THE EFFECTS OF NIACIN AND A SINGLE BOUT OF EXERCISE ON BLOOD LIPID AND LIPOPROTEIN PROFILES IN POSTMENOPAUSAL WOMEN

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BY

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To the Dean of the Graduate School:

I am submitting herewith a dissertation written by Yunsuk Koh entitled "The effects of niacin and a single bout of exercise on blood lipid and lipoprotein profiles in postmenopausal women." I have examined this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy with a major in Kinesiology.

Vic Ben-Ezra, Ph.D., Major Professor

We have read this dissertation and recommend its acceptance:

Department Chair

Accepted:

Dean of the Graduate School

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ABSTRACT

YUNSUK KOH

THE EFFECTS OF NIACIN AND A SINGLE BOUT OF EXERCISE ON BLOOD LIPID AND LIPOPROTEIN PROFILES IN POSTMENOPAUSAL WOMEN

MAY 2008

It has been well documented that independently both exercise and niacin positively alter blood lipids and lipoproteins; however, these interventions have not been studied in postmenopausal women. The purpose of this study was to examine the independent and combined effects of niacin and a single bout of exercise on the blood lipid and lipoprotein profiles in postmenopausal women.

Eighteen sedentary, postmenopausal women (40 – 80 years old), were recruited (mean ± SD; age = 57 ± 6 yrs; height = 161.3 ± 6.7 cm; weight = 75.8 ± 13.9 kg; % body fat = 46.2 ± 6.6 %). The without-niacin (WON) condition was first assigned followed by the with-niacin (WN) condition. The WN condition consisted of ingesting 1,000 mg/day of extended-release niacin for 4 weeks. Rest (R) and exercise (E) trials were randomly assigned within each WON or WN condition. During the E trial treadmill exercise was performed at 60% HRR until 400 kcal were expended. Fasting blood samples were collected immediately before (0 hr) and at 24 and 48 hr post exercise (or rest). All data were reported as mean ± SD. The changes in TC, TG, LDL-C, HDL-C, HDL_2-C, HDL_3-C, and TC to HDL-C ratio were analyzed using a 2 (WON and WN) × 2 (Rest and Exercise) × 3 (0, 24, and 48 hr) ANOVA with repeated measures. The Bonferroni post-hoc test was

applied and the statistical significance was set at $p < .05$.

The concentrations of TC, LDL-C, and TG were not altered in reponses to exercise or niacin. However, the niacin treatment without the exercise intervention significantly ($p < .05$) increased HDL-C (5.4 mg/dl or 12.4 %) and HDL_2-C (3.6 mg/dl or 33.3 %) from baseline (43.5 ± 1.7 and 10.8 ± 1.2 mg/dl, respectively). The current study suggests that the niacin supplement (1,000 mg/day) for 4 weeks increases HDL-C, predominantly HDL_2-C.

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CHAPTER I

INTRODUCTION

Cardiovascular disease (CVD) has been the number one leading cause of death in the United States since 1900 with the exception of 1918. Almost 16.7 million people in the world die of CVD each year, and approximately 2,600 Americans die of CVD everyday. Thirty eight percent of patients who have one or more types of CVD are older than 65 years of age (American Heart Association [AHA], 2006). Coronary heart disease (CHD) results from atherosclerosis of the coronary arteries, and accounts for more than half of all cardiovascular events in older men and women. The chance of developing CHD after age 40 is 49% and 32% in men and women, respectively (Lloyd-Jones, Larson, Beiser, & Levy, 1999). Although men age 49 to 74 years have a higher age-adjusted incidence of CHD than women (Ford, Giles, & Dietz, 2002) the rate of death caused by CHD for both gender becomes similar after age 65 (AHA, 2006; Ford et al., 2002).

The process of atherosclerosis can begin early in childhood, and results from the clustering of multiple factors known as coronary risk factors including genetic, biological, behavioral, and environmental factors (Ross, 1986). According to the Adult Treatment Panel (ATP III) report of the National Cholesterol Education Program (NCEP), coronary risk factors can be categorized into lipid, non-lipid, and emerging risk factors (NCEP, 2001). Atherogenic dyslipidemia is one of the primary lipid risk factors for CHD, and is characterized by elevated concentrations of triglyceride (TG) and low-density lipoprotein

cholesterol (LDL-C), especially small, dense LDL particles, and reduced concentrations of high-density lipoprotein cholesterol (HDL-C). Non-lipid risk factors for CHD include hypertension, cigarette smoking, diabetes mellitus, overweight and obesity, physical inactivity, and an atherogenic diet. Emerging risk factors for CHD include homocysteine, lipoprotein(a) (Lp(a)), thrombogenic and hemostatic factors, inflammatory markers, and the metabolic syndrome (NCEP, 2001).

Dyslipidemia is strongly associated with CHD, and is also a major cause of death in patients with type 2 diabetes (Castelli et al., 1986). An elevated LDL-C concentration, a potent predictor of coronary artery disease (CAD), has a positive relationship with CAD, while a higher HDL-C concentration is inversely related to the incidence of CAD (AHA, 2006; Despres et al., 1989; Wilson, 1990). The American Heart Association reported that 76.1 million people had LDL-C concentrations greater than 130 mg/dl and 46 million people had HDL-C concentrations less than 40 mg/dl (AHA, 2006).

Niacin, also known as pyridine-3 carboxylic acid or nicotinic acid, is a water soluble B complex vitamin (Pieper, 2003). Niacin has been initially studied due to its relationship to pellagra, which is caused by a deficiency of vitamin B3. However, niacin has been widely studied and used for patients with dyslipidemia to improve lipid and lipoprotein profiles (Knopp et al., 1998; Pieper, 2003; Piepho, 2000) since Altschul and colleagues in 1955 first reported its antilipidemic effects (Altschul, Hoffer, & Stephen, 1955). It has been also reported that niacin may reduce the incidence of morbidity and mortality from CVD and stroke by favorably modifying blood lipids and lipoproteins (Brown et al., 1998; Guyton, 2004). Numerous clinical studies with niacin have reported

a significant improvement in serum concentrations of HDL-C, HDL_2-C, and apo-A, as well as reductions in concentrations of total cholesterol (TC), very low-density lipoprotein cholesterol (VLDL-C), LDL-C, TG, apo-B, Lp(a), and TC to HDL-C ratio (Goldberg, 1998; Grundy, Mok, Zech, & Berman, 1981; Knopp et al., 1998; Knopp et al., 1985; Snyder, 1990; Squires, Allison, Gau, Miller, & Kottke, 1992; Wang, Basinger, & Neese, 2000).

Based on the different dissolution rates, three different formulations of niacin such as immediate-release (IR) niacin, extended-release (ER) niacin, and sustained-release (SR) niacin are available. Of these three types of niacin, ER niacin, such as Niaspan, is widely recommended to treat dyslipidemia because it not only improves lipid and lipoprotein profiles, but also has fewer incidences of side effects as compared with IR niacin and SR niacin (Guyton, 2004; Kane, Hamilton, Addesse, Busch, & Bakst, 2001; Knopp et al., 1998; Pan et al., 2002).

Physical activity can favorably modify blood lipids and lipoproteins, and is beneficial in reducing the risk factors for CVD (Durstine, Crouse, & Moffatt, 2000; Lamarche et al., 1997). Both long-term exercise training and a single bout of exercise positively alter blood lipids and lipoproteins (Crouse et al., 1995; Durstine, Grandjean, Cox, & Thompson, 2002; Ferguson et al., 1998). However, according to the published research, responses of TC, VLDL-C, and LDL-C following a single bout of exercise are inconsistent (Crouse et al., 1995; Grandjean, Crouse, & Rohack, 2000; Kantor, Cullinane, Sady, Herbert, & Thompson, 1987), while a reduction of TG (Foger et al., 1994; Gordon et al., 1998; Grandjean et al., 2000; Visich et al., 1996) and an increase in HDL-C

(Ferguson et al., 1998; Gordon et al., 1998; Grandjean et al., 2000; Kantor et al., 1987) are fairly consistently observed following a single bout of aerobic exercise. Although some studies have reported that HDL-C and TG concentrations in women may be more resistant to exercise-induced alterations than men (Imamura et al., 2000; Williams, 1993; Williams, 1996), beneficial changes in lipids and lipoproteins in response to exercise may be similar between men and women (Durstine et al., 2002; Gordon et al., 1998; Kelley, Kelley, & Tran, 2004).

Menstrual status, oral contraceptive use, or hormone replacement therapy can influence blood lipid and lipoprotein profiles in women (Dowling, 2001). Menopause usually occurs at the average age of 50 years in American and European women, and is associated particularly with progressive reductions in reproductive hormones such as estradiol, progesterone, and 17-hydroxoyprogesterone (Asikainen, Kukkonen-Harjula, & Miilunpalo, 2004). Changes in theses hormones, particularly a reduction of estrogen, may be associated with negative alterations of blood lipids and lipoproteins. It has been reported that estrogen generally decreases TC and increases HDL-C (Asikainen et al., 2004; Haddock, Marshak, Mason, & Blix, 2000).

Postmenopausal women are more likely to have higher concentrations of TC, TG, VLDL-C, and LDL-C than men (Shepherd, Betteridge, & Gaal, 2005) or premenopausal women (Blumenthal et al., 1991). In addition, the incidence of chronic diseases such as CHD, type 2 diabetes, and osteoporotic fractures in sedentary women is also significantly increased after menopause (Asikainen et al., 2004, Matthews et al., 1989; Sowers & La Pietra, 1995). Sedentary lifestyle particularly in postmenopausal women is considered

one of the key factors that may enhance body weight gain and decrease cardiorespiratory endurance, muscular strength, and bone mineral density (Sowers & La Pietra, 1995).

Problem Statement

Although many researchers have reported the effects of exercise on lipids and lipoproteins in men, few studies have investigated women, particularly postmenopausal women. Moreover, the results of existing literature examining the effects of a single bout of exercise on blood lipids and lipoproteins in women are equivocal. The majority of studies that examined the effects of a single bout of exercise on lipids and lipoproteins in young individuals, particularly men, utilized various types of aerobic exercise such as walking, stepping, cycling, etc. with an exercise intensity of 50 – 80% VO_2max or 40 – 60% heart rate reserve (HRR) requiring 350 – 1,500 kcal of energy expenditure (Crouse, O'Brien, Grandjean, Lowe, Rohack, Green et al., 1997; Crouse et al., 1995; Ferguson et al., 2003; Ferguson et al., 1998; Grandjean et al., 2000). Therefore, it is necessary to determine how moderate intensity aerobic exercise affects blood lipids and lipoproteins in older women who have increased risk factors for CVD. Thus, the exercise protocol for this study was walking at 60% HRR until 400 kcal are expended.

The majority of studies that examined the effects of niacin on lipid and lipoprotein metabolism used niacin ranging from 1,000 to 3,000 mg/day, and many studies have reported that a minimum of 1,000 mg/day of niacin significantly improved blood lipids and lipoproteins (Goldberg et al., 2000; Guyton et al., 1998; Knopp et al., 1998; Morgan, Capuzzi, & Guyton, 1998; Pan et al., 2002). Higher doses of niacin (> 2,000 mg/day) are associated with adverse effects such as flushing, itching, redness, or

hepatotoxicity. However, Niaspan minimizes these side effects, and is widely used to treat dyslipidemia (Morgan et al., 1998; Pieper, 2003). Therefore, a target dose of 1,000 mg/day of Niaspan was used in this study.

Although it has been well documented that either exercise or niacin positively alters blood lipids and lipoproteins, no published studies have examined the independent and combined effects of niacin and a single bout of aerobic exercise on blood lipids and lipoproteins in postmenopausal women. Therefore, it is important to determine how niacin and exercise influence blood lipids and lipoproteins in this population. The purpose of this study was to investigate the independent and combined effects of niacin (1,000 mg/day) and exercise (60% HRR until expending 400 kcal) on the blood lipid (TC and TG) and lipoprotein (LDL-C, HDL-C, HDL_2-C, and HDL_3-C) profiles in postmenopausal women.

Hypotheses

This study examined the independent and combined effects of 1,000 mg/day of niacin and a single bout of aerobic exercise at 60% HRR requiring 400 kcal of energy expenditure on lipid (TC and TG) and lipoprotein profiles (LDL-C, HDL-C, HDL_2-C, and HDL_3-C) in postmenopausal women. The following hypotheses were tested:

1. Niacin supplementation (1,000 mg/day) for 4 weeks will improve lipid and lipoprotein profiles (Niacin effect).
2. A single bout of exercise at 60% HRR requiring 400 kcal of energy expenditure will improve lipid and lipoprotein profiles (Exercise effect).

3. Niacin supplementation combined with a single bout of exercise will improve lipid and lipoprotein profiles significantly more than exercise or niacin treatment alone (Combination effect).

Definition of Terms

Apolipoproteins: the surface proteins used to identify lipoproteins. Apolipoproteins regulate enzymatic functions, serve as lipid transfer proteins, and are the binding molecules for interaction with lipoprotein receptors.

Atherosclerosis: a multi-factorial process that leads to the accumulation of cholesterol in the intima layer.

Cholesterol ester transfer protein (CETP): a hydrophobic glycoprotein synthesized and secreted by hepatic, muscle, and adipose tissue. An activity of CETP is associated with HDL-C particles and functions of lipids between the HDL-C, LDL-C, and VLDL-C fractions.

Chylomicrons: a class of lipoproteins which transport dietary cholesterol and triglycerides after digestion and absorption of fat in food.

Hematocrit (Hct): a total volume of erythrocytes, expressed as a percentage of blood.

