

# **Exercise and High-Density Lipoprotein: The Effects on Coronary Heart Disease Risk**

*Peter Madsen, 1st year M.Sc. in Exercise Science*

## **INTRODUCTION**

During the last few decades the role of lipoproteins has been a major area of interest in relation to coronary heart disease (CHD) risk. This interest has been sparked by longitudinal observational studies that have found a connection between the blood lipid profile and the risk of coronary heart disease and mortality. This relation between blood lipid profile and CHD has initiated a broad range of clinical investigations that have tried to uncover the complex mechanisms by which blood lipid variables influence certain disease processes in the human cardiovascular system.

It is evident that there exists a relationship between CHD risk and physical exercise. Possible alterations in lipoprotein fractionation due to exercise might be an important change that could explain the relationship between exercise and reduced CHD risk. High-density lipoprotein (HDL) is considered a major CHD risk factor and a low level of this lipoprotein is associated with increased CHD risk. Highly trained endurance athletes exhibit higher levels of HDL cholesterol (HDL-C) than their sedentary counterparts and therefore it is plausible to suggest that exercise induces these beneficial changes. How does exercise change the level of HDL-C? What kind of exercise triggers this response? Answers to these questions could be of great importance in order to reduce CHD risk. As CHD accounts for over one fifth of all mortalities in Ireland, only surpassed by cancer, it is important to keep investigating the interaction between lipoprotein and exercise and the effect this interaction has on CHD risk.<sup>1</sup> Therefore, people at high risk for CHD can be properly advised in order to prevent a CHD event or reduce the risk of multiple CHD incidents.

## **Lipids and Reverse Cholesterol Transport**

Lipid molecules are transported bound to lipoproteins, which are necessary in order for lipids to cross through the intestinal wall and enter the blood stream.<sup>2</sup> Lipoprotein particles consist of triglyceride (TG), cholesterol, phospholipids, carbohydrates, protein (apolipoprotein or apo)<sup>3</sup> and a number of enzymes.<sup>4</sup>

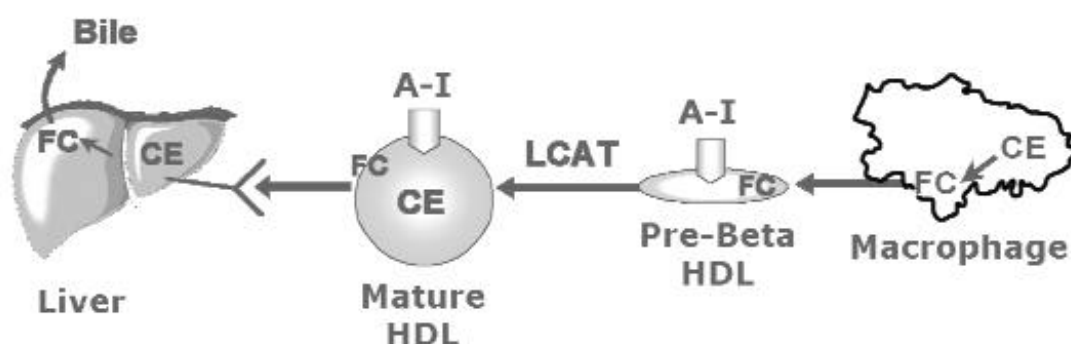
There are four major lipoproteins present in the circulation.<sup>2</sup> The chylomicron is the initial transporter of dietary fats and transports the lipids

from the intestine via the lymph system into the circulation. The majority of the chylomicron-lipids are transferred to another lipoprotein, very-low-density lipoprotein (VLDL), when entering the blood stream.<sup>3</sup> VLDL is mainly synthesized in the liver and is the main transporter of TG in the circulation.<sup>3</sup> As the TG carried in the VLDL is hydrolyzed by lipoprotein lipase (LPL), the VLDL particle becomes a smaller and denser particle known as low-density lipoprotein (LDL).<sup>2</sup> The main role of LDL is to transport cholesterol to peripheral cells and furthermore LDL is thought to be an initiator of the atherosclerotic plaque.<sup>5</sup>

