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ScienceDirect
Journal of Nutritional Biochemistry 21 (2010) 983–990
Journal of Nutritional Biochemistry

Exercise prior to fat ingestion lowers fasting and postprandial VLDL and decreases adipose tissue IL-6 and GIP receptor mRNA in hypertriacylglycerolemic men

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Received 25 May 2009; received in revised form 12 August 2009; accepted 19 August 2009

Abstract

Fasting and postprandial triacylglycerol (TAG) concentrations are risk factors for cardiovascular disease. This study evaluated whether interleukin-6 (IL-6) and incretin hormones [gastric inhibitory peptide (GIP) and glucagon-like peptide-1 (GLP-1) (active)] were associated with fasting and postprandial TAG in response to an oral lipid load, including very-low-density lipoprotein (VLDL) and chylomicron (CM) TAG, following one bout of exercise in nine men (age, 59±2 years; body mass index, 34±2 kg/m^2; waist circumference, 113±3 cm) with high fasting TAG (2.9±0.2 mmol/L). Subjects completed two oral fat tolerance tests (OFTTs), randomized 1 week apart, that consisted of 1g fat/kg body weight emulsified lipids in the absence of carbohydrate and protein. Approximately 16 h prior to one OFTT, subjects completed 60 min of treadmill walking (estimated 55% VO_2 peak; heart rate, 122±4 beats/min). No exercise was performed on the day before the other OFTT. Fasted (0 h) and postprandial (1, 2, 3, 4, 5 and 6 h) blood samples were taken for analysis of TAG, IL-6 and incretins. Subcutaneous adipose tissue biopsies were taken at 0 and 6 h after OFTT ingestion for IL-6 and GIP receptor (GIPr) mRNA quantification. Exercise lowered fasting and postprandial TAG (P<.05) and VLDL TAG (P<.05), while postprandial CM TAG were similar in both OFTT trials (P>.05). Fasting and postprandial plasma IL-6, GIP and GLP-1 did not differ between rest and exercise OFTT trials (P>.05). Exercise reduced IL-6 and GIPr mRNA (P<.05) in adipose tissue. Our results suggest that the reduction in VLDL TAG following an acute bout of exercise is not associated with circulating IL-6 or incretin concentrations, despite reductions in the adipose tissue expression of IL-6 and GIPr.

Keywords: Exercise; Postprandial; Oral fat tolerance test; VLDL; Incretins; Inflammation; Adipose tissue biopsy

1. Introduction

Elevated postprandial triacylglycerol (TAG) concentration is an independent risk factor for cardiovascular disease (CVD) in men and women [1,2]. Furthermore, an exaggerated postprandial TAG response to an oral fat load occurs in individuals with high fasting TAG compared to well-matched individuals with low fasting TAG [3,4]. Fortunately, blood TAG levels may favorably respond to lifestyle interventions such as diet and exercise. Several studies have demonstrated that an acute bout of moderate exercise can reduce fasting and postprandial TAG concentrations. Past investigations have primarily focused on young [5–7] and older [8,9] healthy populations. Gill et al. [10] found that acute moderate exercise in lean and centrally obese middle-aged men resulted in ~25% decreases in both fasting and postprandial TAG. Despite strong evidence that a reduction in very-low-density lipoprotein (VLDL) is responsible for the TAG-lowering phenomenon, supportive studies have used either 1.5 h of walking [7,8] or 2 h of running between 50% and 60% VO_2 peak [11] and have not examined exercise in overweight/obese men with hypertriacylglycerolemia. Individuals with elevated fasting TAG also exhibit the hypotriacylglycerolemic effect of exercise [12]. However, the mechanisms behind the TAG-lowering effect of a single bout of exercise have not been fully explained.

Multiple tissues and systems, such as the liver, gastrointestinal system and adipose tissue, are involved in the regulation of TAG metabolism [13]. In addition to well-recognized factors associated with TAG-rich lipoprotein (TRL) metabolism such as lipoprotein lipase, other factors such as adipokines and incretin hormones are secreted from these tissues and can have metabolic consequences. Interleukin-6 (IL-6) is produced by adipose tissue [14] and exercising muscle [15], and while it acutely stimulates lipolysis and fat oxidation [16], it is also a known CVD risk factor [17,18]. We have previously demonstrated that men with high fasting TAG also exhibit an elevated postprandial IL-6 concentration [4]. In rats, an IL-6 infusion significantly increased fasting TAG, further illustrating a relationship between these CVD factors [19]. The incretin hormone gastric inhibitory peptide (GIP) is also elevated in men with high fasting TAG [20]. On the other hand, GIP administration decreases chylomicron (CM) TAG in dogs undergoing a postprandial challenge [21]. Both GIP and glucagon-like peptide-1 (GLP-1) are responsive to fat

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doi:10.1016/j.jnutbio.2009.08.004

ingestion [22,23], and intravenous administration of GLP-1 completely abolished the postprandial rise in TAG following a high-fat meal [24]. Furthermore, adipose tissue expresses a GIP receptor (GIPr) [25], but the impact of dietary fat and exercise on expression is unknown. While exercise may modulate circulating incretin concentrations [26], it is unknown whether these gut-derived factors are involved in the TAG-lowering effect of exercise.

The purpose of this study was to evaluate the postprandial response to an oral fat load consumed 16 h after 60 min of moderate walking exercise in men with elevated (>2.0 mmol/L) fasting TAG concentrations to determine whether IL-6 and/or incretin hormones are also changed and thus may contribute to the TAG-lowering phenomenon. A previously developed oral fat tolerance test (OFTT) [27] that delivers a fat load consisting solely of emulsified lipids was used as fat challenge. This pure lipid challenge allows for a clear investigation of postprandial response to fat alone. We hypothesized that: (a) the exercise-induced reduction in postprandial TAG will be associated with a decrease in VLDL and CM; however, the proportional decrease will be such that VLDL decreases in a greater manner following exercise; (b) exercise will decrease fasting and postprandial IL-6 and will alter incretin hormones (decrease in GIP and increase in GLP-1); and (c) exercise will decrease the expression of IL-6 and GIPr in subcutaneous adipose tissue.

