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**Exercise Training Reduces Liver Fat and Increases Rates of VLDL Clearance, but not VLDL Production in NAFLD**

**Shojaee-Moradie, F., Cuthbertson, D.J., Barrett, M., Jackson, N.C., Herring, R, Thomas, E.L., Bell, J.D., Kemp, G.J., Wright, J. and Umpleby, A.M.**

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25 **Abstract**

26

27 **Context** Randomised controlled trials in non-alcoholic fatty liver disease (NAFLD) have shown that  
28 regular exercise, even without calorie restriction, reduces liver steatosis. A previous study has shown  
29 that 16 weeks supervised exercise training in NAFLD did not affect total VLDL kinetics.

30 **Objective** To determine the effect of exercise training on intrahepatocellular fat (IHCL) and the  
31 kinetics of large triglyceride-(TG)-rich VLDL<sub>1</sub> and smaller denser VLDL<sub>2</sub> which has a lower TG  
32 content.

33 **Design** A 16 week randomised controlled trial.

34 **Patients** 27 sedentary patients with NAFLD.

35 **Intervention** Supervised exercise with moderate-intensity aerobic exercise or conventional lifestyle  
36 advice (control).

37 **Main outcome** Very low density lipoprotein1 (VLDL<sub>1</sub>) and VLDL<sub>2</sub>-TG and apolipoproteinB (apoB)  
38 kinetics investigated using stable isotopes before and after the intervention.

39 **Results** In the exercise group VO<sub>2max</sub> increased by 31±6% (mean±SEM) and IHCL decreased from  
40 19.6% (14.8, 30.0) to 8.9% (5.4, 17.3) (median (IQR)) with no significant change in VO<sub>2max</sub> or IHCL  
41 in the control group (change between groups p<0.001 and p=0.02, respectively). Exercise training  
42 increased VLDL<sub>1</sub>-TG and apoB fractional catabolic rates, a measure of clearance, (change between  
43 groups p=0.02 and p=0.01, respectively), and VLDL<sub>1</sub>-apoB production rate (change between groups  
44 p=0.006), with no change in VLDL<sub>1</sub> -TG production rate. Plasma TG did not change in either group.

45 **Conclusion** An increased clearance of VLDL<sub>1</sub> may contribute to the significant decrease in liver fat  
46 following 16 weeks of exercise in NAFLD. A longer duration or higher intensity exercise  
47 interventions may be needed to lower plasma TG and VLDL production rate.

48

49 **Introduction**

50 NAFLD, the most prevalent liver disease in the developed world (1), increases the risk of chronic  
51 liver disease, hepatocellular carcinoma and cardiovascular disease, and is associated with increased  
52 visceral fat, hypertriglyceridaemia and insulin resistance (2).

53 Hepatic steatosis is the result of an imbalance between triglyceride (TG) synthesis and TG export.  
54 TGs stored and secreted by the liver are synthesised from fatty acids generated from three main  
55 sources: hepatic de novo lipogenesis; circulating non-esterified fatty acids (NEFA), originating from  
56 adipose tissue; and fatty acids derived from the remnants of the TG rich lipoproteins, VLDL and  
57 chylomicrons (3) which are generated when these lipoproteins are cleared from the circulation by the  
58 lipolytic action of lipoprotein lipase (LPL) and hepatic lipase (4).

59 VLDL secreted by the liver can be separated into large TG-rich VLDL<sub>1</sub> and smaller denser VLDL<sub>2</sub>  
60 which has a lower TG content. There is evidence that these two VLDL species are independently  
61 regulated (5). VLDL is initially assembled as a primordial particle (pre-VLDL) when apolipoprotein  
62 B100 (apoB) is co-translationally lipidated in the endoplasmic reticulum by microsomal transfer  
63 protein (MTP). Pre-VLDL can either be retained and degraded, or further lipidated to form VLDL<sub>2</sub>.  
64 This particle can then either be secreted or converted to VLDL<sub>1</sub> following the addition of more TG in  
65 the liver. The hydrolysis of VLDL<sub>1</sub>-TG by lipoprotein lipase (LPL) also generates VLDL<sub>2</sub> in the  
66 circulation. Thus VLDL<sub>2</sub> has two sources. Insulin regulates VLDL assembly by decreasing apoB  
67 mRNA translation (6), inhibiting the expression of MTP (7) and promoting apoB degradation via  
68 autophagy (8). In NAFLD, with intrahepatic lipids in copious supply, increases in both VLDL-apoB  
69 and VLDL-TG production rate (PR) contribute to the atherogenic lipid profile (9).

70 Lifestyle intervention is the first line of treatment for NAFLD. Weight loss (5-10%) through diet, with  
71 or without exercise, has been shown to reduce hepatic steatosis (10,11). A number of randomised  
72 controlled trials have also shown that regular exercise, even without calorie restriction, reduces liver  
73 steatosis (12,13). A previous study has shown that 16 weeks supervised exercise training in men and  
74 women with NAFLD did not affect total VLDL kinetics (14). In the current study we examined the  
75 effect of 16 weeks supervised exercise training in men with NAFLD on VLDL<sub>1</sub> and VLDL<sub>2</sub> kinetics,  
76 using a protocol which we have shown previously to very effective at increasing fitness (15).

77 **Methods**

78 **Study design** The study was approved by the English National Health Service (NHS) Ethics  
79 Committee and the University of Surrey Ethics Committee. The study was performed at one centre, in  
80 Guildford, Surrey. This study is part of a larger collaborative study investigating the metabolic impact  
81 of exercise supervision in patients with NAFLD (16). Informed consent was obtained from the study  
82 participants prior to inclusion into the study.

83 **Study participants** Twenty nine sedentary male patients, confirmed to have NAFLD were recruited  
84 through the English NHS primary and secondary care providers in the local area. There were two  
85 dropouts, one in each group. Twenty seven patients completed the study (Table 1) The diagnosis of  
86 NAFLD was made in patients who had been referred for investigation of raised serum transaminases,  
87 indication of hepatic steatosis on ultrasound or by liver biopsy (n=4, two in each group; none of these  
88 patients had non-alcoholic steatohepatitis). It was not possible to exclude NASH from subjects who  
89 were not recruited by biopsy. Patients were excluded if the diagnosis of NAFLD was secondary to  
90 drug treatments, if there was evidence of viral hepatitis, autoimmune hepatitis or primary biliary  
91 cirrhosis, or metabolic disorders, if they had a history of type 2 diabetes mellitus, ischaemic heart  
92 disease or had any contraindications to exercise, clinical hyperlipidaemia (fasting plasma TG >3.0  
93 mmol/l or total cholesterol levels > 7.0 mmol/l), if they were current smokers, had a history of  
94 excessive alcohol intake (weekly consumption of >21 units), had MRI contraindications (cardiac  
95 pacemakers, metal implants), or were taking any fibrates or beta blockers.