Hemoglobin (Hb): the iron-containing pigment of the red blood cells, which carries oxygen from the lungs to the tissues, and is expressed as milligrams per deciliter (mg/dl) of blood.

High-density lipoprotein cholesterol (HDL-C): a lipoprotein that picks up cholesterol from cells so that it can be eliminated from the body. Lower concentrations of HDL-C increase the risk of CVD.

Hepatic lipase (HL): bound to the liver endothelial capillary lining, and works in conjunction with CETP in the degradation of HDL_2-C particles.

Lecithin:cholesterol acyltransferase (LCAT): modifies nascent HDL-C particles by transforming cholesterol into cholesteryl ester, shifts the ester to the HDL_3-C core, and develops a chemical gradient that leads to the continual uptake of cholesterol by HDL_2-C.

Lipoprotein (a) [Lp(a)]: a class of plasma lipoproteins similar to LDL-C but containing a large glycoprotein molecule called apolipoprotein (a).

Lipoproteins: particles containing a core of lipids surrounded by a shell of protein and phospholipids.

Lipoprotein Lipase (LPL): involved in the hydrolysis of the triglyceride core of chylomicron and VLDL-C. It is known that LPL is bound to the capillary walls and enhances the uptake of the released fatty acid into the extra-hepatic tissue.

Low-density lipoprotein cholesterol (LDL-C): a lipoprotein that transports cholesterol to cells. Elevated LDL-C increases the risk of CVD.

Maximal Oxygen Consumption (VO_2max): the maximal amount of oxygen that can be consumed during a maximal exercise test.

Menopause: a phase in a woman's life marked by the cessation of ovulation and menstruation as a result of estrogen depletion.

Postmenopause: defined as no more menstruation after which a woman has experienced 12 consecutive months of amenorrhea (lack of menstruation).

Very low-density lipoprotein cholesterol (VLDL-C): large, buoyant lipoproteins secreted by the liver and containing a relatively large amount of triglyceride.

Assumptions and Limitations

Assumptions

The researcher accepted the following assumptions:

1. All participants fasted at least 10 hr preceding each blood collection as requested and abstained from alcohol consumption and exercise over the course of the study.
2. Each participant ingested the same dinner the day before each blood collection.
3. Each participant correctly kept a dietary and physical activity record over the course of the study.
4. Each participant ingested the correct amount of niacin as directed by the researcher during the niacin treatment trial.

Limitations

The researcher accepted the following limitations:

1. Participants in this study were limited to postmenopausal women.
2. Participants in this study were not randomly assigned for niacin trials (with-niacin or without-niacin trial) because of niacin's possible flushing side effects. All participants in this study were first assigned to the without-niacin trial.
3. Any changes in blood lipids and lipoproteins beyond 48 hr after each experimental trial were not considered in this study. Blood samples were collected immediately before and at 24 and 48 hr after each experimental trial (RWN, rest + with-niacin; EWN, exercise + with-niacin; RWON, rest + without-niacin: or EWON, exercise + without-niacin)

Significance of Study

It has been reported that either niacin or exercise independently has favorable effects on blood lipids and lipoproteins. However, there has been no study to date examining the independent and combined effects of niacin and a single bout of exercise on lipid and lipoprotein profiles in postmenopausal women. The present study may provide insight on how the combination of niacin and exercise favorably alters the risk factors associated with dyslipidemia and CAD. In addition, the present study may also provide insight into the development of future research that involves effective dosing of both niacin and exercise on improvement in lipid and lipoprotein profiles.

CHAPTER II

REVIEW OF LITERATURE

Blood Lipids and Lipoproteins

Overview of Lipid and Lipoprotein Metabolism

Lipids are the chemical term for fats or oils (Smolin & Grosvenor, 2002), and have a number of essential roles in the body including serving as an important structural component of cells and providing a source of energy (McArdle, Katch, & Katch, 1999). Lipids are considered the ideal cellular fuels because lipids contain larger quantities of energy per unit weight as compared with carbohydrates and proteins. The human body can obtain lipids primarily from dietary foods containing cholesterol, cholesterol esters, phospholipids, triglycerides (TG), and unesterified free fatty acids (FFAs) (Champe, Harvey, & Ferrier, 2005).

Dietary lipids are digested in the small intestine and absorbed as fatty acids, free cholesterol, monoglycerides, and diglycerides. Most lipids in the body are stored as TG in adipose tissues. Most cholesterol found in plasma is in the esterified form with a fatty acid attached at C-3. Cholesterol and its esters cannot be directly transported into the circulation because of their hydrophobic characteristics. Therefore, cholesterol and its esters are combined with other lipoproteins and apolipoproteins to enter the bloodstream (Champe et al., 2005).

Water-soluble lipids such as short- and medium-chain fatty acids and phospholipids can enter the bloodstream once absorbed into the intestinal mucosal cells while non-water-soluble lipids such as monoglycerides and long-chain fatty acids cannot directly enter the bloodstream. Thus, non-water-soluble lipids are resynthesized into TG by the mucosal cell, which are, in turn, combined with cholesterol, phospholipids, and apolipoproteins to form lipid-rich chylomicrons (Champe et al., 2005; Smolin & Grosvenor, 2002).

The predominant lipid components of chylomicrons (diameter > 75 nm and density < 0.95 g/ml) are TG (Converse & Skinner, 1992). Of the various types of apolipoproteins including apo B-48, apo B-100, apo A-I, and apo A-II, only apo B-48 combines with chylomicrons (Murray, Granner, Mayes, & Rodewell, 2000). The main functions and properties of these apolipoproteins are presented in Table 1. Apo B-48 is named because it constitutes the N-terminal with 48% of proteins coded for by the apo B gene.

On the other hand, apo B-100, which is primarily found in very low-density lipoprotein cholesterol (VLDL-C) and low-density lipoprotein cholesterol (LDL-C), represents 100% of proteins coded for by the apo B gene (Champe et al., 2005). Chylomicrons enter the bloodstream from the intestine via the lymphatic system without passing through the liver.

Table 1

The Functions and Properties of Apolipoproteins and their Association with CAD

Apolipo proteins	Molecular mass (Da)	Lipoproteins	Functions	CAD Risk Factor
A-I	28,016	HDL-C, Chylo	LCAT activator; Ligand for HDL-C receptor.	Inversely related
A-II	17,414	HDL-C, Chylo	HL activator; Inhibitor of LCAT.	Not associated
B-48	264,000	Chylo remnants, Chylo	Secretion of Chylo.	Directly associated
B-100	550,000	LDL-C, VLDL-C, IDL-C	Secretion of VLDL-C, structural protein of LDL-C, receptor-mediated LDL-C catabolism.	Directly associated
C-I	6,600	VLDL-C, HDL-C, Chylo	Possible activator of LCAT.	Not associated
C-II	8,850	VLDL-C, HDL-C, Chylo	Activator of LPL.	Not associated
C-III	8,800	VLDL-C, HDL-C, Chylo	Inhibition of LPL. Inhibition of hepatic uptake of chylo and VLDL-C.	Not associated
E	34,100	VLDL-C, HDL-C, Chylo	Hepatic clearance of chylo remnants and IDL-C.	Not associated

Note. Chylo = chylomicrons, HDL-C = high-density lipoprotein cholesterol, HL = hepatic lipase, IDL-C = immediate-density lipoprotein cholesterol, LCAT = lecithin cholesterol acyl transferase, LDL-C = low-density lipoprotein choleseterol, LPL = lipoprotein lipase, VLDL-C = very low-density lipoprotein cholesterol. Adapted from (Converse & Skinner, 1992; Durstine et al., 2000; Murray et al., 2000).

When a nascent chylomicron particle is transferred to the plasma, the particle is rapidly modified in association with apo E and C-II that are provided by circulating plasma high-density lipoproteins (HDL-C or α-lipoproteins) (Converse & Skinner, 1992; Murray et al., 2000). The characteristics of lipids and lipoproteins are presented in Table 2.

Table 2

The Characteristics of Plasma Lipids and Lipoproteins

Lipid/ Lipoprotein	Density (g/ml)	Diameter (nm)	Source	Composition					
				Protein (%)	Lipid (%)	% of Total Lipid			
						TG	Chol	Phosp	Free Chol
Chylo	<0.95	100-1000	Intestine	1-2	98-99	88	8	3	1
VLDL-C	0.95-1.006	25-75	Liver, intestine	7-10	90-93	56	20	15	8
IDL-C	1.006-1.019	25	VLDL-C, Chylo	11	89	29	26	34	9
LDL-C	1.019-1.063	20-28	VLDL-C, Chylo	21	79	13	28	48	10
HDL_2-C	1.063-1.125	10-20	HDL_3-C	33	67	16	43	31	10
HDL_3-C	1.125-1.210	5-10	Liver, intestine, VLDL-C, Chylo remnants	57	43	13	46	29	6
Chol	-	-	Liver, Diet	-	100	-	-	70-75	25-30
TG	-	-	Liver, Diet	-	100	100	-	-	-

Note. Chylo = chylomicrons, Chol = cholesterol, HDL-C = high-density lipoprotein cholesterol, IDL-C = immediate-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, TG = triglyceride, Phosp = phospholipid, VLDL-C = very low-density lipoprotein cholesterol. Adapted from (Converse & Skinner, 1992; Durstine, Davis, Ferguson, Alderson, & Trost, 2001).

Lipoprotein Lipase (LPL) Activity

Lipoprotein lipase (LPL) is found on endothelial cells and serves as a principal enzyme for TG hydrolysis in lipid-rich lipoproteins. Adipose tissues and muscles are the main sites where LPL is released and transferred to the surface of the endothelial cells of the capillaries (Champe et al., 2005; Lewis & Rader, 2005; Wang & Briggs, 2004). The primary function of LPL is to hydrolyze the lipid core of lipid-rich lipoproteins to release FFAs, diglycerides, and monoglycerides, resulting in the transformation of larger TG-rich particles into smaller TG-depleted remnant lipoproteins (Lewis & Rader, 2005).

The activity of LPL is mediated by apo C-II in the presence of phospholipids. When LPL is activated, FFAs are transported to tissues while the glycerol backbone of TG is returned to the liver and kidney for lipid synthesis, glycolysis, or gluconeogenesis (Champe et al., 2005). Fatty acids transported to tissues may be used as an energy source or resynthesized into TG for storage (Durstine et al., 2000; McArdle et al., 1999; Smolin & Grosvenor, 2002). If FFAs are not immediately used or taken up by cells, FFAs are continuously transported by serum albumin until utilized (Champe et al., 2005).

Very Low-density Lipoprotein Cholesterol (VLDL-C) Metabolism

One of the vital organs for lipid metabolism is the liver. Cholesterol, chylromicron remnants, and TG are synthesized in the liver, and are incorporated into lipoprotein particles called VLDL-C or pre β-lipoproteins. The VLDL particles are smaller (30 – 40 nm) and denser (0.95 – 1.006 g/ml) as compared with chylomicrons (Converse & Skinner, 1992). The VLDL particles contain cholesterol esters, apo B-100, apo E, apo C-I, apo C-II, and apo C-III, and their main role is to transport lipids from the liver to various body cells such as skeletal muscle or adipose tissue for storage or energy sources (Champe et al., 2005).

Nascent VLDL particles containing apo B-100 are released into the circulation from the liver. Like chylromicron hydrolysis, the core of VLDL particles in the presence of apo C-II are also hydrolyzed by LPL, resulting in the release of fatty acids to extra-hepatic tissues. The remaining VLDL-C remnants are removed from the circulation by binding to hepatic apo E receptors. After the hydrolysis of TG in VLDL particles, a smaller, denser intermediate-density lipoprotein (IDL) will be formed (Champe et al.,

2005; Lewis & Rader, 2005).

Immediate-density (IDL-C) and Low-density Lipoprotein Cholesterol (LDL-C) Metabolism

The remaining IDL molecules in an interaction with LPL return to the liver or transform into LDL particles or β-lipoproteins (Shepherd, 1992). A predominant apolipoprotein in LDL particles is apo B-100, a protein with 4536 amino acid residues (Murray et al., 2000). The LDL particles are the primary cholesterol transporters for peripheral tissues, and can be taken up by liver and peripheral cells via receptor-mediated endocytosis when apo B-100, on the surface of LDL-C, binds to the LDL-C apo B-100 cellular receptors on the peripheral cell membrane. During this receptor-mediated endocytosis process, the LDL particles are transported into the cell and exposed to lysomal digestion (Champe et al., 2005; Durstine et al., 2000).

Oxidized LDL particles can easily enter the macrophage through the scavenger receptors, CD 36 and SR-A (Kwiterovich, 2000). Excess intracellular cholesterol is stored after re-esterification by acyl-CoA-cholesterol acyltransferase (ACAT). Individuals with a LDL-C receptor deficiency have significantly elevated plasma LDL-C, and it is well known that high concentrations of LDL-C in the blood are related to heart disease (Converse & Skinner, 1992). Furthermore, smaller, denser LDL particles are strongly associated with the risks of CVD (Rainwater, Mitchell, Comuzzie, & Haffner, 1999). The diameter of LDL particles generally fall within the range of 22 – 29 nm (Rainwater, 1998). Based on size and density, LDL particles can be classified as either phenotype A or phenotype B (Austin et al., 1988). Larger, buoyant LDL particles (> 25.5 nm) are

considered the phenotype A pattern, and LDL particles smaller, denser (< 25.5 nm) than phenotype A are the phenotype B pattern, which are more atherogenic than the phenotype A pattern (Singh et al., 1995).

