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Effect of 6-month supervised exercise on low-density lipoprotein apolipoprotein B kinetics in patients with type 2 diabetes mellitus

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Abstract

Although low-density lipoprotein (LDL) cholesterol is often normal in patients with type 2 diabetes mellitus, there is evidence for a reduced fractional catabolic rate and consequently an increased mean residence time (MRT), which can increase atherogenic risk. The dyslipidemia and insulin resistance of type 2 diabetes mellitus can be improved by aerobic exercise, but effects on LDL kinetics are unknown. The effect of 6-month supervised exercise on LDL apolipoprotein B kinetics was studied in a group of 17 patients with type 2 diabetes mellitus (mean age, 56.8 years; range, 38-68 years). Patients were randomized into a supervised group, who had a weekly training session, and an unsupervised group. LDL kinetics were measured with an infusion of 1-^{13}C leucine at baseline in all groups and after 6 months of exercise in the patients. Eight body mass index–matched nondiabetic controls (mean age, 50.3 years; range, 40-67 years) were also studied at baseline only. At baseline, LDL MRT was significantly longer in the diabetic patients, whereas LDL production rate and fractional clearance rates were significantly lower than in controls. Percentage of glycated hemoglobin A_{1c}, body mass index, insulin sensitivity measured by the homeostasis model assessment, and very low-density lipoprotein triglyceride decreased ($P < .02$) in the supervised group, with no change in the unsupervised group. After 6 months, LDL cholesterol did not change in either the supervised or unsupervised group; but there was a significant change in LDL MRT between groups ($P < .05$) that correlated positively with very low-density lipoprotein triglyceride ($r = 0.51$, $P < .04$) and negatively with maximal oxygen uptake, a measure of fitness ($r = -0.51$, $P = .035$), in all patients. The LDL production and clearance rates did not change in either group. This study suggests that a supervised exercise program can reduce deleterious changes in LDL MRT.

1. Introduction

In type 2 diabetes mellitus, dyslipidemia is characterized by an elevated concentration of triglyceride (TG) and reduced high-density lipoprotein (HDL) cholesterol [1], whereas concentrations of total cholesterol and low-density lipoprotein (LDL) cholesterol are similar to those in the general population [2]. However, an analysis of LDL subclasses reveals a pattern characterized by a predominance of small dense LDL that has been shown to be predictive of coronary events [3-5]. This redistribution of LDL does not occur in isolation but is a result of interrelated lipoprotein changes associated with elevated TG levels [6]. Although measurement of plasma LDL cholesterol concentration provides useful information for the clinical management of dyslipidemia, these values do not provide any mechanistic information relating to LDL metabolism. Stable isotope methodology is an established technique that enables determination of the kinetics (production and catabolism) of lipoproteins in vivo [7]. Previous studies using this technique have shown that LDL apolipoprotein (apo) B metabolism is impaired in patients with type 2 diabetes mellitus compared with healthy control subjects, with both a decreased LDL catabolic rate

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and a diminished synthesis rate [8]. There is however a lack of detailed mechanistic studies examining lipoprotein kinetics after an intervention.

The intervention of lifestyle factors such as physical activity and diet plays an integral role in diabetes management. Structured exercise programs have been shown to be effective in promoting improvements in glycemic control and cardiovascular risk factors such as dyslipidemia in patients with type 2 diabetes mellitus [9-11]. We have recently investigated the effects of a 6-month exercise program on very low-density lipoprotein (VLDL) apo B metabolism using stable isotope methodology in a group of patients with type 2 diabetes mellitus [12]. The exercise program resulted in a decrease in plasma TG concentration, VLDL apo B pool size, and VLDL apo B secretion rate. Information relating to changes in LDL particle kinetics before and after an exercise intervention has not been previously examined. We hypothesize that favorable changes from elevated levels of TG after an intervention would be expected to impact on apo B lipoprotein metabolism. Moreover, a decrease in the production rate (PR) of TG after an exercise intervention would be expected to promote favorable LDL kinetics. Here we describe differences in LDL kinetics between our exercise study groups and show that a supervised exercise program can also reduce deleterious changes in LDL metabolism that may otherwise lead to an increased risk of atherosclerosis.