The last lipoprotein particle is the high-density lipoprotein (HDL). Mature HDL is formed when pre-beta-HDL takes up cholesterol from peripheral cells and the cholesterol subsequently is esterified by the enzyme lecithin cholesterol acyltransferase (LCAT) causing the cholesterol to move into the core of the HDL particle.<sup>6</sup> The most commonly measured HDL sub-fractions in the circulation are the small and dense HDL<sub>3</sub> and the larger and less dense HDL<sub>2</sub>.<sup>6</sup> The HDL<sub>3</sub> particle contains apo-AI while HDL<sub>2</sub> contains both apo-AI and apo-AII.<sup>6</sup> The main role of the HDL is to transport cholesterol from peripheral cells to the liver in order for cholesterol to be excreted in the bile (figure 1).<sup>4</sup> This role of HDL, as the main lipoprotein in reverse cholesterol transport (RCT) offers a link between HDL and CHD risk.<sup>4</sup> An increased level of HDL would be an indicator of enhanced RCT and therefore decreased cholesterol in peripheral cells. Consequently the HDL-C level is usually included in the list of CHD risk factors and is regarded as one of the most important CHD risk factors by the National Cholesterol Education Program.<sup>4</sup> A HDL level <40 mg/dL is an indicator of increased CHD risk. In contrast HDL-C content >60 mg/dL is considered a negative risk factor.<sup>7</sup>

The cholesterol efflux from peripheral cells, which is mediated by apo-AI or HDL, seems to occur through two different mechanisms.<sup>8</sup> Cholesterol efflux can occur by aqueous diffusion and this mechanism seems to account for most of the cholesterol efflux.<sup>8</sup> In this efflux mechanism, cholesterol molecules desorb from the peripheral cell, or donor cell, and then diffuse through to the extracellular fluid until they reach an acceptor particle, which in most instances is HDL particles

Figure 1. The role of HDL in Reverse Cholesterol Transport



Initially free cholesterol (FC) from the peripheral cell, in this case a macrophage, is taken up by Apo A-I (A-I) containing pre-Beta HDL. FC is subsequently esterified by lecithin cholesterol acyltransferase (LCAT) causing the cholesterol esters (CE) to move into the core of the HDL particle. The cholesterol is then transported to the liver where it is undocked and later excreted in the bile. (Adapted from [www.lipidsonline.org](http://www.lipidsonline.org))

containing fully lipidated apo-AI.<sup>8</sup> Large particles generate higher efflux rates than smaller particles.<sup>8</sup> Therefore the HDL<sub>2</sub> particle will be more effective than the HDL<sub>3</sub> particle in triggering cholesterol efflux. Membrane Microsolubilization is the other efflux mechanism. In this mechanism the cholesterol is removed by lipid-poor apo-AI, as found in pre-beta-HDL, and it binds with the donor cell's membrane.<sup>8</sup>

### RCT and Exercise

The inverse relationship between HDL and CHD stresses the importance of finding ways to increase HDL, and possibly cause a decrease in CHD mortality. The majority of the exercise intervention studies that have been conducted in relation to lipoproteins have tried to uncover how exercise changes the blood lipid profile and what type of exercise triggers this response.<sup>9,10,11,12</sup> Unless stated otherwise, the term exercise will be used to describe aerobic exercise since the vast majority of investigations have used aerobic exercise as the intervention. In experiments where the effect of acute exercise was the target it has been reported that plasma HDL-C was elevated and triglycerides decreased following the bout of exercise.<sup>9,10,13</sup> On the other hand, most exercise studies have not reported any significant changes in LDL or total cholesterol (TC).<sup>14,15</sup> It has been suggested that although overall LDL-cholesterol is rarely changed through exercise intervention, the particle size might increase and cause less circulation of small dense LDL particles that have high association with CHD risk, as they are easily oxidized.<sup>16</sup>

