THE EFFECT OF EXERCISE VOLUME ON LIPOPROTEIN METABOLISM IN INDIVIDUALS WITH DIABETES OR PRE-DIABETES

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To the Dean of the Graduate School:

I am submitting herewith a thesis written by Ming Chen Ko entitled "The Effect of Exercise Volume on Lipoprotein Metabolism in Individuals with Diabetes or Pre-diabetes." I have examined this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science with a major in Kinesiology.

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We have read this thesis and recommend its acceptance:

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ABSTRACT

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THE EFFECT OF EXERCISE VOLUME ON LIPOPROTEIN METABOLISM IN INDIVIDUALS WITH DIABETES OR PRE-DIABETES

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Purpose: To determine the relationship between blood lipid and lipoprotein concentrations and the amount of exercise normally performed in individuals with diabetes or pre-diabetes. **Method:** Non-smoking adults who were diabetes or pre-diabetes and 45 to 85 years of age were participants. No attempt was made to alter the participants' medications during this investigation. Fasting blood samples and anthropometric measurements were collected, and were analyzed for blood lipid and lipoprotein-cholesterol concentrations. A Pearson Correlation was used to calculate the relationship between exercise volume and blood lipid and cholesterol concentrations. The exercise volume will be collected by a survey and the FitLinx system used by LEAD-UP. The criterion reference for statistical significance was set at $P \leq 0.05$. **Result:** Thirty participants were included in the final analysis. Within these thirty participants, one was type 1 diabetes, 12 were type 2 diabetes and the rest of the participants were at borderline diabetes. TC concentrations was 188.4 ± 34.5 mg/dl, mean TG concentrations was 137.1 ± 48.6 mg/dl, mean LDL-C concentrations was 104 ± 33.3 mg/dl, and mean HDL-C concentrations was 56.9 ± 8.2 mg/dl. The average calorie expenditures from aerobic exercise were 251±199 kcal/session. The frequency to perform resistance was 1.9 d/week and the frequency to perform aerobic

exercise was 2.1 d/week. **Conclusion:** The results from present study indicated there was no significant relationship between exercise volume and the concentrations of TC, TG, LDL-C, and HDL-C. Therefore, exercise was not related to lipid profiles.

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INTRODUCTION

A report conducted by World Health Organization (WHO) in 2005 indicated that cardiovascular disease (CVD) is one of the most prevalent health problems in the world. Almost 30% of deaths all over the world were attributed to CVD (Erhardt, Moller, & Puig, 2007). For the first time, CVD is the leading cause of death throughout most of the world exceeding infection and cancer (Taylor & Zenovich, 2008). Growing evidence shows that most CVD is preventable and low levels of risk factors are related to healthy lifestyles (Pearson et al., 2002).

Atherosclerosis of the coronary arteries is the precursor of CVD. Atherosclerotic arteries create thrombi, which bulges into the vascular lumen causing obstruction of blood flow or fatal events such as myocardial infarction. This dysfunction of endothelial cells is often characterized by an excess of cholesterol deposition in the subintimal extracellular matrixof the arterial wall (Smith, Marks, & Lieberman, 2005). Varied risk factors can promote the excess of cholesterol concentration such as elevated low-density lipoprotein cholesterol (LDL-C), triglyceride (TG), lipoprotein(a), and decreased high-density lipoprotein cholesterol (HDL-C) concentrations (Schaefer, 2002).Other risk factors also contribute to the development of CVD. These factors are usually categorized based on whether they are modifiable or are non-modifiable. Risk factors such as smoking, hypertension, physical activity level, obesity, and diabetes mellitus are modifiable.

Modifiable risk means can be altered by changing lifestyle to reduce the incidence of CVD (McManus, 2005; Pearson et al., 2002).It is important to realize the impact of non-modifiable factors such as gender and age, which may reduce the beneficial effects of modifiable risk factors. With each additional year of life comes an increased incidence of CVD (Erhard et al., 2007). Therefore, risk factor management should be started early to ensure the beneficial effects.

Four cardiovascular risk factors (hypertension, diabetes, dyslipidemia, and obesity) have been described in clusters in the 1960s and 1970s (Haffner & Taegtmeyer, 2003). During the past two decades, this multifactorial disease has been described with different names, such as Metabolic Syndrome (MetS) and Syndrome X. People with MetS have higher incidence of CVD, thus, increasing the mortality from CVD (Ford, Giles, & Dietz, 2002). In 1998 the World Health Organization stated that individuals with insulin resistance and at least two of four other factors (hypertension, hyperlipidemia, obesity, and microalbuminuria) to be considered as having MetS (Haffner & Taegtmeyer, 2003). The Adult Treatment Program III (ATP III) of the National Cholesterol Education Program (NCEP) developed a different definition for MetS in 2001. Five diagnostic traits are listed in the ATP III version of the MetS (increased waist circumference, fasting TG >150 mg/dl, hypertension, HDL-C < 40 mg/dl in men, < 50 mg/dl in women, and fasting glucose ≥ 110 mg/dl), and the presence of any three of these factors is referred to as the MetS (Wilson & Grundy, 2003). It is very crucial for physicians and patients to realize that there is no risk level that can be considered safe (Erhardt et al., 2007).

Fortunately, the prevention or reversal of these risk factors through exercise can diminish CVD morbidity and mortality (Erhardt et al., 2007).

Almost all mammalian cells can synthesize cholesterol. However, some cells require greater amounts of cholesterol than they can synthesize by themself for the synthesis of membranes or for the formation of steroid hormones (Smith et al., 2005). Via the transportation of TG and cholesterol by lipoproteins, the cholesterol needs of cells can be achieved. Four basic lipoproteins are: chylomicron, very low-density lipoprotein (VLDL), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). These lipoproteins are essential for human function, however, inappropriate lipoprotein cholesterol concentrations can increase the incidence of CVD (Schaefer, 2002).

The impact of the subfractions of HDL-C and LDL-C have been emphasized recently. These subfractions of lipoproteins include lipoprotein(a), HDL_2, and HDL_3. Lipoprotein(a) is a subfraction of LDL containing apolipoprotein (Apo) B-100. Elevated lipoprotein(a) is associated with increased CVD risk (Durstine, Grandjean, Cox, & Thompson, 2002; Schaefer, 2002). The HDL subpopulation, HDL_2 and HDL_3 create a loop which can help the clearance of the excess deposition of cholesterol from the peripheral tissues back to liver for catabolism (Durstine et al., 2002; Smith et al., 2005). It has been suggested that HDL_2 particles are cardioprotective; in contrast, high levels of HDL_3 particles have been suggested to increase CVD risk (Pascot et al., 2007).

Another focal point of CVD risk is the LDL particle size. Lower concentrations of small, dense LDL particles have been observed in more physically

active hypercholesterolemic men, compared to their sedentary hypercholesterolemic counterpart (Halle, Berg, Konig, Keul, & Baumstark, 1996). Low-density lipoprotein (LDL) particle size is not an independent risk factor of CVD while other lipids and lipoproteins have been controlled, therefore, more experiments need to be conducted to confirm these findings (Schaefer, 2002).

Physical activity is a deterrent for developing CVD. Some of the beneficial effects of habitual physical activity are due to its ability to reduce TG, TC, and increase HDL-C concentration (Durstine, Grandjean, Davis, Ferguson, Alderson, & Dubose, 2001). In addition, Slentz et al. (2007) observed after 8 to 9 months of exercise training, the HDL particles size increases significantly in sedentary, overweight individuals. The reduction in atherogenic LDL-C concentrations or an increase in LDL particles size has also been observed after exercise training. However, more often than not, LDL-C concentrations remain unchanged after exercise training. A dose-dependent relationship has been identified when exercise is performed over longer periods of time; the beneficial effects on LDL-C are more likely to occur (Ferguson, Alderson, Trost, Essig, Burke, & Durstine, 1998). In other words, the more calories an individual has been expended per exercise session the better exercise induced lipids responses will occur. The actual amount and intensity of exercise that is sufficient enough to generate beneficial effects on lipid profiles is still unknown and needs more research.

The exercise volume threshold necessary for a TG level change may be similar to that necessary for HDL-C. A weekly energy expenditure > 1200 kcal generally decreases TG and increases HDL-C concentrations (Durstine et al., 2001). The

magnitude of the increment on HDL-C concentrations is similar in both gender and, generally ranges from 4 to 22%. Similarly, a 37% reduction in TG levels has been reported for males after exercise training, but less frequently in females (Durstine et al.).

Different populations might respond differently after exercise training. Reduced TG concentrations were observed after exercise training in untrained individuals; however, TG concentrations are even lower in trained individuals (Magkos, Wright, Patterson, Mohammed, & Mittendorfer, 2005). Individuals with low HDL-C levels along with elevated TG concentrations seem to have the greatest positive responses after endurance training. However, subjects with low HDL-C levels as an isolated trait are much less responsive to training (Couillard et al., 2001).

In general, it is well recognized that exercise plays an important role in altering lipid profiles and reducing CVD risk whenever the changes are large or small. Many studies indicated that physically active middle-aged and older men have better lipid profiles than their age-mached sedentary individuals and it also indicated that the improvement of HDL-C concentrations through exercise training were blunted in obese compared with lean individuals (Niclkas, Katzel, Whitehead, & Goldberg, 1997). In addition, other studies also suggested that weight loss may need to be incorporated with exercise training to elicit changes in lipid metabolism (Katzel et al., 1995). Therefore, the effects of exercise training on lipid profiles in obese individuals remain controversial.

Elevated TG, LDL-C, and decreased HDL-C concentrations are common in people with Type 2 diabetes; exercise has been identified as a major therapeutic way

to treat diabetes (Gordon et al., 2008). Walker et al. (1999) indicated that after 12 weeks of self-paced walking for 60 min per session, five times per week significantly reduced the TC, LDL-C, and non-HDL-C concentrations; however, no change in the HDL-C concentration was observed. Other studies indicated that only reductions in LDL-C concentration were significant with training length ranged from 10 to 26 weeks aerobic exercise intervention (Kelley & Kelley, 2007). A significant increase in HDL-C concentration was observed by Loreto and co-workers (2005). However, the increment of HDL-C concentration will not occur until an individual's energy expenditure achieves 21 METs/hr/week or greater. Thus, the exercise volume threshold that is sufficient enough to induce the alteration of lipid profiles and the responses of people with diabetes after exercise intervention remains unclear.

Statement of Problem

Individuals with diabetes or prediabetes often display more negative lipid profiles than the general population which can lead to an increased incidence of CVD. These negative lipid profiles are elevated TG, LDL-C, TC, and low HDL-C. Although regular physical activity has been recommended as part of a strategy to normalize lipid profiles and prevent the development of CVD, the sufficient amount to alter lipid profiles for individuals with diabetes or prediabetes might be different from the general population. The purpose of this study is to determine the relationship between blood lipid and lipoprotein concentration and the amount of exercise normally performed in individuals with diabetes or pre-diabetes.

Hypothesis

There will be a negative relationship between TC, TG, LDL-C, and a positive relationship between HDL-C and the amount of exercise performed each exercise session in individuals with diabetes or pre-diabetes.

Definition of Terms

1. Apolipoprotein: a protein component within lipoproteins; could increase the water solubility of the lipoprotein, active certain enzymes and act as ligands for specific receptors (Smith et al., 2005).

2. Apolipoprotein A-I (Apo A-I): structural component of high-density lipoprotein; activator of LACT (Smith et al., 2005).

3.Apolipoprotein B-100 (Apo B-100): structural component of VLDL and LDL; ligands for LDL receptors (Smith et al., 2005).

4. Atherosclerosis: a dysfunction of endothelium characterized by cholesterol deposition in the subintimal extracellular matrix of the arterial wall (Smith et al., 2005) associated with thickening and loss of elasticity of the arterial wall.

5. Cardiovascular disease (CVD): any disorder of the heart or arterial vessels. Cardiovascular disease includes coronary heart disease, stroke, congenital heart disease, and other disorders. (American Heart Association [AHA], 2000).

6. Cholesterol: an alicyclic compound, waxy substance in cell membrane and act as precursor for the formation of steroid hormones, the biosynthesis of vitamin D, and the formation of bile salts.

7. Chylomicron: the largest and least dense lipoprotein; rich in TG and synthesized from dietary lipids (Turcotte, Richter, & Kiens, 1995).

8. Exercise duration: how long an individual participates in an exercise session (American College of Sport Medicine [ACSM], 2000).

9. Energy expenditure: how many calories an individual expends per exercise session.

10. Exercise intensity: how hard an individual exerts in an exercise session; 55-69% of maximum heart rate has been defined as moderate intensity, and hard intensity has been defined as 70-90% (ACSM, 2000).

11. Hepatic lipase: bound to the liver capillary endothelium; convert chylomicron and VLDL to LDL and HDL_2 to HDL_3 (Durstine et al., 2002).

12. High-density lipoprotein (HDL): carries cholesterol from peripheral tissues back to liver for catabolizing.

13. High-density lipoprotein-2 (HDL_2): high-density lipoprotein with density 1.063-1.125 mg/ml (Smith et al., 2005).

14. High-density lipoprotein-3 (HDL_3): high-density lipoprotein with density 1.125-1.210 mg/ml (Smith et al., 2005).

15. Lipoprotein lipase: bound to the capillary walls of most tissues and particularly active in adipose tissues, heart muscle, and skeletal muscle. Lipoprotein lipase hydrolyzes TG and release free fatty acid to extrahepatic tissue (Durstine et al., 2002).

16. Lipoprotein (a): a LDL subfraction containing Apo (a) which attached to Apo B-100 on the LDL particle by disulfide bridge (Schaefer, 2002).

17. Low-density lipoprotein (LDL): carries cholesterol from liver to peripheral tissues; density 1.019-1.063 g/ml (Smith et al., 2005).

18. LDL-receptor: located on cells membrane; responsible for the internalization of LDL-C into cells through the interaction with Apo B-100 (Smith et al., 2005).

19. Triglyceride (TG): each TG contains three fatty acids and one glycerol. The linkage between each fatty acid and glycerol is oxygen atom. TGs constitute the vast majority of the lipid consumed in the diet and stored within the body (Brooks, Fahey, & Baldwin, 2005)

20. Very low-density lipoprotein: a lipoprotein rich in TG (80-95%) synthesized by liver for the transportation of TG. (Smith et al., 2005).

21.MET: a MET is a metabolic equivalent or the metabolic rate at rest. 1 MET= 3.5ml/kg/min. (Ainsworth et al., 2000).

Assumptions

This study was conducted based on the following assumption:

The questionnaire is able to truly reflect the participant's exercise, and medication history.

Limitations

This study was conducted with the following limitations:

1. The results may not be able to apply to populations other than individuals with diabetes or pre-diabetes.
2. Small sample size may not provide practical application to other population with different characterization.
3. Previous dietary, medical, or exercise history may influence results.

