL-C by 9%; and plasma triglycerides by 40% ($P < 0.01$), compared with pre-treatment values.
- 3 During exercise, in comparison with placebo, and fluvastatin treatment, respectively, bezafibrate significantly reduced mean fat oxidation: 31% *vs* 39%, $P = 0.035$, 31% *vs* 39%, $P = 0.002$, plasma free fatty acid (FFA) availability, e.g. after 90 min of exercise: (t_{90}) 520 *vs* 662 $\mu\text{mol l}^{-1}$, $P = 0.054$, 520 *vs* 725 $\mu\text{mol l}^{-1}$, $P = 0.016$, and plasma levels of glycerol (t_{90}): 59 *vs* 74 $\mu\text{mol l}^{-1}$, $P = 0.037$, 59 *vs* 73 $\mu\text{mol l}^{-1}$, $P = 0.016$. Fluvastatin had no impact on fat metabolism in comparison with placebo.
- 4 Reduced plasma FFA concentration and lower fat oxidation during prolonged exercise on bezafibrate treatment may be due to an inhibition of hepatic acetyl coenzyme A carboxylase, resulting in reduced FFA release from adipose tissue.
- 5 The possibility that impaired fat metabolism on fibrates could induce premature fatigue during exercise of moderate duration and intensity should be examined in hyperlipidaemic patients.

Keywords bezafibrate fluvastatin exercise fat oxidation

Introduction

Hypercholesterolaemic patients are increasingly being recommended by their doctors to lead active lifestyles or take regular exercise to reduce weight and to supplement lipid-lowering treatment effects on the lipid profile. However, some lipid-lowering agents, such as acipimox [1–3], may inhibit fat metabolism during prolonged exercise, and could make exercising muscle increasingly dependent on glycogen stores, inducing earlier fatigue [4]. A recent study examining the impact of gemfibrozil and simvastatin on exercise metabolism in men [3] found a non-significant trend for a reduction in fat availability during exercise at 50% of maximal oxygen uptake (VO_2 max) on the fibrate compared with placebo, suggesting impaired

release of FFA from adipocytes. Simvastatin had no effect on fat metabolism.

We studied the effects of 3 weeks of bezafibrate, a commonly prescribed fibrate, and fluvastatin, an HMG-CoA reductase inhibitor, on exercise metabolism in both healthy young men and women.

Methods

Subjects

Sixteen healthy normolipidaemic volunteers (eight men and eight women), mean age (s.d.) 21.8 (3.1) years, body weight (s.d.) 68.3 (10.3) kg, body mass index (s.d.) 22.49

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(2.3) kg m⁻² men/22.46 (2.0) kg m⁻² women, participated in the study, which was approved by the South Birmingham Health Authority Ethics Committee, and required informed written consent. All subjects had clinical examinations, and normal haematological (haemoglobin, red blood cell count, haematocrit, white blood cell count) and biochemical (including: total bilirubin, alkaline phosphatase, alanine transferase, albumin, creatinine, creatine kinase, and gamma glutamyl transferase) profiles. Cardiovascular fitness was assessed by measurement of maximal oxygen uptake during a graded test to exhaustion on a motorized treadmill, and a workload corresponding to 50% of VO₂ max was determined during a 90 min walking trial during which subjects were familiarised with the protocol.

Experimental design

The study was a double-blind, randomized, crossover investigation, each subject completing three exercise trials; one following each 3 week period of once-daily treatment with either fluvastatin 40 mg, or bezafibrate 400 mg, or placebo. All treatments were taken once daily, after the evening meal, for 3 weeks, the final dose being taken at 22.00 h on the evening preceding the exercise trial. Each treatment period was followed by a 2 week wash-out period. Subjects recorded food intake and were instructed to follow a similar dietary pattern throughout the study and to replicate the evening meal preceding each trial. Similarly, subjects were asked to replicate exercise patterns for 3 days preceding each trial.

On exercise trial days subjects arrived at the Clinical Investigation Unit at 08.00 h, having starved overnight. A cannula was first inserted into a suitable forearm vein, and a 'fasting' blood sample was taken before subjects ate a fat free 1 MJ carbohydrate breakfast; subjects then rested for 90 min. Resting blood samples were taken 15 min and 5 min before exercise, and at 15 min, 30 min, and 20 h ('fasted' state) post-exercise. Subjects exercised for 90 min at 50% VO₂ max, during which blood samples, measures of heart rate and perceived exertion, and expired air samples, were taken every 15 min.

