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Exercise improves plasma lipid profiles and modifies lipoprotein composition in guinea pigs

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Abstract

These studies were conducted to determine the effects of exercise training on plasma lipoprotein levels and metabolism in the guinea pig to evaluate potential utilization of this model for studies of exercise-mediated effects on the regulation of sterol and lipoprotein metabolism and atherosclerosis regression. Male guinea pigs (n = 5 per group) were randomly assigned to either a control or an exercise group. The exercise protocol consisted of a 7-week training program, 5 days/wk on a rodent treadmill. Final speed and duration were 33 meters/min for 30–40 min per session. Guinea pigs in the exercise group had 33% lower plasma triacylglycerol concentrations ($P < 0.01$), 66% higher HDL cholesterol levels ($P < 0.05$) and 31% lower plasma free fatty acids ($P < 0.05$) than guinea pigs from the non-exercised group. In addition, lipoprotein lipase activity in the heart was 50% higher ($P < 0.025$) in guinea pigs allocated to the exercise protocol. Exercise training resulted in modifications in composition and size of lipoproteins. The concentrations of free cholesterol in LDL and HDL were higher in the exercised guinea pigs. The LDL peak density values were lower in guinea pigs from the exercise group compared to controls suggesting that exercise training resulted in larger LDL particles. In contrast, no significant effects due to exercise were observed in hepatic cholesterol concentrations, hepatic HMG-CoA reductase activity or LDL binding to guinea pig hepatic membranes. These data indicate that exercise had a more pronounced effect on the intravascular processing of lipoproteins than on hepatic cholesterol metabolism. In addition, the pattern of changes in guinea pig lipoprotein metabolism, in response to exercise training, was similar to reported effects in humans.

Keywords: Exercise; Triacylglycerol concentrations; HDL-C; Lipoprotein lipase; Guinea pig

1. Introduction

Exercise has been recommended as a non-pharmacological method for reducing the incidence of coronary heart disease (CHD) and overall mortality [1]. Exercise has numerous health benefits including an improvement in muscle strength, bone structure and density, and cardio-respiratory function. Most epidemiological studies have addressed the influence of physical activity in decreasing the development of CHD since it is the leading cause of death in the United States. Exercise also reduces high blood pressure [2], improves insulin resistance [3] and results in a favorable modification in plasma lipids and lipoprotein concentrations [4]. Observations from many investigators have shown that physically active individuals experience a higher cardiorespiratory fitness and improved lipid profile [5,6,7].

Prolonged exercise results in lower fasting plasma triacyglycerol (TAG) concentrations [8]. It has been shown that exercise training increases lipoprotein lipase (LPL) activity in plasma and in parenchymal cells suggesting a role of exercise in increasing the capacity to clear TAG from circulation, and that LPL is involved in the restoration of muscle TAG stores reduced by exercise [9]. Studies also indicate that moderate intensity training is sufficient to increase plasma HDL cholesterol (HDL-C) concentrations [10,11].

Significant regression and less progression of coronary

Abbreviations: CETP: cholesteryl ester transfer protein, FFA: free fatty acids, HDL-C: HDL- cholesterol, LCAT: lecithin cholesterol acyltransferase, LDL-C: LDL cholesterol, LPL: lipoprotein lipase, TAG: triacylglycerol.

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atherosclerosis has been documented for patients treated with intensive dietary counseling and supervised exercise compared to usual-care control patients [11]. These results were correlated with significant decreases in plasma LDL-C and TAG in the exercise-treated group. Based on the significance of these results; particularly the effects of exercise on coronary artery atherosclerosis, the development of an appropriate animal model to study the mechanisms of exercise-mediated changes on lipoprotein metabolism and atherosclerosis regression is important.

The purpose of this study was to evaluate the guinea pig as a model for determining the mechanisms by which exercise improves lipoprotein metabolism and reduces the risk of CHD. Guinea pigs were chosen for this experiment since substantial data on this animal model support its usefulness in mimicking the human response to dietary factors [12]. In addition, guinea pigs have high levels of LDL relative to HDL, and gender and hormonal status affect lipoprotein metabolism similar to humans [13]. Finally guinea pigs develop atherosclerosis when challenged with a hypercholesterolemic diet, which makes them an appropriate model to study the effects of exercise on atherosclerotic development [14].