2. Materials and methods

2.1. Subjects

Low-density lipoprotein apo B kinetics were measured in 17 patients with type 2 diabetes mellitus (body mass index [BMI] = 30.0 ± 1.3 kg/m^2, mean ± SEM; range, 24.0-41.3) and 8 nondiabetic control subjects matched for age and BMI. Twenty patients were recruited into the study; 2 patients dropped out. Because of technical difficulties, we were unable to measure LDL kinetics in 1 subject. The local ethics committee approved the study, and subjects gave written informed consent. All diabetic patients had failed to show improved glycemic control with diet and tablets and had a percentage of glycated hemoglobin A_{1c} (%HbA_{1c}) greater than 7.5%. Dyslipidemia was not used as an inclusion criterion. Patients with significant ischemic heart disease, significant diabetic complications, uncontrolled hypertension, lipid-lowering medication, and any joint conditions limiting exercise were excluded from the study. All patients were on oral hypoglycemic treatment, which did not change during the study. This consisted of metformin and sulfonylureas, with 3 patients on metformin only. Alcohol intake was similar in both groups. Patients had been diagnosed with diabetes for a minimum of 8 years. The control subjects had no family history of diabetes and were not taking any medication that might affect lipid metabolism.

All diabetic patients were given an initial training session and an individualized exercise program based on the American College of Sports Medicine guidelines [13] and were asked to exercise for 20 to 40 minutes at 60% to 85% of maximal oxygen uptake (VO_{2max}) 4 times per week in a mode of aerobic activity of their choice for a period of 6 months. Patients were taught to use the Rate of Perceived Exertion Borg scale [14] alongside manual heart rate measurement (radial artery over 6 seconds × 10) to help identify the intensity of exercise required when exercising alone. Patients were encouraged to exercise at varying intensities during each exercise session between a Rate of Perceived Exertion of 13 and 16 (60%-85% VO_{2max}). Patients were then randomized into a supervised (n = 8; female, 4; male, 4) or unsupervised (n = 9; female 4; male, 5) group. Supervised patients saw the exercise trainer once every week for an exercise session and an account of their previous week's activity. A plan for the activity for the following week was agreed. The exercise trainer did not see patients in the unsupervised group after their initial contact. Levels of exercise were monitored as VO_{2max} measured using a stepwise maximal exercise test on an electromagnetically braked bicycle ergonometer using a computerized open-loop gas analyzer system (Medical Graphics, St Paul, MN). Electrocardiograph monitoring was used to ensure patients had no latent ischemic heart disease.

2.2. Study protocol

Lipoprotein turnover studies were performed on a single occasion in the control subjects and before and after the period of 6-month exercise in the diabetic patients. All subjects were asked not to exercise for 3 days before the metabolic study day. Subjects were admitted to the metabolic ward at 8:00 AM after an overnight fast. An intravenous cannula was placed in a superficial vein of each arm for blood sampling and administration of tracer. 1-^{13}C-leucine (15 mg/ml, ^{13}C enrichment 99%; Tracer Technologies, Somerville, MA) was administered as a priming dose (1 mg/kg), followed by a constant infusion (1 mg/kg/h) for 9 hours. Baseline blood samples were taken for the measurement of fasting blood glucose, insulin, %HbA_{1c}, total cholesterol, TG, HDL cholesterol, and total apo B. Blood samples were taken at baseline and at 30-minute intervals for 9 hours for the measurement of apo B enrichment. Blood samples for α-ketoisocaproic acid (α-KIC), the deamination product of leucine, which provides a measure of hepatic intracellular leucine enrichment [15], were also taken at regular intervals throughout the study.