Lipoprotein(a)

Lipoprotein(a) (Lp(a)) was first introduced in 1962, and can be found in the same density region as LDL-C and HDL_2-C (Berg, 1994). The structure of Lp(a) is almost identical to LDL particles (Converse & Skinner, 1992). Like LDL particles, apo B-100 is a major apolipoprotein component in Lp(a). However, one of the unique characteristics of Lp(a) as compared to LDL-C is that Lp(a) has an additional apolipoprotein molecule, apo(a), which is covalently linked at a single site of apo B-100 and is highly homologous to plasminogen, a precursor of a blood protease (Champe et al., 2005).

Although Lp(a) concentration is mainly associated with genetics, a trans fat diet can elevate plasma Lp(a) concentrations (Champe et al., 2005) whereas estrogen and progestin lowers Lp(a) concentrations in postmenopausal women with high initial concentrations (Shlipak et al., 2000). All major lipoproteins such as chylomicrons, VLDL-C, LDL-C, and HDL-C are metabolically interrelated and exchange lipid and protein components through the metabolic transformations, but Lp(a) seems to be metabolically unrelated to the other plasma lipoproteins (Converse & Skinner, 1992).

Elevated Lp(a) concentrations (> 25 mg/dl) in plasma appear to be an independent risk factor for CAD (Superko & Hecht, 2001), and promote atherosclerosis via its cholesteryl ester component. Higher concentrations of Lp(a) are also associated with other coronary risks, especially in the presence of elevated LDL-C or apo B

concentrations (Berg, Frey, Baumstark, Halle, & Keul, 1994; Durstine et al., 2000; Kwiterovich, 2000). The conversion of plasminogen to plasmin slows down when Lp(a) competes with plasminogen-binding sites on the surface of endothelial cells, which consequently promotes the process of thrombosis. By stimulating plasminogen activator inhibitor-1 synthesis, Lp(a) can promote thrombosis (Kwiterovich, 2000).

High-density Lipoprotein Cholesterol (HDL-C) Metabolism

The HDL particle is composed of a heterogenous lipoprotein family with cholesterol esters and TG in the core and apolipoproteins, phospholipids, and unesterified cholesterol in the outer amphipathic layer (Kashyap, 1998). The HDL molecule is synthesized *de novo* in the liver and small intestine, and contains various apolipoproteins including apo A-I, apo C-I, apo C-II, and apo E. Approximately 70% of the apolipoprotein content of HDL-C is apo A-I (Lewis & Rader, 2005).

The primary roles of HDL particle in lipid metabolism are to serve as a reservoir of apolipoproteins (e.g., apo E and apo C-II), a site for cholesterol esterification and unesterified cholesterol uptake, and a transporter for cholesterol to the liver (Champe et al., 2005). Since cholesterol cannot directly be hydrolyzed in most cells, a specific lipoprotein such as HDL-C is required to return cholesterol to the liver for catabolism. This process is known as the reverse cholesterol transport (RCT) pathway, and is mediated by HDL-C (Smolin & Grosvenor, 2002; Wang & Briggs, 2004).

The RCT pathway begins with the efflux of cholesterol and phospholipids from the peripheral tissues to lipid-poor apo A-I (Lewis & Rader, 2005; von Eckardstein, Nofer, & Assmann, 2001). This cholesterol and phospholipid efflux is mediated by the ATP-

binding cassette transporter 1 (ABCA 1 or ABC 1). The ABCA 1 transporter is an important mediator for, not only apo A-I lipidation, but the RCT pathway as well (Attie, Kastelein, & Hayden, 2001). Hypoalphalipoproteinemic individuals with mutations in the ABCA 1 gene (Marcil et al., 1999) and patients with Tangier disease (Rust et al., 1999) are associated with extremely low concentrations of HDL-C due to impaired lipidation and rapid catabolism of lipid-poor apo A-I (Lewis & Rader, 2005). Individuals with genetic apo A-I deficiency also have low, or absence of, HDL-C (Schaefer, Heaton, Wetzel, & Brewer, 1982). Although Aiello and colleagues (2002) reported that mice with macrophage-specific ABCA 1 deficiency had minimally reduced HDL-C concentrations, the researchers also reported that these mice had been associated with an increase in atherosclerosis. Thus, macrophage ABCA 1 is believed to be an important transporter for protection from atherosclerosis (Aiello et al., 2002). Hepatic ABCA 1 is also associated with a reduction of HDL-C concentrations and has an important role in the nascent HDL-C lipidation. It has been reported that mice with liver-specific ABCA 1 deficiency had a decrease of almost 80% of HDL-C concentrations (Vaisman et al., 2001).

Two important organs in the process of HDL-C catabolism are the liver and kidney. The clearance process of HDL-C can occur via two different pathways including a selective cholesterol removal pathway and a holoparticle HDL-C uptake pathway (Kashyap, 1998; Kwitcrovich, 1998). The selective cholesterol uptake pathway removes cholesterol from HDL-C without uptake of the whole HDL-C. However, another HDL-C catabolic pathway, known as a holoparticle HDL-C uptake, removes apo A-I by cubulin receptors in the kidney, ileum, and visceral yolk sac (von Eckardstein et al., 2001).

Cubulin, also known as gp280, is a 460-kDa endocytic receptor involved in the HDL-C holoparticle endocytosis and clearance of apo A-I (Hammad et al., 1999).

Two major HDL-C subfractions, HDL_2-C (density, 1.063 – 1.125 g/ml) and HDL_3-C (density, 1.125 – 1.21 g/ml), can be separated after density ultracentrifugation. With immunochemical methods, HDL particles can also be fractionated to either particles containing only apo A-I (LP-AI) and particles containing both apo A-I and apo A-II (LP-AI+AII) (Ganji, Kamanna, & Kashyap, 2003). Apo A-I secreted from the liver or small intestine becomes the discoidal pre-β HDL-C, the nascent form of HDL-C (Kwiterovich, 1998), which contains 2 copies of apo A-I per particle and approximately 10% of free cholesterol and phospholipids (Kunitake, La, & Kane, 1985). It has been reported that LP-AI particles are considered more favorable donors of cholesterol esters than are LP-AI+AII particles because elevated concentrations of LP-AI particles are negatively associated with coronary disease (Puchois et al., 1987; Rinninger et al., 1998). Rubin and colleagues reported that mice with over expression of human apo A-I had increased plasma HDL-C concentrations and been protected from the progression of atherosclerosis (Rubin, Krauss, Spangler, Verstuyft, & Clift, 1991). A transcriptional regulation of the apo A-I gene is primarily mediated by the *cis*-acting sequences in the proximal promoter of the apo A-I gene (Lewis & Rader, 2005).

Lecithin Cholesterol Acyl Transferase (LCAT) Activity

Lecithin cholesterol acyl transferase (LCAT) found on the surface of HDL particles is synthesized in the liver and plays an important role in the maturation of pre-β HDL-C (Lewis & Rader, 2005). After the cholesterol and phospholipid efflux from

peripheral tissues, free cholesterol on the surface of apo A-I is esterified by LCAT. The main function of LCAT is to convert cholesterol and lecithin to cholesterol esters on the surface of HDL particles by transferring a fatty acid from the C-2 position of lecithin to the C-2-OH of cholesterol and lysolecithin (Kwiterovich, 1998; Murray et al., 2000).

The enzymatic activity of LCAT is activated by apo A-I, apo A-IV, apo E, and apo C-I (Jonas, von Eckardstein, Kezdy, Steinmetz, & Assmann, 1991; Steinmetz & Utermann, 1985). After the over-expression of human LCAT in cholesterol-fed rabbits, HDL-C and apo A-I concentrations increased due to a decreased rate of HDL_2-C catabolism (Brousseau et al., 1997). A relative absence of apo A-I and a rapid catabolism of HDL-C caused by LCAT deficiency can result in a reduction of HDL-C (Fielding & Fielding, 1995). With a continuous efflux of free cholesterol to the nascent HDL-C molecules, free cholesterol on the surface of small HDL particles are progressively converted to cholesterol esters and stored in the HDL-C core (Kwiterovich, 1998; Lewis & Rader, 2005). This process will subsequently result in morphological changes of HDL particles from a discoidal disk shape to a spherical shape. The spherical shape of HDL particles, also known as HDL_3-C, continue to become larger particles (HDL_2-C) as they accept more cholesterol from extra hepatic tissues (Converse & Skinner, 1992; Wang & Briggs, 2004). Individuals with LCAT deficiency have elevated the rate of catabolism of cholesterol ester-poor apo A-I, and been significantly associated with lower HDL-C and apo A-I concentrations (Rader et al., 1994).

Scavenger Receptor Class B Type I (SR-BI)

Transferring cholesterol from peripheral tissues to HDL-C is mediated by a scavenger receptor class B type I (SR-BI), consisting of a 509-amino acid and 82-kDa glycoprotein. As a HDL-C receptor, SR-BI mediates HDL-C binding and the selective uptake of HDL-C (Wang & Briggs, 2004). Apo E serves as a facilitator for HDL-C when HDL particles bind to SR-BI on the surface of cells (Kwiterovich, 1998). The mechanism by which SR-BI mediates the selective HDL-C is somewhat different from the uptake of LDL-C via LDL-C receptors (Kozarsky et al., 1997). Since SR-BI has a high affinity to HDL-C, it accepts HDL-derived cholesterol esters without degradation of HDL-C apolipoproteins, which allows apo A-I to be recycled to the circulation (Acton et al., 1996). After the interaction with SR-BI, small, dense HDL particles (HDL_3-C) are formed, and continuously remodeled in plasma to form HDL_2-C particles. Cholesterol derived from HDL-C is eventually removed from the body either as bile acid or free cholesterol in the bile.

Although it is evident that SR-BI plays an important role in cholesterol metabolism, an association with HDL-C metabolism is not clearly understood. It has been reported that when SR-BI activity was reduced, HDL-C concentrations in plasma increased, whereas selective uptake of HDL-C decreased. On the other hand, when SR-BI was highly activated, the activity of HDL-C cholesteryl ester uptake increased while HDL-C concentrations in plasma decreased (Kwiterovich, 1998). Although mice with SR-BI deficiency increased HDL-C concentrations, apo A-I concentrations were not altered due to a defect in the selective uptake of HDL-C. However, mice with SR-BI

over-expression decreased both plasma HDL-C and apo A-I due to enhanced renal and hepatic clearance of cholesterol-depleted HDL particles after the interaction with SR-BI (Kozarsky et al., 1997; Ueda et al., 1999).

Hepatic Lipase (HL)

Hepatic lipase (HL), which is produced in the liver, is a 746-amino acid containing a 23-amino acid signal peptide and four potential glycosylation sites (Champe et al., 2005). The activity of HL influences the remodeling process of chylomicron remnants and other cholesterol particles such as LDL-C and HDL-C, and contributes to the RCT pathway (Deeb, Zambon, Carr, Ayyobi, & Brunzell, 2003). Elevated activity of HL yields smaller, denser lipoprotein particles from IDL-C remnants and large, buoyant LDL particles. It has been reported that individuals with an elevated HL activity produced a greater amount of smaller, denser LDL particles than individuals who had a lower HL activity (Zambon, Austin, Brown, Hokanson, & Brunzell, 1993). Thus, it has been suggested that the elevated HL activity is associated with atherogenic LDL phenotype B. However, it has to be noted that individuals with HL deficiency are associated with elevated TC and TG concentrations and lipid-rich LDL and HDL particles (Zambon, Deeb, Bensadoun, Foster, & Brunzell, 2000).

Unlike the positive relationship between LPL activity and HDL-C, HL is inversely related to HDL_2-C concentrations, but positively related to HDL_3-C concentrations. The main function of HL on HDL-C metabolism is to hydrolyze TG and phospholipids in HDL-C, and convert lipid-rich, buoyant HDL_2-C to smaller HDL_3-C (Deeb et al., 2003; Lokey & Tran, 1898; Lokey & Tran, 1989). After this lipid removal

process, HDL_3-C will return to the circulation and continue the RCT pathway (Kwiterovich, 2000; Wang & Briggs, 2004).

Cholesterol Ester Transfer Protein (CETP)

Cholesterol ester transfer protein (CETP) is a hydrophobic glycoprotein secreted from the liver and adipose tissues. The main role of CETP in lipoprotein metabolism is to transfer TG from apo B containing lipoproteins such as VLDL-C and LDL-C to HDL-C in exchange for cholesterol esters (Kwiterovich, 1998). For instance, CETP transfers cholesterol esters from buoyant, larger HDL_2-C to either VLDL-C or LDL-C in exchange for TG (Durstine et al., 2000; Wang & Briggs, 2004).

The overall effect of increased CETP activity on HDL-C is to deplete cholesterol esters and store more TG in HDL particles, which subsequently results in a reduction in size of HDL-C (Wang & Briggs, 2004). These TG-rich HDL particles will consequently be removed from the circulation via a holoparticle HDL-C uptake pathway in the kidney (Kashyap, 1998). A reduction in CETP activity is associated with anti-atherogenic effects since it retards the catabolic process of HDL_2-C in the liver. Hypertriglyceridemia and obesity are related to increased CETP activity (Riemens, van Tol, Sluiter, & Dullaart, 1998), and individuals with CETP deficiency are associated with hyperalphalipoproteinemia (Inazu et al., 1994).

Relationship between HDL-C and CAD

Apo-B containing lipoproteins such as Lp(a), VLDL-C remnants, and small, dense LDL-C are the major contributors to atherogenesis. Small, dense LDL particles are easily migrated and oxidized in the blood vessel wall and consequently ingested by

inflammatory cells via scavenger receptors. This oxidation process leads to formation of foam cells and ultimately to complex atherosclerotic lesions (Ito, 2002).