2. Materials and methods

2.1. Materials

Enzymatic cholesterol and triacylglycerol kits, cholesterol oxidase, cholesterol esterase and peroxidase were obtained from Boehringer-Mannheim (Indianapolis, IN). Phospholipid and free cholesterol enzymatic kits were obtained from Wako Pure Chemical (Osaka, Japan). Quick-seal ultracentrifuge tubes were from Beckman (Palo Alto, CA) and halothane from Halocarbon (Hackensack, NJ). DL-hydroxy- [3-^{14}C] methyl glutaryl coenzyme A (1.81 GBq/mmol), DL- [5-^{3}H] mevalonic acid (370 GBq/mmol), cholesteryl- [1,2,6,7-^{3}H] oleate (370 GBq/mmol), and DL-3hydroxy-3-methyl glutaryl coenzyme-A were purchased from Amersham (Clearbrook, IL). Cholesteryl oleate, glucose-6-phosphate, glucose-6-phosphate dehydrogenase, NADP, EDTA, NaF, petroleum ether, methylene chloride and sucrose were obtained from Sigma Chemicals (St. Louis, MO). Aluminum silica gel plates were purchased from EM Science (Gibbstown, NJ). Non-purified guinea pig diet was obtained from Teklad (Madison, WI). [^{125}I] Na was purchased from New England Research Productos (Boston, MA). Polyallomer ultracentrifugation tubes were from Beckman (Palo Alto, CA)

2.2. Experimental design

Ten Male Hartley guinea pigs (Harlan Sprague-Dawley, Indianapolis, IN), weighing between 300 and 400 g were randomly assigned to the exercise or the control group. The non-purified diet was reported to contain 17.9% protein (mainly soybean), 1.9% vegetable oil, 49.3% carbohydrates and 14% fiber (mainly alfalfa), 8% minerals and 1% vitamins and 7.9% dietary fiber. Guinea pigs were fed the non-purified diet through the duration of the experiment. Two guinea pigs were kept per metal cage and were housed in a light cycle room (light from 7:00 am to 7:00 pm) with a temperature of 23°C and free access to diet and water. Guinea pigs in the exercise group were initiated on a rodent treadmill. The time and distance was increased gradually from 50 m the first wk to 1485 m during the 7th wk of training utilizing increments of 150 m/week average. Guinea pigs were gradually adapted to the exercise protocol until they demonstrated a final speed of 33 meters/min for 30−45 min per session. Guinea pigs exercised 5 times per week. The control animals were placed on a stationery rodent treadmill twice a wk for about the same period of time as the exercise group. Non-fasted animals were killed by cardiac puncture after halothane anesthesia. Blood (approximately 15 ml per guinea pig) was collected to analyze plasma lipids and to isolate lipoproteins for further characterization. Liver was harvested to determine hepatic lipids and to isolate microsomes to measure HMG-CoA reductase activity and LDL binding. Skeletal, adipose and heart tissue were isolated for determination of lipoprotein lipase activity (LPL). Animal studies were conducted in accordance with U.S. Public Health Service guidelines. Experimental protocols were approved by the University of Arizona Institutional Care and Use Committee.

2.3. Plasma and hepatic measurements

Plasma samples were obtained from blood collected by cardiac puncture from guinea pigs under halothane anesthesia, with EDTA (1.5 mg/ml) as an anticoagulant. 500 μl of plasma from each sample were stored at 4°C for further analysis and the rest was used for lipoprotein isolation. A mixture of aprotinin (0.5 ml/100ml), phenyl methyl sulfonyl fluoride (PMSF 0.1 ml/100 ml), and sodium azide (0.1 ml/100 ml) were added to the samples to prevent changes in lipoprotein concentration during isolation.

Plasma samples were analyzed for cholesterol [15] and TAG [16] by enzymatic methods. Plasma HDL cholesterol was determined using the precipitation method of Warnick et al [17]. Plasma glucose was determined according to the method of Behall et al. [18]. Free fatty acids were measured by use of an enzymatic kit [19].

Hepatic total and free cholesterol and TAG were determined according to Carr et al. [16] following the extraction of hepatic lipids with chloroform-methanol 2:1. Cholesteryl ester concentrations were calculated by subtracting free cholesterol from total cholesterol.

2.4. Lipoprotein characterization

Lipoproteins were isolated by sequential ultracentrifugation in a L8-M ultracentrifuge (Beckman Instruments, Palo Alto, CA) at 125,000 × g at 15°C for 19 h. Separation of lipoproteins was based on the following density fractionations: d <1.019 g/ml for VLDL and IDL, d <1.09 g/ml for LDL and d <1.21 g/ml for HDL. LDL was isolated by similar ultracentrifugation conditions as VLDL, while for the isolation of HDL, samples were submitted to 36 h of ultracentrifugation.