96 Participants were asked to complete a Physical Activity Readiness Questionnaire to identify those not  
97 suitable for physical activity. Motivation was assessed through questions relating to willingness to  
98 increase exercise levels and confidence in complying with exercising four times per week. Suitable  
99 participants were randomised to one of two groups using a list generated by computer randomisation,  
100 (Statistical Analysis System v 9.1, PROC PLAN software). One group received a structured  
101 supervised exercise programme with an exercise physiologist. The other group received standard  
102 lifestyle advice (control group) with no further communication from the exercise physiologist. Both  
103 groups were asked to continue their usual diet.

104

105 **Study measurements** Prior to and following the 16 week intervention period measurements of  
106 physical fitness ( $VO_{2max}$ ) were made and a 7 day diet diary was completed. On a separate visit,  
107 measurements of fasting VLDL<sub>1</sub> and VLDL<sub>2</sub>-apoB and TG kinetics and arterial stiffness (by pulse  
108 wave velocity) were made. Body composition (total, subcutaneous and visceral fat volumes) was  
109 measured by magnetic resonance imaging (MRI) and IHCL, intramyocellular (IMCL) and pancreatic  
110 lipid content was measured by magnetic resonance spectroscopy (<sup>1</sup>H-MRS).

111 **Physical training protocol** Participants allocated to the supervised group exercised at moderate  
112 intensity (40-60% heart rate reserve) for 20 minutes initially (progressing towards 1 hour as the  
113 programme developed) 4-5 times per week for 16 weeks. Types of activities were either gym based  
114 aerobic plus resistance exercise, or outdoor aerobic activities and resistance exercise as discussed with  
115 the exercise physiologist. Participants received weekly exercise supervision by the exercise  
116 physiologist usually in person, otherwise by telephone, to assess their progress.

117 **Measurement of  $VO_{2max}$**   $VO_{2max}$  was performed within four days of the metabolic study using an  
118 electronically braked bicycle ergometer (Lode; Excalibur Sport, Groningen, the Netherlands)  
119 equipped with a computerised breath (oxygen [O<sub>2</sub>]/carbon dioxide [CO<sub>2</sub>]) analyser system (Medical  
120 Graphics, St Paul, MN, USA). An electrocardiogram (ECG) was undertaken during the exercise test  
121 to monitor participants' heart rate and exclude latent ischaemic heart disease.

122 **Measurement of pulse wave velocity** is described in the Supplementary Material.

123 **Diet diaries** Quantification of dietary intake in all participants was assessed by diet diary, and  
124 analysed by Dietplan 6 (Release 6.60b4 with Windows VistaService Pack 1. Forestfield Software Ltd,  
125 Horsham, West Sussex, UK).

126 **Measurement of body composition and intracellular fat** Subjects fasted for 6 hours before the scans.  
127 Whole body MR imaging for body fat content and <sup>1</sup>H MRS measurements of pancreatic fat, IHCL and  
128 IMCL (tibialis anterior and soleus muscle) was measured on an Intera 1.5T Achieva multinuclear  
129 system (Philips Medical Systems, Best, Holland) as previously reported (17, 18). NAFLD was defined  
130 as mean IHCL > 5.5%. For more details see the Supplementary Material.

131 **Metabolic Study Protocol** Participants attended the CEDAR centre, Royal Surrey County Hospital,  
132 Guildford on two occasions before (0 week) and after the intervention (16 weeks). The participants

133 were asked to refrain from vigorous exercise for 72h before the study, abstain from drinking alcoholic  
134 beverages for 24h, and attend after an overnight fast. A primed (1mg/kg) intravenous infusion of 1-  
135 <sup>13</sup>C-leucine (1 mg/kg/h) and a bolus of <sup>2</sup>H<sub>5</sub> glycerol (75μmol/kg) were administered. Blood samples  
136 were taken at regular time intervals for 9 hours.

137 **Laboratory protocols** VLDL<sub>1</sub> (Svedberg flotation rate 60–400) and VLDL<sub>2</sub> (Svedberg flotation rate  
138 20–60) fractions were isolated from plasma by sequential ultracentrifugation (19). ApoB and TG were  
139 isolated from VLDL<sub>1</sub> and VLDL<sub>2</sub> hydrolysed, derivatised and isotopic enrichment measured by gas  
140 chromatography mass spectrometry as described in the Supplementary Material. Concentration  
141 measurements are also described in the Supplementary Material.

142 **Power calculation** The primary endpoint for this study was VLDL-apoB production rate. Based on a  
143 previous study in type 2 diabetes where a 6 month exercise program reduced VLDL-apoB production  
144 rate by 48% (20), the study was powered to detect a 20% within-group reduction in VLDL-apoB  
145 production with 80% power at the 5% level.

146 **Data analysis** The measurements of enrichment of free glycerol in plasma and glycerol enrichment of  
147 TG in VLDL<sub>1</sub> and VLDL<sub>2</sub> particles were used to determine VLDL<sub>1</sub> and VLDL<sub>2</sub>-TG fractional  
148 catabolic rate (FCR) using the modelling software SAAM II (SAAM Institute, Seattle, WA) as  
149 previously described (23). The model was also used to determine the kinetic parameters of VLDL<sub>1</sub>  
150 and VLDL<sub>2</sub> apoB using plasma αKIC enrichment and 1-<sup>13</sup>C leucine enrichment of VLDL<sub>1</sub> and  
151 VLDL<sub>2</sub>-apoB. VLDL<sub>1</sub>-TG and apoB FCR had two components, VLDL<sub>1</sub> FCR transfer (to VLDL<sub>2</sub>) and  
152 VLDL<sub>1</sub> FCR catabolism (direct removal from circulation). Production rate (PR) was calculated as the  
153 product of VLDL<sub>1</sub> and VLDL<sub>2</sub>-FCR and their respective pool sizes. VLDL<sub>1</sub> and VLDL<sub>2</sub>-TG and apoB  
154 pool sizes were calculated from VLDL<sub>1</sub> and VLDL<sub>2</sub>-TG and apoB concentrations in  
155 ultracentrifugation fractions and plasma volume as previously described (21). (For more details of the  
156 models see the Supplementary Material). Total VLDL-TG and VLDL-apoB pool sizes were  
157 calculated by the addition of VLDL<sub>1</sub> and VLDL<sub>2</sub>-TG and apoB pool sizes respectively. Particle sizes  
158 of VLDL<sub>1</sub> and VLDL<sub>2</sub> were calculated by dividing TG pool size by apoB pool size. Total VLDL-TG  
159 PR was calculated by summation of VLDL<sub>1</sub>-TG PR and VLDL<sub>2</sub>-TG hepatic PR.