Significance of the Study

Cardiovascular disease is the leading cause of death, and is responsible for approximately 16.6 million deaths per year throughout the world (Erhardt et al., 2007). Therefore, reducing the risk factors of cardiovascular disease is very important to

decrease the death rate. Cross-sectional data provide evidence that regular aerobic exercise improves the lipid profiles, thus, reducing the risk factors (Kodama et al., 2007). However, the effects of exercise on lipid profiles vary in individuals. Some studies indicated that individuals having the lowest initial HDL-C levels would have the greatest increases in HDL-C after exercise training (Tran, Weltman, Glass, & Mood, 1983). However, others have the opposite opinion (Raz, Rosenblit, & Kark, 1988; Williams, Stefanick, Vranizan, & Wood, 1994). Individuals with diabetes or pre-diabetes have often been diagnosed having low HDL-C concentration and hypertriglyceridemia (Alam et al., 2004). Therefore, to determine the relationship between the lipid profiles (TG, TC, LDL-C, and HDL-C) and the amount or exercise performed in individuals with diabetes or pre-diabetes is crucial to provide more precise knowledge necessary to educate this specific population and have better exercise prescription.

CHAPTER II

REVIEW OF LITERATURE

Triglycerides and cholesterol are specific types of lipids. Lipds are not water soluble. Therefore, lipids must combine with protein to form micelle lipid-protein complexes called lipoproteins. Lipoproteins are spherical, with a measurable dimension, and consist of different apolipoproteins, triglyceride, phospholipid, and free and esterified cholesterol (Shepherd, 1992). Lipoproteins are classified according to size, density and lipid, and apolipoprotein composition (See Appendix A).

Lipoproteins Composition

Apolipoproteins are the protein component of lipoproteins that aid lipids to become soluble (Brewer, Greg, Hoeg, & Fojo, 1988). Apolioproteins are important for lipids transport, nerve regeneration, and directing the regulation of enzymatic function (Brewer et al., 1988; Durstine et al., 2002). There are two major apolipoproteins, Apo A-I and Apo B-100. Apolipoprotein A-I is synthized by intestine and liver, and is the structural component in HDL particle. The metabolic function of Apo A-I is to activate lecithin:cholesterol transfer protein (LCAT), thus increase the HDL-C concentration. Apo B-100 is synthesized by liver. Apolipoprotein B-100 can be observed in VLDL, IDL, and LDL particles and it is also a lignad for LDL receptors (Durstine et al., 2002; Smith et al., 2005).

Chylomicrons are the largest and least dense lipoprotein. This is due to the triglyceride content of chylomicrons. Three major apolipoproteins attach to chylomicron: Apo B-48, Apo E, and Apo C_{II} (Smith et al., 2005).

Apolipoprotein C_{II} (Apo C_{II}) can activate lipoprotein lipase (LPL) which is located in the endothelium of capillary walls of most tissues and is especially active in adipose, heart, and muscle tissue. Triglyceride in the chylomicron core can be hydrolyzed by LPL and released as free fatty acids (FFA). Muscle cells can use those free fatty acids as fuel (Durstine et al., 2002; Smith et al., 2005).

Very low-density-lipoprotein (VLDL), a lipoprotein which is slightly smaller and more dense than chylomicrons, is synthesized by liver and is also involved in triglyceride transportation to peripheral tissues. Apolipoprotein B-100 (Apo B-100), Apo E, and Apo C_{II} are packaged with VLDL. Because VLDL contains Apo B-100, and Apo C_{II}, VLDL can interact with LPL resulting in triglyceride hydrolysis (Smith et al., 2005). The interactions between VLDL and LPL form the smaller and more dense IDL or LDL (Durstine et al., 2002; Shepherd, 1992) depending the resulting density of the lipoprotein. Hepatic lipase (HL) is located in the capillary endothelium at the liver, and it has similar function as LPL. Hepatic lipase indirectly converts VLDL remnants and chylomicrons into LDL. Cholesteryl ester transfer protein (CEPT) is considered a mediator of the exchange of apolar lipids between HDL, VLDL, LDL, and chylomicron remnants in collaboration with HL when converting HDL_2 to HDL_3 particles (Bruce, Chouinard, & Tall, 1998; Durstine et al., 2002; Smith et al., 2005). Low-density lipoprotein is the primary transport mechanism for moving cholesterol to peripheral tissues. High-density lipoprotein (HDL) is the smallest and most dense lipoprotein synthesized by the intestine and liver. The predominant apoproteins in the HDL particle are Apo A-I, Apo A-II, Apo C_I, and Apo C_{II} (Smith et al., 2005).

High-density lipoprotein is central to the transport of cholesterol from peripheral tissues back to the liver to be excreted as bile.

Lipid Metabolism

Several lipoprotein metabolic pathways exist. The LDL receptor pathway and reverse cholesterol transport pathway have critical roles in lipoprotein metabolism and the development of CVD. The low-density lipoprotein receptor pathway consists of a series of chemical steps designed to transport cholesterol to peripheral tissues. The reverse pathway (HDL-C pathway) is designed to transport cholesterol from peripheral tissues back to the liver for catabolism. (Yokoyama, 2000).

Digestion and absorption of dietary fat and cholesterol is involved in the LDL receptor pathway. After a meal, dietary fat and cholesterol will combine with apolipoproteins B-48, A-I, A-II, A-IV, and E, and will be internalized into the core of chylomicrons during intestinal absorption. After combining with chylomicrons, these lipids will be carried to the circulatory system by the lymphatic system, the thoracic duct, and the left subclavian (Shepherd, 1992). In the circulatory system, chylomicrons will interact with LPL and hydrolyze the triglyceride in the core of chylomicrons resulting in FFA release (Durstine et al., 2001; Durstine & Thompson, 2001). Those chylomicron remnants which contain Apo C and E will be removed from the circulation by HDL. In the final step of chylomicron remnants, chylomicron will be assimilated by hepatic cells through the Apo B/E receptor (Durstine et al.; Durstine & Thompson).

A similar process exists for LDL which is formed from VLDL. The interaction between VLDL and LPL will hydrolyze triglyceride in the VLDL core. The

hydrolyzed triglyceride will release fatty acids to be taken up by extrahepatic tissue (Shepherd, 1992). The remnants of VLDL, and IDL, interact with LPL and HL forming LDL. The remnants of VLDL will be removed from the circulation by hepatic Apo E which is located in the liver (Brown & Goldstein, 1986; Smith et al., 2005). The LDL formed from this process is the main cholesterol carrier. Located on cell surfaces, LDL receptors recognize LDL particles, and remove LDL from the circulation into the cell to undergo lysosomal action (Brown et al., 1986). This could activate negative feedback within the cell promoting excess cholesterol storage (Brown & Goldstein, 1986; Smith et al., 2005).

Unlike the LDL-receptor pathway, the reverse cholesterol transport pathway transports cholesterol from the periphery to the liver. It includes several different processes for cholesterol removal (Bruce, et al., 1998; Durstine et al., 2001). The free cholesterol and phospolipid derived from the catabolism of LPL-mediated chylomicrons and VLDL will attach to nascent HDL particles synthesized by the liver (Bruce et al., 1998; Shepherd, 1992). In the presence of Apo A-I, the enzyme lecithin: cholesterol acyl transferase protein (LCAT) will esterify free cholesterol into cholesteryl ester, and transport it into HDL_3 particles (Bruce et al., 1998; Shepherd, 1992). This incremental addition of cholesteryl ester to the HDL_3 core expands the HDL_3 particles and decreases the HDL_3 density resulting in HDL_2 particles. This process induces two other separate chemical cascades. First, the newly formed HDL_2 cholesteryl ester is exchanged for triglyceride from chylomicrons and VLDL remnants by the action of CETP. The remaining VLDL and chylomicron remnants will be delivered to the liver for metabolism and removal (Bruce et al., 1998). Hepatic lipase

will remove the triglyceride from the triglyceride enriched HDL_2. When the removal process is complete, HDL_2 particles are converted back to HDL_3 due to the increased particle density. Thus, HDL_3 is then returned to the circulatory system and the cycle continues (Bruce et al., 1998).

Lipoproteins and Cardiovascular Disease (CVD)

A normal artery consists of three different layers: intima, tunica media, and adventitia. The intima is closest to the lumen of the vessel which is lined by a monolayer of endothelial cells. Beneath the intima is the subintimal extracellular matrix where it is the site for macrophage or foam cell accumulation (Smith et al., 2005).

Role of LDL-C in Atherosclerosis

The first step in the development of atherosclerosis is the formation of a fatty streak. This is formed by an accumulation of lipid-loaded macrophages, or foam cells, in the subintimal lining. When one or more vascular risk factors for atherosclerosis occur, the formation of the fatty streak begins. These risk factors include increased LDL-C, VLDL-C, chylomicron remnants, and low concentrations of circulating HDL-C. When these factors occur, the endothelial cells secrete adhesion molecules that bind to circulating monocytes and slow the speed of movement past the endothelium leading to monocyte accumulation in the arteries (Maiti & Aqrqwql, 2007; Smith et al., 2005).

An accumulation of monocytes transforms into macrophages. Unlike LDL receptors, macrophages are high –capacity, low-specificity receptors. They bind to oxidatively modified fatty acids in the LDL core and become foam cells in the

subintimal space. As the foam cells accumulate, they deform the endothelium and expose these foam cells and extracellular matrix to the blood. Platelets aggregate at the exposed area and form a thrombus. As the plaque matures, a fibrous cap forms and covers the thrombus, which now bulges into the vascular lumen, therefore partially occluding the vascular lumen. If this thrombus completely occludes the remaining lumen of the vessel, an infarction (i.e. myocardial infarction) may occur (Smith et al., 2005).

The LDL receptor is characterized as a high affinity and narrow range of receptor. It recognizes Apo B-100 and Apo E, therefore, this receptor binds VLDL, IDL, and chylomicron remnants in addition to LDL. Via the LDL receptor pathway, cholesterol is internalized by the cells. This internalization processes will continue until it meets cellular needs, leading to the downregulation of LDL receptors (Brunzell et al., 2008). A plasma concentration of 25 mg/dl LDL-C would be sufficient to supply peripheral cholesterol needs (Brown & Goldstein, 1986). Infant LDL-C concentration is in the range of 40-50 mg/dl. In healthy adults LDL-C is 3 to 4 times higher (O'Keefe, Cordain, Harris, Moe, & Vogel, 2004).

People with heterozygous mutations in the LDL receptor produce approximately half of the normal complement of LDL receptors; whereas, the individual with homozygous mutations produce almost no LDL receptor protein. The latter have serum TC concentrations in a range of 500-800 mg/dl (Brunzell et al., 2008; Smith et al., 2005). With these mutations, cholesterol does not enter the target cell from the bloodstream, therefore, the serum cholesterol concentration rises.

If children have this disorder of LDL receptors, the LDL-C concentration will

be 10 times higher than normal, and will, if untreated, lead to CVD in the first decade of life (Brown & Goldstein, 1986). These data suggest that a high concentration of LDL-C can cause atherosclerosis, and all humans should maintain a LDL-C concentration of about 50 mg/dl to prevent atherosclerosis (Brunzell et al., 2008).

Role of High-Density Lipoprotein Cholesterol in Atherosclerosis

High-density lipoprotein-cholesterol (HDL-C) is a heterogeneous lipoprotein made of different subfractions. It has been suggested that it is the large, cholesterol ester-rich HDL_2 subfractions that is cardioprotective (Sich et al., 1998). The benefit of high HDL-C concentration is the ability of HDL to promote reverse cholesterol transport from cells in the vessel wall to the liver for catabolism. Another important property of HDL-C is that it can protect LDL-C from oxidation, thus, inhibiting the formation of foam cells (Brunzell et al. 2008). As a result, this decreases the incidence of having CVD. In general, a HDL-C concentration of 40 mg/dl (0.90 mmol/l) or less is a major risk factor for CVD (World Health Organization [WHO], 1999). In contrast, when HDL-C concentrations are greater than 60 mg/dl (1.60 mmol/l) this creates a negative risk factor for CVD (Leon et al., 2000). Every 1 mg/dl (0.026 mmol/dl) increment of HDL-C level can contribute to a 2% decrease of CVD incidence in men and 3% decrease of CVD incidence in women, respectively (Kodama et al., 2007).

It has also been suggested that abdominal obesity may be a major cause of insulin resistance, increased free fatty acids concentration, and an increase in hepatic TG-rich lipoproteins (Despres, 1993).

These processes will promote the transfer of TG to HDL_2 through the action of CETP. Hepatic lipase then removes the TG from the HDL_2 particles, when the removal of TG is complete, the endproduct, HDL_3, is then returned to the blood circulation (Durstine et al., 2002).

Effects of Exercise on Lipid Profile

It is well established that frequent aerobic activity is good for health and could lower the risk to cardiovascular disease (CVD). The main metabolic benefits of regular physical activity are a rise in HDL-C concentrations, decreased TC, TG, VLDL-C, and LDL-C (Couillard et al., 2001).

Effects of Aerobic Training

Aerobic exercise training frequently leads to an increase in HDL-C concentration and a decrease in TG. These changes corresponded to increased lipoprotein lipase (LPL).Regular aerobic exercise can increase muscle capillary density, which is positively correlated with muscle lipoprotein lipase activity (LPLA) (Kiens & Lithell, 1989). Petibois et al. (2004) trained 20 male rowers for one year. About 70% of the training was consisted of aerobic exercise. There was a significant decrease of TG after 24 weeks of training that remained stable thereafter. At 47 weeks a significant increase in HDL-C was observed accompanied by an increase in LPLA. A significant increase in HDL-C and a decrease in TG were observed in untrained individuals after nine months of moderate or vigorous intensity exercise training (Slentz et al., 2007). An increase in large HDL particle concentration and average size of HDL particles were also observed after training, even without clinically significant weight loss (Kraus et al., 2002). Dalleck et al. (2008) assessed the American College

of Sports Medicine (ACSM) exercise recommendation for exercise indicated that energy expenditure of 1000 kcal/week for 10 weeks is sufficient enough to increase HDL-C concentration and decrease TG concentration. Leon et al. (2000) also indicated that after 20 weeks of exercise training in previously sedentary individuals an average increase of 4.6% in HDL-C concentration and a reduction of 3.7% in TG concentration were observed. Higher HDL-C concentration and lower TC/HDL-C ratio were also observed in highly trained spinal cord injury (SCI) individuals suggested that physical activity plays an important role in this population (Groot, Hjeltnes, Heijboer, Stal, & Birkeland, 2003). However, Kelley and co-workers (2007) indicated that short-term aerobic exercise does not improve HDL-C concentration in children and adolescents (8-16 years), while a reduction in TG concentration was observed. Children and adolescents with lower initial HDL-C concentration can have better responses after exercise training (Kelley & Kelley, 2007). Similarly, Angelopoulos et al. (2007) indicated that after 6 months of training, no changes in HDL-C were observed regardless the gender (healthy sedentary individuals, age 39 ± 2.2 years).

The effects of exercise training on TC and LDL-C have usually been relatively small when compared with TG and HDL-C. Generally, the changes on TC and LDL-C are in the range of 5-10%, and are highly variable (Boreham et al., 2005). Decreased TC and LDL-C have been found after training in overweight and obese populations if accompanied with substantial weight loss (from 2.8 to 11.0 kg) (Halle et al., 1999; Tremblay et al., 1991). Similarly, Helge et al. (2008) found a significant reduction in TC, IDL, and LDL concentration after training in moderately trained individuals with

substantial weight loss. However, Halverstadt et al. (2007) indicated that even without weight loss, decreased TC and LDL-C concentrations can still occur in elderly individuals (50 to 75 years). In addition, a significant decrease in small, dense LDL particle concentration along with an increase in large LDL particle concentration can occur in older adults. Some investigators suggest that individuals with an initially higher LDL-C concentration have the greatest reduction in LDL-C concentration after training (Angelopoulos et al., 2007).