LDL and HDL compositions were calculated by determining free and esterified cholesterol, protein [20], TAG and phospholipids. The number of constituent molecules of LDL was calculated on the basis of one apo B per LDL particle with a molecular mass of 412,000 kD [21]. The number of molecules of TAG, free cholesterol, esterified cholesterol and phospholipids were calculated using molecular weights of 885.4, 386.6, 645 and 734 respectively as previously reported [22].

For calculating peak density, an aliquot of plasma (1.2 ml) was adjusted to a density of 1.3 g/ml with KBr and overlayered with 4 ml NaCl-KBr solution of 1.006 g/ml in a 5.2-ml polyallomer ultracentrifugation tube. A density gradient was generated by ultracentrifugation in a Vti 65.2 vertical rotor for 45 min at 200,000 × g at 10°C and the lipoprotein profile and density distribution were determined by measuring cholesterol and refractive index in all collected fractions as previously described [23]

2.5. Hepatic microsome isolation

Liver tissues were pressed through a tissue grinder into 1:2.5 (wt/v) cold homogenization buffer (50 mmol/L KH_2PO_4, 0.1 mol/L sucrose, 50 mmol/L KCI, 50 mmol/L NaCl, 30 mmol/L EDTA, and 2μmol/L dithiothreitol, pH 7.2) and mixed using a Potter-Elvehjem homogenizer. A microsomal fraction was isolated after two 15-min centrifugation at 10,000 g followed by ultracentrifugation at 100,000 g in a Ti-50 rotor at 4°C. Microsomes were resuspended in the homogenization buffer and centrifuged for an additional hour at 100,000 g. After centrifugation, microsomal pellets were homogenized and stored at −70°C. The protein content of microsomes was measured by the method reported by Markwell et al [20].

2.6. Hepatic LDL binding

Pooled samples of LDL from guinea pigs were radioiodinated with ^{125}I by the iodine monochloride method [24] to give a specific activity between 100–300 cpm/ng. Hepatic microsomes isolated from each group were incubated for 2 h with radiolabeled homologous LDL sample at a concentration of 10 μg/ml in the presence or absence of 1 mg/ml of unlabeled human LDL at 37°C to determine total and non-specific binding. Human LDL has been shown to be an effective competitor for guinea pig LDL at that temperature [25]. After incubation, the membranes were pelleted by ultracentrifugation by overlaying 75 μl of the incubation mixture with 100 μl of bovine serum in Beckman cellulose propionate tubes and centrifuging at 100,000 × g for 45 min in a Ti42.2 rotor. After the supernatant was removed, the membranes were washed with 125 μl of serum and centrifuged at the same speed for 25 min. The supernatant was removed, the tubes were sliced and the pellets counted in a gamma counter to measure radioactivity.

2.7. Hepatic HMG-CoA reductase assay

Hepatic microsomes were used to measure the activity of HMG-CoA reductase as described by Shapiro et al. [26]. 200 μg of microsomal protein were incubated with 7.5 nmol (0.33 GBq/nmol) [3-^{14}C] HMG-CoA, 4.5 μmol glucose-6-phosphate, 3.6 μmol EDTA, 0.45 μmol NADP, and 0.3 IU glucose-6-phosphate dehydrogenase and 0.024 Gbq [^3H] mevalonic acid was added as an internal recovery standard. The reaction was stopped after 15 min with 10 M HCl and 1.2 mg/ml of unlabeled mevalonate was added to increase the recovery. The samples were further incubated at 37°C for 30 min and the microsomal protein precipitated by centrifugation for 1 min and an aliquot of the supernatant (0.1 ml) applied to aluminum silica plates. Plates were developed in acetone-benzene 1:1 and the area containing the mevalonolactone (R_f 0.6–0.9) scraped and mixed with 5 ml of aquasol to measure the radioactivity in a Liquid scintillation counter. HMG-CoA reductase activity was expressed as pmol of [^{14}C] mevalonate produced per min per mg of microsomal protein and the recovery averaged 70 ± 8%.