160

161 Ten-year cardiovascular risk was calculated using the 10 year Framingham Risk Score (FRS) (22).  
162 Homeostatic Model Assessment (HOMA2) was used to assess whole body insulin sensitivity  
163 (HOMA2-%S) (23). Adipose tissue insulin resistance (Adipo-IR) was calculated by multiplying  
164 fasting plasma NEFA concentration with fasting serum insulin concentration.  
165 Percent Change in IHCL was calculated as Pre-Post intervention/Pre x100. Changes in other  
166 measurements were calculated as Pre-Post intervention.

167

168 **Statistical analysis** Statistical analysis of the data was performed using SPSS version 21.0 for  
169 Window (Chicago: SPSS Inc.). IHCL is shown as median (interquartile range). All other results are  
170 means  $\pm$  SEM. Non parametric data was log-transformed. Basal comparisons were performed using  
171 Student's *t* test. Within-group changes between baseline and 16 weeks were compared using paired *t*  
172 tests. The change between baseline and 16 weeks was compared between groups using student's *t* test  
173 for parametric data and Mann-Whitney U test for nonparametric data. Correlations were assessed by  
174 Pearson's correlation coefficient and Spearman's rho correlation coefficient when the data were not  
175 normally distributed. A p value <0.05 was taken as statistically significant.

176



177 **Results**

178 *Baseline characteristics*

179 Body weight, BMI and baseline biochemical characteristics (plasma lipid profile and liver enzyme  
180 concentrations) were not significantly different at 0 weeks between groups (Table 1). Similarly, there  
181 were no significant baseline differences in cardiorespiratory fitness ( $VO_{2max}$ ), IHCL, pancreatic fat or  
182 fat distribution (Table 2). IHCL in all participants (n=27) at 0 week correlated positively with fasting  
183 plasma TG concentration ( $r=0.439$ ,  $p=0.02$ ) and abdominal visceral fat ( $r=0.411$ ,  $p=0.03$ ).

184

185 *Effects of intervention (exercise training vs. control)*

186 *Body weight, BMI and fitness*

187 Body weight and BMI decreased by  $3.6\pm 0.8\%$  and  $3.8\pm 0.9\%$  respectively after 16 weeks exercise  
188 training with no change in controls (change exercise vs. change control  $p<0.001$  and,  $p=0.02$ ) (Table  
189 1). In both groups, total energy intake and macronutrient composition remained unchanged after 16  
190 weeks compared with baseline (Supplementary Table 1).

191 In the exercise group  $VO_{2max}$  increased significantly by  $31\pm 6\%$  after 16 weeks with no change in  
192 controls (change in exercise group vs. control,  $p<0.001$ ) (Figure 1, Table 1).

193 *Liver enzymes (Table 1)*

194 After 16 weeks intervention there were within group decreases in the exercise group in ALT, AST and  
195 GGT concentrations ( $p<0.01$ ,  $p<0.02$  and  $p<0.03$ , respectively). ALT also decreased in controls  
196 ( $p<0.04$ ) with no change in either AST or GGT.

197 *Body composition and ectopic fat (Table 2)*

198 After 16 weeks, there was a significant decrease in IHCL content (% decrease  $52.2\%$  (29.0, 61.8);  
199 median (IQR)) in the exercise group, with no change in controls (change exercise vs. change control  
200  $p=0.02$ ). There was no significant change in pancreatic fat. All measured adipose tissue depots also  
201 significantly decreased with no change in controls (Table 2). The percentage change in IHCL between  
202 0 and 16 weeks in all patients (exercise and control group) correlated negatively with the change in

203  $VO_{2max}$  ( $r=-0.45$ ,  $p<0.02$ ) and correlated positively with the change in total body fat and visceral fat (;  
204  $r=0.54$ ,  $p=0.004$ ;  $r=0.41$ ,  $p=0.03$ ).

205 *Insulin sensitivity, fasting plasma insulin and glucose concentration (Table 1)*

206 After 16 weeks exercise there was a within-group decrease in fasting plasma glucose and serum  
207 insulin concentrations in the exercise group (both  $p<0.01$ ) (between groups for insulin,  $p=0.02$ ).  
208 HOMA2-%S (a measure of insulin sensitivity) increased by  $42.5\pm 11.6\%$  in the exercise group  
209 ( $p=0.002$ ) with no change in controls (between group,  $p=0.003$ ).

210 *Blood pressure, pulse wave velocity and Framingham risk factor scores (Table 2)*

211 Both systolic and diastolic blood pressure measurements decreased by  $5.4\pm 1.8\%$  and  $6.2\pm 2.7\%$  in the  
212 exercise group after 16 weeks exercise ( $p=0.01$ ,  $p=0.04$ ) (between groups  $p=0.04$ ,  $p=0.02$   
213 respectively). After 16 weeks, pulse wave velocity, a measure of arterial elasticity, improved in the  
214 exercise group ( $p=0.05$ ) although between groups this was not significant. The Framingham risk score  
215 decreased  $14\pm 4\%$  ( $p=0.001$ ) after exercise with no change in controls (between groups,  $p<0.05$ ). The  
216 percentage change in IHCL between 0 and 16 weeks in all patients correlated positively with the  
217 change in the FRS ( $r=0.62$ ,  $p=0.001$ ).

218 *Plasma and fraction lipids (Tables 1, 3 and 4)*

219 At baseline, there were no differences in plasma or lipoprotein fraction lipids between groups. Total  
220 cholesterol, TG and HDL cholesterol concentrations did not change from baseline in either group at  
221 16 weeks. After 16 weeks exercise there was a significant within-group decrease ( $p=0.03$ ) in plasma  
222 LDL cholesterol concentration. NEFA concentration did not change in either group. However adipose  
223 tissue IR decreased by  $24\pm 10\%$  in the exercise group ( $p=0.03$ ) with no change in controls (change  
224 between groups,  $p=0.02$ ). After 16 weeks there was no significant change in VLDL1-TG or VLDL1  
225 apoB concentration in either group. However VLDL<sub>2</sub> TG, cholesterol and apoB concentration were  
226 reduced ( $p<0.01$ ,  $p<0.02$ ,  $p=0.04$ ) in the exercise group with no change in controls. The particle size  
227 of VLDL<sub>1</sub> (TG/apoB) was reduced in the exercise group ( $p=0.03$ ), and was different between groups  
228 ( $p=0.04$ ).

229 *VLDL<sub>1</sub>- and VLDL<sub>2</sub>-TG kinetics (Table 3, Figure 2)*

230 At baseline VLDL<sub>1</sub> and VLDL<sub>2</sub>-TG kinetics did not differ between groups. After 16 weeks VLDL<sub>1</sub>-  
231 TG FCR was increased in the exercise group ( $p < 0.05$ ) due to an increase in the VLDL<sub>1</sub>-TG  
232 catabolism FCR ( $p = 0.05$ ). The percent change in IHCL in all participants was negatively correlated  
233 with the change in VLDL<sub>1</sub>-TG catabolism FCR ( $r = -0.74$ ,  $p < 0.001$ ) (Fig 2) and positively correlated  
234 with the change in VLDL<sub>1</sub>-TG transfer FCR ( $r = 0.63$ ,  $p = 0.001$ ). There was no change in VLDL<sub>2</sub>-TG  
235 FCR, VLDL<sub>1</sub>-TG PR, VLDL<sub>2</sub>-TG PR and total VLDL-TG PR within or between groups.