Apolipoprotein B is a major constituent of LDL particles and 95% of LDL particle have only one Apo B (Angleopoulos et al., 2007). Consequently, Apo B concentration could also be a predictor for CVD. Leon et al. (2000) observed no significant changes in Apo B concentration after 20 weeks of training. In contrast, others indicated that a reduction of Apo B concentration was observed after 16 weeks to 12 months of training in middle-aged hypercholesterolemic or overweight men and young, Type 1 diabetic patients (Crouse et al., 1997; Laaksonen et al., 2000; Thompson et al., 1997).

Although the changes on TC, LDL-C, and Apo B are inconsistent, exercise may transiently suppress the increased concentration of these lipid profiles. Therefore, repeated exercise stimulus is important to maintain the positive changes.

Effects of Resistance Exercise

Some investigators use resistance exercise as an intervention for lipid profiles. Unfortunately, the effect of resistance exercise is weak. Kokkinos et al. (1988) divided participants into two resistance training groups, high-repetition with low resistance and low-repetitions with heavy resistance (high-repetition group: 14 to 16 repetitions

maximum; low-repetition group: 4 to 6 repetitions maximum) showed that no changes in TG, TC, HDL-C, and LDL-C concentrations after training. Lemura et al. (2000) trained 12 sedentary but healthy women (age 20.4 ± 1 years) for 3 days/week with an intensity of 60-70% 1RM for 8-10 repetition for each set for 16 weeks. No changes were observed in lipid profiles (TC, TG, LDL-C, HDL-C, and TC:HDL-C) after resistance training. In contrast, the participants in the aerobic exercise training group after 16 weeks of aerobic exercise training (4 days/week, 85% HRR, 45 min/session), TC, LDL-C decreased 10 and 6%, respectively, and HDL-C increased 28%. However, Wallace et al. (1991) indicated that resistance exercise that induced 800 kcal energy expenditures was capable of improving lipid profile in a direction and magnitude comparable to an acute bout of aerobic exercise. Unfortunately, this is not practical for every one.

Therefore, when it comes to lipid response, aerobic exercise would have more favorable effects on lipoprotein cholesterol.

Differences between Physically Active and Inactive Individuals

Generally speaking, obese individuals demonstrate more risk factors for CVD than lean individuals. When an individual's BMI is larger than 30 kg/m^2, it is associated with a two-fold increase in CVD risk (Wannamethee, Shaper, Whincup, & Walker, 2004). Unfortunately, despite many reports reiterating the importance of leanness, much of the reduction in CVD risk associated with habitual exercise is independent of total and regional body fat. Lean individuals could still have a low HDL-C concentration. Furthermore, the relationship between obesity, TG, and HDL-C may not extend to total cholesterol and LDL-C concentrations (Despres,

1994). Therefore, the concentrations of TC and LDL-C might be determined by other factors such as exercise.

Exercise is more important than leanness to alter lipid profiles. O'Donovan et al (2005) compared the CVD risk factors (TG, TC, LDL-C, and HDL-C concentration) in lean habitual exercisers, lean sedentary men, and obese sedentary men. Indeed, in every CVD risk factor, obese sedentary men (BMI > 32 kg/m^2) have the poorest profiles compare with the other two groups. The comparison of the lean groups indicated that at a similar BMI (25.2 ± 2.7 kg/m^2) lean exercisers have lower TC, TG, LDL-C, and Apo B concentrations and are accompanied with higher HDL-C concentrations.

Individuals who are more active have better lipid profiles than their sedentary counterpart even with the same BMI. Tompson et al. (1991) compared the lipid profiles between 10 competitive athletes and 10 physically inactive men. All participants BMI were around 24 kg/m^2 and were, therefore, considered as lean. The average HDL-C concentration was 40% higher in the endurance athletes, in large part because of greater HDL_2-C concentrations. Apolipoprotein A-I concentration was also 25% higher in the athletes. Triglyceride concentration was 45% lower in the athletes. There were no significant differences in LPLA between groups, but a 27% lower in hepatic triglyceride lipase activity (HTGLA) in the athletes was observed. These results indicated that with lower HTGLA, the HDL half life could be longer which in turn would be directly related to HDL-C and, in particular, HDL_2-C concentration.

In summary, many contemporary studies emphasize the importance of maintaining normal weight because of the higher HDL-C and lower TG

concentrations observed in lean individuals. Many cross-sectional studies compare the CVD risk factors such as TC, TG, LDL-C, HDL-C, LPLA, and HTGLA in habitual exercisers and sedentary men indicating that these factors can be altered by exercise. For these reasons, obese individuals who do not exercise constitute a particularly high risk group to have CVD.

Acute Responses After Exercise

In addition to chronic exercise adaptation, acute lipid responses have been shown after prolonged exercise. The alterations in lipid profiles after prolonged exercise are inconsistent. These alterations were first observed in long-distance events ranging from a marathon event to a 70 km skiing event (Enger, Stromme, & Refsum, 1980; Thompson, Cullinane, Henderson, & Herbert, 1980). The discrepancies might be due to the failure to control the potential confounding variables: initial HDL-C level, training level, and exercise duration and intensity.

The concept of exercise volume (how many calories are expended) has been considered as the mechanism responsible for promoting changes in blood lipids after exercise (Crouse et al., 1995; Kodama et al., 2007), rather than the intensity of exercise. Based on this concept Ferguson et al. (1998) observed a 26% decrease in TG and a 22% decrease in VLDL-C after 800 kcal were expended. There were no changes in HDL-C observed until 1100 kcal were expended (15% increase in HDL-C) in trained males. Davis et al (1992) evaluated the acute responses after exercise at different intensities. All participants were well-trained male runners. The exercise protocol consisted of two exercise sessions (50% and 70% VO_2max), and the energy expenditure was held constant (950 kcal/session). No change in HDL-C or any other

lipoprotein component after exercise occurred. In contrast to those studies, Crouse et al. (1996) indicated that 350 kcal of energy expenditure from exercise is sufficient enough to alter lipid profiles in hypercholesterolemic men for ≥ 48 hr. By comparison, Kantor et al. (1987) observed a similar fall in TC and LDL-C, and an increment in HDL-C concentration in untrained normocholesterolemic men. Therefore, we may conclude that individuals with lower initial HDL-C concentration or less physically active will have a better response after a prolonged exercise session on lipid profiles.

Other studies demonstrated a confounded relationship between the acute response of lipid profiles after prolonged exercise and initial HDL-C concentration. Zmuda et al. (1998) demonstrated that individuals with normal, initial HDL-C (> 44 mg/dl) concentration had a better response after exercise. In the normal, HDL-C group, TG, LDL-C, and Apo B concentration were decreased; increased HDL-C was attributable to a 3.8 mg/dl increase in HDL_2-C. On the contrary, in individuals with initial HDL-C (< 40 mg/dl) lipid profiles did not change significantly. Furthermore, Kantor et al. (1984) and Goodyear et al. (1990) indicated that the initial concentration of HDL-C may not limit the acute exercise response. Each participant's initial HDL-C was > 65 mg/dl in the study, and one day after exercise training HDL-C increased by 13%.

In summary exercise volume is more important than intensity for improving blood lipid profiles. However, whether the initial HDL-C concentration can affect the response after prolonged exercise and the threshold of energy expenditure to alter lipid profiles remains unclear.

Responses of Plasma Lipid Profiles after Prolonged Exercise

Most articles indicate that after prolonged exercise (> 1 hr), the acute changes of lipid profiles would be observed (Thompson et al., 2001). The absence or inconsistency of significant acute exercise effects in studies with untrained subjects does not mean that changes would not be detectable with sufficient sample sizes (Thompson et al., 2001). The changes appear to increase while energy expenditure increase and do not require a threshold of work intensity (Cullinane, Siconolfi, Saritelli, & Thompson, 1982). However, untrained individuals may not be capable of expending sufficient calories to induce detectable changes in small studies. The most reproducible results have been obtained in fit subjects performing prolonged endurance events (Thompson et al., 2001).

Triglyceride

Triglyceride (TG) stored within skeletal muscle cells are considered to be a potentially large energy source. It has been estimated that during exercise, intramuscular TG could provide as much as 20-25% of energy for muscles to do work (Klein, Coyle, & Wolfe, 1994; Romijn, coyle, Sidossis, Zhang, & Wolfe, 1995). Enhanced epinephrine and glucagon during exercise activate adenylate cyclase, resulting in an increase in cAMP (Zhang, Thomas, & Ball, 1998). Increased cAMP phosphorylates activates hormone-sensitive LPL. The LPL would hydrolyze intracellular TG in skeletal muscle and myocardium, as well as adipose tissue during exercise to provide free fatty acids (FFA) as an energy source (Reitman, Baldwin, & Holloszy, 1973). After exercise, the endogenous TG that was oxidized needed to be replenished from exogenous TG (Annuzzi, Jansson, Kaijser, Holmquist, & Carlson,

1987). This may cause rapid uptake of FFA from the circulation, thus, increasing the clearance rate of TG from circulation. Therefore, the increased LPL activity in the muscle may play the most important role in the attenuated TG concentration (Lithell, Hellsing, Lundqvist, & Malberg, 1979); whereas LPL activity will reach its peak 18 hr post exercise (Kantor, Cullinane, Herbert, & Thompson, 1984). However, Weise et al. (2005) indicated that LPL activity may actually decrease after exercise in postmenopausal women who have high total cholesterol (≥ 200mg/dl). A decrease in LPLA was observed along with a decrease in blood TG concentration. Perreault et al. (2004) also indicate that LPL activity after exercise is gender specific. This suggests that the regulation of TG concentration might not be modulated by LPL activity alone.

High-Density Lipoprotein-Cholesterol

Like the response of TG, significant changes on HDL-C have been reported after exercise training in most articles. Tran et al. (1983) reported that individuals having the lowest initial HDL-C concentrations would have the greatest increases in HDL-C after exercise training. However, more recent findings have overturned this notion. For example, Raz et al. (1988) indicated that aerobic exercise was ineffective in increasing HDL-C concentration in young men with low initial HDL-C concentration. Similar results have been observed by Williams and co-workers (1994), where it was noted that exercise training increased HDL-C to a greater extent in men with normal baseline HDL-C than in men with low initial HDL-C concentration. Therefore, before undergoing an exercise program, individuals with normal or higher initial HDL-C concentrations might have better exercise-induced responses on HDL-C concentration.

To increase the HDL-C concentration by exercise, many enzymes should be considered. Increased LPL activity hydrolyzes triglycerides from LDL with transfer of the excess surface cholesterol to the HDL particles. This process helps the formation of HDL-C, therefore, increasing the plasma HDL-C concentration (Thompson et al., 2001).

Cholesterol ester transfer protein transfers cholesterol from HDL to other lipoproteins. The reduction of CETP could increase the HDL_2-C concentration (Thompson et al., 2001). Takanmi et al. (1996) observed lower CETP concentrations and elevated HDL_2-C concentrations in male triathletes (35.7 ± 8.3 years) who participated in the '95 Ironman Japan in Lake Biwa (3.8 km swim, 180.2 km bike, 42.2 km run, average duration time: 10 hr and 24 min) immediately and 1 day after a triathlon competition. Therefore, exercise may change CETP activity by changing the lipid composition of the various lipoprotein fractions.

Acute reductions in HTGLA might be observed after prolonged exercise (Gordon et al., 1994; Grandjean, Crouse, & Rohack, 2000). The reduction in HTGLA might diminish the conversion of HDL_2 to HDL_3 resulting in higher HDL_2-C or a greater HDL_2-to-HDL_3-C ratio. However, more frequently this enzyme activity is unaltered (Grandjean et al., 2000).

Lecithin: cholesterol transfer protein (LCAT) is another enzyme which could influence the metabolism of HDL-C. Lecithin: cholesterol transfer protein esterifies free cholesterol into cholesteryl ester that is moved into HDL_3 core to form HDL_2 (Durstine et al., 2002). Some studies indicate that the concentration of LCAT does not change after a moderate exercise training (Berger & Grill, 1987; Grandjean et al.,

2000). Conversely, Frey et al. (1991) indicated that there is an increase in LCAT activity in trained and untrained subjects immediately after prolonged exercise. One possible explanation for the disparate results might be the changes in the elevation of free cholesterol (Dufaux, Order, Muller, & Hollmann, 1986), where the availability of free cholesterol in the HDL fraction can have a great influence on LCAT activity.

In summary, HDL-C concentration is influenced by many enzymes such as LPL, HL, CETP, and LCAT. Fortunately, these enzymes are modifiable. The crucial importance of exercise is that it can modify lipid profiles by altering the concentrations of these enzymes.

Total Cholesterol (TC) and Low-Density Lipoprotein Cholesterol (LDL-C)

Results from most studies indicate that physical activity reduces the risk for the development of CVD when compared with inactive counterparts (Durstine & Thompson, 2001). Nonetheless, there is limited evidence to suggest that those who are physically active have lower concentrations of TC and LDL-C than those who are less active (Durstein et al., 2001). When changes have been reported, participants expended more than 1200 kcal/week (Altekruse & Wilmore, 1973; Durstein et al., 2001; Ready et al., 1995). Aerobic exercise training programs requiring this level of caloric expenditure are most effective at lowering TC and LDL-C in untrained individuals; however, trained individuals do not seem to respond, even with extreme training volume (Barr, Costill, & Fink, 1991).

Some investigators have suggested that exercise-induced reductions in TC and LDL-C are attributed to weight loss or body fat reductions (Superko, 1991). However, several exercise training studies where TC and LDL-C were significantly reduced

were not attributed to weight or body fat reductions (Hill, et al., 1989; Lopez, Vial, Balart, & Arroyave, 1974). Other studies also indicate that TC and LDL-C are often unchanged after exercise-induced weight loss and body fat reduction (Crouse et al., 1996).

The effect of exercise on TC is the summation of changes in the various lipoprotein subfractions; therefore, changes in TC alone have little physiological significance (Thompson et al., 2001). In contrast, even though the total LDL particles do not change by exercise, changes in LDL subfractions have been observed after exercise training (Halle et al., 1996). Two distinct LDL lipoprotein phenotypes have been identified: one characterized by the predominance of large, buoyant particles and the other characterized by the excess of small, dense particles (Austin et al., 1988). An excess of small, dense LDL particles is often accompanied by increased TG concentrations and reduced HDL-C, particularly HDL_2-C, and small, dense LDL particles which have an approximate 50% reduced binding affinity to the LDL receptors (Chen et al., 1994); therefore, those LDL subrfactions have been shown to be associated with premature coronary artery disease. Halle and co-workers (1996) indicated that trained and untrained hypercholesterolemia individuals have the same amount of LDL particles, yet the LDL subfraction profile differed significantly. Trained individuals had significantly less small, dense particles and had higher concentrations of large LDL subfraction particles than untrained individuals.

Although the data are partly inconsistent, the exercise-induced changes in concentration and composition of LDL subfraction particles are thought to be primarily determined by several lipase activities. Increased LPLA along with

decreased hepatic lipase and CETP after exercise have been shown to be associated with the increment of large, buoyant particles and reduced concentrations of small, dense LDL subfraction particles. (Watson et al., 1994).