2. Materials and methods

2.1. Materials

Palm stearin, soybean oil and bleaching clay (Engelhard F105) were generously provided by Bunge Canada (Toronto, ON). Sodium methoxide (Sigma Aldrich) and citric acid (VWR International) were used in lipid interesterification. Myverol 18-99K and Tween80 (both from Nealanders International, Oakville, ON) were used to prepare the emulsified OFTT beverages, which included a commercial food flavoring agent (David Michaels and Co., Philadelphia, PA) and a noncarbohydrate sweetener (SugarTwin Liquid Sweetener; Alberto-Culver, Melrose Park, IL).

2.2. OFTT preparation

To study postprandial metabolic responses, we produced an emulsified, artificially flavored and sweetened beverage that was devoid of protein or carbohydrate, as previously described in detail [27]. Briefly, prior to the experimental trials, a fat blend of palm stearin (63% palmitic acid; 16:0) and soybean oil (53% linoleic acid; 18:2$n-6$) was prepared to achieve the desired P/S ratio of 1.0. The blend was chemically interesterified in order to achieve a completely random distribution of the fatty acids present [27]. The fatty acid composition of the OFTT was confirmed (Table 1) by gas chromatography, as previously described [27].

Table 1
Fatty acid composition of the OFTT beverage consumed by the subjects

Fatty acid[a]	% wt/wt total fatty acids
12:0	0.7
14:0	0.7
16:0	32.0
18:0	4.4
18:1 c9	22.1
18:1 t9	0.6
18:1 c11	0.5
18:2 $n-6$	32.2
18:3 $n-6$	0.3
18:3 $n-3$	4.6
20:0	0.4
22:0	0.3
Total saturated fatty acid	38.5
Total monounsaturated fatty acid	23.1
Total polyunsaturated fatty acid	37.1
P/S ratio[b]	1.0

[a] Only major fatty acids (i.e., >0.2) are presented.
[b] P/S ratio was determined by dividing the total polyunsaturated fatty acid by the total saturated fatty acid.

2.3. Subjects and preliminary screening

This study was approved by the University of Guelph Research Ethics Board. Ten males were recruited to participate in this study through a combination of newspaper, poster and website advertisements. Subjects were required to be between 40 and 70 years of age and to be nonsmokers. In addition, a body mass index (BMI) greater than 27 kg/m^2 was required for inclusion in the study. Individuals taking medications for control of blood lipids and/or inflammation were excluded from participation in this study. Subjects were asked to read and to complete an informed consent form identifying potential risks associated with participation in the study. Subjects were required to attend one pretrial session to complete a subject screening questionnaire and blood screening, and to have weight and height measured. During the preliminary screening visit, subjects arrived in the laboratory following a 12-h fast and following instruction to refrain from exercise for 48 h prior to the visit to the laboratory. Plasma sample was obtained by a medically trained technician via venous puncture for immediate analysis of TAG using Cholestech LDX lipid cassettes (Cholestech Corp., Hayward, CA). To be considered for the study, all subjects were required to have a fasting plasma TAG concentration of ≥2.0 mmol/L. All subjects who met the TAG requirement were required to undergo a 2-h screening with 75 g of oral glucose tolerance test for assessment of glucose tolerance. Any person meeting the criteria for type 2 diabetes [28] was excluded from the study and instructed to consult a physician. Subjects who met all inclusion criteria had their waist circumference measured and body composition determined using bioelectrical impedance analysis (Bodystat, Tampa, FL).

2.3.1. Exercise

All participants were required to attend a preliminary submaximal incremental treadmill exercise session approximately 1 week prior to the OFTTs to determine the speed and gradient required to perform exercise at an estimated 55% VO_2 peak using the heart rate reserve method in accordance with the *ACSM's Guidelines for Exercise Testing and Prescription* [29]. Heart rate was recorded by short-range telemetry (Polar Electro, Lake Success, NY). Subjects then completed a randomized cross-over study consisting of one exercise OFTT and one rest OFTT separated by at least 1 week. On the afternoon (approximately 16 h) before the exercise OFTT, all participants completed 60 min of treadmill walking, maintaining the predetermined speed and gradient. No exercise was performed prior to the rest OFTT.

2.3.2. Pretrial requirements

All subjects were instructed to record their food intake for the 3 days prior to each of the OFTT trials (i.e., a total of 6 days for the entire study). In addition, subjects consumed a standardized meal on the evening prior to each OFTT. Subjects were also required to abstain from alcohol and additional exercise for 48 h prior to each OFTT trial and to arrive at the laboratory following a 12-h fast.

2.4. Study design

2.4.1. Beverage preparation

On each trial day, 1 g lipids/kg subject body weight of the 1.0 OFTT blend was measured into a glass mug. The fat was warmed to approximately 50°C and subsequently emulsified in water (73% wt/wt). To maintain the emulsified pure fat challenge, we added the monoglyceride Myverol (2% wt/wt) and the polysorbate Tween 80 (0.15% wt/wt) using a handheld homogenizer. Each OFTT was sweetened with nonnutritive liquid sweetener (SugarTwin Liquid Sweetener) and flavored with a commercially designed flavor (David Michaels and Co.).

2.5. Experimental trials

Upon the subjects' arrival at the laboratory, a catheter was inserted into a forearm vein for the withdrawal of blood samples. Saline was administered to maintain the catheter for repeated blood sampling. On each day, following an initial fasting blood sample (0 h), subjects ingested the OFTT. Blood was taken at 0.5, 1, 1.5, 2, 3, 4, 5 and 6 h following the OFTT. A subcutaneous adipose tissue sample (~200–300 mg) was obtained by a physician using the percutaneous needle biopsy technique with suction under local anesthetic prior to the start of each OFTT trial (0 h) and at 6 h postingestion of the OFTT. Adipose tissue samples were immediately flash frozen in liquid nitrogen and remained frozen at −80°C until analysis.