2.3. Experimental protocol

After removal of VLDL by sequential flotation for 16 hours at 147 000*g* and intermediate-density lipoproteins at an adjusted density of 1.019 kg/L for 18 hours, LDL was isolated after ultracentrifugation for 20 hours at a density of 1.063 kg/L (Beckman Coulter Optima LE80-K

ultracentrifuge using a Type 50.4 Ti rotor, High Wycombe, United Kingdom). Apolipoprotein B was precipitated from the LDL fraction with tetramethylurea, delipidated, and hydrolyzed with 6 mol/L hydrochloric acid [16]. The isotopic enrichment of leucine in LDL apo B was measured as the *N*-acetyl, *n*-propyl-ester derivative and analyzed by gas chromatography–combustion isotope ratio mass spectrometry (gas chromatograph: Hewlett-Packard 5890, Bracknell, United Kingdom; combustion unit: Orchid, Europa Scientific, Crewe, United Kingdom; isotope ratio mass spectrometer: SIRA 10, VG Isotech, Hellingly, United Kingdom) as described previously [17]. The isotopic enrichment of α-KIC was determined by selected ion monitoring of the quinoxalinol-*tert*-butyldimethylsilyl derivative (Hewlett Packard 5971A MSD). Total plasma apo B and LDL apo B were measured by an immunoturbidimetric method (Immunoturb Kit, Immuno, Dunton Green, United Kingdom; interassay coefficient of variation [CV], 4%). Very low-density lipoprotein apo B was measured using a modified Lowry method as described previously [18]. Plasma cholesterol and TG concentrations were measured by an enzymatic method (ABX, Chicksands, Shefford, Bedfordshire, United Kingdom) using a Cobas Fara II analyzer (Roche, Welwyn Garden City, United Kingdom; interassay CV, 1.6%). Low-density lipoprotein cholesterol was calculated using the Friedewald equation. Serum insulin concentrations were measured in duplicate, using an in-house double-antibody radioimmunoassay (interassay CV, 7%). Hemoglobin A_{1c} (percentage) was measured by anion exchange liquid chromatography (Primus, Kansas City, MO; interassay CV, 8%).

2.4. Data analysis

The fractional secretion rate (FSR) of LDL was calculated using a simple regression model [19], using LDL enrichment values between 4 and 9 hours when the enrichment curves were linear. A total of 9 time points over the 9-hour tracer infusion were included in the linear regression model. The precursor compartment for the incorporation of ^{13}C leucine into LDL particles was the steady-state enrichment of α-KIC. Patients were in a steady state throughout the study as determined by the constant LDL apo B concentration (data not shown). In this case, the FSR equals the fractional catabolic rate (FCR), where:

$$\begin{aligned}&\text{FSR(pools per day)}\\&= [\text{rate of increase of leucine enrichment in LDL apo B}\\&\quad (\text{atoms percentage excess per hour})\\&\quad /\text{steady-state enrichment of } \alpha - \text{KIC}] \times 24.\end{aligned}$$

Low-density lipoprotein apo B production rate (PR) (in milligrams per kilogram per day) was calculated from the product of the FSR (in pools per day) and apo B pool size (in milligrams) divided by body weight. Low-density lipoprotein pool size was calculated from the product of the mean LDL apo B concentration (mean concentration of apo B in 4 pooled samples) and the plasma volume. Plasma volume was calculated using the formula of Pearson et al [20]. Mean residence time (MRT) was calculated as 1/FCR (in pools per day). Insulin resistance was calculated using the homeostasis assessment model (HOMA-IR) [21].

Results are presented as means ± SEM. For between-group comparisons, an unpaired *t* test was used for normally distributed data; and a Mann-Whitney *U* test, for non-normally distributed data. For within-group comparisons, a paired *t* test was used for normally distributed data; and a Wilcoxon signed rank test, for nonnormally distributed data. The change in measurements between 0 and 6 months in the diabetic groups was compared with a *t* test after establishing that these data were normally distributed. A Spearman rank correlation test was used to examine the relationship between the changes in parameters of LDL kinetics with other variables.