Effects of Alcohol Consumption on Lipoprotein Metabolism

Many studies indicate that light to moderate alcohol consumption could lower the risk of developing CVD (Foppa, Fuchs, & Duncan, 2001). The definition of light to moderate alcohol consumption is 1-3 drinks a day or 10-45 g of alcohol a day (Gigleux et al., 2006). Moderate alcohol consumption has been associated with a 30-40% reduction of CVD incidence (Thun, 1997). Studies also indicate that the benefical effect of alcohol consumption is attributed to increased HDL-C concentration (Rimm, Williams, Fosher, Criqui, & Stampfer, 1999). An increase in HDL-C synthesis, a reduction in the degradation of HDL-C, and a higher LDL-C metabolism rate have been observed with regular alcohol consumption (Foppa et al., 2001). Elizabeth et al. (2000) indicated that participants who consume an ethanol diet (0.45 ± 0.19 g/kg/d of alcohol) have 18% a higher HDL-C concentration than those consuming a control diet. Elizabeth et al. also indicated that with an alcohol diet, HL concentration was 8% lower, meanwhile, LPL concentrations were 23% higher when compare to the control diet. These alterations might increase the synthesis rate and decrease the catabolism rate of HDL-C. However, Bantle et al. (2008) indicated that individuals with type 2 diabetes might not respond to alcohol. In this study, participants consumed 24g alcohol for 2 days for acute responses test and consumed 18g alcohol for 30 days for chronic responses test. Both tests showed no changes on TC, TG, HDL-C, and LDL-C.

Diabetes, Lipoprotein Profiles, and Cardiovascular Disease

Individuals with diabetes have 2-4 times higher incidence of CVD than the general population (Laakso & Lehto, 1998). Diabetic patients also have as high a risk of myocardial infarction as non-diabetic patients with previous myocardial infarction, and have higher case fatality when having acute myocardial infarction (Miettinen et al., 1998). Insulin resistance and abdominal obesity in diabetic patients would lead to increased flux of free fatty acids to the liver and result in increased formation of VLDL-C and LDL-C (Gadi & Samaba, 2007). Increased CEPT and hepatic lipase concentrations in individuals with diabetes result from insulin resistance would lead to decreased HDL-C concentration (Gadi & Samaba). Therefore, diabetic patients often possess dyslipidemia (elevated VLDL-C, LDL-C, and TG and low HDL-C concentration) (Assmann & Schulte, 1994; Betteridge, 2004). A typical diabetic patient's lipid concentrations are as follow: TC, 234 mg/dl; TG, 249 mg/dl; LDL-C, 129 mg/dl; HDL-C, 42 mg/dl (Spratt, 2009).

Abdominal Obesity

The lipolysis rate is greater in abdominal than in subcutaneous adipocytes, therefore, central deposition of fat is more strongly related to insulin resistance than peripheral fat depots (Kahn & Flier, 2000). When the abdominal depots are expanded, as in obesity, the concentration of circulating free fatty acids (FFA) becomes elevated. Elevated FFA could be taken up by non-adipocytes. In addition, abdominal obesity has been shown to lower the concentration of acylation stimulating protein (ASP), responsible for TG synthesis within the adipocyte, thereby exaggerating the efflux of FFA from adipocytes (Sniderman, Cianflone,

Arner, Summers, & Frayn, 1998). The increased efflux of FFA to the liver would lead to an increase in the secretion of VLDL (Despres, 2006).

In humans, the TG content of muscle can inversely influence insulin sensitivity. The increased flux of FFA compete with glucose for entry and oxidation by muscle (Randle, Garland, Hale, & Newsholme, 1963) the decreased insulin sensitivity is a consequence of increased TG content of skeletal muscle (Borkman et al., 1993). Insulin stimulates TG synthesis and inhibits lipolysis, thus the decrease of insulin sensitivity will result in decreased fatty acid uptake as well as increased fatty acid release from adipocytes (Sniderman et al., 1998).

When the excess of FFA is trapped within pancreatic islets, ceramide might reach a cytotoxic level. When the ceramide reaches a cytotoxic level, it might lead to impaired β cell function. Furthermore, if all β cells are dysfunctional and the apoptosis rate of β cells exceeds the replacement rate, diabetes will ensue (Unger & Orci, 2000).

VLDL & LDL in Diabetic Patient

Insulin resistance can alter the metabolism of lipoproteins. These alterations include increased VLDL secretion and impaired clearance of VLDL (Krauss, 2004). The retarded clearance of VLDL from plasma results in increased production of IDL particles, and consequently increasing the concentration of small, dense LDL particles (Krauss, 1998). The predominant small, dense LDL particles are more susceptible to be oxidized and tend to be transported into the subendothelial space, leading to atherosclerosis. People with diabetic also have a higher rate of glycation of Apo B, as a result, the affinity of LDL to its receptor decreases (Lyons, 1992). The decreased

rate of LDL clearance from plasma increases the uptake by macrophages resulting in the formation of foam cells. Glycated LDL particles are more susceptible to be oxidation which accelerates the development of atherosclerotic plaque (Lyons).

HDL in People with Diabetes

Insulin resistance also plays a pivotal role in the reduction of HDL particles. Insulin resistance increases the concentration of CEPT and HL activity (Krauss, 2004). Higher CEPT concentrations increase the exchange rate of cholesterol in HDL for triglyceride in chylomicron and VLDL remnants (Krauss). Higher HL activity hydrolyzes the TG-rich HDL particles as a result increasing the catabolism rate of HDL particles (Hopkins & Barter, 1986). Typically, the redistribution of HDL particles in type 2 diabetes patient is manifest in the reduction of HDL_2 particles and the increase in HDL_3 particles (Krauss).

Effects of Exercise on Lipid Profiles in Diabetic Patient

Exercise has been identified as a major therapeutic modality to prevent and delay the development of diabetes and increase insulin sensitivity, thereby improving the lipid profile (Gordon et al., 2008). Diabetic patient also shows a dose-response relationship between amount of physical activity and risk factors for CVD (Loreto et al., 2005). Loreto and co-works (2005) indicated that after 3 months of exercise intervention at moderate intensity (40-60% heart rate reserve), a significant reduction of TC, TG, LDL-C and an increment of HDL-C have been observed. Loreto et al. divided the participants into six groups (with different calorie expenditures per week) indicated when participants expended 1680 kcal/week showed no significant change in any of the selected variables; when participants expended more than 2520

kcal/week, significant decrease in TC, TG, LDL-C concentrations and increase in HDL-C concentration were observed.

Alam et al. (2004) demonstrated that after 6 months of supervised exercise (20-40 min at 60-85% of VO_2max four times per week in any kind of aerobic activities), people with diabetes had a decrease in TG concentration, VLDL Apo B secretion rate, increase in HDL-C concentration and improved insulin sensitivity. There is considerable evidence that suggests insulin regulates the secretion of VLDL Apo B. Watts et al. (1996) indicated that an acute infusion of insulin reduces the secretion of VLDL Apo B in normal participants; however, the secretion of VLDL Apo B is increased in people with diatebes. This result suggests that there may be a loss of sensitivity to the insulin mediated suppression of VLDL Apo B; therefore, these changes on lipid profiles might due to the improved insulin sensitivity after exercise.

Another benefit of exercise in diabetic patients is increasing the concentration of pre ß-HDL particles which is a metabolically active particle in the initial process of removal of cholesterol from cells (Fielding & Fielding, 2001). Sviridov et al. (2003) indicated that after 25 min of exercise at 60% VO_2peak, the formation of pre ß-HDL particles increased by 6.6 fold. There was no difference between non-diabetic and diabetic patients. However, whether this increment is through inefficient conversion of pre ß-HDL particles to mature HDL remains unclear.

CHAPTER III

METHODS

Participants

Nonsmoking males and females, age 45 to 80 years were recruited to participate in this study. All the participants were recruited from the Lifestyle Education Access for Diabetes: a University Program (LEAD-UP). Participants were considered prediabetic if their fasting blood glucose level was 100 to 125 mg/dl, which indicates a high risk of developing diabetes. If a participant's blood glucose was 126 mg/dl or higher, the participant was classified as having diabetes. The information regarding blood glucose level will be obtained from a questionnaire.

Procedures

General Protocol

Fasting blood samples were collected to determine blood lipid and lipoprotein-cholesterol concentrations. Physical activity patterns were assessed to determine the relationship to blood lipid and lipoprotein-cholesterol concentrations by asking each participant to complete one questionnaire regarding medication use, gender, menopausal status, cigarette smoking and the frequency, duration, and intensity of exercise. The questionnaire was modified from Caspersen's YALE physical activity survey (1997). Resistance (sets x reps x weight lifted per session) and aerobic (calorie expenditures) exercise volume were the amount a participant had completed 4 weeks prior to the blood draw.

The total amount of resistance exercise a participant completed for that specific 4 weeks were used to calculate how many pounds the participant had lifted per session. These data were collected by a survey and the FitLinxx system used by LEAD-UP. FitLinxx system uses the Compendium of Physical Activities to calculate calorie expenditures (Ainsworth et al., 2002). Therefore, the calorie expenditures a participant had expended through aerobic and resistance exercise were calculated. The total calorie expenditures through exercise was the combination of the calorie expenditures from aerobic and resistance exercise. Most of the MET value of each activity in the Compendium of Physical Activities guideline was obtained from the 7-Day Recall Physical Activity Questionnaire, the American Health Foundation's Physical Activity List and actual measurement by indirect calorimetry (Montoye et al. 1996).

Anthropometric Measurements

Body mass and height were measured prior to the blood draw. Participants were required to wear light clothes and no shoes while using the Tanita BWB-800 Digital Scale (Tanita Corportation of America, Inc., Arlngton Heights, IL) to obtain body mass. Body mass was measured to the nearest 0.1 kg. Participants were required to look straight forward and barefooted while measuring height. Height was obtained using a portable stadiometer and measured to the nearest 0.1 cm. Body mass index (BMI) will be calculated as the weight in kilograms divided by the square of the height in meters (weight in kilograms/ (height in meters)^2). Dual-energy x-ray absorptiometry (GE Lunar, Lunar Prodigy Advnace) was used to determine body composition and fat distribution. Participants were exposed to a small amount of

radiation during body composition assessment with the DXA scan. The radiation exposure for each participant was approximately the same amount received during a 2 hour airplane flight and less than the normal background radiation an individual is exposed to in one day. Systolic and diastolic blood pressures were measured by using aneroid sphygmomanometer (Aneroid Sphygmomanometer model 108M, Omron Healthcare, Inc.)

Diet

This was a cross-sectional study, and the purpose was to simply observe if the participants' daily activities effect their blood lipids. Therefore, all participants were asked to maintain their dietary habits. Participants were asked to record all dietary consumption for 3 days prior to the blood collection. This record included all food, beverages, and dietary supplements that were consumed. Dietary intake data were analyzed using Nutrition Data System for Research (NDSR) software version 2009 developed by the Nutrition Coordinating Center (NCC), University of Minnesota, Minneapolis, MN. for total caloric consumption and the percent of total calories derived from fat, saturated fat, protein and carbohydrate.

Blood Sampling and Biochemical Analyses

Blood samples were obtained once. Each participant reported to the laboratory after a 12 hr fast in which water was allowed ad libitum. Two 9 ml blood samples were obtained from the antecubital vein (Vacutainer® SST ® .Gel & Clot Activator). The samples were used to obtain serum by centrifugation at 3000 rpm for 10 min. The serum was frozen at −70 ^{0}C so lipoprotein cholesterol and triglyceride concentrations could be determined at a later date. All the samples were analyzed in duplicate. The

concentrations of total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) were measured from serum. Total cholesterol was analyzed by standard enzymatic reagent (KIT#TR13421/2350-250; Thermo Electron, Melbourne, Australia). The analysis of HDL-C concentration was based on isoelectric-polyanionic precipitation of VLDL and LDL (KIT#1335-250; Thermo Electron, Melbourne, Australia). Triglyceride concentrations were analyzed enzymatically (KIT#TR22421/2780-250; Thermo Electron, Melbourne, Australia). The Friedwald equation was used to calculate the concentrations of LDL-C, where LDL-C (mg/dl) = TC – HDL-C – (TG/ 5) (Friedewald, Levy, & Fredrickson, 1972). Coefficient of variation was 5%.

Statistics

A Pearson Correlation was used to calculate the relationships between exercise volume and each of the following blood lipids, TC, TG, LDL-C, and HDL-C concentrations. The independent variable is exercise volume. Significance level was set at p less than *0.05*.

CHAPTER IV

RESULTS

The purpose of this study was to determine the relationship between blood lipid profiles and the amount of exercise normally performed in individuals with diabetes or pre-diabetes. None of the participants consumed alcohol 24 hr prior to the blood draw; therefore, instead of using Partial Correlation technique, a Pearson Correlation was used to determine the relationship between each dependent variable (TC, TG, LDL-C, and HDL-C) and the exercise volume.

Participant Descriptions

Thirty two participants participated in this study (n=32, male=10, female=22). Two participants (both female) did not return the questionnaire for statistical analysis, therefore, these participants were not included in the final analysis. Mean ± standard deviation (SD) for age, weight, height, percent of body fat (fat%) and BMI can be seen in table 1. There were 24 participants did the DXA scan. Within these 30 participants, one had type 1 diabetes, 12 had type 2 diabetes and the rest of the participants were at borderline diabetes. Most participants took more than one medication; the complete medication list can be found in Appendix C.

Table 1

Baseline Characteristics of Participants (n=30)	Mean ± SD
Age (years)	65.1 ± 8.3
Weight (kg)	80.3 ± 4.5
Height (cm)	168 ± 0.2
FAT%	38.7 ± 1.6
BMI (kg/m2)	27.5 ± 4.2

Diet History

A 3-day food record was acquired from each participant. Based on the participants' comments, the 3-day food record could truly reflect the dietary habit of each participant. The average calorie intake, protein, dietary fat, carbohydrate, and cholesterol are showed in Table 2. the complete medication list can be found in Appendix E.

Table 2

Mean Values of Selected Dietary Variables

	Mean ± SD
Calories (kcal)	2619.3 ± 656.2
Protein (g)	89.1 ± 21.7
PUFA (g)	29.1 ± 15.3
MUFA (g)	40.5 ± 30.3
SFA (g)	36.4 ± 10.1
Carbohydrates (g)	236.7 ± 78.4
Cholesterol (mg)	260.7 ± 191.3

PUF, polyunsaturated fat; MUFA, monounsaturated fat; SFA, saturated fat

Exercise History

The information regarding the participant's exercise frequency, intensity, and duration was obtained from the questionnaire and FitLinxx system. Resistance and aerobic exercise volume was the amount a participant had completed four weeks prior to the blood draw. These data are presented in table 3. According to the Compendium of Physical Activities guideline the MET value of light to moderate weight lifting was

3. The mean resistance exercise duration was 25.3 min and the mean body weight was 80 kg, thus, the average total calorie expenditures through resistance was 106 kcal ([(3 MET x 3ml/kg/min x 25.3 min x 80 kg)/1000ml/L] x 5kcal/L). The same way was used to calculate the calorie expenditures through aerobic exercise. According to the Compendium of Physical Activities guideline walking at an intensity of 2.5 mph was equal to 3 MET, thus, the calorie expenditures through aerobic exercise was 99.7 kcal ([(3 MET x 3ml/kg/min x 27.7 min x 80 kg)/1000ml/L] x 5kcal/L). The total calorie expenditures of aerobic exercise per week were 209.4 and for resistance exercise were 203.3 (exercise frequency x kcal/d). The total calorie expenditures through were 412.7 (the combination of aerobic and resistance exercise).