2.6. Blood glucose and plasma TAG measurements

Blood glucose was analyzed in duplicate by a glucose oxidase method (YSI 2300 Stat Plus Glucose Analyzer; Stat Plus, Yellow Springs, OH). At three designated time points (0, 3 and 6 h), 9 ml of blood was drawn into EDTA-treated tubes for plasma TAG analysis. Blood collection tubes were spun immediately at 1000×*g* for 15 min at 4°C. The plasma was collected, pooled for each subject and time point, packaged on ice and shipped overnight to the University of Ottawa for CM and VLDL TAG and cholesterol analysis. Upon receipt, samples were ultracentrifuged in a 50Ti fixed-angle rotor (Beckman Coulter, Inc., Mississauga, ON) at 40,000 rpm for 18 h at 10°C. The lipoprotein fraction VLDL (d<1.006 g/ml) and the sum of intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL)

Table 2
Subject characteristics

Age (years)	59±2
Height (m)	1.8±0.01
Weight (kg)	104.4±4.9
BMI (kg/m^2)	33.8±1.5
Waist circumference (cm)	112.8±3.4
Systolic blood pressure (mmHg)	122.1±7.8
Diastolic blood pressure (mmHg)	71.7±4.7
Fasting TAG (mmol/L)	2.9±0.2
Fasting glucose (mmol/L)	5.5±0.4
HDL cholesterol (mmol/L)	1.0±0.1
LDL cholesterol (mmol/L)	3.2±0.4
Body fat (%)	31.4±1.1
Resting heart rate (beats/min)	73±4
Exercising heart rate (beats/min)	122±4
Power output (estimated % VO_2 peak)	57.0±0.1
Treadmill speed (km/h)	4.2±0.2
Treadmill slope (% grade)	3.1±0.7

All values are presented as mean±S.E.M. (n=9).

(IDL+LDL+HDL; d>1.006 g/ml) fractions were isolated by tube slicing. The cholesterol and TAG in plasma and lipoprotein fractions were measured enzymatically (Genzyme Diagnostics, Framingham, MA) on a Cobas Mira analyzer (Roche Diagnostics, Laval, Quebec). For technical reasons (limitation on the amount of blood withdrawn in accordance with the Research Ethics Board guidelines, sample transportation and processing), we were limited to three time points, as indicated.

2.7. Additional blood measurements

Under resting conditions, 3 ml of blood was drawn into a nontreated tube, allowed to clot at room temperature and centrifuged at 1000×g for 10 min (Beckman Allegra X-12R; Beckman, Fullerton, CA), and the supernatant was frozen at −80°C for analysis of serum free fatty acid (FFA) and serum TAG. Five milliliters was drawn into an EDTA-treated tube on ice and centrifuged at 4°C and 1000×g for 15 min, and the supernatant was stored at −80°C for analysis of plasma IL-6. For incretin and insulin analysis, 6 ml of blood was drawn into an EDTA tube pretreated with dipeptidyl peptidase IV inhibitor and placed on ice following the addition of aprotinin. Tubes were centrifuged at 1000×g for 15 min within 30 min of being drawn. The supernatant was aliquoted into several microcentrifuge tubes and frozen at −80°C for later analysis. Blood samples were analyzed for specific endpoints at each time point, as indicated in Results.

2.8. Subcutaneous adipose tissue mRNA analysis using real-time PCR

Adipose tissue mRNA was extracted using the Trizol reagent method (Invitrogen, Carlsbad, CA). Briefly, approximately 60 mg of frozen adipose tissue was weighed and immediately homogenized using a Polytron 3100 (Kinematica, Bohemia, NY) in 1 ml of ice-cold Trizol reagent. RNA was extracted using chloroform and isopropyl alcohol precipitation, with glycogen (Invitrogen) as carrier, to increase RNA yield. cDNA was synthesized from 1 ng of extracted RNA. Real-time PCR analysis was completed using SybrGreen master mix (Invitrogen) with the ABI 7900HT Fast Real Time PCR system (Applied Biosystems, Forest City, CA) and factory default thermocycler settings, as directed. β-Actin was originally selected as endogenous control. However, after completion of analysis, it was determined that β-actin was not suitable for determining the effect of time (average C_t values, 22.5 at 0 h vs. 20.5 at 6 h; P<.05). The data were reanalyzed using 18S as endogenous control, with no effect of time or treatment, as determined by two-way repeated-measures analysis of variance (ANOVA) (average C_t values, 15.2 at 0 h vs. 14.9 at 6 h; P=.6). The following primers used for IL-6 and 18S analysis have been used previously [30]: IL-6: 5′-TGA AAG CAG CAA ACA GGC ACT-3′ (forward) and 5′-GCA ACT CTC CTC ATT GAA TCC AG-3′ (reverse); 18S: 5′-GAC TCA ACA CGG GAA ACC TCA C-3′ (forward) and 5′-ATC GCT CCA CCA ACT AAG AAC G-3′ (reverse). The following primers were designed for GIPr: 5′-GGG CCA CTT CCG CTA CTA CC-3′ (forward) and 5′-CCA GCA CTG CGT GTT CTC GT-3′ (reverse). The primers for β-actin were as follows: 5′-CCC AAG GCC AAC CGC GAG AAG AT-3′ (forward) and 5′-GTC CCG GCC AGC CAG GTC CAG-3′ (reverse). All primers were determined to have 100% efficiency; therefore, all mRNA data are expressed in terms of relative quantification using the $\Delta\Delta C_t$ method calculated by RQ Manager Software v 1.2 (Applied Biosystems). Expression data were normalized to the rest trial (0 h) expression level for each subject individually (set to an arbitrary unit of 1) to determine the fold change in mRNA in response to exercise and OFTT.