Since the HDL level must be determined by its synthetic and catabolic rate it is plausible to suggest that one of those two factors must be altered in endurance athletes. The high level of HDL-C more often seen in endurance athletes when compared to inactive subjects could be

linked to a decreased catabolic rate of HDL-C<sup>14</sup> and not necessarily an increased HDL-C synthesis.<sup>11,17</sup> Exercise investigations have reported that the biological half-life of the HDL molecule in runners was almost twice as long as that of sedentary subjects while others have found more modest increases in HDL half-life.<sup>14,17</sup> As little evidence has been provided for increased HDL synthesis in trained subjects, a decreased catabolic rate is thought to be responsible for the elevated HDL-C level.<sup>17</sup> Furthermore studies that have measured HDL subfractions have found that the increased level of HDL-C seen in endurance athletes seems to be almost entirely caused by an increase in the HDL<sub>2</sub> subfraction while HDL<sub>3</sub> is similar to that of the sedentary population.<sup>17</sup> The link between the elevated HDL<sub>2</sub> and exercise could be mediated through the enzyme lecithin cholesterol acyltransferase (LCAT). Increases in LCAT activity have been reported in some investigations after exercise training and that could subsequently result in more cholesterol being esterified and transported to the core of the HDL particle.<sup>18</sup> That enables the HDL molecule to bind more unesterified cholesterol on its surface and give rise to more HDL<sub>2</sub>.<sup>18</sup> Increase in HDL<sub>2</sub> particles results in reduced amounts of unesterified cholesterol in the plasma entering peripheral cells.<sup>18</sup> It has been suggested that the major factor leading to an improved blood lipid profile, following an exercise regime, is the weight loss and decrease in body fat often seen with exercise training.<sup>12</sup> In contrast to that theory, Thompson *et al.* (1997) showed that exercise training improved lipid profiles in a study where the subjects weight and body fat stayed constant during one year of exercise training.<sup>14</sup>

An interesting finding by Gupta *et al.* (1993) showed that cholesterol ester transfer protein (CETP) had a positive relationship to cholesterol transport in and out of peripheral

cells.<sup>18</sup> An elevated CETP level causes a decrease in HDL, but could still be anti-atherogenic by ensuring that the elevated LCAT level, as seen in athletes, does not cause cholesterol overload in the HDL particles and thereby inhibit further cholesterol uptake by HDL.<sup>18</sup> If this is the case it appears that the RCT could be enhanced despite unchanging HDL mass. This suggests that even if HDL-C fails to increase after an exercise-training regime there could still be positive alterations in the RCT taking place in an individual. Just measuring the HDL-C in the plasma can therefore underestimate the effect exercise training has on the RCT.<sup>18</sup> This is important for health professionals prescribing training programs to keep in mind, as an unchanged HDL-C level does not necessarily mean that the patient's health status is unimproved. Other factors in the RCT could still have been changed favourably.

### **Enzymes of RCT and Exercise**

The enzyme lipoprotein lipase is a key enzyme when trying to link both enhanced RCT and increased HDL-C with exercise. LPL resides in the endothelium wall of capillaries and is found in most tissues throughout the body. Its activity, especially in adipose tissue, is important in regulating body weight, besides playing a vital role in ensuring free fatty acid (FFA) availability for skeletal and cardiac muscles. LPL is the rate limiting enzyme in hydrolyzing plasma TG either in the form of free TG or TG bound to the lipoproteins VLDL and chylomicrons.<sup>19</sup> Most of the hydrolysis of lipoprotein-TG takes place when the lipoproteins interact with the endothelial cell.<sup>20</sup> The remnants of chylomicrons and VLDL can be transferred to HDL<sub>3</sub>, which is subsequently converted to the larger HDL<sub>2</sub> particle.<sup>19</sup> LPL activity seems to be an indicator of an increased RCT and a significant relationship between LPL activity and HDL-C has been reported in male subject populations.<sup>21</sup> On the other hand, a decrease in LPL could decrease the chylomicron-TG hydrolysis, which would cause more TG to return to the liver and then lead to increased synthesis of TG rich lipoproteins such as VLDL.<sup>20</sup> An increased VLDL mass will result in more cholesterol being transferred from HDL by the CETP in exchange of TG. The resulting TG rich HDL-molecules are degraded faster causing a decreased HDL and apo-AI level.<sup>20</sup> This suggests that increased LPL activity indicates decreased CHD risk.