Indirect calorimetry

Oxygen uptake and carbon dioxide excretion were measured using the Douglas bag technique. The percentages of oxygen and carbon dioxide in aliquots of expired air were measured using a paramagnetic oxygen (Beckmann OM11) and infra-red carbon dioxide meter (Beckmann LB2) previously calibrated with standard gases (BOC Special Gases) certified to an accuracy of 0.05%. Total resistance to flow of the gas collection system was 2.0 cm of water at a constant flow of 200 l min⁻¹, and gas volume was measured at a constant flow using a dry gas meter (Harvard, UK). Oxygen uptake and carbon dioxide excretion were calculated using the Haldane transformation [5], and rates of energy expenditure and the proportion of carbohydrate

and fat metabolism calculated using standard equations [6].

Analytical method

Each blood sample (8 ml) was distributed between evacuated septum sealed test tubes (Vacutainer®) containing: sodium fluoride and potassium oxalate; lithium heparin; ethylenediaminetetraacetic acid (EDTA); and no additives, for subsequent measurement of: plasma glucose (coefficient of variation, CV=1.6%) [7], lactate (CV=3.6%) [8], free fatty acids (CV=2.5%) [9], triglycerides (CV=3.6%) [10], and glycerol (CV=3.2%) [11] (samples were deproteinized using 0.77 M perchloric acid), haemoglobin and haematocrit, and lipid fraction (total cholesterol, LDL-C, HDL-C) concentrations, respectively. Samples of approximately 150–200 µl were pipetted into Cobas Bio® cups and frozen at -70°C for subsequent analysis on a Cobas Bio® colourimeter.

Calculation and statistical analysis

Data were analysed using repeated measures two factor (time and treatment) analysis of variance (ANOVA), corrected for related means (Greenhouse-Geiser Epsilon), taking $P < 0.05$ to indicate a significant treatment/time interaction effect. One-factor ANOVA determined differences between treatments at individual time points, and *t*-tests were employed to evaluate the effect of treatment on lipid concentrations. Results are given as the mean and 95% confidence intervals.

Results

Effects of treatment

Pre-treatment cholesterol measures were comparable. There were significant changes in the lipid profiles of these normolipidaemic subjects following treatment with fluvastatin 40 mg, and bezafibrate 400 mg (see Table 1). Bezafibrate reduced total cholesterol by 11%, LDL-C by 9%, and triglyceride concentration by 40%. Fluvastatin reduced total cholesterol by 23%, LDL-C by 33%, and plasma triglyceride concentration by 11%. HDL-C concentration was unaffected following treatment with either bezafibrate; 1.3 (0.7–1.9) to 1.3 (0.8–1.8) mmol l⁻¹, or fluvastatin; 1.3 (0.8–1.9) to 1.3 (0.8–1.8) mmol l⁻¹.

Cardiorespiratory/Energy expenditure data

Mean maximal oxygen uptake (VO₂ max) values for men ($n=8$); 52.9 (48.3–57.5) ml kg⁻¹ min⁻¹, and women ($n=8$); 38.62 (34.0–43.2) ml kg⁻¹ min⁻¹, indicated that the subjects were moderately fit but not specifically endurance trained. Mean exercise heart rate was 133 (128–138) beats min⁻¹ in men, and 138 (135–142) beats

Table 1 Effects of 3 weeks' treatment with bezafibrate, and fluvastatin, on the lipid profiles of normolipidaemic subjects ($n=16$)

Effects of treatment on mean lipoprotein concentrations (95% confidence intervals) (mmol l^{-1}).						
Treatment	Total cholesterol		LDL-cholesterol		Triglycerides	
	Pre-T	Post-T	Pre-T	Post-T	Pre-T	Post-T
Placebo	4.7 (3.4–6.0)	4.4 (2.4–6.4)	3.0 (2.0–4.1)	2.7 (1.2–4.2)	1.0 (0.4–1.6)	0.9 (0.2–1.6)
Bezafibrate	4.7 (3.3–6.0)	4.1** (2.5–5.8)	2.8 (1.9–3.6)	2.5 (1.3–3.8)	1.2 (0.0–2.5)	0.7** (0.3–1.1)
Fluvastatin	4.09 (3.4–6.4)	3.8**** (2.6–5.0)	3.1 (1.7–4.5)	2.1**** (1.3–2.9)	1.0 (0.2–1.8)	0.9 (0.1–1.6)