2.9. Assays

Whole-blood glucose was analyzed by a glucose oxidase method (YSI 2300 Stat Plus Glucose Analyzer). Plasma IL-6 was determined using separate high-sensitivity quantitative sandwich enzyme immunoassays performed in accordance with the manufacturer's direction (Quantikine HS; R&D Systems, Minneapolis, MN). Incretin [GIP and GLP-1(active)] and insulin analyses were performed from the same sample using a multiplex immunoassay (Milliplex Human Gut Hormone panel HGT-68K; Millipore Corp., St. Charles, MO) and a Bio-Plex 200 analyzer (Bio-Rad, Hercules, CA), in accordance with the manufacturer's guidelines. Serum 3-hydroxybutyrate (3HB) was analyzed by a cyclic enzymatic method (Autokit 3-HB; Wako Bioproducts, Richmond, VA) using the microtiter procedure provided by the manufacturer. Serum FFA was calculated by colorimetric assay (NEFA kit; Wako Bioproducts). Serum TAG was determined by an autoanalyzer (Synchron CX Systems; Beckman Coulter, Inc.) at Guelph General Hospital (Guelph, ON, Canada).

2.10. Calculations and statistical analysis

Food record analysis was completed using ESHA Food Processor SQL v9.04 software. Two-tailed paired Student's t test was used to examine differences between fasting values and area under the curve (AUC) for TAG, GIP and GLP-1(active). AUC was calculated with Prism software (Prism v. 3.03, 2002) using the trapezoidal method. For all other data, the effects of Treatment, Time and Treatment×Time interactions were assessed using a two-way repeated-measures ANOVA. When statistical significance was indicated, a Tukey post hoc test was applied for multiple comparisons analysis. Significance was set at P<.05. Statistical procedures were performed using Sigma Stat version 2.03. Most data were not normally distributed and were therefore log-transformed prior to statistical analysis. The data are reported as geometric mean±pooled S.E.M., as indicated.

3. Results

3.1. Subject characteristics and fasting blood measurements

In total, 10 subjects were recruited, and they completed the protocol. Despite meeting the screening criteria, one subject subsequently demonstrated a fasting TAG of <2.0 mmol/L (1.12 mmol/L) during rest (nonexercise trial) and was excluded from subsequent analysis. The physical and clinical characteristics (including fasting blood measurements), as well as the exercise results, of the remaining subjects (n=9) are summarized in Table 2. There was no difference in energy intake or macronutrient content between the exercise trial and the rest trial during the 3 days prior to each trial (2286±214 kcal, 34±2% fat, 17±1% protein, 48±4% carbohydrate and 3±1% alcohol). Subjects described their lifestyles as ranging from sedentary (<30 min of exercise per week) to low activity with walking (1–2 h/week), the most commonly reported mode of physical activity.

3.2. Fasting and postprandial TAG and cholesterol

Two measures of TAG were made: total serum TAG at 0, 1, 2, 3, 4, 5 and 6 h, and plasma TAG (total, CM, VLDL and IDL+LDL+HDL) at 0, 3

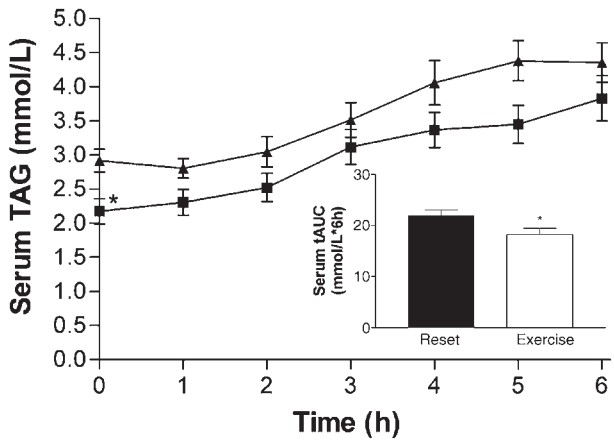

Fig. 1. Outset: Postprandial serum TAG with and without exercise (55% VO_2 peak) 16 h prior to an OFTT in men with high fasting TAG (n=9). Data are presented as geometric mean±pooled S.E.M. Rest is represented by triangles (▲), and exercise is represented by squares (■). Fasting serum TAG is lower following exercise (main effect; P<.05). The OFTT raised postprandial TAG in both exercise and rest (P<.05). Exercise prior to the OFTT lowered postprandial serum TAG (P<.05). Inset: Serum TAG total AUC was lowered by exercise treatment (P<.05).