3. Results

3.1. Subject characteristics, fitness, and body composition

Age and BMI in diabetic subjects were not different from the control group, with similar ranges in the variables measured. There was no difference in age, BMI, $\%HbA_{1c}$, HOMA-IR score, or VO_{2max} between the supervised and unsupervised diabetic groups at baseline (Table 1). After 6 months of exercise, in the supervised group, there was a significant within-group decrease in $\%HbA_{1c}$ (7.7% ± 0.5%, $P = .01$), BMI (28.8 ± 2.0, $P < .02$), and HOMA-IR score (8.4 ± 1.8, 0 month to 5.3 ± 1.8; $P = .01$), with no significant change in these measurements in the unsupervised group including HOMA-IR (7.4 ± 1.4, 0 month vs 8.8 ± 1.3, 6 months). The change in measurements from 0 to 6 months between diabetes groups was significant for $\%HbA_{1c}$ ($P = .006$). Patients in the supervised exercise group also significantly increased their VO_{2max}, indicating an increase in aerobic fitness in this group that was not apparent in the unsupervised group (Table 2).

Table 1
Baseline characteristics (mean ± SEM) in the supervised and unsupervised exercise diabetes groups and a healthy control group

	Diabetic patients		
	Supervised (n = 8)	Unsupervised (n = 9)	Controls (n = 8)
Age (y)	59 ± 3	55 ± 3	50 ± 3
BMI	30 ± 2	31 ± 2	28 ± 3
Male	4	5	2
Plasma TG (mmol/L)	1.1 ± 0.2	1.7 ± 0.4	0.9 ± 0.2
Plasma cholesterol (mmol/L)	4.5 ± 0.4	4.4 ± 0.3	5.0 ± 0.4
LDL cholesterol (mmol/L)	3.0 ± 0.3	2.9 ± 0.3	2.7 ± 0.3
HDL cholesterol (mmol/L)	1.0 ± 0.1	0.8 ± 0.1	1.6 ± 0.1*
HbA_{1c} (%)	8.6 ± 0.4	9.3 ± 0.4	-
HOMA	8.4 ± 1.8	7.4 ± 1.5	-

* $P < .001$, controls vs supervised and unsupervised diabetic patients.

Table 2
Patient characteristics, lipid profiles, and fitness levels in the supervised and unsupervised groups at baseline and after 6 months of exercise

	Supervised group (n = 8)		*P* value 0 vs 6 mo	Unsupervised group (n = 9)		*P* value 0 vs 6 mo	*P* value Δ supervised vs Δ unsupervised
	0 mo	6 mo		0 mo	6 mo		
BMI	30 ± 2.0	28.8 ± 2.0	<.2	31.2 ± 1.0	30.6 ± 2.0	NS	NS
HbA_{1c} (%)	8.6 ± 0.4	7.7 ± 0.5	.01	9.3 ± 0.4	9.2 ± 0.5	NS	.006
HOMA-IR	8.4 ± 1.8	5.3 ± 1.8	.01	7.4 ± 1.4	8.8 ± 1.3	NS	<.02
TG (mmol/L)	1.1 ± 0.2	0.87 ± 0.2	<.03	1.7 ± 0.4	1.9 ± 0.4	NS	NS
LDL cholesterol (mmol/L)	3.0 ± 0.3	2.1 ± 0.4	NS	2.9 ± 0.3	2.8 ± 0.4	NS	NS
Total cholesterol (mmol/L)	4.5 ± 0.4	3.8 ± 0.4	NS	4.4 ± 0.3	4.6 ± 0.4	NS	NS
Total apo B (g/L)	0.9 ± 0.08	0.8 ± 0.07	<.02	1.1 ± 0.1	1.0 ± 0.1	NS	NS
VO_{2max} (mL/[kg min])	22.4 ± 2.8	25.6 ± 2.6	.002	23.1 ± 2.5	23.9 ± 2.6	NS	<.05

NS indicates not significant.