** $P < 0.01$, **** $P < 0.0001$, vs pre-treatment mean. T, treatment.

min^{-1} in women. Total energy expenditure during 90 min of exercise at 50% VO_2 max averaged 3307 (2253–4361) kJ in males, and 2063 (1461–2665) kJ in females.

Fat oxidation

Fat oxidation increased steadily throughout the 90 min exercise period on all treatments ($P=0.0001$). The total percentage contribution of fat to energy expenditure for 90 min of exercise at 50% VO_2 max was reduced on bezafibrate; 31% (5–56), compared with both placebo; 39% (8–69), $P=0.035$, and fluvastatin; 39% (19–60), $P=0.002$. During the last 30 min of the exercise period, mean fat oxidation was approximately 29% lower on bezafibrate, compared with placebo or fluvastatin. The increase in fat oxidation with time was also greater on placebo compared with bezafibrate ($P=0.054$), and on fluvastatin compared with bezafibrate ($P=0.013$). Overall, fat oxidation was similar on fluvastatin and placebo (see Table 2 and Figure 1).

Plasma free fatty acids (FFA)

Mean plasma FFA concentrations are shown in Figure 2 and Table 3. Pre-exercise concentrations were significantly lower on bezafibrate ($16 \mu\text{mol l}^{-1}$ [0–35]) than on placebo ($28 \mu\text{mol l}^{-1}$ [0–75], $P < 0.05$), and tended to remain lower during and after exercise ($P=0.054$). They were lower on bezafibrate than on fluvastatin pre-exercise ($38 \mu\text{mol l}^{-1}$ [0–124]), and were significantly lower ($P=0.016$) during exercise. The overall increase

Figure 1 Mean ($\pm$ s.e. mean) percentage contribution of fat oxidation to energy expenditure during 90 min of exercise at 50% VO_2 max on placebo ($\circ$), fluvastatin ($\blacksquare$), and bezafibrate (Δ). Bezafibrate vs placebo: $P < 0.05$. Bezafibrate vs fluvastatin: $P < 0.01$.

in plasma FFA concentration from rest (15 min pre-exercise) to 15 min post-exercise was depressed on bezafibrate treatment ($771 \mu\text{mol l}^{-1}$) compared with both placebo ($983 \mu\text{mol l}^{-1}$), and fluvastatin ($1042 \mu\text{mol l}^{-1}$). Plasma FFA levels continued to rise sharply on all treatments immediately post-exercise, but decreased following 15–30 min rest.

Plasma glycerol

Plasma glycerol concentration increased steadily during the 90 min exercise period on all treatments ($P=0.0001$),

Table 2 Mean ($n=16$) percentage contribution of fat oxidation to energy expenditure (and 95% confidence intervals), measured at 15 min time (t) intervals during exercise at 50% VO_2 max on placebo, fluvastatin, and bezafibrate treatment

Mean fat oxidation (% contribution to energy expenditure) during exercise						
Treatment	$t15$	$t30$	$t45$	$t60$	$t75$	$t90$
Placebo	25 (0–56)	30 (1–59)	35 (5–66)	43 (7–80)	48 (31–66)	51 (51–82)
Fluvastatin	23 (0–47)	30 (4–56)	36 (7–65)	44 (21–68)	48 (30–66)	54 (33–75)
Bezafibrate	19 (0–44)	25 (0–50)	30 (2–58)	31 (4–58)	38 (8–67)	41 (10–71)

Table 3 Mean ($n=16$) plasma free fatty acid concentration (and 95% confidence intervals), measured at 15 min time (t) intervals during exercise at 50% VO_2 max on placebo, fluvastatin, and bezafibrate treatment