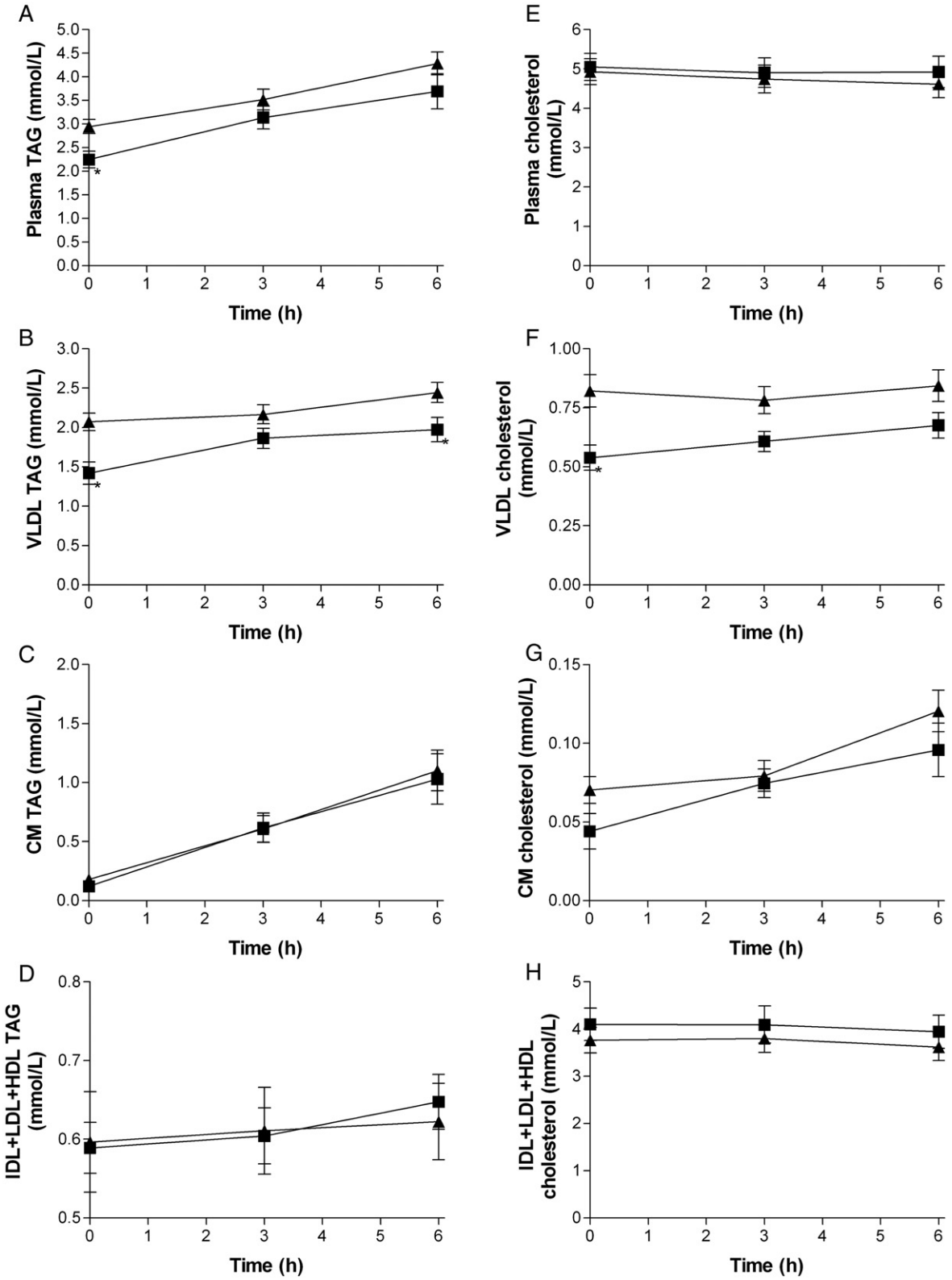

Fig. 2. Postprandial total, CM, VLDL and IDL+LDL+HDL plasma TAG and cholesterol with and without exercise (55% VO_2 peak) 16 h prior to an OFTT in men with high fasting TAG (n=9). Data are presented as geometric mean±pooled S.E.M. Rest is represented by triangles (▲), and exercise is represented by squares (■). Specific significant differences are marked by (*). (A) Exercise lowered fasting plasma TAG (P<.05). (B) Exercise lowered fasting VLDL TAG (P<.05). VLDL TAG increased following OFTT ingestion and was lower at 0 and 6 h following exercise (P<.05). (C) Exercise did not alter fasting CM TAG. CM TAG increased following OFTT ingestion (P<.05) and was not changed by exercise. (D) Exercise did not alter IDL, LDL and HDL TAG. The sum of IDL, LDL and HDL TAG did not change following OFTT ingestion and was not changed by exercise. (E) Exercise did not alter fasting total cholesterol. Total plasma cholesterol decreased following OFTT ingestion (P<.05) and was not changed with exercise. (F) Exercise lowered fasting VLDL cholesterol (P<.05). VLDL cholesterol was not increased following OFTT ingestion and was lower following exercise (P<.05). (G) Exercise lowered fasting CM cholesterol (P<.05). CM cholesterol increased following OFTT ingestion (P<.05) and was not changed by exercise. (H) Exercise did not alter fasting IDL, LDL and HDL cholesterol. The sum of IDL, LDL and HDL cholesterol decreased following OFTT ingestion (P<.05) and was not changed by exercise.

Table 3
Fasting and postprandial glucose, insulin, IL-6, GIP and GLP-1 following an OFTT with (exercise) and without (rest) an acute bout of moderate exercise in men with high fasting TAG

	Time (h)	0	0.5	1	1.5	2	4	6
Glucose (mmol/L) *	Rest	4.76±0.2		4.50±0.2		4.60±0.1	4.55±0.1	4.40±0.1
	Exercise	4.96±0.2		4.56±0.2		4.75±0.1	4.56±0.1	4.45±0.1
Insulin (pmol/L) *	Rest	56.09±11.7	78.15±16.7	65.26±11.8	60.42±12.7	52.99±9.5	51.06±6.7	47.16±7.1
	Exercise	56.61±9.4	80.81±12.2	60.57±8.1	48.76±7.7	54.96±9.6	52.52±9.1	49.12±8.3
GIP (pg/ml) **	Rest	21.53±4.5	69.56±15.8	67.35±16.6	95.14±31.4	103.73±29.1	130.22±20.4	121.77±12.9
	Exercise	21.84±5.0	78.34±17.9	76.88±14.4	69.84±18.0	98.36±27.3	140.96±22.5	145.78±32.2
GLP-1(active) (pg/ml) **	Rest	18.31±1.3	28.07±2.9	26.87±4.9	26.67±4.4	29.18±4.1	35.94±4.3	40.86±4.4
	Exercise	15.73±0.9	30.94±5.1	29.09±3.5	22.77±2.6	26.43±3.4	30.95±5.4	39.33±6.0
IL-6 (pg/ml) **	Rest	2.01±0.2				1.99±0.2	2.31±0.2	3.30±0.4
	Exercise	1.68±0.2				1.70±0.1	2.37±0.3	3.08±0.2

All values are presented as geometric mean±pooled S.E.M. (n=9).
* Significant decrease in concentration over the postprandial period (two-way repeated-measures ANOVA, P<.05).
** Significant increase in concentration over the postprandial period (two-way repeated-measures ANOVA, P<.05). There was no effect of exercise on these measurements (P>.05).