It is well documented that HDL-C has antiatherogenic and anti-inflammatory properties. The HDL particles may protect against atherosclerotic events via the RCT pathway and inhibit the LDL-C oxidation process (Kwiterovich, 2000). Accumulated lipid droplets from oxidized LDL particles in macrophages are associated with the formation of foam cells, which contribute to the development of atherosclerosis. In macrophages SR-A mediates the endocytosis of chemically modified LDL particles including oxidized lipids and apo B. Unlike LDL-C receptors, SR-A is not down-regulated in response to increased intracellular cholesterol concentrations. Thus, oxidized lipids accumulated in macrophages eventually lead to the formation of atherosclerotic plaque (Champe et al., 2005; Kwiterovich, 1998).

The HDL particles are primary acceptors for free cholesterol in macrophages and mediate the cholesterol efflux to remove cholesterol from macrophage cells. During the process of cellular cholesterol efflux the ABCA 1 transporter plays a key role. The continuous cholesterol removal process from macrophages to pre-β HDL particles is facilitated by the ABCA 1 and produces larger HDL_3-C, which eventually becomes HDL_2-C. This cholesterol efflux process is considered one of the direct inhibitory effects of HDL-C on the formation of foam cells and atherosclerotic lesions (Brewer, 2004; Wang & Briggs, 2004).

Decreased nitric oxide (NO) production caused by endothelial cell dysfunction is associated with atherosclerosis (Ramet et al., 2003). It is known that HDL-C has a

positive inhibitory effect on endothelial dysfunction during the development of atherosclerosis (Wang & Briggs, 2004). Endothelial cells release several relaxing factors such as NO, endothelium derived hyperpolarizing factor (EDHF), prostacyclin (PGI2), and endothelium-derived contracting factors (EDCFs). The impairment of endothelium-dependent vasodilations affect both NO and EDHF-mediated response, and are one of the risk factors for atherosclerosis (Ramet et al., 2003). It has been reported that HDL-C can stimulate the endothelial NO (eNOS) synthase expression (Kuvin et al., 2002; Ramet et al., 2003) and bioavailability (Spieker et al., 2002). Peroxidized lipids including monocyte chemotractic protein -1 (MCP-1) are formed during the oxidation of LDL-C, and promote an atherosclerotic process. The HDL particles contain antioxidant enzymes such as paraoxonase and platelet-activating factor acetylhydrolase, which degrade oxidized lipid droplets and inhibit LDL-C oxidation. Oxidized lipids in LDL-C can be reduced via CETP by transferring oxidized lipids from LDL-C to HDL-C (Christison, Rye, & Stocker, 1995).

Niacin and Lipids and Lipoproteins Metabolism

Overview of Niacin

Pellagra is a disease caused by a nutritional deficiency of vitamin B3 (Smolin & Grosvenor, 2002), and was first described approximately 300 years ago by Casal as "mal de la rosa." The symptoms of this disease include dermatitis, diarrhea, and dementia, which consequently leads to death (Cervantes-Laurean, McElvaney, & Moss, 1998). Although niacin was initially studied because of its association with pellagra, Altschul and colleagues in 1955 first introduced niacin as an antilipidemic agent since niacin in

gram doses favorably altered TC concentrations in both normo- and hypercholesterolemic individuals (Altschul et al., 1955).

Nicotinic acid or pyridine-3-carboxylic acid, another chemical term for niacin, is a water soluble B-complex vitamin (vitamin B3) (Drood, Zimetbaum, & Frishman, 1991). The recommended dietary allowance (RDA) of niacin for adult males and females is 16 mg/day and 14 mg/day, respectively (Institute of Medicine, 1998). Significant amounts of niacin can be found in red meat, liver, legumes, milk, eggs, alfalfa, cereal grains, yeast, fish, and corn (Smolin & Grosvenor, 2002).

Niacin Metabolism

The main biological functions of niacin in the body include the synthesis of fatty acids, cholesterol, and steroids, signal transduction, and the regulation of gene expression. Niacin is required as an important precursor for two essential enzymes, nicotinamide adenine dinucleotide (NAD^+) and nicotinamide adenine dinucleotide phosphase (NADP) (Ganji et al., 2003). The oxidized (NAD^+) and reduced (NADH) forms of enzymes are involved in many biological oxidation-reduction reactions such as mitochondrial electron transport and numerous enzyme reactions. In metabolic reactions NAD^+ is used to transfer the potential free energy stored in carbohydrates, lipids, and proteins to NADH to form adenosine triphosphate (ATP) (Cervantes-Laurean et al., 1998).

Figure 1 describes a detailed biochemical pathway of niacin and nicotinamide. In niacin metabolism, dietary L-tryptophan is first converted to nicotinic acid monoucleotide (NicMN), which is, in turn, converted to nicotinic acid dinucleotide (NicAD). In the presence of NAD synthetase, NicAD is converted to NAD^+, which has a

number of metabolic opportunities including the formation of nicotinamide, NADP, nicotinamide 5'-mononucleotide (NMN), cyclic ADP-ribose and nicotinic acid dinucleotide phosphate (NAADP). Nicotinamide is converted to either NA via the enzyme nicotinamidase or NMN via nicotinamide-5-phosphorobosyltransferase (NamRPTase), which can be converted to NAD+ (Cervantes-Laurean et al., 1998; Hageman & Stierum, 2001).

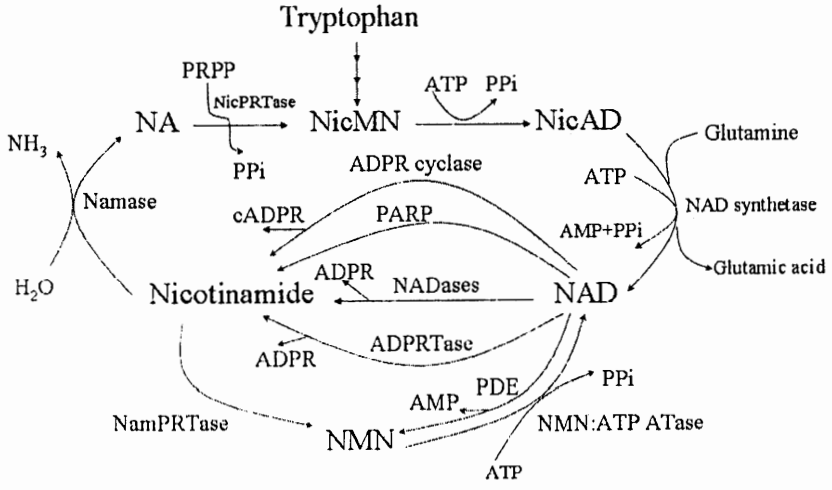

Figure 1. The biochemical pathways of niacin and nicotinamide metabolism.

Note. Adapted from *Modern Nutrition in Health and Disease* (p. 403), by Cervantes-Laurean, N. D., McElvaney, G., & Moss, J., 1998, Baltimore, MD: Lippincott Williams & Wilkins. Copyright 1998 by the Lippincott Williams & Wilkins. ADPRTase = adnosine diphosphate ribosyltransferase, NA = niacin, NAD = nicotinamide adenine dinucleotide, NamPRTase = nicotinamide-5-phosphoribosyltransferase, NicAD = nicotinic acid adenine dinucleotide, NicMN = nicotinic acid mononucleotide, NicPRTase = nicotinic acid phosphoribosyltransferase, PARP = polyadenosine diphoshate ribosylpolymerase, PDE = phosphodiesterase.

Absorption of low doses of niacin is mediated by sodium-dependent facilitated diffusion whereas the passive diffusion is the principal mechanism of absorption of niacin at higher doses (Berg, 1997). According to its dissolution and absorption rate, niacin is metabolized in the liver via two different pathways, the conjugative and the amidation pathways as described in Figure 2.

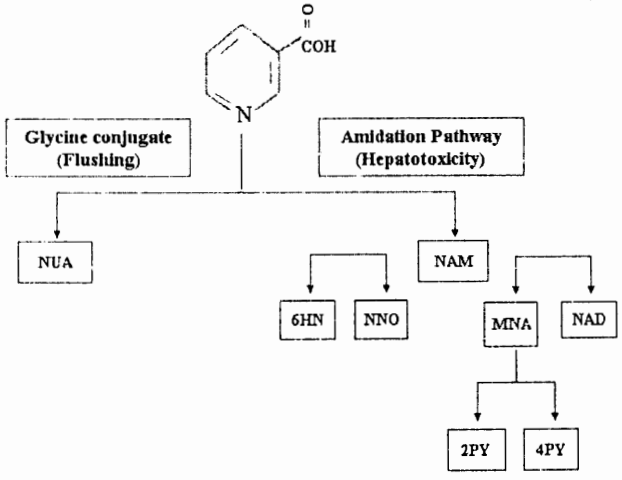

Figure 2. Two different pathways of niacin metabolism.

Note. Adapted from "Overview of niacin formulations: Differences in pharmacokinetics, efficacy, and safety," by Pieper, A. J., 2003, *American Journal of Health-System Pharmacists, 60*, p. S10. Copyright 2003 by American Society of Health-System Pharmacists. MNA = N-metylnicotinamide, NAD = nicotinamide adenine dinucleotide, NAM = nicotinamide 6-hydroxynicotinamide, NNO = nicotinamide-N-oxide, NUA = nicotinuric acid, 2PY = 2 pyridine metabolites, 4PY = 4 pyridine metabolites.

It is known that IR niacin has a rapid dissolution and absorption rate, and quickly saturates the amidation pathway causing most of niacin to be metabolized via the conjugative pathway. The conjugative pathway leads to the formation of glycine conjugates of niacin, such as nicotinuric acid (NUA), which is associated with vasodilation and flushing side effects (Pieper, 2003). However, SR niacin is more slowly released and metabolized, causing the most of niacin metabolized via the amidation pathway. This amidation pathway is associated with the hepatotoxicity side effect due to its slow dissolution rate in the liver, and forms nicotinamide and its oxidized products, 2- and 4-pyridine metabolites (Piepho, 2000).

Pharmacokinetics of Different Types of Niacin

As briefly mentioned above, niacin, based on its dissolution rate, can be classified to three different formulations such as IR-, SR-, and ER niacin. It has been reported that IR niacin favorably modifies blood lipids and lipoproteins, but at the same time it causes a relatively high incidence of flushing side effects characterized by redness and itching (Knopp et al., 1985).

In the mid 1960's, SR niacin was introduced to replace ER niacin by reducing the flushing side effects. However, SR niacin failed to be approved by the Food and Drug Administration (FDA) because it caused other adverse effects such as gastrointestinal intolerance and hepatotoxicity. A dissolution rate of ER niacin is between IR and SR niacin formulations, and ER niacin such as Niaspan® (KOS pharmaceuticals, Miami FL) is widely recommended to treat dyslipidemia because it positively alters blood lipids and lipoproteins and minimizes the adverse effects as well (Knopp et al., 1998; McKenney,

2003; Morgan et al., 1998). The characteristics of the three different formations of niacin and its common side effects are presented in Table 3.

Table 3

The Characteristics of Three Different Niacin Formulations and its Side Effects

Forms	Dissolution Rate	FDA	Side Effects
IR	Immediate release	Yes	Flushing, redness, and itching
SR	Sustained release	No	Gastrointestinal intolerance and hepatotoxicity
ER	Between IR and ER	Yes	Improved tolerability and safety characteristics

Note. FDA = Food and Drug Administration, ER = extended-release, IR = immediate-release, SR = sustained-release.

To compare the efficacy of IR and SR niacin, 71 hyperlipidemic patients randomly received either IR or SR niacin for 6 months. During the first month, the dose was increased up to 1,500 mg/day and the final dose of 3,000 mg/day thereafter. As compared with SR niacin (9%), IR niacin significantly increased HDL-C (26%) from baseline concentrations. However, the overall reductions in TC and LDL-C were similar for both IR and SR niacin (Knopp et al., 1985).

Knopp and colleagues have also examined the efficacy of IR and ER niacin using 223 dyslipidemic patients, who received placebo, IR, or ER niacin for 16 weeks. After gradually increasing doses, the final dose of 3,000 mg/day of IR niacin (3 × 1,000 mg/day) was given to the IR niacin group, while the final dose of 1,500 mg/day of ER niacin was given once a day at bedtime to the ER niacin group. At the same doses of 1,500 mg/day, both ER and IR niacin had similar lipid modifying effects including

reductions in TG (17%), TC (8%), apo B (12%), apo E (8%), Lp(a) (13%), and LDL-C (12%), and increases in total HDL-C (19%), HDL_2-C (35%), HDL_3-C (16%), and apo A (7%). When the dose of IR niacin was increased up to 3,000 mg/day, lipid modifying effects were almost doubled as compared with the IR niacin dose of 1,500 mg/day (Knopp et al., 1998).

Each niacin formulation has a different time to reach peak serum concentrations. For instance, IR niacin reaches its peak serum concentration in 45 min while ER niacin takes 4 to 5 hr after ingestion. The bioavailability of niacin can be maximized when niacin is ingested with food (Pieper, 2003). One of the common side effects of niacin is flushing in the face, neck, and chest, which is caused by an increased blood flow in cutaneous blood vessels. The niacin-induced flushing side effect is transient and tolerated with continued administration of niacin. The flushing side effect usually occurs within 20 min following niacin ingestion, and IR niacin is highly associated with the flushing side effect. However, ER niacin taken once daily either as monotherapy or in combination with other lipid-lowering drugs has the same antilipidemic effects with less flushing and hepatotoxicity side effects than IR and SR niacin, respectively (Goldberg, 2004; Morgan et al., 1998).