2.8. Lipoprotein lipase activity

Skeletal muscle from the Soleus, epididymal adipose tissue and cardiac muscle were isolated from guinea pigs and LPL activities were assayed in the supernatant fraction as previously reported [27]. One gram of tissue was homogenized in buffer (0.025 M NH_3, 5 mM EDTA, 8 mg Triton X-100, 0.4 mg SDS/ml, 5 IU heparin/ml, 10 μg pepstatin/ml, 25 IU trasylol/ml) and centrifugation at 10,000 g for 20 min at 4°C. The homogenate was incubated with [^3H] triolein (50 × 10^6 dpm) for 30 min at 25°C in a water bath and reaction stopped by addition of 3.25 ml methanol-chloroform-heptane (1.41:1.24:1) by volume. The methanol-water upper phase was removed and free-fatty acid radioactivity determined in a scintillation counter. Results are expressed as nmol fatty acid released/min per g of tissue at 25°C.

2.9. Statistical analysis

Student's t test was used to determine differences in total plasma cholesterol, LDL and VLDL cholesterol, hepatic

Table 1
Plasma total cholesterol (TC), VLDL-cholesterol (VLDL-C), LDL-cholesterol (LDL-C) and HDL-cholesterol (HDL-C), triacylglycerol (TAG), glucose and free fatty acids (FFA) of control guinea pigs and guinea pigs following an exercise protocol for 7 weeks

Parameter	Group[1]	
	Control	Exercise
TC (mmol/L)	0.93 ± 0.26	0.75 ± 0.10
VLDL-C (mmol/L)	0.20 ± 0.09	0.15 ± 0.02
LDL-C (mmol/L)	0.42 ± 0.08	0.38 ± 0.05
HDL-C (mmol/L)	0.21 ± 0.06[a]	0.34 ± 0.08[b]
TAG (mmol/L)	0.90 ± 0.16[a]	0.54 ± 0.05[b]
Glucose (mg/dL)	185.4 ± 38.4	181.2 ± 29.6
FFA (mEq/L)	0.51 ± 0.11[a]	0.35 ± 0.14[b]

[1]Values are expressed as mean ± SD for n = 5 guinea pigs group. Values in the same row with different superscripts are significantly different ($P < 0.05$) as determined by Student's *t-test.*

lipids, HMG-CoA reductase, hepatic LDL binding, lipoprotein composition, FFA, lipoprotein lipase activity and plasma glucose between exercise and control groups. Pearson Product-Moment Correlation's were used to evaluate associations between lipoprotein and LPL activity. Data are presented as mean ± SD and differences were considered significant when the probability of a type I error was ≤0.05.

3. Results

3.1. Plasma lipids and lipoproteins

There were no statistical differences in weight gain between trained and untrained guinea pigs. Final weights were 852 ± 92 g for the control and 850 ± 126 g for the exercised group. Plasma total, VLDL and LDL-C were not different between the exercise and the control group (Table 1). In contrast plasma HDL-C concentrations were 66% higher and plasma TAG 32% lower in the exercised guinea pigs when compared to the control guinea pigs ($P < 0.01$, Table 1). In addition, no differences in plasma glucose between groups were observed while the concentration of free fatty acids in plasma was 32% lower in exercised guinea pigs (Table 1).

Significant differences in LDL and HDL composition were also observed due to exercise. The number of molecules of free cholesterol was higher in the exercised guinea pigs $P < 0.05$) (Table 2). LDL peak density, a measure of LDL size, was lower in the trained compared to the untrained guinea pigs suggesting that the exercise intervention resulted in larger LDL particles. Similarly, HDL composition was also altered by exercise. HDL isolated from the exercise group had a significantly higher percentage of free cholesterol than those HDL isolated from control guinea pigs ($P \leq 0.05$, Table 3).

Table 3
Percent composition of HDL of control guinea pigs and guinea pigs following an exercise protocol for 7 weeks

Parameter	(g/100g)	
	Control	Exercise
Cholesteryl Ester	22.3 ± 7.0	20.5 ± 1.8
Free Cholesterol	1.2 ± 1.1[a]	3.0 ± 1.3[b]
Phospholipids	19.1 ± 4.5	16.9 ± 3.6
Triacylglycerol	15.9 ± 1.6	13.4 ± 2.0
Protein	39.5 ± 8.6	46.3 ± 4.5

[1]Values are expressed as mean ± SD for n = 5 guinea pigs per group. Values in the same row with different superscripts are significantly different ($P < 0.05$) as determined by Student's *t*-test.

3.2. Hepatic lipids, HMG-CoA reductase activity and LDL binding

Hepatic lipids and other parameters of hepatic cholesterol metabolism were not affected by exercise. Hepatic free or esterified cholesterol concentrations did not differ between the control and exercise groups (Table 4). In addition, the activity of the regulatory enzyme for cholesterol synthesis, HMG-CoA reductase, was not affected by exercise. LDL binding to hepatic membranes, a measurement of receptor activity, was also not modified by exercise (Table 4).