Treatment	Plasma FFA concentration ($\mu\text{mol l}^{-1}$) during exercise, at time t (min)					
	$t15$	$t30$	$t45$	$t60$	$t75$	$t90$
Placebo	91 (0–286)	218 (0–561)	339 (0–760)	430 (0–859)	542 (62–1021)	662 (136–1188)
Fluvastatin	80 (0–186)	214 (0–445)	350 (43–657)	463 (156–769)	587 (260–913)	725 (334–911)
Bezafibrate	41 (0–147)	121 (0–391)	216 (0–629)	307 (0–820)	421 (0–1041)	520 (0–1192)

Figure 2 Mean ($\pm$ s.e. mean) plasma free fatty acid concentration at rest (-15 and -5 min, before exercise and $+15$ and $+30$ min, post-exercise), and during exercise at 50% VO_2 max for 90 min ($t15$ – $t90$), on placebo ($-○-$), fluvastatin ($-■-$), and bezafibrate ($-△-$) treatment. Bezafibrate *vs* placebo: $P=0.054$. Bezafibrate *vs* fluvastatin: $P<0.05$.

but was lower on bezafibrate treatment than on placebo ($P=0.037$), and fluvastatin ($P=0.016$). After 60 min of exercise, plasma glycerol concentration on placebo, fluvastatin, and bezafibrate was 53 (4–102); 53 (16–89); and 43 (0–95) $\mu\text{mol l}^{-1}$, and by 90 min had increased to 74 (21–127), 73 (30–116), and 59 (3–115) $\mu\text{mol l}^{-1}$, respectively (see Figure 3).

Figure 3 Mean ($\pm$ s.e. mean) plasma glycerol concentration at rest (-15 and -5 min, before exercise, and $+15$ and $+30$ min, post-exercise), and during exercise at 50% VO_2 max for 90 min ($t15$ – $t90$), on placebo ($-○-$), fluvastatin ($-■-$), and bezafibrate ($-△-$) treatment. Bezafibrate *vs* placebo: $P<0.05$. Bezafibrate *vs* fluvastatin: $P<0.05$.

Plasma triglycerides

Plasma triglycerides increased steadily during exercise on all treatments ($P=0.0001$), but were lower on bezafibrate than on either placebo ($P=0.027$), or fluvastatin ($P=0.005$). After 60 min of exercise, plasma triglyceride concentration on placebo, fluvastatin, and bezafibrate was 70 (23–117); 72 (21–122); and 59 (7–111) mg dl^{-1} , and by 90 min had increased to 76 (24–128), 79 (24–134), and 63 (27–99) mg dl^{-1} , respectively.

Plasma lactate

There were no significant effects of treatment on plasma lactate levels. Mean plasma lactate concentration decreased steadily with time from: 1440.8 (471–2411), 1448.2 (770–2126), and 1423.1 (637–2209) $\mu\text{mol l}^{-1}$, at 5 min pre-exercise ($T-5$), to 828.2 (372–1285), 849.0 (345–1353), and 907.4 (329–1486) $\mu\text{mol l}^{-1}$ following 90 min of exercise ($t90$), on placebo, fluvastatin, and bezafibrate, respectively.

Perceived exertion

There was no apparent effect of treatment, in comparison with placebo, on perceived exertion during exercise.

Discussion

Reduced fat metabolism during prolonged exercise may induce premature fatigue [4]. Acipimox, a nicotinic acid analogue, has been shown to reduce FFA availability during exercise [1–3], but no well-designed cross-over trials, employing adequate treatment periods, have been conducted with the fibrates or statins. In this randomized, crossover study, we investigated the effects of 3 weeks of treatment with bezafibrate (400 mg), and fluvastatin (40 mg), compared with placebo, on fat metabolism during moderate intensity exercise in healthy young men and women.

Despite the normolipidaemic profiles of the subjects, lipid-lowering therapy produced substantial changes in cholesterol and triglycerides. Treatment with fluvastatin 40 mg reduced total mean cholesterol by 22.9%, $P<0.00001$, and LDL-C by 32.9%, $P<0.0001$, and

treatment with bezafibrate 400 mg reduced cholesterol by 11%, $P < 0.01$, and triglycerides by 40.0%, $P < 0.01$. Similar changes in lipid profile are achieved in hypercholesterolaemic patients (fluvastatin [12], bezafibrate [13]). There was no effect of placebo treatment on measures of total cholesterol, LDL-C, or triglycerides (see Table 1).