Recommended doses of IR and ER niacin for adults are up to 3,000 mg/day and 2,000 mg/day, respectively. Administration of niacin on an empty stomach is not recommended. The use of a 325 mg dose of aspirin or ibuprofen (200 mg) 30 min prior to taking niacin helps minimize the potential for flushing side effects (Whelan, Price, Fowler, & Hainer, 1992).

Antilipidemic Effects of Niacin

Figure 3 describes the antilipidemic effects of niacin. It has been reported that niacin lowers TC, LDL-C, VLDL-C, Lp(a), apo B-100, and TG concentrations and increases apo A and HDL-C concentrations (Abourjaily, 2001; Carlson, 2005). Although the mechanism by which niacin positively modifies lipid and lipoprotein profiles is not clearly established, it is known that the primary antilipidemic action of niacin begins with a reduction in adipose lipolysis, resulting in decreased mobilization of plasma FFAs (#1 in Figure 3) (Carlson, 2005; Crouse, 1996; Grundy et al., 1981; Piepho, 2000; Snyder, 1990).

Non-esterified fatty acids in plasma are precursors for hepatic TG synthesis, leading to the secretion of VLDL. Niacin also lowers apo B, a necessary componenet for VLDL synthesis in the liver (#2 in Figure 3). A reduced mobilization of FFAs from adipose tissues contributes to a decrease in uptake of FFAs by the liver and thereby reduces the hepatic synthesis of TG (#3 in Figure 3) and VLDL (Karpe & Frayn, 2004). This reduced hepatic synthesis of TG is considered a secondary effect of niacin in the liver. However, Ganji and colleagues (2004) reported that niacin directly decreases a hepatic synthesis of TG by inhibiting hepatic diacylglycerol acyltransferease 2, the rate limiting enzyme for TG synthesis. In addition, niacin can decrease the formation of fatty acyl CoA, a substrate for TG, by directly inhibiting acetyl CoA in the liver (Ganji et al., 2004).

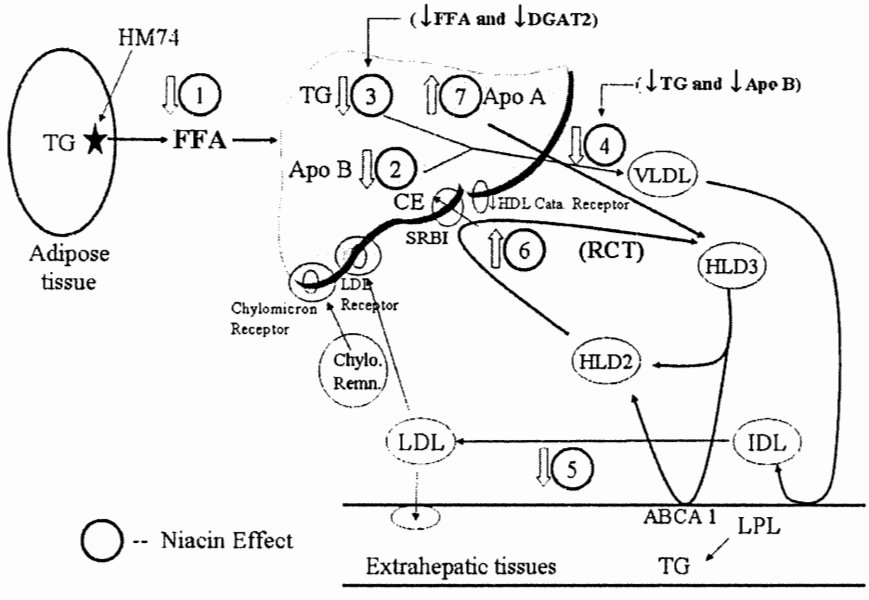

Figure 3. Effects of niacin on blood lipid and lipoprotein metabolism.

Note. ABCA1 = ATP (adenosine triphosphate)-binding cassette transporter 1, Apo = apolipoprotein, CE = cholesterol ester, Chylo Remn. = chylomicron remnants, DGAT2 = diacylglycerol acyltransferase 2, FFA = free fatty acids, HDL = high-density lipoprotein, HM 74 = human homologue of murine PUMA-G (protein upregulated in macrophages by interferon-γ), IDL = immediate-density lipoprotein, LDL = low-density lipoprotein, Lp(a) = lipoprotein (a), LPL = lipoprotein lipase, RCT = reverse cholesterol transport, SRB1 = scavenger receptor class B type 1, TG = triglyceride, VLDL = very low-density lipoprotein.

A reduced hepatic synthesis of TG may result in the secretion of smaller VLDL particles containing less TG (#4 in Figure 3). The majority of LDL particles are produced by catabolism of VLDL particles via a formation of IDL or VLDL remnants (Carlson,

2005; Ganji et al., 2003; Ito, 2002). Therefore, a reduction in the amount of VLDL-C available for catabolism may contribute to a reduction in LDL-C concentrations (#5 in Figure 3) (Drood et al., 1991). Grundy and colleagues suggested other possible explanations for niacin-induced LDL-C reduction, including an increase in hepatic clearance of IDL-C, thereby limiting the conversion of IDL-C to LDL-C, and consequently decreasing VLDL-independent synthesis of LDL-C (Grundy et al., 1981).

Another antiatherogenic effect of niacin is to shift the LDL particle size distribution from more atherogenic small, dense particles (phenotype B) to buoyant, large particles (phenotype A) that are less atherogenic. This positive phenotype shift may result from the niacin-induced reduction of TG-rich VLDL particles, which, in turn, inhibit the formation of small, dense LDL particles (Morgan et al., 2003; Morgan, Carey, Lincoff, & Capuzzi, 2004). Niacin may indirectly stimulate some nuclear transcription factors such as a peroxisome proliferator activated receptor γ (PPARγ) to translocate into the nuclesus (Rubic, Trottmann, & Lorenz, 2004). It is known that PPARγ has anti-diabetic and anti-atherosclerotic effects in both adipocytes and skeletal muscles (Kota, Huang, & Roufogalis, 2005).

The most beneficial antilipidemic effect of niacin is to increase HDL-C (Sprecher, 2000). The relationship between niacin and HDL-C metabolism is not clearly understood. However, one of the possible explanations for a niacin-induced increase in HDL-C concentrations in plasma is caused by selectively blocking hepatic catabolism of HDL particles containing apo A-I, without affecting cholesterol ester removal (Ganji et al., 2003; Jin, Kamanna, & Kashyap, 1997; Sprecher, 2000), which thereby augments the

RCT pathway (#6 in Figure 3) (Kashyap, 1998). Another explanation may be related to an increase in apo A-1 production (#7 in Figure 3) and a shift in the distribution of HDL-C subfractions such as an increase in the HDL_2-C to HDL_3-C ratio (Jin et al., 1997; Sakai, Kamanna, & Kashyap, 2001). As an antiatherogenic agent, niacin stimulates the ABCA 1-induced transfer of cholesterol from macrophages for uptake by HDL-C. This direct effect of niacin on macrophages may explain its antiatherosclerotic mechanism and be directly related to the HDL-C-raising effect (Rubic et al., 2004).

Niacin Receptors: HM 74A & PUMA-G

The niacin-induced reduction of lipolysis in adipose tissue is caused by inhibiting hormone-sensitive triglyceride lipase. As described in Figure 3, the antilipolytic activity occurs when the stimulation of cyclic adenosine monophosphate (cAMP) in adipose tissue is inhibited by a G_i-protein-mediated inhibition of adenylyl cyclase (Benyo et al., 2005; Mahboubi et al., 2005; Tunaru et al., 2003; Zhang et al., 2005).

The human homologue of murine PUMA-G (protein upregulated in macrophages by interferon-γ, HM 74A) is considered a niacin receptor, which has a high affinity for niacin (Knowles, Te Poele, Workman, & Harris, 2006). There are two G protein-coupled receptors (GPCRs) for niacin such as high (HM 74A; GPR 109A) and low (HM 74; GPR 109B) affinity receptors (Mahboubi et al., 2005; Zhang et al., 2005). These niacin receptors are mostly found in white and brown adipose tissues with a few in spleen and macrophages, suggesting that antilipidemic effects of niacin observed in the liver are secondary to alterations in lipids and lipoproteins (Lorenzen et al., 2001).

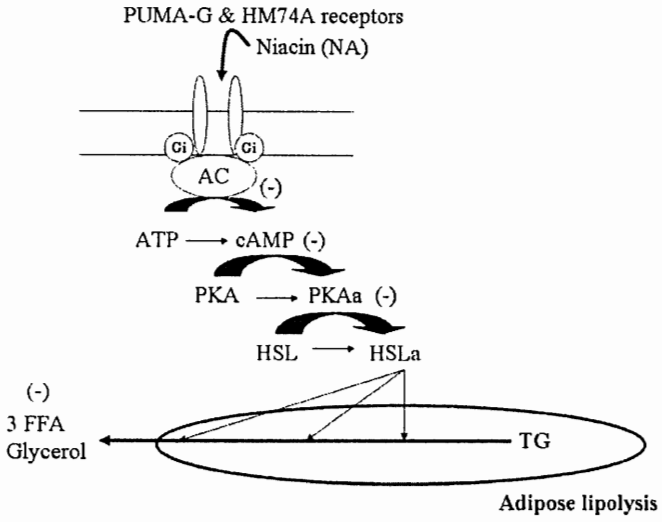

Figure 4. Niacin receptors, PUMA-G and HM74 A, and anti-lipolytic properties of niacin in adipose tissue.

Note. AC = adenylyl cyclase, ATP = adenosine triphosphate, cAMP = cyclic adenosine monophosphate, FFA = free fatty acids, HM 74A = human homologue of murine PUMA-G, HSL = hormone-sensitive triglyceride lipase, HSLa = HSL activated, PKA = protein kinase, PKAa = PKA activated, PUMA-G = protein upregulated in macrophages by interferon-γ, TG = triglycerides.

However, Ganji and colleagues reported that niacin directly inhibits acetyl CoA and diacylglycerol acyltransferase 2 in the liver, leading to a reduced formation of TG and apo B (Ganji et al., 2004). Binding of niacin to PUMA-G or HM 74A in adipose tissues results in a G_i-protein-mediated decrease in cAMP activities. The niacin-induced reductions of plasma FFAs and TG concentrations were abrogated in mice with PUMA-G

deficiency, indicating that PUMA-G mediates the antilipolytic and lipid-lowering effects of niacin (Tunaru et al., 2003).

Niaspan and its Antilipidemic Effects on Lipids and Lipoproteins

Niaspan is a widely prescribed ER niacin to treat dyslipidemia, and it has been reported that the doses of 1,000 – 2,000 mg/day of Niaspan reduces LDL-C and TG concentrations by 10 – 25% and 20 -- 50%, respectively and increases HDL-C concentrations by 10 – 35% (Abourjaily, 2001). Several clinical studies have investigated the effects of Niaspan (1,000 – 4,000 mg/day) on lipids and lipoproteins, and found a positive influence of Niaspan on almost all lipids and lipoproteins including a reduction of TG, VLDL-C, LDL-C, apo B, Lp(a), and small, dense LDL particles, and an elevation in apo A, total HDL-C, and ratio of HDL_2-C to HDL_3-C (Goldberg, 1998; Goldberg et al., 2000; Guyton et al., 1998; Kane et al., 2001; Knopp et al., 1998; Morgan et al., 1998; Pan et al., 2002; Sakai et al., 2001).

Pan and colleagues (2002) examined the effects of Niaspan on the atherogenic lipid profile (APL) in 36 diabetic patients (30 men and 6 women), and the APL was defined by LDL peak particle diameter $\leq$ 26.3 nm, HDL_2-C < 40% of total HDL-C, and Lp(a) $\geq$ 25 mg/dl. All participants ingested Niaspan with an initial dose of 500 to 750 mg/day, and the doses increased continuously over a period of 1 to 4 months (mean dose of 2,819 mg/day, ranging from 1,000 to 4,000 mg/day). The results indicated that Niaspan increased LDL peak particle diameter by 0.9 nm while small, dense LDL-C concentrations decreased from 30 to 17 mg/dl. A total concentration of HDL-C increased from 42 to 57 mg/dl, HLD_2-C increased from 34 to 51%, and Lp(a) decreased from 37 to

23 mg/dl. Total LDL-C and TG concentrations were also reduced by 18 and 48%, respectively (Pan et al., 2002).

Knopp and colleagues (1998) reported that after 8 weeks of 1,500 mg/day of Niaspan treatment in 223 hypercholesterolemic men and women, all blood lipids and lipoproteins were favorably altered from baseline including reductions in TC (-8%), TG (-16%), LDL-C (-12%), apo B (-12%), apo E (-9%), and Lp(a) (-15%) and elevation in HDL-C (20%), HDL_2-C (37%), HDL_3-C (17%), and apo A-I (8%) (Knopp et al., 1998). With the Niaspan treatment (an average dose of 2,000 mg/day) for almost two years, patients with CAD increased HDL-C by 28% and decreased LDL-C, TG, and Lp (a) by 20%, 28%, and 40%, respectively (Capuzzi et al., 1998; Guyton & Capuzzi, 1998). In another study, Niaspan therapy (an average dose of 2,000 mg/day) for 48 and 96 weeks decreased LDL-C (18%), apo B (15%), TC (10%), Lp(a) (34%), and TC to HDL-C ratio (30%) and increased HDL-C (28%) (Guyton & Capuzzi, 1998).