236 *VLDL<sub>1</sub>- and VLDL<sub>2</sub>-apoB kinetics (Table 4, Figure 2)*

237 VLDL<sub>1</sub>- and VLDL<sub>2</sub>-apoB kinetics were not different at baseline between groups. VLDL<sub>1</sub>-apoB FCR  
238 was increased at 16 weeks in the exercise group ( $p = 0.02$ ) with no change in controls (between groups,  
239  $p = 0.01$ ). This was due to a increase in the catabolism FCR ( $p < 0.01$ ) while the transfer FCR (to  
240 VLDL<sub>2</sub>) was decreased ( $p = 0.005$ ). There was no change in VLDL<sub>2</sub>-apoB FCR. VLDL<sub>1</sub>-apoB PR and  
241 total VLDL-apoB PR increased in the exercise group ( $p = 0.003$ ,  $p = 0.004$ ) (between groups  $p = 0.006$ ,  
242  $p = 0.02$ ). The percent change in IHCL between 0 and 16 weeks in all participants correlated  
243 negatively with the change in VLDL<sub>1</sub>-apoB PR ( $r = -0.48$ ,  $p = 0.01$ ) (Fig 2).

245 **Discussion**

246 We have demonstrated for the first time that a 16 week supervised exercise intervention which  
247 significantly improved cardiorespiratory fitness and reduced liver fat by over 50% in men with  
248 NAFLD increased the FCR (a measure of clearance) of both VLDL<sub>1</sub>-TG and apoB.

249 It is well documented that VLDL<sub>1</sub>-TG and apoB FCR increases with acute exercise (24) but this effect  
250 is not sustained 48h after exercise (25). In the current study subjects abstained from exercise for 72h  
251 prior to the measurement of VLDL kinetics in order to measure the chronic, rather than the acute,  
252 effects of exercise. NAFLD is highly associated with peripheral and hepatic insulin resistance (26,27),  
253 as observed in our participants who had a fasting insulin concentration double that reported in healthy  
254 subjects. There was an improvement in insulin sensitivity, as measured by HOMA %S, with exercise  
255 training, as has also been demonstrated previously in type 2 diabetes mellitus and overweight subjects  
256 (20,15). We have also shown in a different subset of patients with NAFLD that 4 months of exercise  
257 training (with a similar-sized effect on fitness and IHCL to the current study) improved peripheral but  
258 not hepatic insulin sensitivity (16). In the current study an improvement in peripheral insulin  
259 sensitivity was also demonstrated with the decrease in adipose-IR. LPL activity is regulated by insulin  
260 (28) and 20-weeks endurance exercise training in healthy men, which increased VO<sub>2max</sub> by 13%, has  
261 previously been shown to significantly increase post-heparin plasma lipoprotein lipase (29). Increased  
262 LPL activity would provide a mechanism for the increase in VLDL<sub>1</sub>-TG and apoB FCR observed in  
263 the current study. Notably for VLDL<sub>1</sub>-TG and apoB FCR it was the catabolic pathway that was  
264 increased rather than the transfer of TG to VLDL<sub>2</sub>. The increased clearance of TG from the systemic  
265 circulation, while the production rate of TG was simultaneously maintained, would enable the liver to  
266 export some of the stored TG for hydrolysis in skeletal muscle to sustain increased demand for fatty  
267 acids during exercise.

268 The reduction in body weight in the exercise group is unlikely to have mediated the increase in  
269 VLDL<sub>1</sub>-TG and apoB clearance since previous studies have shown weight loss in obese men,  
270 following a low calorie diet, reduces VLDL-apoB production rate with no effect on VLDL-apoB FCR

271 (30). Similarly in obese women, a hypocaloric diet has been shown to have no effect on either VLDL-  
272 TG or VLDL-apoB FCR (31).

273 The failure of exercise training to lower VLDL<sub>1</sub>-apoB and TG production rate and to increase  
274 VLDL<sub>1</sub>-apoB production rate was unexpected. This differs from a study in patients with type 2  
275 diabetes where exercise training for 6 months, resulting in a 16% increase in VO<sub>2max</sub>, reduced VLDL-  
276 apoB production rate (20). Liver fat was not measured in the latter study, patients were on oral  
277 hypoglycemic treatment (metformin and sulphonylureas) and some of the participants were African-  
278 Caribbean, a group known to have a lower propensity for NAFLD (32). The increase in VLDL<sub>1</sub>-apoB  
279 production rate following exercise training in the current study may be explained by the marked  
280 decrease in fasting insulin concentration in response to the improved peripheral insulin sensitivity,  
281 while at the same time hepatic insulin resistance was maintained. Insulin regulates VLDL assembly  
282 (6,7,8), thus a lowering of insulin will increase apoB secretion. It has also been shown in mice that  
283 triglycerides can rescue apoB from posttranslational degradation (33). The up-regulation of VLDL<sub>1</sub>-  
284 apoB production rate in response to exercise training could increase TG export and therefore assist in  
285 the reduction of liver fat. This could also explain the maintenance of plasma TG levels despite a  
286 decrease in liver fat.

287 The findings of this study differ from a previous study of patients with NAFLD where 16 weeks  
288 exercise training at an exercise intensity comparable to the current study had no effect on VLDL-TG  
289 and apoB kinetics (14). The discordant findings most likely reflect a greater improvement in both  
290 cardiorespiratory fitness and thus a greater reduction in IHCL in our study participants. VO<sub>2max</sub>  
291 increased by 31% in the current study compared to only a 9% increase in the previous study (14). An  
292 alternative or additional explanation is that total VLDL-TG and apoB (sf 20-400) were measured in  
293 the previous study, rather than VLDL<sub>1</sub> and VLDL<sub>2</sub> as in the current study. There is evidence that  
294 VLDL<sub>1</sub> and VLDL<sub>2</sub> are independently regulated (5) and that exercise primarily affects VLDL<sub>1</sub>  
295 kinetics (34), and so the effect of exercise on VLDL<sub>1</sub> may not be revealed by measurements on total  
296 VLDL. VLDL<sub>1</sub> carries more TG compared to VLDL<sub>2</sub> per particle and LPL has been shown to have a  
297 preference for TG-rich particles (35).

298 In NAFLD, CV events are the most common cause of mortality (36). Both the FRS, which has been  
299 shown to accurately predict the actual 10-year CV disease risk in patients with NAFLD (37), and  
300 arterial stiffness, an indicator of CVD and independent predictor of the corresponding risk and LDL  
301 cholesterol were decreased following exercise training. The reduced LDL cholesterol may be related  
302 to the small weight loss (38). These measures demonstrate that 16 weeks exercise training can reduce  
303 CVD risk in NAFLD.