The steady increase in the plasma concentration of free fatty acids and glycerol observed during exercise in this study is well recognized [14, 15] and results primarily from an increase in the rate of lipolysis [15]. Concomitant with this rise in FFA was a decline in the respiratory exchange ratio (RER), indicating that a greater proportion of the energy was being supplied by oxidation of FFA [14, 15]. Following 90 min of exercise at 50% VO_2 max, fat oxidation provided more than 60% of the required energy in some subjects. Albumin-bound FFA is considered to be the major source of FFA, although some may be supplied by the removal of triglycerides from the VLDL particle, a process which involves adipose lipoprotein lipase (LPL) [16]. The sharp rise in plasma FFA concentration observed between 15–30 min post-exercise is believed to be important for the early recovery of both muscle glycogen and triglyceride stores [17].

Bezafibrate treatment had a significant impact on exercise metabolism, reducing plasma free fatty acid availability, fat oxidation, plasma glycerol levels, and plasma triglyceride levels, in comparison with both placebo, and fluvastatin, whereas fluvastatin had no adverse effect on the availability of energy substrates or fat oxidation, in comparison with placebo.

The mechanism of action of the fibrates is only partially established, but the hypotriglyceridaemic effect, and the reduced levels of plasma FFA observed at rest and during exercise in this study, may relate to the following mechanisms. Firstly, fibrates may inhibit hepatic acetyl coenzyme A carboxylase, which is a key enzyme controlling the synthesis of triglycerides in the liver [18], and, there have been reports of fibrates interfering with the hepatic production of very low-density lipoprotein triglyceride in laboratory animals [19]. In addition, there is evidence for clofibrate reducing fasting levels of FFAs in humans by inhibiting their release from adipose tissue [20–22]. A reduction in circulating levels of FFAs should decrease the availability of FFAs to the liver to serve as substrate for the synthesis of triglycerides for very low-density lipoprotein [23], and result in a reduced formation of hepatic very low-density lipoprotein-triglyceride. Fibrates have been shown to increase muscle lipoprotein lipase activity [24], which could enhance the catabolism of plasma triglycerides [25, 26], and decrease levels of LDL-C via an enhanced hepatic clearance of VLDL and IDL [27].

A significant compensatory increase in fat metabolism in working muscle in response to reduced plasma free fatty acid availability during exercise following bezafibrate treatment is not thought to have occurred since overall fat oxidation was also reduced. FFA and glucose are the main providers of energy substrates during prolonged, moderate intensity exercise [28], and

the lower rate of fat oxidation was compensated for by a greater rate of carbohydrate oxidation. Despite this, euglycaemia was maintained, suggesting that more glycogen was oxidized and/or the rate of blood glucose turnover was increased following bezafibrate treatment [2]. It has been demonstrated that the interference of fat metabolism by certain lipid-lowering agents during prolonged exercise [1–3] could have the effect of inducing premature fatigue [4]. The effects observed on fat metabolism in this study warrant similar investigations in hyperlipidaemic patients.

Interestingly, it is thought that the maintenance of elevated plasma concentration of FFAs during the post-exercise period may be important for the early recovery of both the muscle glycogen and triglyceride stores [17]. This may have implications for patients on bezafibrate therapy who undertake regular exercise; a depleted glycogen supply as a result of one exercise bout reducing the potential for carbohydrate metabolism during the subsequent session, and inducing early symptoms of fatigue.

HMG-CoA reductase inhibitors predominantly affect the liver, and are reversible inhibitors acting upon catalysis of an early rate-limiting step in cholesterol synthesis. Inhibition of cholesterol synthesis in the liver leads to upregulation of the LDL receptor and increased catabolism of LDL and precursor particles [29]. Treatment with fluvastatin had no impact on exercise metabolism, in comparison with placebo, a finding which supports the claim that fluvastatin is a 'metabolically neutral' drug, 'isolating' its cholesterol-lowering mechanism to the liver.

The findings from this study suggest that during moderately intense, prolonged exercise, fluvastatin has no significant impact on metabolism compared with placebo, but bezafibrate reduces the availability of fat as an energy substrate. These effects should be investigated in hypercholesterolaemic patients, to evaluate the effects of decreased fat metabolism and increased use of glycogen stores on exercise fatigue.