Dose-response efficacy of Niaspan (from 500 to 3,000 mg/day) was examined using 131 patients with primary hyperlipoproteinemia. Participants were randomly assigned to the placebo (n = 44) or Niaspan group (n = 87). Participants in the Niaspan group ingested 375 mg of Niaspan per day during the first week, and the dose was increased to 500 mg/day at the second week. Dosing was then continuously increased by 500 mg/day at 4-week intervals to a maximum of 3,000 mg/day for 25 weeks. There were significant reductions in LDL-C (3% at 500 mg, 9% at 1,000 mg, 14% at 1,500 mg, 17% at 2,000mg, 22% at 2,500 mg, and 21% at 3,000 mg) and apo B (2% at 500 mg, 7% at 1,000 mg, 14% at 1,500 mg, 16% at 2,000 mg, 22% at 2,500 mg, and 20% at 3,000 mg).

Significant dose-dependent reductions from baseline were observed in TC (16%), TG (44%), VLDL-C (45%), Lp(a) (26%), and the ratio of TC to HDL-C (35%) while HDL-C (30%), HDL_2-C (72%), and apo A-I (12%) concentrations increased with the Niaspan treatment (Goldberg et al., 2000).

Five double-blind, placebo-controlled studies related to ER niacin were analyzed to examine possible gender differences in blood lipids and lipoproteins. A total of 432 participants with dyslipidemia (mean age = 54 yrs, men (n) = 277, and women (n) = 155) received ER niacin at various doses (from 500 to 3,000 mg/day). The results of this meta-analysis revealed that women may experience more beneficial effects of niacin than do men at various doses. For example, a reduction of LDL-C from the baseline in women was significantly greater than in men at 1,000 mg (women = 7% vs. men = 0.2%), 1,500 mg (women = 11% vs. men = 6%), 2,000 mg (women = 15% vs. men = 7%), and 3,000 mg (women = 29% vs. men = 18%). A significant reduction of TG concentrations in women was also observed at doses of 1,500 mg (women = 29% vs. men = 20%). With the Niaspan treatment, HDL-C increased and Lp(a) decreased in both groups, but there were no significant gender differences in these lipoproteins (Goldberg, 2004).

The antilipidemic effects of Niaspan seem to plateau when the doses are greater than 2,000 mg/day, but the incidence of side effects increases with doses higher than 2,000 mg/day. Therefore, the recommended maximum dosage of Niaspan is 2,000 mg/day. However, as low as 500 mg/day of Niaspan can positively alter blood lipids and lipoproteins, and women may benefit from the lower end of the dosing ranges more than men (Goldberg, 1998).

The effects of niacin on glucose and insulin responses are not entirely clear. The mechanism by which niacin causes hyperglycemia or insulin resistance in patients with type 2 diabetes (Garg & Grundy, 1990) or in healthy individuals (Kahn et al., 1989), respectively, is not fully understood. To investigate the effects of niacin on insulin sensitivity, 15 non-diabetic male participants received 500 mg/day of ER niacin during the first week of the study and the dose was increased to 1,000 mg/day at the second week. Insulin sensitivity was assessed by a euglycemic-hyperisulinemic clamp. The results indicated that ER niacin reduced mean insulin sensitivity by approximately 15% (glucose infusion rate, 49.6 vs. 42.5 μmol/L) (Poynten et al., 2003). In another study, 13 patients with type 2 diabetes, who received 4,500 mg/day of IR niacin (3 × 1,500 mg/day) for 8 weeks, showed deteriorated glycemic control. Fasting glucose concentrations rose an average of 16% (from 7.8 to 9.1 mmol/L), and concentrations of glycosylated hemoglobin increased by 21% (Garg & Grundy, 1990).

However, several studies reported that niacin improved or maintained blood glucose concentrations (Pan et al., 2002; Squires et al., 1992). For instance, mean hemoglobin A1c concentrations were reduced (from 7.5% to 6.5%) in 36 diabetic patients after the Niaspan treatment (mean dose, 2,819 mg/day, ranging from 1,000 to 4,000 mg/day) (Pan et al., 2002). Squires and colleagues (1992) also reported that the niacin treatment for 7 months (mean of 1,297 mg/day of time-release niacin) improved lipid and lipoprotein profiles in 63 dyslipidemic individuals and fasting glucose concentration was not changed (99 mg/dl to 101 mg/dl) by the niacin treatment (Squires et al., 1992). Unlike SR niacin, Niaspan may not change the liver enzymes including aspartate

aminotransferase (AST) and alanine aminotransferase (ALT) (Goldberg et al., 2000; Guyton et al., 1998; Morgan et al., 1998).

Summary of Niacin and Lipid and Lipoprotein Profiles

Many investigators have reported the beneficial effects of niacin on blood lipid and lipoprotein profiles including a reduction of TG, TC, VLDL-C, LDL-C, apo B, and Lp(a), and an increase in HDL-C, apo A-I, and HDL_2-C to HDL_3-C ratio. Although these changes are dependent upon the dosage, a minimum of 500 mg/day of Niaspan may lead to significant changes in lipid and lipoprotein profiles. A common side effect of flushing occurs with IR niacin due to its fast metabolism rate by the glycine conjugate pathway, and SR niacin develops a hepatotoxicity side effect because of its slow metabolism rate by the amidation pathway. However, Niaspan is highly recommended to treat dyslipidemia because it favorably alters lipids and lipoproteins and minimizes the adverse side effects as well.

Exercise and Lipid and Lipoprotein Metabolism

Physical activity can improve CVD risk factors and other health problems by positively modifying blood lipids and lipoproteins (Dowling, 2001; Durstine et al., 2000; Lamarche et al., 1997). Extensive research examining the effects of exercise on blood lipid and lipoprotein profiles has been conducted on men (Bermingham, Mahajan, & Neaverson, 2004; Crouse, O'Brien, Grandjean, Lowe, Rohack, & Green, 1997; Crouse, O'Brien, Grandjean, Lowe, Rohack, Green et al., 1997; Ferguson et al., 2003; Grandjean et al., 2000; Houmard et al., 1994; Sgouraki, Tsopanakis, Kioussis, & Tsopanakis, 2004; Thompson et al., 1997), whereas few studies have investigated women, particularly

postmenopausal women (Alhassan et al., 2006; Binder, Birge, & Kohrt, 1996; Blumenthal et al., 1991; Boutcher, Meyer, Craig, & Astheimer, 2003; Grandjean, Crouse, O'Brien, Rohack, & Brown, 1998; Weise, Grandjean, James, Womack, & Crouse, 2005). Moreover, the results of existing research examining the responses of lipids and lipoproteins to exercise in women are equivocal and inconclusive due to a lack of information available. Nevertheless, based on the existing publications, it has been carefully stated that exercise may be less effective in women than men on positive changes in blood lipids and lipoproteins (Hill et al., 1989; Williams, 1993; Williams, 1996).

Although there are some physiological and metabolic differences between men and women including total body fatness and distribution, bone structure, hormonal difference, etc., both men and women can equally benefit from exercise (Asikainen et al., 2004; Durstine et al., 2002; Gordon et al., 1998; Kelley et al., 2004; Leon et al., 2000; Savage, Brochu, & Ades, 2004). It has been well documented that not only long-term exercise training (Alhassan et al., 2006; Andersen et al., 1999) but also a single bout of exercise favorably alters blood lipids and lipoproteins (Durstine et al., 2002; Ferguson et al., 2003; Grandjean et al., 2000; Weise et al., 2005).

Effects of Chronic Exercise Training on Blood Lipids and Lipoproteins

According to the cross-sectional studies, physically active or trained individuals have generally lower TC, LDL-C, TG, and TC to HDL-C ratio, and higher HDL-C concentrations as compared with inactive or untrained individuals (Durstine et al., 2000; Kelley et al., 2004; Lippi et al., 2006). In spite of the fact that exercise positively

influences the blood lipid and lipoprotein profiles, the responses of TC and LDL-C to exercise training are inconsistent (Alhassan et al., 2006; Altena, Michaelson, Ball, Guilford, & Thomas, 2006; Andersen et al., 1999; Boreham et al., 2005; Grandjean et al., 1998; Wilund, Ferrell, Phares, Goldberg, & Hagberg, 2002), while the increased HDL-C and decreased TG concentrations are often observed in response to exercise training (Alhassan et al., 2006; Fahlman, Boardley, Lambert, & Flynn, 2002; Houmard et al., 1994; Seip et al., 1993; Thompson et al., 1997).

The Response of TC to Chronic Exercise. It is evident that plasma TC concentrations generally do not increase in response of exercise training. However, the response of TC to exercise training is equivocal and not completely understood. Some studies have reported no change in TC (Boreham et al., 2005; Grandjean et al., 1998; Houmard et al., 1994; Maclean, Tanner, Houmard, & Barakat, 2001; Ready et al., 1996; Sunami et al., 1999; Szmedra, LeMura, & Shearn, 1998; Wilund et al., 2002), while some have reported a 4 – 20% (7 – 27 mg/dl) reduction of TC after exercise training (Alhassan et al., 2006; Andersen et al., 1999; Binder et al., 1996; Blumenthal et al., 1991; Grandjean, Oden, Crouse, Brown, & Green, 1996).

Different study settings including age, gender, and intensity, volume, and mode of exercise have been utilized to examine the response of plasma TC to exercise training. For example, Grandjean and colleagues had postmenopausal women exercise at 50 – 70% VO_2max for 12 weeks until 800 – 1,200 kcal/wk were expended, and reported no change in TC concentrations after the training program (Grandjean et al., 1998). Step exercise at moderate intensity (70 – 85% VO_2max) for 8 – 14 weeks did not alter plasma

TC in men (Houmard et al., 1994) and sedentary young women (Boreham et al., 2005; Sunami et al., 1999). Similarly, plasma TC concentrations did not change in older men (Sunami et al., 1999) and women (Fonong et al., 1996; Ready et al., 1996; Svendsen, Hassager, & Christiansen, 1994) after 8 – 24 weeks of exercise training (3 – 5 day/wk for 45 – 60 min/day) at a moderate intensity (50 – 75% VO_2max) on either the treadmill or cycle ergometer.

In contrast, a significant reduction of TC was observed in men and women after exercise training. For instance, following 10-weeks of exercise training at 70% HRmax requiring 1,500 – 2,000 kcal/wk of energy expenditure, TC concentrations decreased by 13% (25 mg/dl) in men (Hill et al., 1989). Similarly, an approximate 5 – 6% (11 – 13 mg/dl) reduction of TC was observed in women after moderate exercise training (60% VO_2max) (Binder et al., 1996; Blumenthal et al., 1991; Ready et al., 1995). Interestingly, a significant exercise-induced reduction of TC was no longer significant when confounding factors such as body weight, caloric intake, alcohol consumption, and smoking were statistically controlled (Durstine et al., 2002).

The Response of LDL-C to Chronic Exercise. The relationship between exercise training and LDL-C is not completely understood although exercise training generally does not increase LDL-C concentrations. A significant exercise-induced reduction (19 – 28 mg/dl) of LDL-C was reported in some studies (Alhassan et al., 2006; Andersen et al., 1999; Binder et al., 1996; Boreham et al., 2005; Fahlman et al., 2002; Grandjean et al., 1996), whereas some have reported no change in LDL-C in response to exercise training (Blumenthal et al., 1991; Crouse, O'Brien, Grandjean, Lowe, Rohack, Green et al., 1997;

Fonong et al., 1996; Grandjean et al., 1998; Szmedra et al., 1998; Thompson et al., 1997; Wilund et al., 2002).

A reduction of LDL-C was observed after exercise training in sedentary men and women. For example, Altena and colleagues (2006) reported that either 4-weeks of continuous or intermittent exercise training significantly decreased LDL-C (8.4% or 7.0 mg/dl) in sedentary men and women (Altena et al., 2006). Similarly, following stair climbing exercise for 8 weeks, LDL-C was reduced by 8% (6.6 mg/dl) from baseline (83.1 mg/dl) in sedentary women (Boreham et al., 2005). However, Crouse and colleagues reported no change in LDL-C after 24-weeks of cycling exercise at two different intensities (80% or 50% VO_2max) in hypercholestrolemic men (Crouse, O'Brien, Grandjean, Lowe, Rohack, Green et al., 1997). Grandjean and colleagues also reported no change in LDL-C in women after a 12-week walking or jogging exercise training program (Grandjean et al., 1998).

The Response of TG and HDL-C to Chronic Exercise. Numerous studies, but not all (Blumenthal et al., 1991; Boreham et al., 2005; Crouse, O'Brien, Grandjean, Lowe, Rohack, Green et al., 1997), have frequently reported that exercise training decreases TG concentrations by 5 – 38 mg/dl and increases HDL-C concentrations by 2 – 8 mg/dl in men (Houmard et al., 1994; Seip et al., 1993; Thompson et al., 1997) and women (Alhassan et al., 2006; Andersen et al., 1999; Fahlman et al., 2002; Hill et al., 1989). In additional, several cross-sectional studies have reported that trained or active individuals have generally lower TG (18 to 77 mg/dl) and higher HDL-C (4 to 24 mg/dl) concentrations than untrained or sedentary counterparts (Dowling, 2001; Durstine et al.,

2002; Lippi et al., 2006).