Table 2
Characteristics of LDL of control guinea pigs and guinea pigs following an exercise protocol for 7 weeks

Parameter	Group	
Number of molecules	Control	Exercise
Cholesteryl Ester	482 ± 41	492 ± 122
Free Cholesterol	210 ± 58[a]	314 ± 42[b]
Triacylglycerol	269 ± 33	232 ± 8
Phospholidids	203 ± 30	232 ± 17
LDL Peak Density (g/ml)	1.093 ± 0.007[a]	1.070 ± 0.014[b]

[1]Values are expressed as mean ± SD for n = 5 guinea pigs per group. Values in the same row with different superscripts are significantly different ($P < 0.05$) as determined by Student's *t*-test.

Table 4
Hepatic cholesterol, HMG-CoA reductase activity and LDL binding to hepatic microsomes of guinea pigs in the control or exercise group

Parameter	Group	
	Control	Exercise
Total Cholesterol (mmol/g)	6.92 ± 0.46	7.26 ± 0.0.64
Free Cholesterol (mmol/g)	6.33 ± 0.0.62	6.59 ± 0.0.70
Esterified Cholesterol (mmol/g)	0.59 ± 0.33	0.66 ± 0.20
HMG-CoA Reductase Activity (pmol/min.mg)	26.2 ± 13.1	28.6 ± 3.1
Hepatic LDL Binding (ng/mg membrane protein)	265 ± 33	245 ± 35

[1]Values are expressed as mean ± SD for n = 5 guinea pigs per group.

Table 5
Lipoprotein lipase activities in adipose, skeletal and heart tissue of guinea pigs in the control or exercise group

Activity (nmol/min per g)	Group	
	Control	Exercise
Adipose Tissue	760 ± 345[a]	1049 ± 402[a]
Soleus Muscle	304 ± 65[a]	289 ± 8[a]
Heart	1744 ± 432[a]	2741 ± 626[b]

[1]Values are expressed as mean ± SD for n = 5 guinea pigs per group. Values in the same row with different superscripts are significantly different ($P < 0.05$) as determined by Student's *t*-test.

3.3. Lipoprotein lipase activity

Epididymal adipose and Soleus (skeletal) muscle LPL activities were not different between the exercise and the control group (Table 5). In contrast LPL activity was 57% higher in the heart indicating that exercise had differential modulation of this enzyme's activity in these tissues. There was a significant negative correlation between plasma TAG concentrations and lipoprotein lipase activity in heart ($r = -0.71$, $P < 0.025$) for all guinea pigs suggesting an important role for this enzyme in determining plasma TAG concentrations in guinea pigs.

4. Discussion

In this study we have demonstrated that exercise training resulted in significant modifications in plasma lipids in guinea pigs. These changes are similar to those reported to occur with exercise in humans. The observed decreases in plasma TAG and increases in HDL cholesterol in guinea pigs are considered to be the main effects on plasma lipids as a result of physical activity in humans [28]. Significant modifications of lipoprotein composition were also observed, which may be related to specific changes in the processing of LDL and HDL occurring in the intravascular compartment.

Numerous reports have established a clear link between exercise and a more desirable plasma lipid profile. Sedentary individuals, for example, experience beneficial changes in their plasma lipids and lipoprotein concentrations after exercise training [29]. Lowering of plasma TAG and VLDL-C and increases in HDL-C have been reported for hypercholesterolemic individuals undergoing high intensity (90% VO_2 max) or moderate intensity (50% VO_2 max) exercise [30]. In addition, short-term sessions of aerobic exercise have resulted in a 10.7% increase in HDL-C and a 25% decrease in TAG in trained men [31]. Walking has also been linked to elevations in plasma HDL-C [28]. The elevation in HDL in that study however, was related to the distance walked rather than to the intensity of the walking [28].

Results from the current study with guinea pigs, are in agreement with reported data in humans [28–31]. An increase in plasma HDL-C and a decrease in plasma TAG were observed in guinea pigs running at a pace of 33 m/min for 30 to 40 min. Exercise interventions, which increase plasma HDL-C concentrations, appear to be more effective when subjects are starting with low HDL-C levels [32]. This may partially explain why the exercise intervention was effective in guinea pigs since these animals have low levels of cholesterol carried by this lipoprotein.