Nikkila *et al.* (1978) reported significantly higher skeletal muscle LPL activity in endurance trained individuals compared to a sedentary control group.<sup>21</sup> Additionally, the adipose tissue LPL activity was significantly

higher for endurance trained males than the sedentary control group. Interestingly there was no significant difference between sprinters and the control group in the lipid parameters mentioned above.<sup>21</sup> Since the training regime of sprinters mostly consists of anaerobic exercise activities (sprint drills, heavy resistance training) and little aerobic component, this study indicates that explosive type exercise training has little effect on the blood lipid profile.<sup>21</sup>

LPL activity is increased after a single aerobic exercise bout.<sup>10,14,19,22</sup> Increased post-exercise LPL activity is believed to cause the decrease of serum TG that often is reported post exercise.<sup>23</sup> In relation to this Kiens and Richter *et al.* (1998) conducted a study where muscle TG stores was measured after a high intensity glycogen depleting exercise bout.<sup>22</sup> They found that LPL was significantly elevated over baseline level up to 30 hours post exercise and at the same time TG in muscle was significantly decreased despite the fact that muscle TG was not depleted during exercise.<sup>22</sup> This shows that after high intensity exercise, muscle TG is oxidized at a high rate in order to meet energy demand and TG from the circulation is hydrolyzed in order to make more free fatty acids (FFA) available for the muscle cells. In the study, the fat oxidation accounted for over 50% of the oxidative muscle metabolism post exercise, despite that the subjects were taking in a high carbohydrate diet post exercise.<sup>22</sup> The authors suggested that this high post exercise FFA oxidation indicates that glycogen restoration has metabolic priority and therefore TG is broken down in order to cover muscle energy expenditure.<sup>22</sup> This illustrates the importance of looking at post-exercise alterations in blood lipids and enzymes when prescribing exercise programs.

Another key enzyme in the RCT is the hepatic triglyceride lipase (HTGL). Thompson *et al.* (1997) found a decrease in this enzyme after a training period and this could indicate less HDL catabolism since HTGL is believed to delipidate HDL causing catabolism of the particle.<sup>14</sup> This finding has been documented in other studies as well.<sup>17</sup> It has been reported that the LPL/HTGL ratio is significantly increased following exercise training, which indicates exercise training causes more TG rich lipoproteins (i.e. Chylomicrons and VLDL) to be hydrolyzed.<sup>16</sup> This subsequently results in HDL<sub>3</sub> being converted to HDL<sub>2</sub> as the chylomicron remnants attaches to the HDL<sub>3</sub> particle.

Although the majority of investigations have looked at the anti-atherogenic role of HDL in the RCT, recent research suggests that HDL has other beneficial interactions that could result in

decreased CHD risk. HDL contains Paraonase, which is an enzyme thought to inhibit the formation of oxidized LDL.<sup>4</sup> As oxidized LDL is associated with increased monocyte adherence to the endothelium and foam cell formation this role of HDL is important in reducing the development of the atherosclerotic plaque. To support this theory a study by Lupatelli *et al.* (2003) found that a low HDL-C level predicted increased levels of vascular cell adhesion molecule-1 (VCAM-1) and that high levels of oxidized LDL predicted high VCAM-1 in hyperlipidaemic subjects.<sup>24</sup> Additionally oxidized LDL is believed to cause the formation of peroxy nitrates, which diminish the artery dilating effectiveness of nitric oxide (NO).<sup>4</sup>