304 The correlation between liver fat and cardiorespiratory fitness suggests the latter is the main driver for  
305 reduced IHCL in the exercise group. However the small weight loss in the exercise group will have  
306 contributed to the reduction in IHCL (11). Both endurance and resistance exercise with and without  
307 weight loss have been shown to reduce liver fat (39). The decrease in IHCL following exercise was  
308 not accompanied by any change in IMCL. This has also been reported in a previous exercise study in  
309 obese subjects (13). A recent meta-analysis of 33 studies examining the effect of lifestyle  
310 interventions on ectopic fat deposition in overweight and obese adults showed only a non-significant  
311 trend toward reductions in IMCL (40). Although the meta-analysis suggested pancreatic fat reduced  
312 with exercise, this was not found in the current study. There have been few studies specifically  
313 addressing effects of exercise intervention on pancreatic fat.

314 In conclusion, with an exercise intervention in non-diabetic men with NAFLD that significantly  
315 improved fitness and cardio-metabolic health, and produced a significant reduction in IHCL, the liver  
316 continued to export excessive amounts of TG in VLDL. This may reflect the failure to normalise  
317 IHCL and restore hepatic insulin sensitivity. A longer duration or higher intensity exercise  
318 intervention, or a combined approach with calorie restriction, may be required to achieve this and to  
319 lower plasma TG and VLDL production rate.

320

321

322 **Acknowledgements**

323 We are grateful to Dr Roman Hovorka, University of Cambridge, UK for creating the VLDL TG and  
324 apolipoprotein B models.

325

326

327 **Contribution statement**

328 AMU, DJC, FSM and GJK designed the study, FSM. JW and RH performed the clinical studies. MB  
329 supervised the exercise intervention. FSM and NCJ performed the laboratory work, supervised by  
330 AMU. JB and ELT performed the MRI and MRS measurements, AMU was the lead writer. All  
331 authors reviewed the manuscript. AMU is the guarantor of this work and, as such, had full access to  
332 all the data and takes responsibility for the integrity of the data and the accuracy of the data analysis.

333

334 **Figure legends**

335 Figure 1:  $VO_{2max}$  at 0 and 16 weeks in a) Exercise group and b) Control group

336 Figure 2. a) VLDL<sub>1</sub> (V1) apoB FCR, b) VLDL<sub>1</sub>-TG FCR c) VLDL<sub>1</sub>-apoB production rate and d)  
337 VLDL<sub>1</sub>-TG production rate, at 0 weeks (solid bar) and 16 weeks (hatched bar) in the exercise and  
338 control groups, e) relationship between percent change in IHCL and the change in VLDL<sub>1</sub>-apoB  
339 production rate and f) relationship between percent change in IHCL and the change in VLDL<sub>1</sub>-TG  
340 catabolism FCR. Black circles: exercise group; open circles: control group.

341

342 **References**

- 343 1. **Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M.** Global  
344 Epidemiology of Non-Alcoholic Fatty Liver Disease-Meta-Analytic Assessment of  
345 Prevalence, Incidence and Outcomes. *Hepatology*. 2016;64 (1):73-84.
- 346 2. **Marchesini G, Brizi M, Morselli-Labate AM, et al.** Association of nonalcoholic fatty liver  
347 disease with insulin resistance. *Am J Med*. 1999;107(5):450-455.
- 348 3. **Donnelly KL, Smith CI, Schwarzenberg SJ, Jessurun J, Boldt MD, Parks EJ.** Sources  
349 of fatty acids stored in liver and secreted via lipoproteins in patients with nonalcoholic fatty  
350 liver disease. *J Clin Invest*. 2005;115(5):1343-1351.
- 351 4. **Dallinga-Thie GM, Franssen R, Mooij HL, et al.** The metabolism of triglyceride-rich  
352 lipoproteins revisited: new players, new insight. *Atherosclerosis*. 2010;211(1):1-8.
- 353 5. **Malmstrom R, Packard CJ, Caslake M, et al.** Effects of insulin and acipimox on VLDL1  
354 and VLDL2 apolipoprotein B production in normal subjects. *Diabetes*. 1998;47(5):779-787.
- 355 6. **Sidiropoulos KG, Pontrelli L, Adeli K.** Insulin-mediated suppression of apolipoprotein B  
356 mRNA translation requires the 5' UTR and is characterized by decreased binding of an  
357 insulin-sensitive 110-kDa 5' UTR RNA-binding protein. *Biochemistry*. 2005;44(37):12572-  
358 12581.
- 359 7. **Au WS, Kung HF, Lin MC.** Regulation of microsomal triglyceride transfer protein gene by  
360 insulin in HepG2 cells: roles of MAPKerk and MAPKp38. *Diabetes*. 2003;52(5):1073-1080.
- 361 8. **Sparks JD, O'Dell C, Chamberlain JM, Sparks CE.** Insulin-dependent apolipoprotein B  
362 degradation is mediated by autophagy and involves class I and class III phosphatidylinositide  
363 3-kinases. *Biochem Biophys Res Commun*. 2013;435(4):616-620.
- 364 9. **Adiels M, Taskinen MR, Packard C, et al.** Overproduction of large VLDL particles is  
365 driven by increased liver fat content in man. *Diabetologia*. 2006;49(4):755-765.
- 366 10. **Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI.** Reversal of  
367 nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate  
368 weight reduction in patients with type 2 diabetes. *Diabetes*. 2005;54(3):603-608.
- 369 11. **Lazo M, Solga SF, Horska A, et al.** Effects of a 12-month intensive lifestyle intervention on  
370 hepatic steatosis in adults with type 2 diabetes. *Diabetes Care*. 2010;33(10):2156-2163.
- 371 12. **Hallsworth K, Fattakhova G, Hollingsworth KG, et al.** Resistance exercise reduces liver  
372 fat and its mediators in non-alcoholic fatty liver disease independent of weight loss. *Gut*.  
373 2011; 60(9):1278-1283.
- 374 13. **Johnson NA, Sachinwalla T, Walton DW, et al.** Aerobic exercise training reduces hepatic  
375 and visceral lipids in obese individuals without weight loss. *Hepatology*. 2009;50(4):1105-  
376 1112.