Exercised guinea pigs also presented lower concentrations of plasma FFA than the untrained group. These results suggest that exercised guinea pigs have a greater uptake of fatty acids by muscle. It is well established that the preferred substrate for the heart is FFA [33]. Since we found a significant negative correlation between the concentration of plasma FFA and LPL activity in heart muscle, our results suggest greater uptake of fatty acids by this organ in the exercised guinea pigs. Physical training induces changes that enhance the uptake of FFA [34] and it has long been demonstrated that physical training of muscle causes elevated lipid oxidation in the exercised limb [35]. Our results are consistent with these findings.

The composition and size of lipoproteins were also affected by exercise in guinea pigs. Both LDL and HDL had a greater content of free cholesterol, which is a surface component that may contribute to the density and size of these lipoproteins. Studies aimed at evaluating the association between physical fitness and LDL subfractions have shown that young healthy men with the lowest physical fitness, as assessed by maximum oxygen uptake and activity scores, had increased concentrations of small dense LDL particles [36]. Our study is in agreement with these results, guinea pigs in the exercise group had a less dense LDL particle while LDL from the control group was more dense, demonstrating that exercise induced changes in the composition and size that are consistent with a less atherogenic LDL particle [37].

In addition, Berglund et al. [38] conducted an experiment assessing lovastatin (an HMG-CoA reductase inhibitor) treatment on LDL metabolism in guinea pigs. Similar to LDL from exercised guinea pigs in the current study, LDL isolated from guinea pigs fed a control diet had higher concentrations of free cholesterol than LDL from lovastatin treated guinea pigs [37]. The authors reported that LDL particles with higher concentrations of free cholesterol, as we observed for the exercised guinea pigs in this study, had an increased fractional catabolic rate when injected into control and lovastatin treated animals [37]. The results from these studies suggest that the content of fee cholesterol in LDL may play a regulatory role in the fractional catabolic rate of the LDL particle.

In contrast to effects on plasma, exercise did not affect hepatic lipids, HMG-CoA reductase activity, or LDL binding to hepatic membranes, an indirect measurement of LDL receptor activity. These results suggest that the compositional changes in lipoproteins induced by exercise, occurred

in the intravascular compartment possibly through the action of LPL. It is also known that cholesteryl ester transfer protein (CETP) and lecithin cholesteryl acyltransferase (LCAT) activities are modified by exercise. For example, postmenopausal women participating in an exercise program had lower CETP activity compared to sedentary individuals [39] while young athletes presented an increased reverse cholesterol transport after exercise, which was correlated with higher CETP and LCAT activities [40]. Increases in LCAT activity due to exercise have been reported in other studies [41]

A major effect observed in this study was significant changes in cardiac LPL activity in the exercised guinea pigs. LPL has been suggested to play a major role by replenishing tissue lipid stores during exercise and an increase of LPL activity has been shown in physically active individuals [9]. A recent study evaluating the effect of a LPL D9N mutation on plasma lipids, and the interaction with exercise in a Dutch population of 379 individuals [42], indicated a highly significant interaction between the D9N mutation and physical activity. Physically inactive carriers (of the D9N mutation) had higher plasma cholesterol, TAG and apo B levels and lower HDL-C than the non-carriers. The physically active D9N carriers on the other hand, were not different from the non-carriers. These studies indicate the importance of LPL in mediating plasma lipids through exercise and how unfavorable lipid profiles can be counteracted by physical activity [38].

Increases in LPL mRNA abundance and protein have been observed in the heart of rats with severe aorta constriction, a procedure designed to increase cardiac overload. These results suggest that the up-regulation of LPL in the heart enhanced fatty acid availability to compensate for the increased energy requirement by this organ under these experimental conditions [43]. In this study, there was a statistically significant increase in LPL activity from the heart muscle of the exercised guinea pigs. The increased activity in heart LPL suggests greater mobilization of FFA in the heart muscle to compensate for the higher energy demands of the exercised guinea pig's heart.

In summary, exercise induces similar alterations in plasma lipids and lipoprotein metabolism in guinea pigs and humans. Results from this preliminary study support the premise that the guinea pig could be an appropriate model to evaluate the effects of exercise on different parameters of lipoprotein metabolism as well as the exercise induced mechanisms on regression of atherosclerosis.

References

[1] J. Busby, M. Notelovitz, K. Putney, T. Grow, Exercise, high-density lipoprotein cholesterol and cardiovascular function in climateric women, South Med. J. 78 (1985) 769–773.

[2] S. N. Blair, H.W. Kohl, R.S. Pafferbafter, D.G. Clark, K.G. Cooper, L. W. Gibbons, Physical fitness and all cause mortality: a prospective study of healthy men and women, JAMA 262 (1989) 2395–2401.