#### TRAINING AND ACUTE EXERCISE: WHAT ALTERS THE BLOOD LIPIDS?

The exercise intervention studies conducted in relation to lipoproteins can be divided up into two categories, exercise training studies and acute exercise studies. The training studies have subjects follow a training regime for a minimum of 10 weeks and up to several years. The acute exercise studies are less depended on subject adherence and therefore include both studies of very long duration, and high intensity exercise sessions. Subjects may only be required to do the relevant exercise on a few occasions.

#### **Exercise Training Response**

It has already been described how endurance athletes exhibit a significant higher level of HDL-C than non-trained individuals and therefore it is likely that exercise training will cause an increased HDL-C level in an untrained individual. Despite numerous investigations in the area of exercise training and changes in blood lipid profile there still is some uncertainty regarding what level of exercise intensity is needed to induce improvements in the blood lipid profile and also whether there is an optimum exercise intensity.<sup>15</sup> Stein *et al.* (1990) found no improvements in HDL-C cholesterol following a 12 week aerobic training program at 65% of maximal heart rate ( $HR_{max}$ ), but reported that the higher intensity groups (75% and 85% of  $HR_{max}$ ) of the experiment showed significant improvements in HDL-C after the training period.<sup>25</sup> These results could indicate that there is an exercise threshold between 65% and 75% of  $HR_{max}$  that is necessary to reach in order to improve the blood lipid profile. Other training investigations have also found lipoprotein improvements when exercising subjects at 60-80% of  $HR_{max}$ .<sup>18</sup> Some studies have reported that exercising at a higher intensity caused no further

changes in lipoprotein levels.<sup>15</sup> In relation to training volume, some studies have found that the blood lipid response is related to the volume by comparing two different training volumes.<sup>15</sup> Brownell *et al.* (1982) reported a significant increase in HDL and HDL/LDL for male subjects after a 10-week exercise program consisting of low volume aerobic training.<sup>26</sup> The weekly exercise training consisted of 3 exercise sessions of 15-20 min. aerobic exercise at 70%  $V_{O2max}$ . According to the report, the exercise energy expenditure of each session should equal about 300-350 Kcal or around 1000 Kcal/week if all 3 sessions were attended.<sup>26</sup> This is below the exercise volume threshold described in other reports and indicates that different subject populations might respond in differently to exercise training.<sup>18</sup>

Although there is a general agreement that highly fit endurance athletes have a higher level of HDL-C, some studies have not found a relationship in training studies between fitness level ( $V_{O2max}$ ) and improvements in HDL-C.<sup>21,25,26</sup> If this is the case, exercise intervention could diminish cardiac risk factors without having to increase the individuals fitness level. Despres and Lamarche *et al.* (1994) introduced the term "metabolic fitness".<sup>16</sup> Being metabolically fit, according to this notion, translates into having metabolic properties that are associated with low CHD risk and not necessarily involve increased exercise performance.

#### **Acute Exercise Response**

The transient response to a single exercise bout may also be an important area to investigate in order to understand how exercise alters lipoprotein levels. A substantial number of acute exercise studies have described an increase in HDL-C following exercise.<sup>11,13,27,28</sup> However, some investigations have not reported HDL-C response to be significant following a single exercise bout.<sup>29</sup> Another common finding is a delayed decrease in serum TG. That decrease is likely to be caused by a delayed increase in LPL activity.<sup>30,31</sup> These conflicting results are possibly caused by the various exercise protocols used and different subject characteristics. Most studies have used endurance trained subjects in their studies.<sup>29,30</sup> That particular population might respond differently to an exercise bout than the sedentary population. This view may be regarded as valid when one takes into account the findings from a number of training studies that have reported supportive results for blood lipid changes due to prolonged exercise training.<sup>14,25,32</sup>