Table 3

Exercise Mod, Frequency, Volume, Duration

Mode	Frequency (d/wk)	Intensity	Duration (min)	Calories (kcal/d)	Kg
Aerobic	2.1	2.3±0.9 mph	27.7±14.4	99.7 ±35	
Resistance		25.3±11.3	107±57.2	2902.8 ± 2475.5	

LM, low or moderate; HLM, high and low or moderate

The Concentrations of TC, TG, LDL-C, and HDL-C

The participants' mean concentrations ± SD for TC, TG, LDL-C and HDL-Care found in table 4. According to the ATPIII Guidelines (NCEP, 2001) the optimal range for TC, TG, LDL-C, HDL-C concentrations, the majority of the participants' lipid concentrations were within normal ranges.

Table 4

Lipid Concentrations

Variable	Range	Mean ± SD
TC (mg/dl)	137.8 - 275.3	188.4 ± 34.5
TG (mg/dl)	47.9 - 207.6	137.1 ± 48.6
LDL-C (mg/d	40.8 - 176.4	104 ± 33.3
HDL-C (mg/dl)	35 - 76.4	56.9 ± 8.2

TC, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol

Relationship between Lipid Concentrations and Exercise Volume

A graphic depiction of the relationship between the selected lipid concentrations and exercise volume can be seen in Figures 1 through 4. A complete report of selected lipid concentrations for each participant can be found in Appendix D.

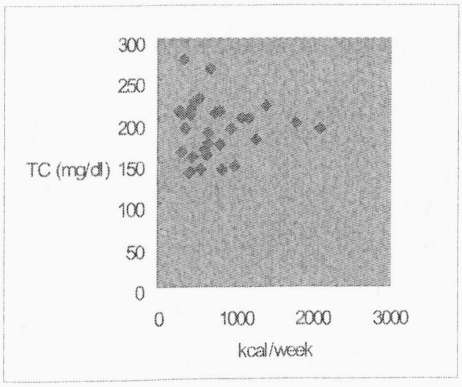

Figure 1. The relationship between total calorie expenditures and TC concentration

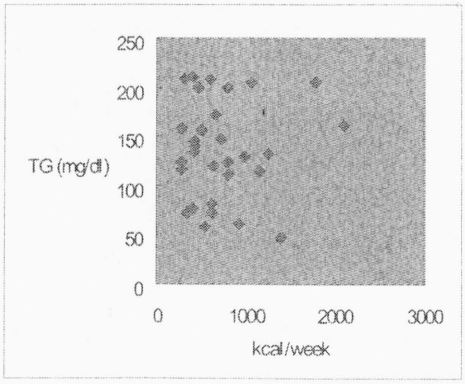

Figure 2. The relationship between total calorie expenditures and TG concentration

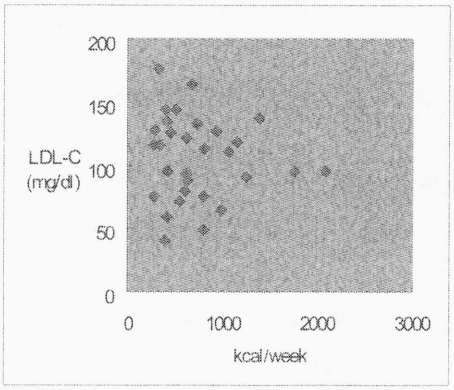

Figure 3. The relationship between total calorie expenditures and LDL-C concentration

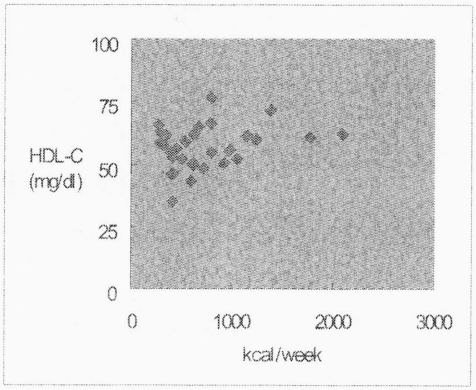

Figure 4. The relationship between total calorie expenditures and HDL-C concentration

It was hypothesized that there would be a negative relationship between TC, TG, LDL-C , and a positive relationship between HDL-C concentrations and the amount of exercise performed in individuals with diabetes or pre-diabetes. However, figures 1 through 8 as can be seen there was no significant relationship between exercise volume and the concentrations of TC, TG, LDL-C, and HDL-C. Therefore, exercise was not related to lipid profiles.

CHAPTER V

DISCUSSION AND CONCLUSIONS

Discussion

Exercise has been identified as a major therapeutic modality to prevent and delay the development of diabetes and increase insulin sensitivity, thereby improving the lipid profile (Gordon et al., 2008). Individuals with diabetes also show a dose-response relationship between amount of physical activity and risk factors for CVD (Loreto et al., 2005). Sviridov et al. (2003) also indicated that there were no differences between nondiabetic and diabetic patients. However, in the present study no significant relationship between exercise amount and lipid profiles was found.

In studies where significant reductions were seen in TC and LDL-C concentrations, participants were often required to expend more than 1200 kcal/week (Altekruse & Wilmore, 1973; Durstine et al., 2001; Ready et al., 1995). In the present study, the total caloric expenditures through aerobic and resistance exercises were 412.7 which might be too low to result in any change in TC and LDL-C concentrations. Similarly, to decrease TG concentration and increase HDL-C concentration a caloric expenditure of 1200 to 2200 kcal/week is required (Durstine et al., 2001). Thus, due to the small amount of calories expended by the participants through aerobic exercise in the present study, no relationships between exercise amount and TC, TG, LDL-C, and HDL-C concentrations were observed.

The lack of any relationship between exercise amount and TC, TG, LDL-C, and HDL-C concentrations may be due to the timing of the blood draw.

The majority of the articles suggested decreased TG and increased HDL-C concentrations after exercise are expected due to increased LPL activity (Thompson et al., 2001; Zhang, Thomas, & Ball, 1998). Kantor et al. (1984) indicated LPL activity would reach its peak 18 hr post exercise. Most articles reported significant decreases in TC, TG, and LDL-C concentrations and increases in HDL-C concentrations within 24 hr after the most recent exercise bout (Leon et al., 2000; Slentz et al., 2007; Wallace et al., 1991). According to the previous studies, it was concluded that exercise could have acute effects on lipid profiles. In the present study participants randomly chose a day to do the blood draw after a 12 hr fast. Hence, the timing of the blood draw for each participant may have been different, with some of the participants having the blood draw immediately after the most recent exercise bout and some >48 hr after the most recent exercise bout. It is difficult to clarify whether the high HDL-C concentration and low TC, TG, and LDL-C concentrations are due to the acute effects after exercise or long term exercise effects.

Previous studies suggested exercise volume (amount of calories expended) was responsible for promoting changes on blood lipid profiles rather than the intensity of exercise (Crouse et al., 1995; Kodama et al., 2007). However, the mode of exercise performed and exercise intensity might have some influence on lipid profiles. It is common for aerobic exercise training to increase HDL-C concentration and decrease TG concentration (Dustine et al., 2001). Exercise performed at range from 45 to 90% of VO_2max or 40 to 85% of heart rate reserve (HRR) may elicit significant changes in HDL-C and TG concentrations (Dalleck et al., 2008; Leon et al., 2000; Slentz et al., 2007). Nevertheless, the aerobic exercise intensity the participants performed in the

present study may be too low to have significant impacts on lipid profiles. Based on the information acquired from the questionnaire and FitLinxx system, the majority of participants in this study walked at speeds of 2.3 mph as their mode of aerobic training. Consequently, it might be difficult to have impacts on lipid profiles.

Most research is in agreement with the present study in that after resistance exercise the lipid profile did not change significantly (Kokkinos et al., 1988; Lemura et al., 2000). However, other data have indicated that resistance exercise could be another intervention to alter lipid profiles (Wallace et al., 1991). Wallace et al. (1991) showed an increase on HDL-C concentration and decreases in TC and TG after resistance activities when intensity was set at 70 to 80% of 1 RM for 8-12 repetitions and 49 sets. In the present study all participants performed resistance exercise with intensity lower than 50% of 1 RM for 3 sets. It was concluded that resistance exercise would not be an optimal strategy to induce any change in TC, TG, LDL-C, and HDL-C concentrations.

The differences at baseline characteristics between groups might influence the responses after exercise intervention. The baseline cholesterol level may influence the responses of lipid profiles after exercise training which could be an important factor to explain why in the present study no significant relationship between lipid profiles and exercise volume was observed. Some studies indicated TC and LDL-C concentrations in hypercholesterolemic (TC >200 mg/dl) men were significantly decreased after aerobic exercise training when compared with baseline level (Crouse et al., 1995; Grandjean et al., 2000). The mean TC and LDL-C concentrations in the present study were 188 mg/dl and 104 mg/dl respectively which were lower than the

TC and LDL-C concentrations in the previous studies. Thus, it might decrease the magnitude of the overall reduction in TC and LDL-C concentrations after exercise training.

The lack of a significant relationship between exercise amount and the HDL-C concentration in the present study disagreed with previous studies on initial HDL-C concentration and the responses after exercise training. Previous studies have suggested that individuals with normal to high initial HDL-C concentrations might have better responses in HDL-C concentration after exercise training (Raz et al., 1988; Williams et al., 1994). However, according to the ATPIII Guidelines (NCEP, 2001), the mean HDL-C concentration (56.9 mg/dl) in the present study was considered high. Tran et al. (1983) reported that individuals with low initial HDL-C concentrations would have the greatest increases in HDL-C concentration after exercise training. Therefore, with the results from present study it is difficult to figure out whether initial HDL-C concentration can influence the responses after exercise training.

Gender differences in lipids metabolism after exercise might be another issue which could obstruct any alteration on lipid profiles occurred. Perreault et al. (2004) pointed out LPL activity after exercise is gender specific. Weise et al. (2005) also indicated that LPL activity may actually decrease after exercise in postmenopausal women who have high total cholesterol ($\geq$ 200 mg/dl). In the present study, two thirds of the participants were female and only two of them were premenopausal. Hence, LPL activity after exercise in those female participants might not reach the point to lead to any changes on lipid profiles.

Other studies that have included both men and women also reported that changes in TC, TG, LDL-C, and HDL-C were in the direction of benefit, but, the changes were not significant (Kelley et al., 2007).

Furthermore, no significant relationship between exercise volume and the lipid concentrations may be explained by age. In similar studies, the participants' age range was 28-53 years (Dalleck et al., 2008; Petibois et al., 2004; Slentz et al. 2007). After exercise training (45-85% of VO_2max, calorie expenditures of 1000 kcal to 21400 kcal/ week) , significant decreases in TC, TG, LDL-C and increases in HDL-C concentrations were observed (Dalleck et al.; Petibois et al.; Slentz et al.). The participants' mean age in the present study was 65 years which was more than 12 years older than the participants in previous studies. In the study by Kelley et al. (2007), which was a cross-sectional study, the participants' age range was 45-75 years which was similar with the present study. Kelley et al. indicated that after 10-26 weeks of exercise training (65-73% VO_2max, 30-75 min per session, 3-7 d/week) no significant changes in any lipid variable were observed. Accordingly, it could be concluded that with similar exercise training regimen, older participants may have less benefit from exercise. Therefore, older age range in the present study could be another factor to impede any changes on lipid profiles.

In the present study, the majority of the participants took more than one medication. Some of the medications (Humalog, Metformin, Niacin, Lipitor, Simcor, Simvastain, Crestor, and Pravastatin) have the ability to decrease TC, TG, LDL-C and increase HDL-C concentrations. No attempt was made to alter the participants' medications during the investigation. Moreover, the results in the present study

showed the majority of the participants' lipid concentrations were within normal ranges which might due to the influences of the medications. Therefore, the effects of exercise training might be confounded by medications.

There are several limitations which might be able to explain the results observed in the present study, such as medications, exercise amount calculation, food intake, and small sample size. Medications can have a substantial influence on lipid concentrations; although it would be a better study design, it is too risky to ask participants to stop taking medications.

The small sample size and exclusive population reduce the applicability of the results in the present study to the general population. The small sample size might also impede the observation of any change on lipid profiles.

The information regarding exercise amount was based on the questionnaire and FitLinxx system. Unfortunately, not every weight machine and treadmill can automatically record how much weight have been lifted or calories been expended. Some participants walked on the track and did resistance exercise with free weights, therefore, those participants need to input information in FitLinxx system manually, which could have resulted in under or over reporting of the exercise amount completed. There were some limitations of using the Compendium of Physical Activities to calculate calorie expenditures. Most of the MET value of each activity was obtained through actual measurement by indirect calorimetry (Montoye et al.1996). However, for some activities the values were not obtained by actual measurement. Furthermore, individual variation in exercise patterns might influence the energy cost of activities. The MET value of each activity in the compendium was

merely averages and did not take into account the performance differences between individuals. For some individuals may rate his or her resistance exercise intensity as light while another might rate the same amount of weights as heavy. Thus, individual differences might reduce the preciseness of calculating the calorie expenditures.

A 3-day food record was required for each participant. However, it may not have accurately reflected participants' habitual dietary intakes. Furthermore, there was not a registered dietitian participated in this study, thus, the influences from diet could confound the effects after exercise training. A more controlled diet might be helpful to clarify the effects from exercise training; however, allowing the participants to consume their habitual diet is easier to conduct and apply to the general population.

Conclusion and Recommendations

In conclusion, the results of the present study showed no significant relationship between exercise amount and TC, TG, LDL-C, and HDL-C concentrations. Therefore, the exercise training routines (low calorie expenditures, low exercise intensity) for the participants in the present study might not suitable for having any effect on lipid profiles.

Recommendations for future studies may include:

1. The timing for blood draw should be carefully arranged. To reduce errors, every participant should have blood drawn at the same time period (such as immediate, 24 hr, or 48 hr after the most recent exercise session).
2. A registered dietitian should be used in future studies if the purpose of the studies is to clarify the effects from exercise not diet.
3. To more accurately record and calculate the exercise amount an individual has

completed, instead of asking the participants to input any information regarding exercise amount the researchers should record that information themselves.

4. Future studies should recruit those participants who do not take any medication to control serum lipids.
5. More studies are needed to determine the calorie expenditures threshold through exercise training to decrease TC, TG, LDL-C and increase HDL-C concentrations in individuals with diabetes or prediabetes.

REFERENCES

Adult Treatment Panel III (2001). Executive summary of the third report of the national cholesterol education program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. *The Journal of the American Medical Association. 285*, 2486-2497.

American Heart Association (2000). 2000 heart and stroke statistical update. Dallas: American Heart Association.

Ainsworth, B.E., Haskell, W.L., Whitt, M.C., Irwin, M.L., Swartz, A.M., Strath, S.J. et al. (2000). Compendium of physical activities: an update of activity codes and MET intensities. *Medicine and Science in Sports and Exercise. 32 (9 suppl)*, S498-504.