3.2. Lipid profile

There was no difference in fasting plasma TG, cholesterol, and LDL cholesterol between the control group and the diabetic patients or between the 2 diabetic groups at baseline. High-density lipoprotein cholesterol was significantly higher in the control group ($P < .001$, Table 1). After 6 months of exercise in the diabetic patients, there was a significant decrease in fasting plasma TG concentration (0 month: 1.12 ± 0.23, 6 months: 0.87 ± 0.18 mmol/L; $P < .03$) and total apo B concentration (0.90 ± 0.08 to 0.80 ± 0.07 g/L, $P < .02$) in the supervised group. In the unsupervised group, plasma TG increased (0 month: 1.7 ± 0.4, 6 months: 1.9 ± 0.4 mmol/L), although this was not significant. There was also no significant change in total apo B concentration (1.1 ± 0.1 to 1.0 ± 0.1 g/L) in the unsupervised group after 6 months of exercise. Plasma total cholesterol and LDL cholesterol were not significantly altered after 6 months of exercise in either the supervised group (4.5 ± 0.4 to 3.8 ± 0.4 mmol/L, 3.0 ± 0.3 to 2.1 ± 0.4 mmol/L) or the unsupervised group (4.4 ± 0.3 to 4.6 ± 0.4 mmol/L, 2.9 ± 0.3 to 2.8 ± 0.4 mmol/L) (Table 2).

3.3. LDL kinetics

Low-density lipoprotein FCR and PR were significantly lower ($P < .02$ and $P < .001$) and LDL MRT was significantly higher ($P < .001$) in the diabetic patients compared with the control group (Table 3). In the diabetic patients, at baseline, there was a correlation between LDL MRT and plasma TG ($r = 0.52$, $P = .025$). There was also a significant correlation between the size of the training effect as estimated by the percentage of change in VO_{2max} and the percentage of change in LDL MRT ($r = -0.51$, $P = .035$).

There was a between-group change in LDL MRT and FCR from 0 to 6 months ($P < .05$, $P = .07$). A within-group analysis showed an increase in LDL MRT in the unsupervised group ($P = .05$). Although there were a 14% decrease in mean LDL apo B MRT and a 34% increase in FCR after 6 months of exercise in the supervised group, these were not significant in a within-group analysis. There were no changes in LDL PR or LDL apo B pool size in either the supervised or unsupervised group (Table 4). Although at baseline the mean LDL apo B pool size and MRT were higher in the unsupervised group than the supervised group, these differences were not statistically significant. However, although not significantly different, the greater plasma apo B pool size, plasma TG, and LDL apo B100 pool size of the patients in the unsupervised group may indicate a greater likelihood of the presence of small dense LDL in the unsupervised compared with the supervised group at baseline.

There was a significant correlation in all diabetic patients between the change in LDL MRT from 0 to 6 months and the change in VLDL TG ($r = 0.51$, $P < .04$) and the change in plasma TG ($r = 0.50$, $P < .05$).

Table 3
Low-density lipoprotein kinetics in the healthy control group and diabetic patients at baseline (0 months)

	Controls (n = 8)	Diabetic patients (n = 17)
FCR (pools/d)	0.41 ± 0.03	0.3 ± 0.04**
PR (mg/kg/d)	9.0 ± 0.63	3.8 ± 0.24*
Pool size (mg)	1706 ± 214	1356 ± 185
MRT (h)	61.6 ± 4.5	95.9 ± 9.4**

* Significantly different from control subjects, $P < .02$.
** Significantly different from control subjects, $P < .001$.