Regarding the intensity of acute exercise, low intensity exercise (~50%  $HR_{max}$ ), has been

reported to cause significant improvements in HDL-C.<sup>31</sup> Most studies have used an exercise intensity at least equal to this, or even higher.<sup>9,11,30,33</sup> It is therefore possible that the intensity threshold for lipid changes could be below 50% HR<sub>max</sub>. Crouse *et al.* (1995) did not find a significant difference between two different exercise intensities, which suggests that there is not a dose-response relationship regarding exercise intensity and blood lipid changes.<sup>33</sup> It should be noted that the subjects were hypercholesterolaemic men and they may exhibit a different exercise response than normocholesterolaemic subjects. Supporting this, Hicks *et al.* (1987) showed that higher intensity acute exercise elicits a greater response than lower intensity in normocholesterolaemic active men.<sup>11</sup> In regards to acute exercise volume, a caloric expenditure of 350 kcal has been sufficient to raise HDL significantly in some exercise studies.<sup>9,33</sup> A higher volume might induce a more pronounced increase in HDL as oxidation of fat is necessary and therefore likely to increase LPL activity.

Extreme exercise such as marathon running might induce different blood lipid responses than normally seen in training or acute exercise studies. A significant decrease in LDL and total cholesterol has been reported up to 66 hours after a marathon run, a finding that is unusual since most studies have failed to find any alterations in these variables post-exercise.<sup>23</sup> This indicates that going far beyond the normal training stimulus in both exercise intensity and volume could induce a more beneficial blood lipid response. Despite the positive changes of the blood lipid profile seen in post-exercise in this study it has limited practical application. For the general population this type of exercise is too severe to undertake on a daily or even weekly basis.

Most exercise studies have used either a motorized treadmill or cycle ergometer on which the subjects have performed continuous exercise. The degree of exercise is then calculated either by time spent, or number of calories consumed.<sup>9,11,25,28,29,30</sup> Future studies looking at other aerobic exercise modes or types might offer additional information in regard to how lipoproteins can be altered. Popular team sports such as soccer, rugby and basketball, where many individuals get most of their physical exercise, could be interesting areas for investigation. A difficulty is that high intensity continuous exercise can cause previous sedentary individuals to fatigue early into the exercise session. If high intensity exercise is mixed with brief rest periods, as in interval training, it is possible a greater exercise volume could be accumulated. Greater transient blood lipid response could then result,

due to higher post exercise metabolic rate. If LPL activity can be elevated in the capillary bed of active skeletal muscles it is likely that high intensity exercise that involves recruitment of additional motor units will cause an increase in LPL activity in a larger proportion of the overall capillary bed.

## **Detraining**

Follow-up studies have shown that middle age individuals that were highly physically active in their youth, but later became sedentary, are in a similar CHD risk category as individuals that never undertook physical activity. This suggests that the positive lipoprotein changes following exercise training are reversible once exercise ceases. Yanagibori *et al.* (1998) found a significant decrease in HDL-C and LPL following 21 days of bed rest in healthy males and females.<sup>34</sup> These results support the theory of a negative detraining effect on lipoproteins. Maximum program adherence should therefore be a main objective for health professionals prescribing an exercise program in order to lower CHD risk in patients.

## **CONCLUSION**

There seems to be little doubt based on the literature that HDL has anti-atherogenic properties and that exercise has the capability to increase serum HDL and positively alter the RCT. It is also clear that RCT is a complex mechanism that involves many interactions and that elevated HDL-C may only be a small part of the transport mechanism responsible for decreased CHD risk. Furthermore HDL exhibits other critical roles in regards to reducing CHD risk, mainly by influencing LDL oxidation.