Alam, S., Stolinski, M., Pentecost, C., Boroujerdi, M.A., Jones, R.H. et al. (2004). The effect of a six-month exercise program on very low-density lipoprotein apolipoprotein B secretion in type 2 diabetes. *The Journal of clinical Endocrinology & Metabolism. 89*, 688-694.

Altekruse, E.B., & Wilmore, J.H. (1973). Changes in blood chemistries following a controlled exercise program. *Journal of Occupational Medicine. 15*, 110-113.

Angelopoulos, T.J., Sivo, S.A., Kyriazis, G.A., Caplan, J.D., Zoeller, R.F., Lowndes, J. et al. (2007). Do age and baseline LDL cholesterol levels determine the effect of regular exercise on plasma lipoprotein cholesterol and apolipoprotein B levels? *European Journal of Applied Physiology, 101*, 621-628.

Annuzzi, G., Jansson, E., Kaijser, L., Holmquist, L. & Carlson, L.A. (1987). Increased removal rate of exogenous triglycerides after prolonged exercise in man: time course and effect of exercise duration . *Metabolism, 36*, 438-443.

Assmann, G., Shulte, H. (1994). Identification of individuals at high risk for myocardial infarction. *Atherosclerosis, 110*, 11-21.

Austin, M.A., Breslow, J.L., Hennekens, C.H., Buring, J.E., Willett, W.C., & Krauss, R.M. (1988). Low-density lipoprotein subclass patterns and risk of myocardial infarction. *The Journal of the American Medical Association, 260*, 1917-1921.

Bantle, A.E., Thomas, W., & Bantle, J.P. (2008). Metabolic effects of alcohol in the form of wine in persons with type 2 diabetes mellitus. *Metabolism, 57*. 241-245.

Barr, S., Costill, D. & Fink, W. (1991). Effects of increased training volume on blood lipids and lipoproteins in male collegiate swimmers. *Medicine and Science in Sports and Exercise, 23*, 795-800.

Berger, G., & Grill, M. (1987). Acute effects of moderate exercise on plasma lipoprotein parameters. *International Journal of Sports Medicine, 8*, 336-341.

Betteridge, D.J., (2004). Treating dyslipidaemia in the patient with type 2 diabetes. *European Heart Journal Supplements, 6*, C28-C33

Boreham, C.A., Kennedy, R.A., Murphy, M.H., Tully, M., Wallace, W.F., & Young, I.(2005). Training effects of short bouts of stair climbing on cardiorespiratory fitness, blood lipids, and homocysteine in sedentary young women. *British Journal of Sports Medicine, 39*, 590-593.

Borkman, M., Storlien, L.H., Pan, D.A., Jenkins, A.B., Chisholm, D.J., & Campbell, L.V. (1993).The relation between insulin sensitivity and the fatty-acid composition of skeletal-muscle phospholipids. T*he New England Journal of Medicine, 328*, 238-244.

Brewer, H.B., Greg, R.E., Hoeg, J.M., & Fojo, S.S. (1988). Apolipoproteins and lipoproteins in human plasma: an overview. *Clinical Chemistry, 34*, B4-B8.

Brooks, G.A., Fahey, T.D., & Baldwin, K.M. (2005). Exercise physiology: human bioenergetics and its applications. NY: McGraw-Hill.

Brown, M.S., & Goldstein, J.L. (1986). A receptor-mediated pathway for cholesterol homeostasis. *Science, 232*, 34-37.

Bruce, C., Chouinard Jr, R.A., & Tall, A.R. (1998). Plasma lipid transfer proteins, high-density lipoproteins, and reverse cholesterol transport. *Annual Review of Nutrition, 18*, 297-330.

Bruzell, J.D., Howard, B.V., Davidson, M., Stein, J.H., Furberg, C.D., Witztum, J.L. et al. (2008). Lipoprotein management in patients with cardiometabolic risk. *Journal of the American College of cardiology, 51*. 1512-1524.

Caspersen C.J. (1997). YALE physical activity survey. *Medicine & Science in Sprots & Exercise, 29*. s130-s140.

Chen, G.C., Liu, W., Duchateau, P., Allaart, J., Hamilton, R.L., Mendel, C.M., et al. (1994). Conformational differences in human apolipoprotein B-100 among subspecies of low density lipoproteins (LDL). Association of altered proteolytic accessibility with decreased receptor binding of LDL subspecies from hypertriglyceridemic subjects. *The Journal of Biological Chemistry, 269*, 29121-29128.

Couillard, C., Despres, J.P., Lamarche, B., Bergeron, J., Gagnon, J., Leon, A.S. et al. (2001). Effects of endurance exercise training on plasma HDL cholesterol levels depend on levels of triglycerides. *Arteriosclerosis, Thrombosis, and Vascular Biology. 21*, 1226-1232.

Crouse, S.F., O'Brien, B.C., Grandjean, P.W., Lowe, R.C., Rohack, J.J., Green, J.S. et al. (1996). Training intensity, blood lipids and apolipoproteins in men with high cholesterol. *Journal of Applied Physiology, 82*, 270-277.

Crouse, S.F., O'Brien, B.C., Grandjean, P.W., Lowe, R.C., Rohack, J.J., & Green, J.S. (1997). Effects of training and a snigle session of exercise on lipids and apolipoproteins in hypercholesterolemic men. *Journal of Applied Physiology, 6*, 2019-2028.

Crouse, S.F., O'Brien, B.C., Rohack, J.J., Lowe, R.C., Green, J.S., Tolson, H. et al., (1995). Changes in serum lipids and apolipoproteins after exercise in men with high cholesterol: influence of intensity. *Journal of Applied Physiology, 79*, 279-286.

Cullinane, E., Siconolfi, S., Saritelli, A., & Thompson, P.D. (1982). Acute decrease in serum triglycerides with exercise: is there a threshold for an exercise effect? *Metabolism, 31*, 844-847.

Dalleck, L.C., Borresen, E.C., Wallenta, J.T., Zahler, K.L., & Boyd, E.K. (2008). A moderate-indensity exercise program fulfilling the American College of Sports Medicine net energy expenditure recommendation improves health outcomes in premenopausal women. *Journal of Strength and Conditioning Research, 22*, 256-262.

Dallmeijer, A.J., Hopman, M.T., & van der Woude, L.H. (1997). Lipid, lipoprotein, and apolipoprotein profiles in active and sedentary men with tetraplegia. *Archives of Physical Medicine and Rehabilitation, 78*, 1173-1176.

Davis, P.G., Bartoli, W.P., & Durstine, J.L. (1992). Effects of acute exercise intensity on plasma lipids and apolipoproteins in trained runners. *Journal of Applied Physiology.72*, 914-919.

Definition, diagnosis and classification of diabetes mellitus and its complications: report of a WHO consultation. Geneva, Switzerland: department of Noncommunicable disease Surveillance, World Health Organization, 1999.

Despres, J.P. (2006). Is visceral obesity the cause of the metabolic syndrome? *Annals of Medicine, 38*, 52-63.

Despres, J.P. (1993). Abdominal obesity as important component of insulin-resistance syndrome. *Nutrition, 9*, 452-459.

Despres, J.P. (1994). Dyslipidaemia and obesity. *Baillière's Clinical Endocrinology and Metabolism, 8*, 629-660

Di Loreto, C., Fanelli, C., Lucidi, P., Murdolo, G., De Cicco, A., Parlanti, N., et al. (2005). Make your diabetic patients walk: long-term impact of different amounts of physical activity on type 2 diabetes. *Diabetes Care, 28,* 1295-1302.

Dufaux, B., Order, U., Müller, R., & Hollmann W (1986). Delayed effects of prolonged exercise on serum lipoproteins. *Metabolism, 35,* 105-109.

Durstine, J.L. *Exercise and lipid disorders.* N Y: McGraw-Hill.

Durstine, J.L., Grandjean, P.W., Davis, P.G., Ferguson, M.A., Alderson, N.L., & Dubose, K.D. (2001). Blood lipid and lipoprotein adapations to exercise: a quantitative analysis. *Sports Medicine, 31,* 1033-1062.

Durstine, J.L., Grandjean, P.W., Cox, C.A., & Thompson, P.D. (2002). Lipids, lipoproteins, and exercise. *Journal of Caridopulmonary Rehabilitation, 22,* 385-398.

Durstine, J.L., & Thompson, P.D. (2001). Exercise in the treatment of lipid disorders. *Cardiology Clinics, 19,* 1-19.

Enger, S.C., Stromme, S.B., & Refsum, H.E. (1980). High density lipoprotein cholesterol, total cholesterol and triglycerides in serum after a single exposure to prolonged heavy exercise. *Scandinavian Journal of Clinical and Laboratory Investigation, 40,* 341-345.

Erhardt, L., Moller, R., & Puig, J.G. (2007). Comprehensive cardiovascular risk management-what does it mean in practice? *Vascular Health and Risk Management, 3,* 587-603.

Ferguson, M.A., Alderson, N.L., Trost, S.G., Essig, D.A., Burke, J.R., & Durstine J.L. (1998). Effects of four different single exercise sessions on lipids, lipoproteins, and lipoprotein lipase. *Journal of Applied Physiology, 85,* 1169-1174.

Fielding, C.J., & Fielding, P.E. (2001). Cellular cholesterol efflux. *Biochimica Et Biophysica Acta, 1553*, 175-189.

Frey, I., Baumstark, M.W., Berg, A., & Keul, J (1991).Influence of acute maximal exercise on lecithin:cholesterol acyltransferase activity in healthy adults of differing aerobic performance. *European Journal of Applied Physiology and Occupational Physiology, 62*, 31-35.

Foppa, M., Fuchs, F.D., & Duncan, B.B. (2001). Alcohol and atherosclerosis. *Arquivos Brasilerios de Cardiologia, 76.* 171-176.

Ford, E.S., Giles, W.H., & Dietz, W.H. (2002). Prevalence of the metabolic syndrome among US adults. *JAMA : The Journal of the American Medical Association. 287*, 356-359.

Gadi, R., & Samaba, F.F., (2007). Dyslipidemia in typ 2 diabetes mellitus. *Current Diabetes Reports, 7.* 228-234.

Gigleux, I., Gagnon, J., St-Pierre, A., Cantin, B., Dagenais, G.R., Meyer, F., et al. (2s06). Moderate alcohol consumption is more cardioprotective in men with the metabolic syndrome. *The Journal of Nutrition, 136,* 3027-3032.

Gill, J.M., & Hardman, A.E. (2000). Postprandial lipemia: effects of exercise and restriction of energy intake compared. *The American Journal of Clinical Nutrition, 71*,465-71.

Gordon L.A., Morrison, E.Y., McGrowder, D.A., Yong, R., Fraser, Y.T.P., Zamora, E.M., et al. (2008). Effect of exercise therapy on lipid profile and oxidative stress indicators in patients with type 2 diabetes. *BMC Complementary and Alternative Medicine, 8*, 21.

Gordon, P.M., Goss, F.L., Visich, P.S., Warty, V., Denys, B.J., Metz, K.F., & Robertson, R.J. (1994). The acute effects of exercise intensity on HDL-C metabolism. *Medicine and Science in Sports and Exercise, 26*, 671-677.

Goodyear, L.J., Van Houten, D.R., Fronsoe, M.S., Rochio, M.L., Dover, E.V., & Durstine, J.L. (1990). Immediate and delayed effects of marathon running on lipids and lipoproteins in women. *Medicine and Science in Sports and Exercise, 22*, 588-589.

Grandjean, P.W., Crouse, S.F., & Rohack, J.J. (2000). Influence of cholesterol status on blood lipid and lipoprotein enzyme responses to aerobic exercise. *Journal of Applied Physiology, 89*, 472-480.

Groot, P.C., Hjeltnes, N., Jeijboer, A.C., Stal, W., & Birkeland, K. (2003). Effect of training intensity on physical capacity, lipid profile and insulin sensitivity in early rehabilitation of spinal cord injured individuals. *The Official Journal of the International Medical Society of Paraplegia, 41*. 673-679.

Haffner, S., & Taegtmeyer, H. (2003). Epidemic obesity and the metabolic syndrome. *Circulation, 108*, 1541-1545.

Halle, M., Berg, A., Garwers, U., Baumstark, M.W., Knisel, W., Grathwohl, D. et al. (1999). Influence of 4 weeks intervention by exercise and diet on low-dentisy lipoprotein subfractions in obese men with type 2 diabetes. *Metabolism, 5*, 641-644.

Halle, M., Berg, A., König, D., Keul, J., & Baumstark, M,W. (1996). Differences in the concentration and composition of low-density lipoprotein subfraction particles between sedentary and trained hypercholesterolemic men. *Metabolism, 46*, 186-191.

Halverstadt, A., Phares, D.A., Ferrell, R.E., Wilund, K.R., Goldberg, A.P., & Hagberg, J.M. (2003). High-density lipoprotein-cholesterol, its subfractions, and responses to exercise training are dependent on endothelial lipase genotype. *Metabolism, 52*, 1505-1511.

Halverstadt, A., Phares, D.A., Wilund, K.R., Goldberg, A.P., & Hagerg, J.M. (2007). Endurance exercise training raises high-density lipoprotein cholesterol and lowers small low-density lipoprotein and very low-density lipoprotein independent of body fat phenotypes in older men and women. *Metabolism Clinical and Experimental, 56*, 444-450.

Helge, J.W., Damsgaard, R., Overgaard, K., Andersen, J.L., Donsmark, M., Dyrskog, S.E. et al. (2008). Low intensity training dissociates metabolic from aerobic fitness. *Scandianvian Journal of Medicine & Science in Sports, 18*, 86-94.

Hill, J.O., Thiel, J., Heller, P.A., Markon, C., Fletcher, G., & DiGirolamo, M. (1989) Differences in effects of aerobic exercise training on blood lipids in men and women. *The American Journal of Cardiology, 63*, 254-256.

Hopkins, G.J., & Barter, P.J. (1986). Role of triglcer9de-rich lipoproteins and hepatic lipase in determining the particle size and composition of high density lipoproteins. *Journal of Lipid Research, 27*, 1265-1277.

Kahn, B.B, & Flier, J.S., (2000). Obesity and insulin resistance. *The Journal of Clinical Investigation. 106*, 473-481.

Kantor, M.A., Cullinane, E.M., Herbert, P.N., & Thompson, P.D. (1984). Acute increase in lipoprotein lipase following prolonged exercise. *Metabolism, 33*, 454-457.

Kantor, M.A., Cullinane, E.M., Sady, S.P., Herbert, P.N., & Thompson, P.D. (1987). Exercise acutely increases high density lipoprotein-cholesterol and lipoprotein lipase activity in trained and untrained men. *Metabolism, 36*, 188-192.

Katsanons, C.S., Grandjean, P.W., & Moffatt, R.J. (2003). Effects of low and moderate exercise intensity on postprandial lipemia and postheparin plasma lipoprotein lipase activity in physically active men. *Journal of Applied Physiology, 96*, 181-188.

Katzel, L.I., Bleecker, E.R., Colman, E.G., Rogus, E.M., Sorkin, J.D., & Goldberg, A.P. (1995). Effects of weight loss vs aerobic exercise training on risk factors for coronary disease in healthy, obese, middle-aged and older men. A randomized controlled trial. *JAMA : The Journal of the American Medical Association, 274*, 1915-1921.