4. Discussion

The main findings of this study are that a 6-month exercise program in patients with type 2 diabetes mellitus resulted in unchanged LDL cholesterol concentrations in both diabetic groups, but in a significant change in LDL MRT between the supervised and the unsupervised group and that the change in LDL MRT after 6 months correlated with the change in plasma VLDL TG concentrations in both diabetic groups. It was also shown that the subjects who had the most improved physical activity levels had the most favorable changes in LDL MRT, whereas in the subjects in whom physical activity levels decreased, there was deterioration in this risk factor.

A previous kinetic study in patients with type 2 diabetes mellitus showed that, although LDL cholesterol concentration was comparable with control subjects, LDL apo B

Table 4
Kinetic characteristics of LDL metabolism in supervised and unsupervised diabetes exercise groups (mean ± SEM)

	Supervised (n = 8)			Unsupervised (n = 9)			*P* value Δ supervised vs Δ unsupervised
	0 mo	6 mo	*P* value 0 vs 6 mo	0 mo	6 mo	*P* value 0 vs 6 mo	
FCR (pools/d)	0.32 ± 0.04	0.43 ± 0.12	NS	0.28 ± 0.06	0.21 ± 0.03	NS	.07
PR (mg/kg/d)	4.00 ± 0.57	4.49 ± 0.35	NS	3.65 ± 0.30	3.39 ± 0.54	NS	NS
Pool size (mg)	1186 ± 81	1058 ± 87	NS	1465 ± 140	1567 ± 128	NS	NS
MRT (h)	84.8 ± 11.6	72.8 ± 10.8	NS	105.8 ± 14.1	134.1 ± 17.4	.05	<.05

metabolism in patients with type 2 diabetes mellitus was impaired, with an increase in LDL MRT, a reduction in FCR, and a trend toward a decrease in LDL PR [8]. In the present study, we confirmed these findings with an age- and BMI-matched control group. A low LDL catabolism with a concomitant decrease in the production of LDL provides an explanation for the lack of high LDL cholesterol concentrations apparent in type 2 diabetes mellitus. Intervention by insulin treatment of patients with type 2 diabetes mellitus has been shown to normalize both LDL apo B FCR and LDL residence time [22]. Small dense LDL particles, found in patients with type 2 diabetes mellitus, are easily oxidized, leading to an increase in atherogenic potential [23]. A reduction in MRT of LDL is therefore of major importance in patients with type 2 diabetes mellitus because it reduces the time during which LDL can be exposed to glycative and oxidative modifications [22]. It appears that there is a positive correlation between oxidative modification of LDL particles and mean LDL residence time, suggesting that the longer a given LDL particle remains in the circulation, the greater is the chance that it will be modified [24]. Thus, the atherogenic potential of LDL particles depends not only on quantitative aspects (mainly assessed as LDL cholesterol) but also on qualitative aspects (small dense LDL) and kinetic parameters, such as increased residence time.

The LDL particles isolated in this study were composed of a single fraction, with a density range of 1.019 to 1.063 g/mL. This fraction contains a continuum of particles that differ in their physicochemical, immunologic, and atherogenic properties. A number of distinct LDL subclasses can be separated, with the predominance of small dense LDL particles accepted as a cardiovascular risk factor [3,25]. Various studies in patients with type 2 diabetes mellitus have shown that an improvement in glycemic control, as a result of a modification of treatments including lifestyle factors such as exercise, can result in an improvement in LDL particle size, with a shift toward larger LDL particles [25-27]. Small dense LDL particles have been shown to have reduced affinity for the LDL receptor, resulting in increased plasma residence time [28]. Thus, the observed change in LDL MRT after 6 months in our study may be a reflection of a relative remodeling in LDL subclasses between the 2 groups of subjects.