and 6 h. Exercise significantly lowered fasting (24% decrease; P<.05) and postprandial (main effect; P<.05) serum TAG compared to the rest trial (Fig. 1). Total serum TAG increased significantly during the postprandial period following OFTT ingestion (P<.05). Likewise, fasting total TAG in plasma (Fig. 2A) was significantly lower (23% decrease) following exercise (main effect; P<.05). More specifically, fasting plasma TAG in the VLDL fraction was significantly lower (30% decrease) following exercise (Fig. 2B; P<.05). Postprandial VLDL TAG increased following OFTT ingestion in both exercise and rest, but was significantly lower following exercise at 0 and 6 h (interaction; P<.05). Fasting CM TAG was not altered by exercise. Postprandial CM TAG increased significantly with OFTT ingestion (P<.05), but was not different between rest and exercise at any time point (Fig. 2C). The sum of IDL, LDL and HDL TAG did not change with exercise at fasting, nor was there a significant postprandial response in either trial (Fig. 2D). Fasting total plasma cholesterol was not altered with exercise (Fig. 2E). A very small but statistically significant decrease in total plasma cholesterol was observed throughout the postprandial period (Fig. 2E; P<.05), but was not altered by exercise. Fasting VLDL cholesterol was significantly lowered (34%) following exercise (Fig. 2F; P<.05). VLDL cholesterol did not change following OFTT. VLDL cholesterol remained significantly lower throughout the postprandial period following exercise (P<.05). Fasting CM cholesterol was significantly lower (27%) following exercise (Fig. 2G; P<.05). CM cholesterol increased significantly following OFTT ingestion (P<.05) in both exercise trial and rest trial, with no effect of exercise treatment. Exercise did not alter the fasting sum of IDL, LDL and HDL cholesterol (Fig. 2H), and decreased significantly during the postprandial period (P<.05). The postprandial response of the sum of IDL, LDL and HDL did not change with exercise.

3.3. Whole-blood glucose and serum insulin

Exercise did not alter fasting glucose and insulin (Table 3). Mean glucose and insulin decreased significantly (P<.05) during the postprandial period, but were not altered with exercise (Table 3).

3.4. Serum FFA and 3HB

There was no difference in fasting FFA or 3HB between the exercise trial and the rest trial. OFTT ingestion significantly raised postprandial FFA and 3HB (Fig. 3A and B; P<.05), and exercise induced a significantly greater increase in postprandial FFA and 3HB compared to rest (P<.05).

3.5. Postprandial plasma IL-6

Plasma IL-6 data are summarized in Table 3. Fasting concentrations of IL-6 did not change with exercise. IL-6 increased significantly throughout the postprandial period in both the exercise trial and the rest trial. Exercise did not significantly affect the postprandial IL-6 response despite a 17% nonsignificant (P>.05) reduction in fasting plasma IL-6 following exercise.

3.6. Postprandial plasma GIP and GLP-1(active)

Fasting concentrations of GIP and GLP-1(active) did not change with exercise (Table 3). Both incretin hormones GIP and GLP-1 (active) increased following the ingestion of OFTT (P<.05). Exercise did not alter the postprandial concentration of GIP or GLP-1 (Table 3), and there was no significant difference in AUC for either incretin hormone (data not shown).

3.7. IL-6 and GIPr mRNA expressed in subcutaneous adipose tissue

All data are presented with fasting levels of expression during the rest trial (rest, 0 h), established as the reference level of expression. Due to a scheduling conflict, resting biopsy samples could not be obtained for one subject. Thus, due to lack of paired adipose tissue expression data, this subject has been removed from analysis, and the expression data shown are for n=8. Exercise significantly lowered IL-6 and GIPr mRNA (both main effects; P<.05) as compared to rest (Fig. 4).

4. Discussion

Several important aspects of postprandial lipid metabolism had not been previously investigated following an acute bout of exercise. The purpose of this study was to lower fasting and postprandial TAG through a single bout of exercise in a population of older men with elevated fasting TAG to determine whether inflammation (as measured by IL-6) and gut hormones (as measured by the incretins GIP and GLP-1) are involved in modifying postprandial response to an oral fat load. This study considered several tissues other than muscle, namely, the liver, gut and adipose tissue, which could be involved in the reduction of fasting and postprandial TAG following a novel OFTT containing emulsified lipids as the only nutrient stimulus. While the amount of fat consumed by subjects in each OFTT trial was substantial (100 g on average), it is noteworthy that this amount of fat can be achieved in a single fast-food meal (e.g., double cheeseburger, large fries and milkshake) and thus is representative of the amount of fat that could be consumed in one meal in today's society. Age [31], as well as both fasting and postprandial TAG [32], is an independent risk factor for CVD. To our knowledge, hypertriacylglycerolemic men have only been investigated in one previous study of similar design, but with a younger cohort of subjects [33]. Unlike most other postprandial studies, we extended our TAG investigation to include lipoprotein subfractions. We demonstrated that VLDL TAG is the only TRL fraction to be altered with acute exercise. The circulating concentration of IL-6,