Kelley, G.A., & Kelley, K.S. (2007). Aerobic exercise and lipids and lipoproteins in children and adolescents: a meta-analysis of randomized controlled trials. *Atherosclerosis. 191*, 447-453.

Kiens, B., & Lithell, H. (1989). Lipoprotein metabolism influence by training-induced changes in human skeletal muscle. *The Journal of Clinical Investigation, 83*,558-564

Klein, S., Coyle, E.F., & Wolfe, R.R. (1994). Fat metabolism during low-intensity exercise in endurance-trained and untrained men. *The American Journal of Physiology, 267*, 934-940.

Kodama, S., Tanaka, S., Saito, K., Shu, M., Sone, Y., Onitake F. et al. (2007). Effect of aerobic exercise training on serum of high-density lipoprotein cholesterol. *Archives of Internal Medicine,167*, 999-1008.

Kokkinos, P.F., Hurley, B.F., Vaccaro, P., Patterson, J.C., Gardner, L.B., Ostrove, S.M., & Goldberg, A.P. (1988). Effects of low- and high –repetition resistive training on lipoprotein-lipid profiles. *Medicine and Science in Sports and Exercise, 20*, 50-54

Krauss, R.M. (1998). Atherogenicity of triglyceride-rich lipoproteins. *The American Journal of Cardiology, 81*, 13-17.

Krauss, R.M. (2004). Lipids and lipoproteins in patients with type 2 diabetes. *Diabetes Care, 27*, 1496-1504.

Krauss, W.E., Houmard, J.A., Duscha, B.D., Knetzger, K.J., Wharton, M.B., McCartney, J.S., (2002). Effects of the amount and intensity of exercise on plasma lipoproteins. *The New England Journal of Medicine, 347*,1522-1524.

Laakso, M., Lehto, S. (1998). Epidemiology of risk factors for cardiovascular disease in diabetes and impaired glucose tolerance. *Atherosclerosis, 137*, 65-73

Laaksonen, D.E., Atalay, M., Niskanen, L.K., Mustonen, J., Sen, C.K., Lakka, T.A. et al. (2000). Aerobic exercise and the lipid protile in type 1 diabetic men: a randomized controlled trail. *Medicine and Science in Sports and Exercise, 9*, 1541-1548.

Lemura, L.M., VonDuvillard, S.P., Andreacci, J., Klebez, J.M., Chelland, S.A., & Russo, J (2000). Lipid and lipoprotein profiles, cardiovascular fitness, body composition, and diet during and after resistance, aerobic and combination training in young women. *European Journal of Applied Physiology, 82*, 451-458.

Leon, A.S., Rice, T., Mandel, S., Despres, J.P., Bergeron, J. Gagnon, J. et al. (2000). Blood lipid response to 20 weeks of supervised exercise in a large biracial population: the heritage family study. *Metabolism, 49*, 513-520.

Lithell, H., Hellsing, K., Lundqvist, G., & Malberg, P. (1979). Lipoprotein –lipase activity of human skeletal-muscle and adipose tissue after intensive physical exercise. *Acta Physiologica Scandinavica, 105*, 312-315.

Lopez, A., Vial, R., Balart, L., & Arroyave, G. (1974). Effect of exercise and physical fitness on serum lipids and lipoproteins. *Atherosclerosis,* 20, 1-9.

Loreto, C.D., Ranchelli, A., Fanelli, C., Fatone, C., Lucidi, P., Taglioni, C., et al. (2005). Make your diabetic patients walk long-term impact of different amounts of physical activity on type 2 diabetes. *Diabetes Care, 28*, 1295-1302.

Lyons, T.J., (1992). Lipoprotein glycation and its metabolic consequences. *Diabetes, 41*, 67-73.

Magkos, F., Wright, D.C., Patteron, B.W., Mohammed, B.S., & Mittendorfer, B. (2005). Lipid metabolism response to a single, prolonged bout of endurance exercise in healthy young men. *American journal of physiology. Endocrinology and metabolism, 290*, 355-362.

Maiti, R., & Aqrqwql, N.K. (2007). Atherosclerosis in diabetes mellitus: role of inflammation. *Indian Journal of Medical Sciences, 61*, 292-306.

McManus, B. (2005). INTERHERAR: nine factors that could save your life. *Healthcare Quarterly, 8*, 28.

Miettinen, H., Lehto, S., Salomaa, V., Mähönen, M., Niemelä, M., Haffner, S.M. et al., (1998) .Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. *Diabetes Care. 21*, 69-75.

Nicklas, B.J., Katzel, L.L., Whitehead, J.B., & Goldberg, A.P. (1997). Increases in high-density lipoprotein cholesterol with endurance exercise training are blunted in obese compared with lean men. *Metabolism, 46*, 556-561.

O'Donovan, G., Owen, A., Kearney, E.M., Jones, D.W., Nevill, A.M., Woolf-May, K., et al., (2005). Cardiovascular disease risk factors in habitual exercisers, lean sedentary men and abdominally obese sedentary men. *International Journal of Obesity, 29*, 1063-1069.

O'Keefe, J.H., Cordain, L., Harris, W.H., Moe, R.M., & Vogel, R. (2004). Optimal low-density lipoprotein is 50 to 70 mg/dl: lower is better and physiologically normal. *Journal of the American College of Cardiology, 43*, 2124-2126.

Pascot, A., Lemieux, I., Prud'homme, D., Tremblay, A., Nadeau, A., Couillard, C. et al. (2007). Reduced HDL particle size as an additional feature of the atherogenic dyslipidemia of abdominal obesity. *Journal of Lipid Research, 43*, 2007-2014.

Pearson, T., Blair, S., Daniels, S., Eckel, R., Fair, J., Fortmann, S., et al. (2002). AHA guidelines for primary prevention of cardiovascular disease and stroke: 2002 update. *Circulation. 106*, 388-391.

Perreault, L. Lavely, J.M., Kittelson, J.M., & Horton, T.J. (2004). Gender differences in lipoprotein lipase activity after acute exercise. *Obesity Research, 12*, 241-249.

Petibois, C., Cassaigne, A., Gin, H., & Deleris, G. (2004). Lipid profile disorders induced by long-term cessation of physical activity in previously highly endurance-trained subjects. *The Journal of Clinical Endocrinology & Metabolism, 89*, 3377-3384.

Randle, P.J., Garland, P.B., jales, C.N., & Newsholeme, E.A., (1963). The glucose fatty-acid cycle: its role in insulin sensitivity and the metabolic disturbances of diabetes mellitus. *Lancet, 1963*, 785-789.

Raz, I., Rosenblit, H., & Kark, J.D. (1988). Effect of moderate exercise on serum lipids in young men with low high density lipoprotein cholesterol. *Arteriosclerosis, 8*, 245-251.

Ready, A.E., Drinkwater, D.T., Ducas, J., Fitzpatrick, D.W., Brereton, D.G., & Oades, S.C. (1995). Walking program reduces elevated cholesterol in women postmenopause. *The Canadian Journal of Cardiology, 11*, 905-912.

Reitman, j., Baldwin, K.M., & Holloszy, J.O. (1973). Intramuscular triglyceride utilization by red, white and intermediate skeletal muscle and heart during exhausting exercise. *Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N.Y.), 142*, 628-631.

Rimm, E.B, Williams, P., Fosher, K., Criqui, M., & Stampfer, M.J. (1999). Moderate alcohol intake and lower risk of coronary heart disease: meta-analysis of effects on lipids and haemostatic factors. *BJM, 319.* 1523-1528.

Romijn, J.A., Coyle, E.F., Sidossis, L.S., Zhang, X.J., & Wolfe, R.R. (1995). Relationship between fatty acid delivery and fatty acid oxidation during strenuous exercise. *Journal of Applied Physiology, 79*, 1939-1945.

Schaefer, E. (2002). Lipoproteins, nutrition, and heart disease. *American Journal of Clinical Nutrition, 75*, 191-212.

Schwartz, R.S., Cain, K.C., Shuman, W.P., Larson, V., Stratton, J.R., Beard, J.C. et al. (1992) Effect of intensive endurance training on lipoprotein profiles in young and older men. *Metabolism, 41*, 649-654.

Shepherd J. (1992). Lipoprotein metabolism: an overview. *Ann Acad Med, 21*, 106-113.

Slentz, C.A., Houmard, A.J., Johnson, J.L., Bateman, L.A., Tanner, C.J., McCartney, J.S. et al. (2007). Inactivity, exercise training and detraining, and plasma lipoproteins. *Journal of Applied Physiology, 103*, 432-442.

Smith, C., marks, A.D., & Lieberman, M. (1996). *Basic medical biochemistry a clinical approach,* MD: Lippincott Williams & Wilkins.

Sniderman, A.D., Cianflone, K., Arner, P., Summers, L.K.M., & Frayn, K.N., (1998). The, adipocyte, fatty acid trapping, and atherogenesis. *Arteriosclerosis, Thrombosis, and Vascular Biology, 18*, 147-151.

Sich, D., Saidi, Y., Giral, P., Largrost, L., Egloff, M., Auer, C., et al. (1998). Hyperalphalipoproteinemia: characterization of a cardioprotective profile association increased high-density lipoprotein 2 levels and decreased hepatic lipase activity. *Metabolism, 47,* 965-973.

Spratt, K.A. (2009). Managing diabetic dyslipidemia: aggressive approach. *Journal of American Osteopathic Association, 109*. s2-s7.

Superko, H.R. (1991). Exercise training, serum lipids, and lipoprotein particles: is there a change threshold? *Medicine and science in sports and exercise*, 23, 677-685.

Sviridov, D., Kingwell, B., Hoang, A., Dart, A., & Nestel, P. (2003). Single session exercise stimulates formation of preβ$_1$-HDL in leg muscle.

Takanami, Y. , iwane, H., Kawai, Y, Katsumura, T. & Shimomitsu, T. (1996). Influence of strenuous endurance exercise on cholesteryl transfer protein and HDL metabolism in serum. *Medicine and Science in Sports and Exercise, 28*, s29.

Taylor, D.A., & Zenovich, A.G. (2008). Cardiovascular cell therapy and endogenous repair. *Diabetes, Obesity & Metabolism. 10*, 5-15.

Tran, Z.V., Weltman, A., Glass, G.V., & Mood, D.P. (1983). The effects of exercise on blood lipids and lipoproteins: a meta-analysis of studies. *Medicine and Science in Sports and Exercise, 15*, 393-402.

Thompson, P.D., Crouse, S.F., Goodpaster, B., Kelley, D., Moyna, N., & Pescatello, L. (2001). The acute versus the chronic response to exercise. *Medicine & Science in Sports & Exercise, 33*, s438-s445.

Thompson, P.D., Cullinane, E.M., Henderson, O., & Herbert, P.N. (1980). Acute effects of prolonged exercise on serum lipids. *Metabolism, 29*, 62-665.

Thompson, P.D., Cullinane, E.M., Sady, S.P., Flynn, M.M., Chenevert, C.B., & Herbert, P.N (1991). High density lipoprotein metabolism in endurance athletes and sedentary men. *Circulation, 84*, 140-152.

Thompson, P.D., Yurgalevitch, S.M., Flynn, M.M., Zmuda, J.M., Spannaus-Martin, D., Saritelli, A. et al. (1997). Effect of prolonged exercise training without weight loss on high density lipoprotein metabolism in overweight men. *Metabolism, 2*, 217-223.

Thun, M.J., Peto, R., Lopez, A.D. et al. (1997). Alcohol consumption and mortality among middle-aged and elderly US adults. *The New England journal of Medicine, 337,* 705-1714.

Tremblay, A., Despres, J.P., Maheux, J. Pouliot, M.C., Nadeau, A., Moorjani, S. et al. (1991). Normalization of the metabolic profile in obese women by exercise and a low fat diet. *Medicine and Science in Sports and Exercise, 12*, 326-1331.

Turcotte, L., Richter, E., & Kiens, B. (1995). *Lipid metabolism during exercise,* IL: Human Kinetics Publishers.

Unger, R.H., & Orci, L. (2000). Lipotoxic diseases of nonadipose tissues in obesity. *International Journal of Obesity, 24*, suppl 4, S28-S32.

Visich, P.S., Goss, F.L., Gordon, P.M., Robertson, R.J., Warty, V., Denys, B.G. et al. (1996). Effects of exercise with varying energy expenditure on high-density lipoprotein-cholesterol. *European Journal of Applied Physiology, 72*, 242-248.

Wallace, M.B., Moffatt, R.J., Haymes, E.M., & Green, N.R. (1991). Acute effects of resistance exercise on parameters of lipoprotein metabolism. *Medicine & Science in Sports & Exercise, 23*, 199-204.

Wannamethee, S.G., Shaper, G.A., Whincup, P.H., & Walker, M. (2004). Overweight and obesity and the burden of disease and disability in elderly men. *International Journal of Obesity and Related Metabolic Disorders : Journal of the International Association for the Study of Obesity, 28,* 1374-1382.

Watson, T.D., Caslake, M.J., Freeman, D.J., Griffin, B.A., Hinnie ,.J, Packard, C.J. et al. (1994). Determinants of LDL subfraction distribution and concentrations in young normolipidemic subjects. *Arteriosclerosis and Thrombosis : a Journal of Vascular Biology / American Heart Association, 14*, 902-910.

Watts, G.F., Cummings, M.H., Kelly, J.M., Umpleby, A.M., O'Brien, S.F., & Sonksen, P.H. (1996). Acute hyperinsulinaemia decreases hepatic secretion of very low density lipoprotein apolipoprotein B-100 in normolipidaemia non diabetic subjects. *The Journal of Clinical Endocrinology and Metabolism, 3*, 253-263.

Weise, S.D., Grandjean, P.W., Rohack, J.J., Womack, J.W., & Crouse, S.F. (2005). Acute changes in blood lipids and enzymes in postmenopausal women after exercise. *Journal of Applied Physiology, 99*, 609-615.

Wilson, P., & Grundy, S.M. (2003). The metabolic syndrome practical guide to origins and treatment. *Circulation, 108*, 1422-1425.

Williams, P.T., Krauss, R.M., Vranizan, K.M., Stefanick, M.L., Wood, P.D., & Lindgren, F.T. (1992). Associations of lipoproteins and apolipoproteins with gradient gel electrophorisis estimates of high density lipoprotein subfractions in men and women. *Arteriosclerosis and Thrombosis : a Journal of Vascular Biology / American Heart Association, 12*, 332-340.

Williams, P.T., Stefanick, M.L., Vranizan, K.M., & Wood PD. (1994). The effects of weight loss by exercise or by dieting on plasma high density lipoprotein (HDL) levels in men with .L ow, intermediate, and normal-to-high HDL at baseline. *Metabolism, 43*, 917-924.

Yokoym, S. (2000). Release of cellular cholesterol molecular mechanism for cholesterol homeostasis in cells and in the body. *Biochimica Et Biophysica Acta, 1529*, 231-244.

Zhang, J.Q., Thomas, T.R., & Ball, S.D. (1998). Effect of exercise timing on postprandial lipemia and HDL cholesterol subfractions. *Journal of Applied Physiology, 85*, 1516-1522.