[3] V.R. Joman, A.K. Veikko, D. Deibert, Increased insulin sensitivity and insulin binding to monocytes after physical training, N. Engl. J. Med. 301 (1979) 200.

[4] NIH consensus development panel on physical activity and cardiovascular health. JAMA 276 (1986) 241–246.

[5] J.L. Dustin, W.L. Hakerl, Effects of exercise training on plasma lipids and lipoproteins, Exer. Sport Sci. Rev. 22 (1994) :477–521.

[6] C.B. Eaton, Physical activity, physical fitness and coronary heart disease risk factors, Med. Sci. Sport Exerc. 27 (1995) 340–346.

[7] E.R. Skinner, C. Watt, R.J. Maughan, The acute effects of marathon running on plasma lipoproteins in female subjects, Europ. J. Appl. Phys. Occup. Phys. 56 (1987) 451–456.

[8] R. Savard, C.Bouchard, Genetic effects in the response to adipose tissue lipoprotein lipase activity to prolonged exercise. A twin study, Int. J. Obesity 14 (1990) 771–777.

[9] L.B. Oscai D.A. Essig, W.K. Palmer, Lipase regulation of muscle triglyceride hydrolysis, J. Appl. Physiol. 69 (1990) 1571–1577.

[10] T. Spate-Douglas, R.E. Keyser, Exercise intensity. Its effect on the high-density lipoprotein profile, Arch. Phys. Med. Rehabil. 80 (1999) 691–695.

[11] Schlierf, G., Schuler, G., Hambrecht, R., Niebauer, J., Hauer, H., Vogel G. & Kubler, W., Treatment of coronary heart disease by diet and exercise, J. Cardiovasc. Pharmacol. 25 (1985) S32–S34.

[12] M.L. Fernandez, Guinea pigs as models for cholesterol and lipoprotein metabolism, J. Nutr. 131 (2001)10–20.

[13] S. Roy, S. Vega-Lopez, M.L. Fernandez, Gender and hormonal status affect the hypolipidemic mechanisms of dietary soluble fiber in guinea pigs, J. Nutr. 130 (2000) 600–607.

[14] E.B. Cos, S. Roy, S., Yoganathan, R. J. Nicolosi, M.L. Fernandez, Soluble fiber and soybean protein reduce atherosclerotic lesions in guinea pigs. Sex and hormonal status determine lesion extension, Lipids 36 (2001) 1209–1216.

[15] C.C. Allain, L.C. Poon, G.S. C. Chan, W. Richmond, P.C. Fu, Enzymatic determination of total serum cholesterol, Clin. Chem. 20 (1974) 470–475.

[16] T. Carr, C. J. Andressen, L.L. Rudel, Enzymatic determination of triglyceride, free cholesterol, and total cholesterol in tissue lipid extracts, Clin. Biochem. 26 (1993) 39–42.

[17] G.R. Warnick, J. Benderson, J.J. Albers, Dextran-sulphate-Mg^{+2} precipitation procedure for quantitation of high-density lipoprotein cholesterol, Clin. Chem. 28 (1982) 1379–1388.

[18] K.M. Behall, D.J. Schofield, K.H. Lee, P.B. Moser, Blood glucose and hormone levels in adult males fed four refined fibers, Nutr. Rep. Intl. 30 (1984) 537–543.

[19] A. Widjaja, R.J. Morris, J.C. Levy, K.N. Faryn, S.E. Manley, R.C. Turner, Within and between subject variations in commonly measured anthropometric and biochemical variables, Clin.Chem. 4 (1999) 561–566.

[20] M.A. S. Markwell, L. Haas, L. Bieber, N.E. Tolbert, A modification of the Lowry procedure to simplify protein determination in membrane and lipoprotein samples, Anal. Biochem. 87 (1978) 206–210.

[21] J.M. Chapman, G.L. Mills, J.H. Ledford, The distribution and partial characterization of the serum apolipoproteins in the guinea pig, Biochem. J. 149 (1975) 423–436.

[22] M.L. Fernandez, K. Conde, L. Ruiz, C. Montano, D.J. McNamara, Carbohydrate type and amount alter intravascular processing and catabolism of plasma lipoproteins in guinea pigs, Lipids 30 (1995) 619–626.

[23] M.L. Fernandez, D-M. Sun, M.A. Tosca, D. J. McNamara, Citrus pectin and cholesterol interact to regulate hepatic cholesterol homeostasis and lipoprotein metabolism. A dose response study in guinea pigs, Am. J. Clin. Nutr. 59 (1994) 869–878.