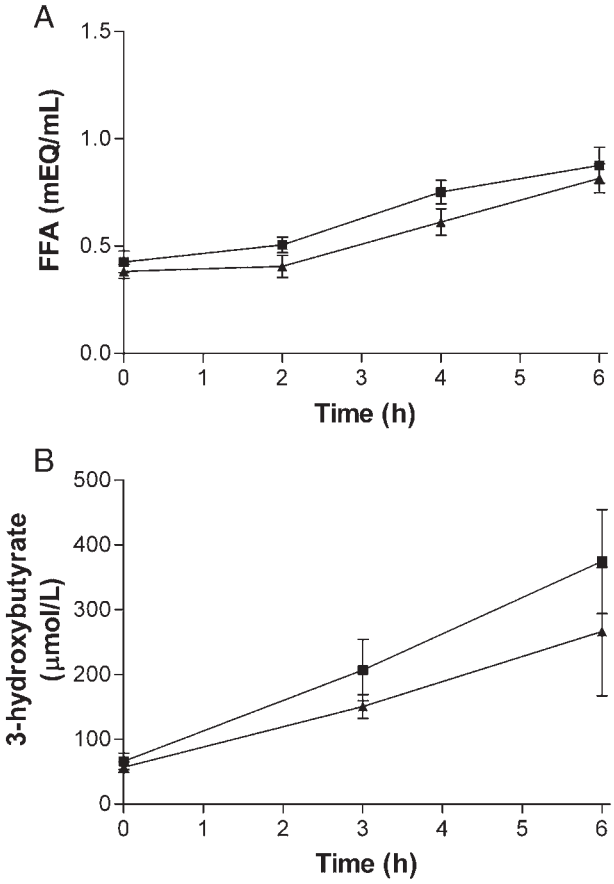

Fig. 3. (A) Postprandial serum FFA with and without exercise (55% VO_2 peak) 16 h prior to an OFTT in men with high fasting TAG (n=9). Data are presented as geometric mean±pooled S.E.M. Rest is represented by triangles (▲), and exercise is represented by squares (■). Exercise raised postprandial FFA concentrations (P<.05). OFTT administration raised FFA in both exercise and rest trials (P<.05). (B) Postprandial serum 3HB with and without exercise (55% VO_2 peak) 16 h prior to an OFTT in men with high fasting TAG (n=9). Data are presented as geometric mean±pooled S.E.M. Rest is represented by triangles (▲), and exercise is represented by squares (■). Exercise raised postprandial 3HB concentrations (P<.05). OFTT administration raised 3HB in both exercise and rest trials (P<.05).

a key inflammatory mediator secreted from adipose tissue [14], was not altered, but subcutaneous adipose tissue expression of IL-6 was significantly decreased following exercise, which may have substantial implications for local tissue regulation [34]. Gut-derived incretin hormones are responsive to dietary fat ingestion [22,23], but they have not been investigated within the context of acute exercise with the intent of lowering TAG. Although our data showed that the postprandial GIP and GLP-1 response to an oral fat load was not affected by exercise, adipose tissue expression of GIPr mRNA was decreased following a single bout of moderate-intensity exercise. Taken together, these data suggest that the liver and adipose tissue are indeed modified following exercise.

In the current study, 60 min of moderate exercise at an estimated 55% VO_2 peak on the day before a pure fat load resulted in a significant decrease in fasting and postprandial TAG. Moderate treadmill walking (between 50% and 60% VO_2 peak; 45–90 min) on the day prior to a mixed-meal oral fat load has been established as a means to significantly decrease fasting and postprandial TAG [8,33,35–38]. The measurements of CM and VLDL in this study cannot be used to determine the relative contributions of the production and clearance of TAG. However, our observed decrease in fasting and postprandial VLDL TAG and cholesterol, but not in postprandial CM TAG and cholesterol, strongly suggests that the liver contributed substantially to the TAG-lowering effect of exercise during the postprandial response to a pure lipid OFTT. An additional metabolic process, on top of increased peripheral clearance, is likely responsible for the reduction in circulating TAG [35], as CM particles are preferentially bound to lipoprotein lipase before being cleared from the circulation [39]. Both large and small VLDL particles are decreased following moderate exercise [8], but the number of gut-derived TAG particles (fasting and postprandial) is not reduced following exercise despite a decreased fasting TAG concentration [40]. Exercise has been shown to alter fasting and postprandial TAG differently compared to energy restriction alone [38]. However, exercise may alter these TAG concentrations when the energy deficit following exercise is replaced [41,42]. Subjects consumed a standardized meal on the evening before both exercise and rest trials, and they were instructed to consume only the standardized meal on the evening before both fat loads. The results of this study can therefore be attributed to the addition of the exercise bout, although the contribution of energy deficit and caloric expenditure requires further analysis.

The reduction in VLDL can be attributed to an increased hepatic catabolism of fatty acids and/or a decreased secretion of TRL particles from the liver. We have found that FFA and 3HB, a marker of hepatic fatty acid oxidation, are increased following exercise. Others have previously demonstrated that prior exercise increased not only 3HB but also whole-body endogenous and exogenous fatty acid oxidation following a high-fat mixed meal [7]. Taken together, these data

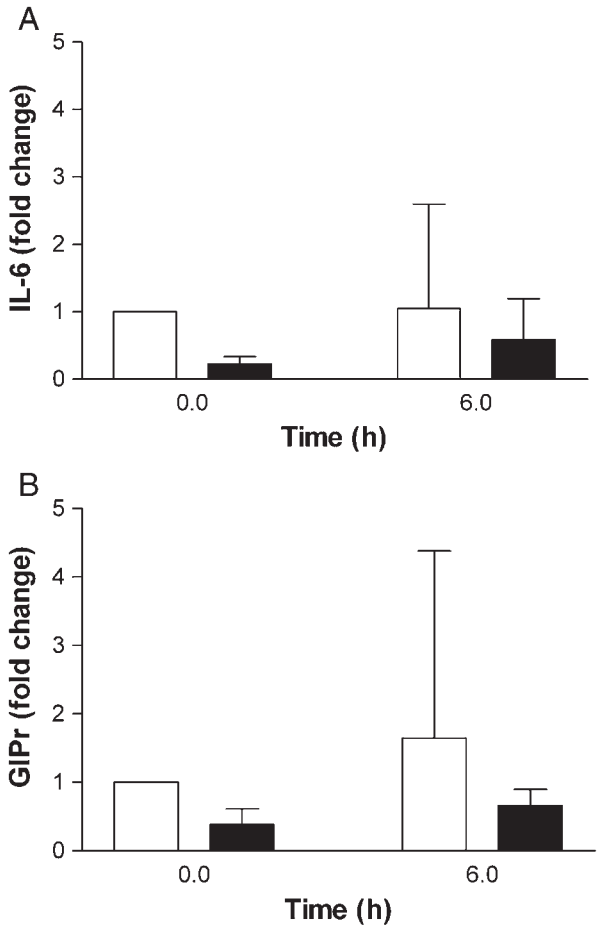

Fig. 4. IL-6 and GIPr expression in subcutaneous adipose tissue taken from men (n=8) with high fasting TAG with and without exercise (55% VO_2 peak) 16 h prior to an OFTT. Open bars represent the rest trial, and black bars represent the exercise trial. Significant effect of exercise is noted by (*). (A) IL-6 expression was lowered with exercise (main effect; P<.05). (B) GIPr expression was lowered with exercise (main effect; P<.05).

suggest that exercise increased hepatic fatty acid oxidation, thereby reducing the partitioning of fatty acids into TAG formation and VLDL assembly. This reduced the appearance of VLDL in the blood and subsequently lowered fasting and postprandial TAG. As the rate of VLDL production is dependent on substrate provision [43], fatty acid oxidation likely exceeds FFA delivery, resulting in the observed decrease in VLDL. It is not known whether oxidation is solely responsible for the decrease in VLDL, or whether other as of yet unknown factors participate in this process.