There appears to be both a training and acute exercise training response. The training response seems to be increased HDL particle half-life resulting in an elevated base level HDL. This is often seen in highly trained individuals. Acute exercise seems to increase HDL level and decrease TG level in the hours following exercise. Exercise has not been found to have a significant effect on LDL and TC levels, but LDL particle size could possibly be altered in response to exercise. The positive lipoprotein exercise response seems reversible when exercise training ceases. The challenge for future research is to conduct a range of investigations with the aim of establishing an optimal exercise regime with regards to lipoprotein change. In addition focus should be directed at trying to identify particular exercise modes that are most likely to generate high program adherence.

## REFERENCES

1. Health Promotion Unit (Ireland). Ireland's changing heart – Second report on implementation of the Cardiovascular Health Strategy. Dublin: 2003. Available from: URL: <http://www.healthpromotion.ie/>
2. Riccardi G, Rivallese A, Williams C. The Cardiovascular System. In: Gibney MJ, Macdonald IA, Roche HM, editors. Nutrition & Metabolism. Oxford: Blackwell Publishing; 2003. p. 224-240.
3. Thomas TR, LaFontaine T. Exercise and Lipoproteins. In: Roitman JL, editor. ACSM's Resource Manual for Guidelines for Exercise Testing and Prescription. 3rd ed. Baltimore: Lipincott Williams and Wilkins; 1998. p. 284-301.
4. Kwiterovich PO. The antiatherogenic role of high-density lipoprotein cholesterol. *Am. J. Cardiol.* 1998; 82: 13Q-21Q.
5. Berliner JA, Navab M, Fogelman AM, Frank JS, et al. Atherosclerosis: basic mechanisms oxidation, inflammation, and genetics. *Circulation* 1995; 91 (9): 2488-2494.
6. Leaf DA. The effect of physical exercise on reverse cholesterol transport. *Metabolism* 2003; 52(8):950-957.
7. Chong PH, Kezele R, Franklin C. High-density lipoprotein cholesterol and the role of statins. *Circulation* 2002; 66: 1037-1044.
8. Phillips MC, Gillote KL, Haynes MP, Johnson WJ, et al. Mechanisms of high density lipoprotein-mediated efflux of cholesterol from cell membranes. *Atherosclerosis* 1998; 137 (Suppl.): S13-S17.
9. Crouse SF, O'Brien BC, Grandjean PW, Lowe RC, et al. Effects of training and a single session of exercise on lipids and apolipoproteins in hypercholesterolemic men. *J. Appl. Physiol.* 1997; 83(6): 2019-2028.
10. Grandjean PW, Crouse SF, Rohack JJ. Influence of cholesterol status on blood lipid and lipoprotein enzyme responses to aerobic exercise. *J. Appl. Physiol.* 2000; 89: 472-480.
11. Hicks AL, MacDougall JD, Muckle TJ. Acute changes in high-density lipoprotein cholesterol with exercise of different intensities. *J. Appl. Physiol.* 1987; 63(5): 1956-1960.
12. Sharma AM, Mascitelli L, Pezzetta F, Slentz CA, et al. Effects of exercise on plasma lipoproteins. *NEJM.* 2003; 448 (15): 1494-1496.
13. Dufaux B, Order U, Muller R, Hollman W. Delayed effects of prolonged exercise on serum lipoproteins. *Metabolism* 1986; 35(2): 105-109.
14. Thompson PD, Yurgalevitch SM, Flynn MM, Zmuda JM, et al. Effect of exercise training without weight loss on high-density lipoprotein metabolism in overweight men. *Metabolism* 1997; 46(2): 217-223.
15. Kraus WE, Houmar JA, Duscha BD, Knetzger KJ, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. *NEJM.* 2002; 347: 1483-1492.