- 377 14. **Sullivan S, Kirk EP, Mittendorfer B, Patterson BW, Klein S.** Randomized trial of  
378 exercise effect on intrahepatic triglyceride content and lipid kinetics in nonalcoholic fatty  
379 liver disease. *Hepatology*. 2012;55(6):1738-1745.
- 380 15. **Shojaee-Moradie F, Baynes KC, Pentecost C, et al.** Exercise training reduces fatty acid  
381 availability and improves the insulin sensitivity of glucose metabolism. *Diabetologia*..  
382 2007;50(2):404-413.
- 383 16. **Cuthbertson DJ, Shojaee-Moradie F, Sprung VS, et al.** Dissociation between exercise-  
384 induced reduction in liver fat and changes in hepatic and peripheral glucose homeostasis in  
385 obese patients with non-alcoholic fatty liver disease. *Clin Sci (Lond)*. 2016;130(2):93-104.
- 386 17. **Thomas EL, Hamilton G, Patel N, et al.** Hepatic triglyceride content and its relation to  
387 body adiposity: a magnetic resonance imaging and proton magnetic resonance spectroscopy  
388 study. *Gut*. 2005;54(1): 122-127.
- 389 18. **Thomas EL, Fitzpatrick JA, Malik SJ, Taylor-Robinson SD, Bell JD.** Whole body fat:  
390 content and distribution. *Prog Nucl Magn Reson Spectrosc*. 2013;73:56-80.
- 391 19. **Watts GF, Mandalia S, Brunt JN, Slavin BM, Coltart DJ, Lewis B.** Independent  
392 associations between plasma lipoprotein subfraction levels and the course of coronary artery  
393 disease in the St. Thomas' Atherosclerosis Regression Study (STARS). *Metabolism*.  
394 1993;42(11):1461-1467.
- 395 20. **Alam S, Stolinski M, Pentecost C, et al.** The effect of a six-month exercise program on  
396 very low-density lipoprotein apolipoprotein B secretion in type 2 diabetes. *J Clin Endocrinol*  
397 *Metab*. 2004;89(2):688-694.
- 398 21. **Sarac I, Backhouse K, Shojaee-Moradie F, et al.** Gender differences in VLDL1 and  
399 VLDL2 triglyceride kinetics and fatty acid kinetics in obese postmenopausal women and  
400 obese men. *J Clin Endocrinol Metab*. 2012;97(7):2475-2481.
- 401 22. **D'Agostino RB, Vasan RS, Pencina MJ, et al.** General cardiovascular risk profile for use  
402 in primary care the Framingham Heart Study. *Circulation*. 2008;117(6):743-753.
- 403 23. **Levy JC, Matthews DR, Hermans MP.** Correct homeostasis model assessment (HOMA)  
404 evaluation uses the computer program. *Diabetes Care*. 1998;21(12): 2191-2202.
- 405 24. **Al-Shayji IA, Caslake MJ, Gill JM.** Effects of moderate exercise on VLDL and Intralipid  
406 kinetics in overweight/obese middle-aged men. *Am J Physiol Endocrinol Metab*.  
407 2012;302(3):E349-355.
- 408 25. **Bellou E, Magkos F, Kouka T, et al.** Effect of high-intensity interval exercise on basal  
409 triglyceride metabolism in non-obese men. *Appl Physiol Nutr Metab*. 2013;38(8):823-829.
- 410 26. **Kotronen A, Seppälä-Lindroos A, Bergholm R, Yki-Järvinen H.** Tissue specificity of  
411 insulin resistance in humans: fat in the liver rather than muscle is associated with features of  
412 the metabolic syndrome. *Diabetologia*. 2008;51(1):130-138.
- 413 27. **Bugianesi E, Gastaldelli A, Vanni E, et al.** Insulin resistance in non-diabetic patients with

- 414 non-alcoholic fatty liver disease: sites and mechanisms. *Diabetologia*. 2005;48(4):634-642.
- 415 28. **Pollare T, Vessby B, Lithell H.** Lipoprotein lipase activity in skeletal muscle is related to  
416 insulin sensitivity. *Arterioscler Thromb*. 1991;11(5):1192-1203.
- 417 29. **Bergeron J, Couillard C, Després JP, et al.** Race differences in the response of postheparin  
418 plasma lipoprotein lipase and hepatic lipase activities to endurance exercise training in men:  
419 results from the HERITAGE Family Study. *Atherosclerosis*. 2001;159(2):399-406.
- 420 30. **Chan DC, Gan SK, Wong AT, Barrett PH, Watts GF.** Association between skeletal  
421 muscle fat content and very-low-density lipoprotein-apolipoprotein B-100 transport in  
422 obesity: effect of weight loss. *Diabetes Obes Metab*. 2014;16(10):994-1000.
- 423 31. **Mittendorfer B, Patterson BW, Klein S.** Effect of weight loss on VLDL-triglyceride and  
424 apoB-100 kinetics in women with abdominal obesity. *Am J Physiol Endocrinol Metab*.  
425 2003;284(3):E549-556.
- 426 32. **Kallwitz ER, Guzman G, TenCate V, et al.** The histologic spectrum of liver disease in  
427 African-American, non-Hispanic white, and Hispanic obesity surgery patients. *Am J*  
428 *Gastroenterol*. 2009;104(1):64-69.
- 429 33. **Zhang YL, Hernandez-Ono A, Ko C, Yasunaga K, Huang LS, Ginsberg HN.** Regulation  
430 of hepatic apolipoprotein B-lipoprotein assembly and secretion by the availability of fatty  
431 acids. I. Differential response to the delivery of fatty acids via albumin or remnant-like  
432 emulsion particles. *J Biol Chem*. 2004;279(18):19362-19374.
- 433 34. **Gill JM, Al-Mamari A, Ferrell WR, et al.** Effects of a moderate exercise session on  
434 postprandial lipoproteins, apolipoproteins and lipoprotein remnants in middle-aged men.  
435 *Atherosclerosis*. 2006;185(1):87-96.
- 436 35. **Bjorkegren J, Packard CJ, Hamsten A, et al.** Accumulation of large very low density  
437 lipoprotein in plasma during intravenous infusion of a chylomicron-like triglyceride  
438 emulsion reflects competition for a common lipolytic pathway. *J Lipid Res*. 1996;37(1): 76-  
439 86.
- 440 36. **Targher G, Day CP, Bonora E.** Risk of cardiovascular disease in patients with nonalcoholic  
441 fatty liver disease. *N Engl J Med*. 2010;363(14): 1341-1350
- 442 37. **Vlachopoulos C, Manesis E, Baou K, et al.** Increased arterial stiffness and impaired  
443 endothelial function in nonalcoholic Fatty liver disease: a pilot study. *Am J Hypertens*. 2010;  
444 23(11):1183-1189.
- 445 38. **Dattilo AM, Kris-Etherton PM.** Effects of weight reduction on blood lipids and  
446 lipoproteins: a meta-analysis. *Am J Clin Nutr*. 1992;56(2):320-328.
- 447 39. **Musso G, Cassader M, Rosina F, Gambino R.** Impact of current treatments on liver  
448 disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease  
449 (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia*.  
450 2012;55(4):885-904

451 40. **Hens W, Taeyman J, Cornelis J, Gielen J, Van Gaal L, Vissers D.** The Effect of Lifestyle  
452 Interventions on Excess Ectopic Fat Deposition Measured by Noninvasive Techniques in  
453 Overweight and Obese Adults: A Systematic Review and Meta-Analysis. *J Phys Act Health.*  
454 2016;13(6):671-694  
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**Table 1 Subject characteristics and biochemistry**