Our data demonstrate that an acute bout of moderate-intensity walking decreased IL-6 mRNA in adipose tissue in men with high fasting TAG. As an elevated IL-6 concentration is a risk factor for developing CVD [17,18] and as about 30% of circulating IL-6 originates from subcutaneous adipose tissue [14], this significant change in IL-6 mRNA may represent a positive phenotype shift towards CVD risk reduction in a lower inflammatory state. Lowering the inflammatory profile in at-risk subjects might be of clinical importance, as a low-grade inflammatory state characterizes many obesity-related chronic diseases such as CVD [18]. Men with elevated fasting TAG also have a concurrent elevation in plasma IL-6 [4], and an IL-6 injection increased TAG secretion in rats [19]. IL-6 is secreted from subcutaneous adipose tissue, and previous work has shown that the expression of IL-6 mRNA in this fat depot is increased throughout the acute exercising period [44]. Although we did not see a difference in circulating IL-6, exercise training has decreased IL-6 in lean men and obese men with and without type 2 diabetes [45]. Thus, IL-6 could have varying acute and chronic responses to exercise.

Our data suggest that IL-6 mRNA in adipose tissue is sensitive to the last bout of exercise. Morbidly obese individuals who have completed a lifestyle intervention to reduce obesity demonstrate a significant decrease in subcutaneous IL-6 mRNA [46]. However, IL-6 mRNA may, in fact, be increased following weight stabilization when the timing of the last bout of exercise is controlled for [47]. Based on our data, it seems noteworthy that future intervention studies examining IL-6 expression should account for the last bout of exercise.

Our use of the novel OFTT has allowed us to conclude that dietary fat alone can induce a postprandial incretin response. Despite the significant changes in fasting and postprandial VLDL TAG observed with exercise, we were unable to detect differences in fasting or postprandial GIP or GLP-1. It is possible that postprandial TAG can still be altered by incretin hormones via modulation of the CM response, and that the lack of carbohydrate in our test meal resulted in an insufficient stimulus for GLP-1 and/or GIP secretion in order for differences in postprandial incretin measurements to be observed. Incretin hormones are responsive to dietary fat in mixed meals that include carbohydrate and protein, and modulate postprandial response to fat ingestion [22,23]. GLP-1, in particular, has been shown to be responsive to exercise [26]. GIP administration decreased CM TAG in dogs [21] and activated lipoprotein lipase in adipocytes *in vitro* [48]. Intravenous administration of GLP-1 abolished the postprandial rise in TAG [24]. Further work is necessary to determine whether the nutrient composition of a meal leads to differences in gut-derived incretin hormones and can account for the differences seen between studies.

Subcutaneous adipose tissue expresses a GIPr [25]. Furthermore, the pharmaceutical antagonism of GIPr prevented obesity and reduced TAG in mice fed various high-fat diets [49,50], and transgenic GIPr knockout mice have resisted the obesity and insulin resistance typically induced by a high-fat diet [51]. We therefore considered that exercise, a potent stimulus for decreasing obesity and promoting insulin sensitivity, might decrease GIPr expression in adipose tissue. Exercise significantly decreased GIPr mRNA in subcutaneous adipose tissue in men with high fasting TAG. Although these data suggest that acute exercise promotes a favorable expression profile of GIPr in subcutaneous adipose tissue, the function of GIPr in adipose tissue remains largely unknown [52]. Furthermore, it is noteworthy that our measurement of the relative expression of mRNA might not fully convey the effects of a functional protein on adipose tissue. Nevertheless, our data suggest that further research using different models such as animal models and/or microdialysis would be most beneficial to our understanding of adipose tissue physiology in response to the interaction between acute exercise and dietary fat.

The addition of moderate exercise on the day before an OFTT significantly lowered fasting and postprandial measures of TAG in men with elevated TAG. Most notably, liver-derived VLDL (TAG and cholesterol) was the major lipid component affected by exercise. We also found that circulating concentrations of IL-6, GIP and GLP-1 (active) do not appear to play a role in the TAG-lowering effect of exercise. In addition, we have shown that one bout of exercise altered the expression of IL-6 and GIPr in subcutaneous adipose tissue. Thus, this study illustrates that one bout of exercise can significantly improve factors implicated in CVD in men with high fasting TAG. Although the current study only measured mRNA expression following a single bout of exercise, beneficial changes in adipose tissue protein expression might be observed with repetitive bouts of exercise.

Acknowledgments

The authors would like to acknowledge the following persons for their contribution to this study: the subjects for volunteering their time; Dr. Deborah Robinson, MD, and Dr. Erin Turvey, MD, for performing the adipose tissue biopsies; Premila Sathasivam for providing logistical and technical support throughout the study; Marion Cousins for completing the ultracentrifugation analysis of plasma lipids; Brennan Smith for completing the gas chromatography analysis; and Holly Freill for completing the 3HB analysis and for contributing to subject recruitment and protocol completion.

The authors also acknowledge the Natural Sciences and Engineering Research Council of Canada for financial support: a Discovery Grant to L.E.R. and a Postgraduate Doctoral (PGSD3) scholarship to M.J.D.

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