16. Despres JP, Lamarche B. Low-intensity endurance training, plasma lipoproteins and the risk of coronary heart disease. *J. Intern. Med.* 1994; 236: 7-22.
17. Herbert PN, Bernier DN, Cullinane EM, Edelstein L, et al. High-density lipoprotein metabolism in runners and sedentary men. *JAMA.* 1984; 252: 1034-1037.
18. Gupta AK, Ross EA, Myers JN, Kashyap ML. Increased reverse cholesterol transport in athletes. *Metabolism* 1993; 42 (6): 694-690.
19. Eckel RH. Lipoprotein Lipase: A multifunctional enzyme relevant to common metabolic diseases. *NEJM.* 1989; 320 (16): 1060-1068.
20. Goldberg IJ. Lipoprotein lipase and lipolysis: central role in lipoprotein metabolism and atherogenesis. *J. Lipid. Res.* 1996; 37: 693-707.
21. Nikkila EA, Taskinen MR, Rehunen S, Harkonen M. Lipoprotein lipase activity in adipose tissue and skeletal muscle of runners: Relation to serum lipoproteins. *Metabolism* 1978; 27 (11): 1661-1671.
22. Kiens B, Richter EA. Utilization of skeletal muscle triacylglycerol during postexercise recovery in humans. *Am. J. Physiol.* 1998; 275: E332-E337.
23. Thompson PD, Cullinane E, Henderson LO, Herbert PN. Acute effects of prolonged exercise on serum lipids. *Metabolism* 1980; 29(7): 662- 665.
24. Lupattelli G, Marchesi S, Lombardini R, Siepi D, et al. Mechanism of high-density lipoprotein cholesterol effects on the endothelial function in hyperlipemia. *Metabolism* 2003; 52(9): 1191-1195.
25. Stein RA, Michielli DW, Glantz MD, Sardy H, et al. Effect of different exercise intensities on lipoprotein cholesterol fractions in healthy middle aged men. *Am. Heart. J.* 1990; 119: 277-283.
26. Brownell KD, Bachorik PS, Ayerle RS. Changes in plasma lipid and lipoprotein levels in men and women after a program of moderate exercise. *Circulation* 1982; 65(3): 477- 483.
27. Sgouraki E, Tsopanakis A , Tsopanakis C. Acute exercise: response of HDL-C, LDL-C lipoproteins and HDL-C subfractions level in selected sport disciplines. *J. Sports. Med. Phys. Fitness* 2001; 41: 386-391.
28. Kantor MA, Cullinane EM, Sady SP, Herbert PN, et al. Exercise acutely increases high density lipoprotein lipase activity in trained and untrained men. *Metabolism* 1987; 36(2): 188-192.
29. Davis PG, Bartoli WP, Durstine JL. Effects of acute exercise intensity on plasma lipids and apolipoproteins in trained runners. *J. Appl. Physiol.* 1992; 72(3): 914-919.
30. Gordon PM, Fowler S, Warty V, Danduran M, et al. Effects of acute exercise on high density lipoprotein cholesterol and high density lipoprotein subfractions in moderately trained females. *Br. J. Sports Med.* 1998; 32: 63-67.
31. Follansbee WP, Orije JE, Rahko SE, Curtiss EI, et al. The acute response of HDL to exercise: Is it determined by intensity? *Circulation* 1984; 70 (Suppl. 2): II-280 (Abstr.)
32. Thompson PD, Cullinane EM, Sady SP, Flynn MM, et al. Modest changes in high-density lipoprotein concentration and metabolism with prolonged exercise training. *Circulation* 1988; 78: 25-34.
33. Crouse SF, O'Brien BC, Rohack JJ, Lowe RC, et al. Changes in serum lipids and apolipoproteins after exercise in men with high cholesterol: influence of intensity. *J. Appl. Physiol.* 1995; 79(1): 279-286.
34. Yanagibori R, Kondo K, Suzuki Y, Kawakubo K, et al. Effect of 20 days' bed rest on the reverse cholesterol transport system in healthy young subjects. *J. Intern. Med.* 1998; 243: 307-312.