Following exercise training for nearly one year, HDL-C concentrations increased 5% or 3 mg/dl, while TG concentrations decreased 20% or 26 mg/dl in both older men and women (Seip et al., 1993). Similarly, obese women (average BMI = 33 kg/m^2) significantly decreased plasma TG concentrations (18% or 24 mg/dl) and increased HDL-C concentrations by 9% or 5 mg/dl after exercise training (Andersen et al., 1999). Fahlman and colleagues also reported a reduction of TG (150 to 129 mg/dl) and TC to HDL-C ratio (4.2 to 3.4) and an increase in HDL-C (45 to 54 mg/dl) in older women after 10-weeks of exercise training (Fahlman et al., 2002). Interestingly, Savage and colleagues have suggested that there may be a gender-specific response of HDL-C to exercise training in individuals with CVD. After 12-weeks of cardiac rehabilitation exercise training, women, regardless of baseline HDL-C concentrations, significantly increased HDL-C, whereas only men who had lower baseline HDL-C increased HDL-C (Savage et al., 2004).

In contrast, several studies have failed to confirm the beneficial effects of exercise training on HDL-C and TG concentrations. For example, no changes in HDL-C and TG were observed in sedentary individuals after exercise training on a cycle ergometer at 75% VO_2max for 7 consecutive days (Maclean et al., 2001). Additionally, neither step nor cycle training increased HDL-C and reduced TG concentrations in sedentary young (Boreham et al., 2005) and older women (Fonong et al., 1996).

The Response of HDL-C Subfractions to Chronic Exercise. According to the recent meta-analysis research, exercise training can increase HDL_2-C by 11% (2.6 mg/dl)

in men and women (Kelley & Kelley, 2006), and promote a shift in small, dense HDL_3-C to large, less-dense HDL_2-C (Altena et al., 2006; Blumenthal et al., 1991; Crouse, O'Brien, Grandjean, Lowe, Rohack, Green et al., 1997).

Plasma HDL_2-C concentrations significantly increased by 1.2% or 0.2 mg/dl, while HDL_3-C concentrations decreased by 1.4% or 0.5 mg/dl in sedentary men and women after 4-week exercise training (Altena et al., 2006). Similarly, Sunami and colleagues also demonstrated an increase in both HDL_2-C (32.9 to 40.0 mg/dl) and HDL_2-C to HDL_3-C ratio (1.83 to 2.55) and a reduction in HDL_3-C (18.4 to 16.2 mg/dl) in older men and women after 20-weeks of cycle ergometer training (Sunami et al., 1999). Although total HDL-C concentrations do not change in response to exercise training, HDL-C subfractions may be favorably altered (Thompson et al., 2001). For example, Crouse and colleagues did not observe an increase in total HDL-C concentrations in hypercholesterolemic men following 24-weeks of exercise training, but HDL_2-C increased 82% (6.1 to 11.1 mg/dl) and HDL_3-C decreased 13% (39.5 to 34.2 mg/dl) (Crouse, O'Brien, Grandjean, Lowe, Rohack, Green et al., 1997).

In summary, the responses of TC and LDL-C to exercise training are equivocal, and only 25% of publications have reported a positive effect of exercise training on TC and LDL-C (Durstine et al., 2001). Exercise training alone may not influence TC and LDL-C in either healthy individuals or patients with CVD (Kelley, Kelley, & Franklin, 2006). However, exercise training can favorably shift small, dense LDL particles (phenotype B) to large, less-dense particles (phenotype A) (Altena et al., 2006; Halle et al., 1999). It has been noted that the exercise-induced reductions of TC or LDL-C

concentrations were generally associated with a minimum of 1,200 kcal/wk of energy expenditure (Durstine et al., 2001) and decreased body weight or percent body fat (Durstine et al., 2000; Kelley et al., 2004).

Sedentary or untrained individuals may increase HDL-C concentrations up to 6 mg/dl and reduce TG concentrations up to 20 mg/dl when they engage in aerobic exercise training requiring 1,500 to 2,200 kcal/wk (15 – 20 miles/wk) of energy expenditure (Durstine et al., 2001; Durstine et al., 2002). It has been reported that every 1 mg/dl increase in HDL-C is associated with a 2 – 3% reduction of CHD risks in men and women (Gordon et al., 1989). The Health, Risk Factors, Exercise Training and Genetics (HERITAGE) family study revealed that individuals with high initial TG and low HDL-C significantly increased HDL-C concentrations by 4.9% (Couillard et al., 2001), particularly the HDL_2-C subfraction with an increase in apo A-I (Leon et al., 2000). The HDL_2-C subfraction has a higher apo A-I to apo A-II ratio than does HDL_3-C. Therefore, an increase in the ratio of HDL_2-C to HDL_3-C indicates a favorable index in lowering CVD risks (Blumenthal et al., 1991).

Effects of a Single Bout of Exercise on Blood Lipids and Lipoproteins

Although many researchers have investigated the effects of a single bout of exercise on blood lipids and lipoproteins in men (Bermingham et al., 2004; Ferguson et al., 2003; Grandjean et al., 2000; Sgouraki et al., 2004; Vuorimaa, Ahotupa, Irjala, & Vasankari, 2005) and women (Imamura et al., 2000; Weise et al., 2005), the results of existing publications are inconsistent and equivocal. One of the explanations for this inconsistency is that each study had a different study setting such as gender, age, training

status, preexisting lipid concentrations, and different exercise mode, intensity, and volume (Crouse, O'Brien, Grandjean, Lowe, Rohack, Green et al., 1997; Durstine et al., 2000; Grandjean & Crouse, 2001).

However, it has been generally reported that a single bout of exercise may not influence TC, VLDL-C, and LDL-C concentrations, whereas a reduction of TG and an elevation in HDL-C are frequently observed in response to a single bout of aerobic exercise (Bermingham et al., 2004; Crouse et al., 1995; Ferguson et al., 2003; Grandjean et al., 2000; Kantor et al., 1987; Sgouraki et al., 2004; Weise et al., 2005).

The Response of TC to a Single Bout of Exercise. The response of TC immediately following or several days after a single bout of exercise is equivocal. Following a single bout of exercise, TC concentrations were elevated (Crouse, O'Brien, Grandjean, Lowe, Rohack, & Green, 1997; Sgouraki et al., 2004), reduced (Crouse et al., 1995; Ferguson et al., 2003; Foger et al., 1994; Grandjean et al., 2000; Kantor et al., 1987; Vuorimaa et al., 2005) or not changed (Angelopoulos, Robertson, Goss, Metz, & LaPorte, 1993; Bermingham et al., 2004; Davis, Bartoli, & Durstine, 1992; Durstine et al., 1996; Gordon et al., 1994; Imamura et al., 2000; Visich et al., 1996; Weise et al., 2005).

Grandjean and colleagues observed an approximate 3% reduction (217 to 210 mg/dl) of TC concentrations in sedentary normo- and hypercholesterolemic men immediately following a single bout of exercise requiring 500 kcal of energy expenditure (Grandjean et al., 2000). In another study, TC concentrations were reduced by 18% (19 mg/dl) in moderately trained men after a single bout of exercise expending more than 1,000 kcal of energy expenditure of (Ferguson et al., 2003). However, it has been noted

that if TC concentrations were reduced in response to a single bout of exercise, the magnitude of this reduction was relatively small (3 – 5%) and disappeared 24 hours after exercise (Grandjean & Crouse, 2001).

In contrast, some studies reported an elevation of TC immediately following or several days after a single bout of exercise in sedentary normo- (Crouse et al., 1995; Kantor et al., 1987) and hypercholesterolemic men (Crouse, O'Brien, Grandjean, Lowe, Rohack, & Green, 1997). In one study, TC concentrations increased by 13% (173 to 195 mg/dl) in trained and untrained men after the completion of maximal treadmill exercise until exhaustion (Sgouraki et al., 2004).

Following a relatively low volume (400 kcal) of a single bout of exercise (70% VO_2peak), TC concentrations did not change in normo- and hypercholesterolemic postmenopausal women (Weise et al., 2005). Similarly, both low (300 – 350 kcal) and high (600 – 700 kcal) volumes of a single bout of exercise at moderate exercise intensity (60 – 65% VO_2max) did not change TC concentrations in men (Biggerstaff, 2000; Kushnick, 2003).

The Response of LDL-C to a Single Bout of Exercise. Based on the existing literature, it is difficult to determine the effects of a single bout of exercise on LDL-C due to inconsistent results. Some studies have reported that following a single bout of exercise, plasma LDL-C concentrations decreased (Ferguson et al., 2003; Ferguson et al., 1998; Foger et al., 1994; Goodyear et al., 1990; Kantor et al., 1987; Vuorimaa et al., 2005), increased (Sgouraki et al., 2004; Thomas et al., 2004), or were not changed (Bermingham et al., 2004; Crouse, O'Brien, Grandjean, Lowe, Rohack, Green et al.,

1997; Davis et al., 1992; Grandjean et al., 2000; Visich et al., 1996; Weise et al., 2005).

Ferguson and colleagues reported a 9% reduction (170 to 155 mg/dl) of LDL-C concentrations following a single bout (70% VO_2max), high volume (> 1,100 kcal of energy expenditure) of exercise (Ferguson et al., 2003). In addition, an approximate 14% reduction of LDL-C was observed in trained men following prolonged-walking exercise (6 hours/day) for 2 days (Vuorimaa et al., 2005). In contrast, LDL-C concentrations in trained and untrained men were elevated by almost 12% (90 to 101 mg/dl) following the completion of maximal treadmill exercise testing (Sgouraki et al., 2004). Thomas and colleagues also observed elevated LDL-C (79.7 to 84.6 mg/dl) in recreationally active men after a single bout of treadmill exercise at 60% VO_2max for 60 min (Thomas et al., 2004).

Alternatively, total LDL-C concentrations were not altered in either normo- or hypercholesterolemic women following a single bout of exercise at 70% VO_2peak until 400 kcal were expended (Weise et al., 2005). Bemingham and colleagues observed no change in LDL-C in response to an acute 15-min interval arm ergomety exercise at 65 – 75% HRmax (Bermingham et al., 2004). Similarly, total LDL-C did not change in sedentary men following acute treadmill exercise at 60% VO_2max until expending either 350 (low volume) or 700 kcal (high volume) (Biggerstaff, 2000).

The Response of TG and HDL-C to a Single Bout of Exercise. The responses of TG and HDL-C to a single bout of exercise seem to be fairly consistent. The majority of studies often reported a significant decrease in TG and an increase in HDL-C concentrations immediately following and several days after a single bout of exercise

(Angelopoulos et al., 1993; Ferguson et al., 1998; Gordon et al., 1998; Grandjean et al., 2000; Kushnick, 2003; Weise et al., 2005).

It has been reported that both high-volume (> 800 kcal) and relatively low-volume (300 – 600 kcal) exercise yielded a reduction of plasma TG in men (Ferguson et al., 2003; Ferguson et al., 1998) and women (Weise et al., 2005). For example, an approximate 30% reduction of TG concentrations was observed in trained men after performing a single bout of exercise (70% VO_2max) until expending at least 800 – 1,500 kcal (Ferguson et al., 2003; Ferguson et al., 1998). After a single bout of exercise at 70% VO_2peak until expending 400 kcal, TG concentrations decreased by 8.5% (from 128 to 118 mg/dl) 24 hours following exercise in both normal- and hypercholesterolemic postmenopausal women. In addition, a non-significant exercise-induced reduction (122 mg/dl) of TG remained until 48 hours after exercise (Weise et al., 2005). Following a single bout of treadmill walking (65% VO_2max) requiring 600 kcal of energy expenditure, plasma TG concentrations in sedentary men were reduced by 25% (23 mg/dl), 27% (26 mg/dl), and 22% (21 mg/dl) at the 12-hour, 24-hour, and 48-hour period following exercise, respectively. In addition, an approximate 19% (18 mg/dl) reduction of TG was observed 12-hours after exercise when expending 300 kcal of energy expenditure (Kushnick, 2003).

It has been reported that total HDL-C concentrations may be elevated up to 34% in response to a single bout of exercise, and this exercise-induced elevation of HDL-C may last up to 4 days following exercise (Grandjean & Crouse, 2001). However, it has been suggested that a minimal exercise threshold may exist to significantly increase

HDL-C in different individuals (Durstine et al., 2001; Ferguson et al., 1998).

For instance, total HDL-C concentrations increased in trained individuals after a single bout of exercise expending more than 800 kcal. For example, after a single bout of exercise expending 1,100, 1,300, or 1,500 kcal of energy expenditure, total HDL-C in trained men increased 6, 6, or 12 mg/dl, respectively, at the 24-hour period following exercise, and this exercise-induced elevation of HDL-C remained 48 hours after exercise when expending 1,500 kcal of energy expenditure (Ferguson et al., 1998). Similarly, Gordon and colleagues also observed an increase in HDL-C in trained women 48 hours after a single bout of exercise requiring 800 kcal of energy expenditure (Gordon et al., 1998). However, in one study, increased HDL-C concentrations following repeated exercise bouts (65% VO_2max) declined to baseline 48 hours after exercise (Angelopoulos et al., 1993).

Kushnick reported that sedentary men increased HDL-C from baseline (46 mg/dl) 12 hours (48 mg/dl), 24 hours (50 mg/dl), and 48 hours (48 mg/dl) following a single bout of exercise until expending 600 kcal of energy expenditure. However, 72 hours following exercise HDL-C concentrations decreased to 47 mg/dl, and this reduction of HDL-C was significantly lower than the 24-hour value (Kushnick, 2003). Similarly, Biggerstaff observed an increase in HDL-C following both low (350 kcal) and high (700 kcal) volumes of a single exercise bout in sedentary men with lower initial HDL-C concentrations (< 42 mg/dl). Total HDL-C concentrations were significantly elevated from baseline (36 mg/dl) at the 12-hour (42 mg/dl), 24-hour (42 mg/dl), and 48-hour period (40 mg/dl) following the low volume exercise session. With the high volume of

exercise, HDL-C was also elevated up to 25% from baseline (37 mg/dl) 12 hours (46 mg/dl), 24 hours (45 mg/dl), and 48 hours (45 mg/dl) post exercise (Biggerstaff, 2000).