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Appendix

Indirect calorimetry

a) Principle

Indirect calorimetry is a validated method for using oxygen uptake as a basis for measuring energy expenditure. Measurement is made of the volume of air breathed, and expired air is analysed for oxygen and carbon dioxide content. Since the composition of inspired air is constant (O_2 : 20.93%; CO_2 : 0.04%; N_2 : 79.04%), it is possible to calculate the total volume of oxygen consumed (and the volume of carbon dioxide produced) over any given period of time.

Expired air contains more carbon dioxide (usually 2.5 to 5.0%), less oxygen (usually 15.0 to 18.5%), and more nitrogen (usually 79.04 to 79.60%). Nitrogen, however, is inert in terms of metabolism and any change in its concentration reflects the fact that the number of oxygen molecules removed from the inspired air are not replaced by the same number of carbon dioxide molecules produced in metabolism; this results in the volume of expired air (VE) being unequal to the inspired volume (VI). VI can be determined from VE using the relative change in nitrogen in an equation known as the Haldane transformation [5]:-

$$\text{VI} = \text{VE} \times \frac{\% \text{N}_2 \text{E}}{\% \text{N}_2 \text{I}}$$

$\% \text{N}_2 \text{I} = 79.04$

$\% \text{N}_2 \text{E} = \% \text{ nitrogen in expired air computed from gas analysis as } [(100 - (\% \text{O}_2 \text{E} + \% \text{CO}_2 \text{E}))]$.

$\% \text{O}_2 \text{E} = \% \text{ expired oxygen and } \% \text{CO}_2 \text{E} = \% \text{ expired carbon dioxide}$

b) Oxygen consumption

The volume of O₂ removed from inspired air (VO₂) each minute can be determined as follows:

$$\text{VO}_2 = \{[(\text{VE} \times \% \text{N}_2 / 79.04\%) \times 20.93\%] - (\text{VE} \times \% \text{O}_2 \text{E})\}$$

VO₂ = volume of oxygen consumed/min (ml), and VE = expired air volume/min).

The final form of the equation is:-

$$\text{VO}_2 = \text{VE}[(\% \text{N}_2 \text{E} \times 0.265) - \% \text{O}_2 \text{E}]$$

The value obtained within the brackets is referred to as the 'true O₂'; this represents the 'oxygen extraction', or, the percentage of oxygen consumed for any volume of air expired.

c) Carbon dioxide production

The carbon dioxide production per minute (VCO₂) is calculated as follows:

$$\text{VCO}_2 = \text{VE} (\% \text{CO}_2 \text{E} - \% \text{CO}_2 \text{I})$$

%CO₂E = percent carbon dioxide in expired air determined by gas analysis, and

%CO₂I = percent carbon dioxide in inspired air, which is essentially constant at 0.04%.

d) Calculation of respiratory quotient

Because of the inherent chemical differences in the composition of carbohydrates, fats, and proteins, different amounts of oxygen are required to oxidise the

carbon and hydrogen atoms in the molecule to the end products, carbon dioxide and water. Thus the quantity of carbon dioxide produced in relation to oxygen consumed varies somewhat depending on the substrate metabolised. This ratio of metabolic gas exchange is termed the respiratory quotient (R.Q.).

$$\text{R.Q.} = \frac{\text{CO}_2 \text{ produced (VCO}_2\text{)}}{\text{O}_2 \text{ consumed (VO}_2\text{)}}$$

During the complete oxidation of a glucose molecule, six molecules of carbon dioxide are produced and six molecules of oxygen are consumed, giving an R.Q. equal to 1.0.

Fats contain considerably fewer oxygen atoms in proportion to atoms of carbon and hydrogen. Consequently, when fat is broken down, relatively more oxygen is required to oxidise fat to carbon dioxide and water. When palmitic acid, a typical fatty acid, is oxidised to carbon dioxide and water, 16 carbon dioxide molecules are produced for every 23 oxygen molecules consumed. This exchange is summarised by the equation:-

Thus, the R.Q. for this fatty acid is 0.696 (16 CO₂/23 O₂). Generally, the R.Q. is considered to be 0.70. Having established that for carbohydrate oxidation, R.Q.=1, and for fat oxidation, R.Q.=0.7, it follows that R.Q. values between 1 and 0.7 represent a combination of carbohydrate and fat oxidation.