	Pre Ex n=15	Post Ex n=15	Within group p value	Pre Control n=12	Post Control n=12	Within group p value	Between group p value
Age yr	52.4 ±2.2			52.8±3.0			NS
Body weight kg	101.3±2.64	97.3±12.2	< <b>0.001</b>	102.3±6.1	102.9±6.4	NS	< <b>0.001</b>
BMI kg/m <sup>2</sup>	31.6±0.8	30.5±1.0	< <b>0.001</b>	31.7±1.0	31.6±1.2	NS	<b>0.02</b>
Waist circumference cm	109.3±1.9	105.0±2.5	<b>0.005</b>	110.0±3.9	109.6±4.3	NS	<b>0.03</b>
VO <sub>2max</sub> ml kg <sup>-1</sup> min <sup>-1</sup>	25.5±1.1	33.0±1.5	< <b>0.001</b>	23.3±1.0	23.8±1.3	NS	< <b>0.001</b>
Fasting glucose mmol/l	6.0±0.2	5.8±0.2	<b>0.005</b>	5.9±0.2	5.6±0.1	<b>0.02</b>	NS
Fasting insulin pmol/l	183±17	138±16	<b>0.007</b>	164±17	170±17	NS	<b>0.02</b>
HOMA2 %S	32.5±2.9	45.6±4.9	<b>0.002</b>	36.1±3.7	34.5±3.2	NS	<b>0.003</b>
Adipose tissue-IR	79.8±8.0	58.2±8.8	<b>0.03</b>	75.9±9.4	86.6±15.7	NS	<b>0.02</b>
NEFA mmol/l	0.45±0.03	0.41±0.04	NS	0.48±0.05	0.50±0.05	NS	NS
Total Cholesterol mmol/l	5.0±0.2	4.7±0.2	NS	5.1±0.2	5.1±0.2	NS	NS
TG mmol/l	2.0±0.2	1.8±0.2	NS	1.6±0.2	1.9±0.2	NS	NS
LDL-Cholesterol mmol/l	3.8±0.1	3.3±0.2	<b>0.03</b>	3.6±0.2	3.2±0.2	<b>0.07</b>	NS
HDL-Cholesterol (mmol/l)	1.01±0.06	1.03±0.06	NS	1.09±0.09	1.09±0.08	NS	NS
Alanine transaminase U/l	51.1±5.3	36.8±5.2	<b>0.01</b>	40.9±6.2	31.1±4.7	<b>0.04</b>	NS
Aspartate transaminase U/l	36.9±3.2	29.4±3.5	<b>0.02</b>	29.0±2.5	26.3±1.84	NS	NS
Gamma glutamyl transaminase U/l	53.5±10.2	36.3±7.5	<b>0.03</b>	37.0±4.5	33.8±4.9	NS	NS

**Table 2 Body composition and vascular measurements**

	Pre Ex n=15	Post Ex n=15	Within group p value	Pre Control n=12	Post Control n=12	Withi n group p value	Betwee n group p value
IHCL %	19.6(14.8,30.0)	8.9(5.4,17.3)	<b>&lt;0.001</b>	12.5(6.9,32.9)	12.6(9.2,26.1)	NS	<b>0.02</b>
IMCL (Sol)	21.7 ± 3.8	19.0 ± 3.5	<b>0.09</b>	19.2±1.8	20.5 ± 2.6	NS	<b>0.07</b>
IMCL (Tib)	8.8 ± 1.0	8.8 ± 1.4	NS	13.2±5.4	8.2 ± 1.2	NS	NS
Pancreatic fat	13.7 ± 5.0	8.8 ± 1.6	NS	8.2±3.3	10.9 ± 3.5	NS	NS
Total Internal fat kg	9.5 ± 0.6	7.9 ± 0.6	<b>&lt;0.001</b>	9.9 ± 0.9	9.6 ± 0.9	NS	<b>0.03</b>
Visceral Fat kg	5.7 ± 0.4	4.7 ± 0.4	<b>&lt;0.001</b>	5.7 ± 0.55	5.4 ± 0.6	NS	<b>0.06</b>
Abdominal Subcut Fat kg	7.0 ± 7.2	6.3 ± 0.7	<b>&lt;0.001</b>	7.8 ± 1.0	7.91 ± 1.1	NS	<b>0.003</b>
Total body fat kg	31.6±2.0	27.3±1.9	<b>&lt;0.001</b>	34.8 ± 3.2	34.5 ± 3.5	NS	<b>0.004</b>
Total subcut fat kg	22.1 ± 1.7	19.5 ± 1.6	<b>&lt;0.001</b>	24.9 ± 2.4	24.9 ± 2.6	NS	<b>0.001</b>
Systolic BP mm Hg	133.4 ± 4.2	128.8 ± 4.2	<b>0.01</b>	131.3 ± 4.5	134.4 ± 3.8	NS	<b>0.04</b>
Diastolic BP mm Hg	83.4 ± 2.3	78.2 ± 2.6	<b>0.04</b>	83.8 ± 3.0	86.3 ± 3.0	NS	<b>0.02</b>
PWV (m/s)	7.94 ± 0.26	7.67 ± 0.25	<b>0.05</b>	7.58 ± 0.27	7.77 ± 0.28	NS	NS
Framingham Risk scores	14.4 ± 1.4	12.4 ± 1.4	<b>0.001</b>	14.2 ± 2.5	13.6 ± 1.9	NS	<b>&lt;0.05</b>

**Intrahepatocellular fat (IHCL)** presented as median (interquartile range)

Sol, soleus; Tib, tibialis; visc, visceral; subcut, subcutaneous; PWV, pulse wave velocity