A number of studies have failed to demonstrate a direct correlation between LDL size and insulin resistance in patients with type 2 diabetes mellitus [29,30]. Instead, the distribution in LDL size has been related to hypertriglyceridemia, where LDL size has been explained by the effects of insulin resistance and/or hyperinsulinemia on VLDL metabolism. Increased hepatic secretion and an impaired clearance of large TG-rich VLDL have been reported to be of central importance to the formation of small dense LDL [31]. More specifically, the elevation of TG above a threshold value of 1.5 mmol/L has been suggested to be a major metabolic condition that leads to the formation of small dense LDL [32,33]. The difference in plasma TG found in the present study may explain the increase in LDL MRT in the unsupervised group with no significant change in LDL MRT in the supervised group.

The effects of physical activity on LDL metabolism may be a direct effect or due to a decrease in BMI. The significant inverse correlation between the percentage of change in VO_{2max} and percentage of change in LDL MRT shows the importance of an individual's status of aerobic fitness in relation to effects on LDL metabolism. The possibility that dietary changes could have accounted for some of the changes seen in LDL kinetics cannot be ruled out. There was no significant correlation between BMI and LDL kinetics at baseline. Changes in BMI after 6 months also did not correlate with changes in LDL kinetics. Weight loss due to dietary intervention (−12%) has been shown to significantly increase the catabolism of LDL apo B-100 (+27%, $P < .05$) in a group of men with metabolic syndrome but did not affect LDL apo B PR [34]. However, in the current study, weight loss was much lower at only 2.1%. The subjects in this study were not given any formal dietary guidelines but were asked not to change their dietary intakes.

Despite improvements in insulin sensitivity, HbA_{1c}, and plasma TGs in the supervised group, at 0 month in the supervised group, mean plasma TG was less than 1.5 mmol/L, whereas in the unsupervised group, mean plasma TG was greater than 1.7 mmol/L. At baseline, there was a correlation between MRT and plasma TG. When the subjects were divided into 2 groups at baseline based on a threshold value of 1.5 mmol/L TG, LDL MRT was higher ($P = .06$) in the subjects with TG greater than 1.5 mmol/L (data not shown). After 6 months, in the unsupervised exercise group, mean plasma TG concentration was 1.9 ± 0.4 mmol/L, with an increase in plasma and VLDL TGs in 5 of the 9 patients. Those in the supervised group showed a significant decrease in VLDL TG and plasma TG. The significant correlation

between the change in LDL apo B MRT and the change in VLDL and plasma TG after 6 months supports the suggestion that differences in LDL apo B MRT in the 2 groups may have been due to differences in plasma TG composition. Our previous study showed that the decrease in plasma TG after exercise was caused by a reduction in VLDL apo B PR, as clearance rates remained the same in the supervised group after 6 months of exercise. It may be expected that a decrease in VLDL apo B pool size would decrease LDL apo B PR; however, we did not show this effect. Instead, there was a trend to increase LDL clearance, which resulted in an improvement in the residence time of LDL in the circulation. The model used measures total LDL apo B PR and is not able to distinguish between input from VLDL1, VLDL2, intermediate-density lipoprotein, or direct LDL secretion from the liver. The LDL pool examined also represented the sum of all LDL subfractions (small and large LDL). It is likely that many of these individual inputs to each of the various LDL subfractions may have changed differentially as a direct result of a decrease in plasma TG levels. We speculate that, in the supervised group, a decrease in the conversion of large VLDL into the smaller denser LDL subclasses may have resulted in the normalization of the lipoprotein delipidation cascade and promoted the flux of other LDL precursors. In such a case, changes in VLDL metabolism could have primarily elicited changes in the conformation of LDL, affecting residence time characteristics with high TG levels and the production of larger LDL with lower TG concentrations.

In conclusion, our data show that, after a 6-month exercise program, the unsupervised control group showed a significant increase in LDL apo B MRT that was not apparent in the supervised control group. The increase in LDL apo B MRT may have been due to remodeling of LDL resulting from the high plasma TG level in the unsupervised group after 6 months. The study highlights the important relationship between LDL MRT and plasma TG.

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