Zmuda, J.M., Yurgalevitch, S.M., Flynn, M.M., Bausserman, L.L., Saratelli, A., Spannaus-Martin, D.J., et al. (1998). Exercise training has little effect on HDL levels and metabolism in men with initially low HDL cholesterol. *Atherosclerosis, 137*, 215-221.

APPENDICES

Appendix A

Characteristics of the Major Lipoproteins

Characteristics of the Major Lipoproteins

Lipoprotein	Density (g/ml)	Diameter (mm)	TG%	Chol%	PL%
Chylomicrons	0.930	75-12000	80-95	2-7	3-9
VLDL	0.930-1.006	30-80	55-80	5-15	10-20
IDL	1.006-1.019	25-35	20-50	20-40	15-25
LDL	1.019-1.063	18-25	5-15	40-50	20-25
HDL_2	1.063-1.125	9-12	5-10	15-25	20-30
HDL_3	1.125-1.210	5-9			

Abbreviations: TG, Triacylglycerols; Chol, free and esterified cholesterol; PL, phospholipid; VLDL, very-low-density lipoprotein; IDL, intermediate-density lipoprotein;LDL, low-density lipoprotein; HDL, high-density lipoprotein. (Smith, Marks & Lieberman, 2005).

Appendix B

Medical and Exercise History Questionnaire

Questionnaire

Date_____

Personal Information

Name:_____ Birth

Date(mm/dd/yyyy):_____

Gender: Male Female Age: _____ years

Pre/Post menopausal status_____

Address:_____

City/State_____ Zip:_____

Home Phone:_____ Cell Phone:_____

Email:_____

Emergency Contact:

Name:_____ Relationship:_____

Phone:_____

Health History Information

1. Weight: _____kg
2. Height: _____cm
3. Blood pressure:_____/_____mmHg(systolic/diastolic)
4. Have you been diagnosed with diabetes_____ or borderline diabetes____?

If yes, how long?_____

5. What medications are you currently taking? (please list all)_____

Exercise

1. How many times per week you participate in vigorous aerobic exercise which lasts at least 10 minutes and cause large increases in breathing, heart rate, leg fatigue or cause you to perspire? (ex: jogging)

Score: 0= not al all (go to question 3)
1= 1-2 times per week
2= 3-4 times per week
3= more than 5 times per week
4= don't know Frequency score_____

2. How long do you do vigorous intensity aerobic exercise each session?

Score: 0= not applicable
1= 10-30 minutes
2= 31-60 minutes
3= more than 60 minutes
4= don't know

Duration score _____
Weight=2

Vigorous activity index score: FREQ score ____ x DUR score____ x weight ____ = ____

3. How many times per week you participate in low or moderate intensity aerobic exercise which lasts for at least 10 minutes or more without stopping and is not strenuous enough to cause large increases in breathing, heart rate, leg fatigue or cause you perspire? (ex: walking)

Score: 0= not al all
1= 1-2 times per week
2= 3-4 times per week
3= more than 5 times per week
4= don't know

Frequency score_____

4. How long do you do low or moderate intensity aerobic exercise each session?

Score: 0= not applicable
1= 10-30 minutes
2= 31-60 minutes
3= more than 60 minutes
4= don't know

Duration score _____
Weight=1

Walking index score: FREQ score ____ x DUR score____ x weight ____ = ____

5. How many times per week you do resistance exercise (ex: weight lifting)? _____

6. The intensity of the resistance exercise (light, moderate, heavy)?_____

Appendix C

Medication History

Medication History

Participant	Medication
01	Humalog Metformin Cozaar
02	Insulin Warfarin Glyburide Metformin Metorpolol Salsalate Spironolactone Terazppsom Niacin Lisinopril
03	Januvia Metformin Glipizide Nexium Accupril Lodopin
04	Nexium Synthroid Singulair Betnanacol Lipitor Trazodone
05	Flomax Simcor Fish oil Calcium

06	Avapro Zestril Clonidine Metoprolol Bumex Potassium Flax seed oil Calcium Fish oil
07	None
08	Insulin
09	Synthoid Metformin
10	Hydrocodone Skelzxin Benicar
11	None
12	None
13	Lumigan
14	Synthroid
15	Synthroid Calicum Hydrocholorothiazide Crestor
16	Cosopt Alphagan Xibrom Xalatan
17	Zocor
18	None
19	None
20	Simvastain Levothyroxine HydroxyzinePamoate

21	Levothyroxine Metoprolol Simvastain Co Q 10
22	Estradiol Dehydroepiandrosterone Progesterone
23	Omeprazole Citalopram
24	Metformin Pravastatin Lisinopril Glucosamine sulfate Calcium citrate
25	None
26	Metformin Januvi
27	None
38	Metformin Synthroid Diovan Crestor Nifedipin Metoprolol Pantoprazole
29	Omnaris Bisoprolol Estradiol Testosterone
30	Prilosec Albuterol sulfate Advari discus Pravastatin

Appendix D

Selected Lipid Concentrations

Selected Lipid Concentrations

Participant	Gender	Age	Menopausal	TC(mg)	TG(mg)	LDL-C(mg)	HDL-C(mg)	Glucose(g)	FAT %
01	F	74	Post	159.5	73	94.3	50.6	132	40.1
02	M	76		137.8	209.8	40.8	55	124	
03	M	71		164.7	208.7	79.6	43.3	128	31.7
04	F	69	Post	141.5	57.6	70.7	59.2	112	43.5
05	M	75		189.7	60.8	127.2	50.3	103	35.9
06	F	73	Post	210	146	132.8	48	100	41.8
07	M	67		218.2	47.9	137.3	71.3	124	23.2
08	F	66	Post	196.7	204.5	95	60.8	161	39.5
09	F	62	Post	163.2	122.3	75.7	63	153	37.9
10	F	46	Pre	208.7	115.4	127.1	58.5	102	
11	M	69		213.8	76.6	144	54.4	144	21.8
12	F	65	Post	212.9	157.8	115.4	65.9	122	
13	F	73	Post	262.6	171.8	163.3	64.9	98	50.1
14	F	57	Post	189.7	161.7	94.9	62.4	106	51.1
15	F	83	Post	191.2	72.2	115.6	61.1	112	
16	F	67	Post	157.2	134.3	95.3	35	104	
17	M	59		186.5	80.8	121	49.3	115	32.9
18	F	48	Pre	207.5	139.1	133.6	46	108	48.6
19	F	56	Post	203.4	203.9	111.1	51.5	153	
20	M	64		140.3	145.8	58.6	52.5	120	28.8
21	M	68		145.6	128	64.6	55.4	99	22.9
22	F	67	Post	174.1	119.3	88.5	61.7	107	40.1
23	F	63	Post	178.2	132.7	91.5	60.1	113	45.4
24	M	65		140.7	123.2	49.5	66.5	172	38.7
25	F	60	Post	227.9	155.6	144.6	52.1	166	50.2
26	M	60		212.5	110.8	113.9	76.4	130	6.9
27	F	63	Post	222.6	199.7	126.3	56.3	157	55
28	F	60	Post	170.6	199.2	76	54.7	149	50.8
29	F	57	Post	202.7	114	118.5	61.4	119	47.7
30	F	64	Post	275.3	207.6	176.4	57.3	106	45.3

Appendix E

Dietary Intake Summary

Dietary Intake Summary

Participant	Total kcal	SFA (g)	MUFA (g)	PUF (g)	Carb (g)	Chol (mg)	Protein (g)
01	3329	34	61	32	300	196	83
02	3138	29.3	49	55	362	177	121
03	4179	43.2	186	69	336	134	75
04	1746	22.4	27	16	162	128	69
05	3404	54.8	77	52	253	789	163
06	1672	35.2	36	33	179	253	95
07	2296	30.3	32	12	291	153	77
08	3012	50	43	28	188	166	86
09	2473	40	42	18	293	137	93
10	1486	20.4	23	21	153	110	62
11	3240	52	56	57	289	281	123
12	3581	49.2	37	41	299	540	114
13	2553	33	41	31	164	133	72
14	2491	45.7	34	28	201	312	64
15	2987	43	22	34	155	208	76
16	1775	24	28	8	388	190	84
17	1808	22.1	35	14	183	885	94
18	2746	44	36	20	211	377	99
19	2711	38.7	24	20	204	130	72
20	2493	34	19	6	446	192	80
21	3470	46.3	25	24	222	381	76
22	1835	21.3	26	19	214	176	85
23	2011	36	33	31	205	504	120
24	2763	34.8	26	37	137	123	63
25	2499	52	53	46	244	249	78
26	2510	33.6	30	24	221	121	92
27	3042	42	27	27	138	189	77
28	3007	29.3	31	39	156	278	86
29	2336	27	26	13	207	188	95
30	1987	24.5	30	16	301	125	101

Appendix F

Informed Consent

TEXAS WOMAN'S UNIVERSITY

CONSENT TO PARTICIPATE IN RESEARCH

Title of Study: The effect of exercise volume on lipoprotein metabolism in diabetes or pre-diabetes patient

Investigator's Name: Ming-Chen Ko

Investigator's Phone: (469) 879-3259 Investigator's Email: ko_ming_chen@hotmail.com

Advisor's Name: Kyle D. Biggerstaff, Ph.D.

Advisor's Phone: (940) 898-2596

Explanation and Purpose of the Research

You are being asked to participate in a research study for Ming-Chen Ko's thesis at Texas Woman's University. The purpose in this study is to determine whether exercise duration per week is inversely related to blood lipid and lipoprotein-cholesterol concentrations in those with diabetes or prediabetes.

Research Procedures

For this study, participants only need to visit the laboratory for several measurements. Participantion in the study will require approximately 4 hours of your time, including one hour for the dual-energy X-ray scan, one hour for the interview and questionnaire, and one hour for the blood draw and all anthropometric measurements. The time for you to complete dietary consumption is approximately 1 hours. Participants in this study is voluntary, you have the right to withdraw from the study at any time without penalty. If you choose to participate, you will be required to wear light clothes and no shoes to obtain body weight. Height will be obtained using a portable stadiometer. A Dual-energy X-ray machine (bone scan) will be used to determine body composition, fat distribution, and bone density. You will be asked to lie face up, fully clothed, on a table for the scan. A trained technician will perform all scaning measurements. Systolic and diastolic blood pressures will be measured by using blood pressure cuff. Blood will be drawn from the antecubital forearm vein in your elbow by a standard venipuncture technique. An individual trained in phlebotomy (blood draws) following universal precautions will draw blood. You will be required to visit the laboratory in the morning after a 12 h fast you may drink water during the fast. You will be seated for 10 minutes prior to the blood draw. The blood will be analyzed for total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol, and triglyceride concentrations. Prior to the blood draw, you will be asked if you are allergic to latex. If you inform the phlebotomist that you are allergic to latex, another type of glove and tourniquet will be used to obtain the blood

sample. Each participant will be asked to complete one questionnaire regarding medication use, gender, pre/post-menopausal status, alcohol consumption, cigarette smoking and the frequency, duration, and intensity of exercise.

_____Participant or Parent/Guardian Initials

Potential Risks

Potential risks related to your participation in this research include loss of confidentiality, infection, latex allergy, radiation, and bruising. There is a risk of loss of confidentiality in all email, downloading, and internet transactions, therefore, the passwords for all internet activities should keep in an unreachable place.To minimize the risk of loss of confidentiality, all data will be kept in a locked file cabinet in a locked office, 116, Pioneer Hall, Texas Woman's University. The original data will be coded with a numerical system rather than the participant's name. A single identification form will be used to line the names to the code. This is the only way to decipher the numerical system to names. This form will be kept in a separate file than all other data in the principal investigator's office. The data will be kept for an unspecified period of time. This project is the beginning of a long-term study of the effect of exercise on metabolic parameters in people with diabetes or pre-diabetes. The code sheet identifying participants will be shredded by September 1th 2013. Confidentiality will be protected to the extent that is allowed by law.

To minimize the risk of infection, all blood draws will be performed by trained personnel. Sites for the blood draws will be sterilized with alcohol prior to the venipuncture. Each new needle that is opened will be disposed of in biohazard boxes immediately after use.

During the blood draw, the phlebotomist will wear latex gloves. To minimize the risk of latex allergy, the participant will be asked if he/she is allergic to latex prior to each blood draw. If the participant is allergic to latex, another type of glove and tourniquet will be used.

To minimize the risk of bruising resulting from blood draws, all procedures will be performed by trained personnel. Universal precautions will be used during all blood draw procedures. After each blood draw, pressure will be applied to the site for approximately five minutes to minimize bruising.

The risk of radiation is trivial. Participants will be exposed to a small amount of radiation during body composition assessment with the Dual-energy X-ray scan.

The radiation exposure for each participant will be approximately the same amount received during a 2 hour airplane flight and less than normal background radiation an individual is exposed to in one day.

The researchers will try to prevent any problem that could happen because of the study. You should let the investigators know if you have any problem and they will help you. However, Texas Woman's University does not provide medical services or financial assistance for injuries that might happen because you are participating in this research.

_____Participant or Parent/Guardian Initials

Participation and Benefits

Participation in this study is voluntary. You have the right to withdraw from the study at any time without penalty. Participating in this study or not will not impact the services which LEAD-UP program provided to you. If you withdraw from the study at any point, you can still have the access to any data collected from you that has been analyzed at any time point.

You will benefit from involvement in this study by learning about your current risks for CVD, body composition and bone density.

Questions Regarding the Study

A copy of this singed and dated consent will be given to you. If you have any question about the study you should ask the investigators; their phone numbers are on the top of this form. If you have any question about your rights as participant in this study, you may contact the Texas Woman's University Office of Research and Sponsored Programs at (940) 898-3378 or via email at IRB@twu.edu.

_____

_____

Signature of Participant

Date

*If you would like to receive a summary of the result of this study, please provide an address to which this summary should be sent:

_____

_____

Appendix G

IRB Approval Letter

TWU
TEXAS WOMAN'S UNIVERSITY
DENTON DALLAS HOUSTON

Institutional Review Board
Office of Research and Sponsored Programs
P.O. Box 425619, Denton, TX 76204-5619
940-898-3378 Fax 940-898-3416
e-mail: IRB@twu.edu

October 28, 2009

Mr. Ming-Chen Ko

Dear Mr. Ko:

Re: The Effect of Exercise Volume on Lipoprotein Metabolism in Diabetes or Pre-Diabetes Patient

The above referenced study has been reviewed by the TWU Institutional Review Board (IRB) and appears to meet our requirements for the protection of individuals' rights.

If applicable, agency approval letters must be submitted to the IRB upon receipt PRIOR to any data collection at that agency. A copy of the approved consent form with the IRB approval stamp and a copy of the annual/final report are enclosed. Please use the consent form with the most recent approval date stamp when obtaining consent from your participants. The signed consent forms and final report must be filed with the Institutional Review Board at the completion of the study.

This approval is valid one year from August 7, 2009. According to regulations from the Department of Health and Human Services, another review by the IRB is required if your project changes in any way, and the IRB must be notified immediately regarding any adverse events. If you haye any questions, feel free to call the TWU Institutional Review Board.

Sincerely,

Dr. Kathy DeOrnellas, Chair
Institutional Review Board - Denton

enc.

cc. Dr. Charlotte Sanborn, Department of Kinesiology
Dr. Kyle D. Biggerstaff, Department of Kinesiology
Graduate School