**Table 3. VLDL TG kinetics (mean ± SEM)**

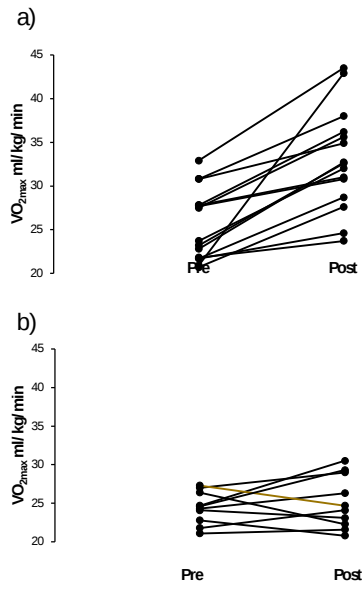
	Pre Ex n=15	Post Ex n=15	Within group P	Pre Control n=12	Post Control n=12	Within group P	Between group P
VLDL <sub>1</sub> -TG mmol/l	1.24 ±0.15	1.04±0.11	NS	1.00±0.12	1.05±0.15	NS	NS
VLDL <sub>2</sub> -TG mmol/l	0.17±0.02	0.11±0.01	<b>&lt;0.01</b>	0.13±0.02	0.14±0.02	NS	<b>0.01</b>
VLDL-TG mmol/l	1.41±0.17	1.15±0.11	<b>&lt;0.01</b>	1.13±0.15	1.19±0.16	NS	<b>0.08</b>
VLDL <sub>1</sub> -Chol mmol/l	0.31 ±0.04	0.29±0.04	NS	0.29±0.04	0.32±0.05	NS	NS
VLDL <sub>2</sub> -Chol mmol/l	0.10 ±0.07	0.07±0.01	<b>&lt;0.02</b>	0.09±0.03	0.09±0.02	NS	<b>&lt;0.01</b>
VLDL-Chol mmol/l	0.41 ±0.04	0.36±0.04	<b>0.02</b>	0.38±0.06	0.40±0.06	NS	<b>0.01</b>
VLDL <sub>1</sub> -TG FCR pools/d*	8.25±1.07	9.80±1.51	<b>&lt;0.05</b>	9.09±0.80	8.62±1.02	NS	<b>0.06</b>
VLDL <sub>1</sub> -TG catabolism FCR pools/day**	6.82±1.16	8.14±1.31	<b>0.05</b>	7.46±0.78	5.92±0.53	NS	<b>0.02</b>
VLDL <sub>1</sub> -TG transfer FCR pools/day**	1.22±0.16	1.44±0.38	NS	1.63±0.48	2.71±1.35	NS	NS
VLDL <sub>1</sub> -TG PR mg/kg/d*	230.9 ±20.3	232.5±12.9	NS	218.4±30.6	213.9±24.1	NS	NS
VLDL <sub>2</sub> -TG FCR pools/d**	10.44 ±0.70	11.62±1.48	NS	12.05±1.52	13.16±3.18	NS	NS
VLDL <sub>2</sub> -TG PR mg/kg/d**	40.7 ±4.6	33.9±5.1	NS	37.6±5.5	49.6±10.7	NS	NS
VLDL <sub>2</sub> -TG hepatic PR mg/kg/d**	5.03±0.83	4.23±0.93	NS	6.7±1.3	8.3±3.1	NS	NS
VLDL-TG PR mg/kg/d**	235.6±20.2	236.4±13.0	NS	225.1±30.4	222.3±25.5	NS	NS
VLDL <sub>1</sub> to VLDL <sub>2</sub> - TG transfer mg/kg/d**	35.7 ± 4.7	29.7±4.6	NS	30.9±4.8	41.3±8.5	NS	NS

460 \*n=13 and \*\*n=12 in exercise group due to problems with sample analysis

**Table 4. VLDL apoB kinetics (mean±SEM)**

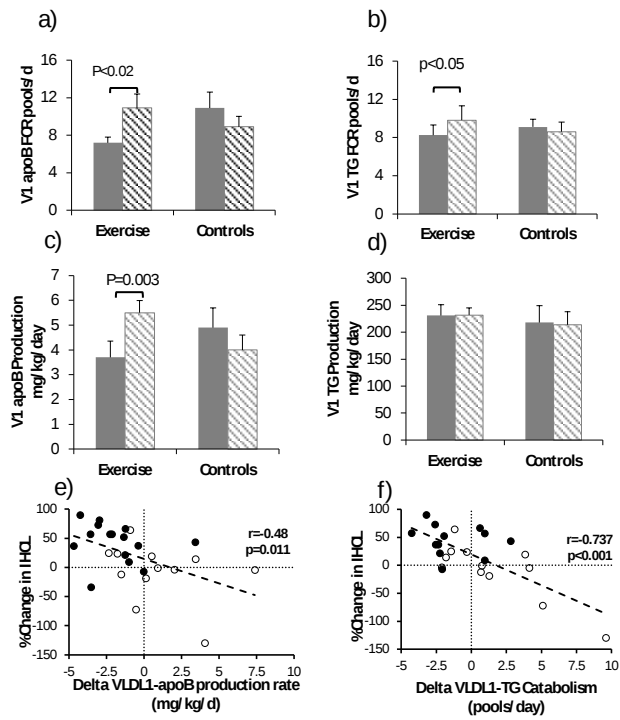
	Pre Ex n=15	Post Ex n=15	Within group p value	Pre Control n=12	Post Control n=12	Within group p value	Between- group p value
VLDL <sub>1</sub> apoB concentration mg/l	18.4±2.2	20.2±2.8	NS	16.7±1.5	17.3±2.3	NS	NS
VLDL <sub>2</sub> -apoB concentration mg/l	12.9±1.4	9.7±1.0	<b>0.04</b>	11.2±1.8	11.1±1.1	NS	NS
VLDL <sub>1</sub> - TG/V <sub>1</sub> apoB	66.2±7.0	49.8±4.0	<b>0.03</b>	56.5±7.2	60.12±8.7	NS	<b>0.04</b>
VLDL <sub>2</sub> - TG/V <sub>2</sub> apoB	12.9±1.5	11.6±1.1	NS	12.1±1.4	14.8±3.5	NS	NS
VLDL <sub>1</sub> -apoB FCR pools/day	7.18±0.57	10.93±1.49	<b>0.02</b>	10.91±1.76	8.88±1.06	NS	<b>0.01</b>
VLDL <sub>1</sub> -apoB catabolism FCR pools/day	5.98± <b>0.66</b>	10.39±1.49	<b>&lt;0.01</b>	9.87±1.86	7.89±1.23	NS	<b>0.01</b>
VLDL <sub>1</sub> -apoB transfer FCR pools/day	1.19±0.16	0.54±0.1	<b>0.005</b>	1.04±0.25	0.99±0.3	NS	<b>0.06</b>
VLDL <sub>2</sub> -apoB FCR pools/day	12.3±1.3	11.8±1.3	NS	16.9±3.0	12.9±1.8	NS	NS
VLDL <sub>1</sub> -apoB PR mg/kg/d	3.67±0.65	5.54±0.49	<b>0.003</b>	4.92±0.80	3.96±0.60	NS	<b>0.006</b>
VLDL <sub>2</sub> -apoB PR mg/kg/d	4.05±0.42	3.22±0.44	NS	4.93±1.00	3.98±0.60	NS	NS
VLDL <sub>2</sub> -apoB hepatic PR mg/kg/d	0.52±0.09	0.50±0.10	NS	0.74±0.23	0.89±0.24	NS	NS
VLDL <sub>1</sub> - to VLDL <sub>2</sub> transfer mg/kg/d	3.52±0.04	2.72±0.01	NS	4.19±1.09	3.09±0.69	NS	<b>0.013</b>
VLDL apoB PR mg/kg/d	4.19±0.66	6.04±0.50	<b>0.004</b>	5.66±0.95	4.85±0.49	NS	<b>0.02</b>

Figure 1



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Figure 2



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