[24] J.L. Goldstein, S.K. Basu, M.S. Brown, Receptor-mediated endocytosis of low density lipoprotein in cultured cells, Meth. Enzymol. 98 (1983) 241–260.

[25] M.L. Fernandez, E.C.K. Lin, A. Trejo, D.J. McNamara, Prickly pear (*opuntia sp*) reverses low density lipoprotein (LDL) receptor suppres-

sion induced by a hypercholesterolemic diet in guinea pigs, J. Nutr. 122 (1992) 2330–2340.
[26] D.L. Shapiro, R.L. Imblum, V.W. Rodwell, Thin-Layer chromatographic assay for HMG-Coa reductase and mevalonic acid, Anal. Biochem. 31 (1969) 383–390.
[27] M.L. Fernandez, B.E. McDonald, A.E. Soscia, G.-S. Sun, D. J. McNamara, Olive oil and rapeseed oil differ in their effect on plasma low-density lipoprotein metabolism in the guinea-pig, Brit. J. Nutr. 76 (2002) 869–880.
[28] A.E. Hardmann, Interaction of physical activity and diet: implications for lipoprotein metabolism, Pub. Health Nutr. 2 (1999) 369–376.
[29] J.L. Durstin, W.L. Haskell, Effects of exercise training on plasma lipids and lipoproteins, Exercise Sports Sci. Rev. 22 (1994) 477–521.
[30] S.F. Crouse, B.C. O'Brien, J. Rohack, R.C. Lowe, J.S. Green, H. Tolson, J.L. Reed, Changes in serum lipids and apolipoproteins after exercise in men with high cholesterol: influence of intensity, J. Appl. Physiol. 79 (1995) 279–286.
[31] R.G. Bounds, P.W. Grandjean, B.C. O'Brien, C. Iman, S.F. Crouse, Diet and short term plasma lipoprotein-lipid changes after exercise in trained men, Int. J. Nutr. Sport Exerc. Metab. 10 (2000) 114–127.
[32] P.H. Kokkinos, B. Fernahll, Physical activity and high density lipoprotein cholesterol levels. What is the relationship?, Sports Med. 28 (1999) 307–314.
[33] J.R. Neely, H.E. Morgan, Relationship between carbohydrate and lipid metabolism and the energy balance of heart muscle, Annu. Rev. Physiol. 36 (1974) 413–459.
[34] B. Saltin, P.-O. Astrand, Free fatty acids and exercise, Am. J. Clin. Nutr. 57 (1993) 752S–758S.
[35] J. Henrikssson, Training induced adaptations of skeletal muscle and metabolism during submaximal exercise, J. Physiol. 270 (1977) 677–690.
[36] M. Halle, A. Berg, M.W. Baumstark, J. Keul, Association of physical fitness with LDL and HDL subfractions in young healthy men, Int. J. Sports Med. 20 (1999) 464–469.
[37] R. M. Krauss, Dense low density lipoproteins and coronary artery disease, Am. J. Cardiol. 75 (1995) 53B–57B.
[38] L. Berglund, M.F. Sharkey, R.L. Elam, J.L. Witztum, Effects of lovastatin therapy on guinea pig low density lipoprotein and composition and metabolism, J. Lipid Res. 30 (1989) 1591–1600.
[39] T. Al-Sarraj, K. Greaves, S. Anderson, T. Lohman, S Going, M.L. Fernande, CETP and LCAT activities in postmenopausal women, Exercise and hormone replacement therapy, FASEB J. 11 (1997) A 887.
[40] A.K. Gupta, E.A. Ross, J.N. Myers, M.L. Kashyup, Increased reverse cholesterol transport in athletes, Metabolism 42 (1993) 684–690.
[41] M.W. Baumstark, A. Barg, J. Keul, Influence of acute maximal exercise on LCAT in healthy adults of differing aerobic performance, Eur. J. Appl. Physiol. Occup. Physiol. 62 (1991) 31–35.
[42] J.M. Boer J.A. Kuivenhoven, E.J. Feskens, E.G. Schouten, L.M. Havekes, J.C. Seidell J.J. Kastelein, D. Kromhout, Physical activity modulates the effect of a lipoprotein lipase mutation (d9n) on plasma lipids and lipoproteins, Clin. Genet. 56 (1999) 158–163.
[43] N.D. Vaziri, K. Lian, C.H. Barton, Effect of increased afterload on cardiac lipoprotein lipase and VLDL receptor expression, Biochim. Biophys. Acta 1436 (1999) 577–584.