The Response of HDL-C Subfractions to a Single Bout of Exercise. It is difficult to determine the exact mechanism by which a single bout of exercise alters HDL-C subfractions. Some researchers reported an increase in both HDL_2-C and HDL_3-C (Biggerstaff, 2000; Ferguson et al., 1998; Park & Ransone, 2003), while others reported an increase or decrease in either one of the HDL-C subfractions (Angelopoulos et al., 1993; Gordon et al., 1994; Kushnick, 2003; Sgouraki, Tsopanakis, & Tsopanakis, 2001; Visich et al., 1996) or no change in both subfractions (Gordon et al., 1998; Imamura et al., 2000; Weise et al., 2005; Zhang et al., 2002) following a single bout of exercise.

The HDL_2-C concentrations in trained men increased approximately 43% (14 to 20 mg/dl) following a single bout of exercise expending 1,500 kcal, and this elevated HDL_2-C remained up to 48 hours. In addition, HDL_3-C also increased by 25% (28 to 35 mg/dl) 24 hours following exercise (Ferguson et al., 1998). Similarly, Biggerstaff also reported a significant increase (11% or 3 mg/dl) in both HDL_2-C and HDL_3-C concentrations in sedentary men with low initial HDL-C concentrations (< 39 mg/dl) 48 hours after moderate exercise expending 700 kcal of energy expenditure (Biggerstaff, 2000).

Alternatively, HDL_2-C was reduced 48 hours after exercise while HDL_3-C increased immediately following and 48 hours after exercise at 65% VO_2max in sedentary men (Angelopoulos et al., 1993). Following maximal treadmill exercise, HDL_2-C concentrations increased, but HDL_3-C did not change in highly trained men. The

results revealed that HDL_2-C was correlated (r = 0.37) with VO_2max, and long distance runners had the highest HDL-C concentrations when compared with swimmers, wrestlers, and basketball players (Sgouraki et al., 2001). Elevated total HDL-C following exercise expending 800 kcal was mainly attributed to an elevation of HDL_3-C, but not HDL_2-C, in recreational runners (Gordon et al., 1994) and endurance trained runners (Visich et al., 1996). However, Kantor and colleagues reported that increased total HDL-C in trained and untrained men after a single session of cycling exercise was produced by an increase in HDL_2-C (3 mg/dl) in trained men, but by an increase in HDL_3-C (2 mg/dl) in untrained men (Kantor et al., 1987). No changes in HDL_2-C and HDL_3-C were reported after a single bout of exercise in young (Imamura et al., 2000) and postmenopausal (Weise et al., 2005) women. Zhang and colleagues did not observe any improvement in HDL_2-C in hyperlipidemic and normolipidemic men after 1-hour treadmill exercise at 60% VO_2max (Zhang et al., 2002).

Table 4 and Figure 5 summarize the responses of blood lipids, lipoproteins, and enzymes to exercise. Exercise may lower the concentration of TG by increasing muscle (#1 in Figure 5) and adipose (#2 in Figure 5) tissue LPL activity (Durstine et al., 2000; Grandjean & Crouse, 2001). It is known that LCAT is an important factor for the maturation of pre β-1 HDL-C (Lewis & Rader, 2005; Smolin & Grosvenor, 2002), and exercise may increase LCAT activity (#3 in Figure 5) (Weise et al., 2005), which consequently promotes conversion of HDL_3-C to HDL_2-C. Increased LCAT activity also promotes the initiation of the RCT pathway (#4 in Figure 5). Reduced CETP activity may delay the catabolism of HDL_2-C (Inazu et al., 1994). It has been suggested that exercise

may reduce CETP activity (#5 in Figure 5), which thereby decreases the rate of cholesterol transfer from HDL-C to LDL-C or VLDL-C, leading to an increase in the cholesterol carrying capacity of HDL-C (Grandjean & Crouse, 2001).

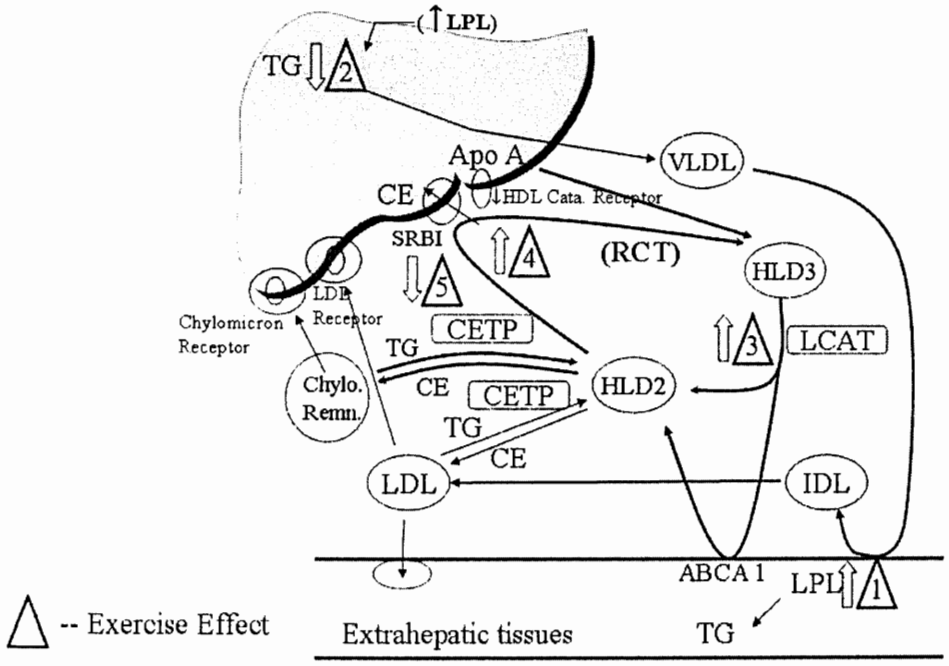

Figure 5. Effects of exercise on blood lipid and lipoprotein metabolism.

Note. ABCA1 = ATP (adenosine triphosphate)-binding cassette transporter 1, Apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transport protein, Chylo Remn. = chylomicron remnants, HDL = high-density lipoprotein, IDL = immediate-density lipoprotein, LCAT = lecithin cholesterol acyl transferase, LDL = low-density lipoprotein, LPL = lipoprotein lipase, RCT = reverse cholesterol transport, SRB1 = scavenger receptor class B type 1, TG = triglyceride, VLDL = very low-density lipoprotein.

Table 4

The Responses of Blood Lipids, Lipoproteins, and Lipoprotein Enzymes to Exercise

Lipid/lipoprotein	Chronic Exercise Training	Acute Exercise
TG	↓ 4% - 37% (mean 24%)	↓ 7% - 69% (mean 20%)
Chol	↔	↔
LDL-C	↔	↔
Small, dense LDL particles	↑ LDL particle size usually with TG lowering	↔
Lp(a)	↔	↔
HDL-C	↑ 4% - 18% (mean 8%)	↑ 4% - 18% (mean 10%)
Chylo and VLDL-C	Usually lower	Usually lower
Postprandial lipemia	↓	↓
Apo A-I	↑	↔
Apo B	Parallels LDL-C changes	Parallels LDL-C changes
Enzymes/Proteins		
LPL	↑	Delayed change (≥ 4 hours)
HL	↔ or ↓ with weight loss	↔
LCAT	↑ or ↔	↑ or ↔
CETP	↔ or ↑	↔

Note. Apo = apolipoprotein, CETP = cholesterol ester transport protein, Chylo = chylomicrons, Chol = cholesterol, HDL-C = high-density lipoprotein cholesterol, HL = hepatic lipase, IDL-C = immediate-density lipoprotein cholesterol, LCAT = lecithin cholesterol acyl transferase, LDL-C = low-density lipoprotein cholesterol, Lp(a) = lipoprotein (a), LPL = lipoprotein lipase, TG = triglyceride, Phosp = phospolipid, VLDL-C = very low-density lipoprotein cholesterol. Adapted from (Fletcher et al., 2005).

Based on existing literature, it can be summarized that exercise and niacin independently have favorable effects on blood lipids and lipoproteins. For example, exercise can decrease the concentration of TG and increase HDL-C (Durstine et al., 2002; Fletcher et al., 2005; Grandjean & Crouse, 2001). Niacin also positively alters all classes of lipids and lipoproteins including a reduction of VLDL-C, LDL-C, TG, apo B, Lp(a), and small, dense LDL particles, and an elevation of total HDL-C, a ratio of HDL_2-C to HDL_3-C, apo A-I, and a ratio of LP-AI to LP-AI+AII (Goldberg, 2004; Meyers, Kamanna, & Kashyap, 2004; Morgan et al., 2004; Pan et al., 2002). Figure 6 describes how niacin and exercise influence the blood lipid and lipoprotein metabolism.

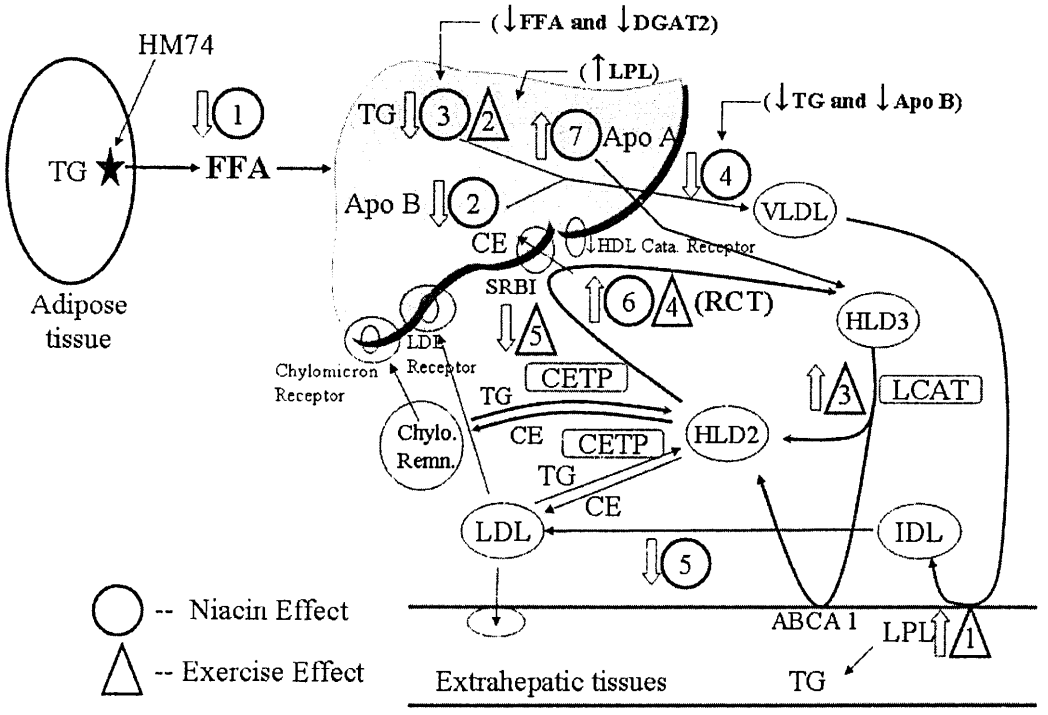

Figure 6. Effects of exercise and niacin on blood lipid and lipoprotein metabolism.

Note. ABCA1 = ATP (adenosine triphosphate)-binding cassette transporter 1, Apo = apolipoprotein, CE = cholesterol ester, CETP = cholesterol ester transport protein, Chylo Remn. = chylomicron remnants, DGAT2 = diacylglycerol acyltransferase 2, FFA = free fatty acids, HDL = high-density lipoprotein, HM 74 = human homologue of murine PUMA-G (protein upregulated in macrophages by interferon-γ), IDL = immediate-density lipoprotein, LCAT = lecithin cholesterol acyl transferase, LDL = low-density lipoprotein, Lp(a) = lipoprotein (a), LPL = lipoprotein lipase, RCT = reverse cholesterol transport, SRB1 = scavenger receptor class B type 1, TG = triglyceride, VLDL = very low-density lipoprotein.

CHAPTER III

METHODS

Participants

Eighteen postmenopausal women volunteers ($N = 18$) between 40 and 80 years of age were recruited by advertisements in announcement flyers. All participants met the following criteria to participate in the study: a) had been postmenopausal at least one year (naturally or surgically), b) were not engaged in any exercise program (any physical activity accumulated more than 20 min) for the previous 6 months, c) were not taking any medication known to alter lipid and lipoprotein metabolism, d) were non-smokers or had quit smoking for the past 6 months, and e) self-reported no diagnoses of cardiovascular diseases, type 1 or 2 diabetes, or any known metabolic disorder. All study methods and procedures were reviewed and approved by the Institutional Review Board of Texas Woman's University. Participants who had agreed to volunteer for the study additionally provided written informed consent and completed medical history forms. Before performing any study procedures, all participants were also requested to provide a written permission letter from the primary care physician to participate in the study. All participants refrained from any types of exercise training throughout the study periods other than the exercise treatment as part of this investigation.

Determination of Appropriate Exercise Intensity

Participants performed a submaximal exercise test using a treadmill walking

exercise protocol on a Quinton Q65 motor driven treadmill (Quinton Instruments, Bothell, WA). Data obtained from the submaximal exercise testing were used to determine the appropriate exercise intensity (60% HRR in this study) for the exercise trial. After 2 min of warm-up at a speed of 2.0 mph with 0% grade, the treadmill exercise protocol started at 3.0 mph with 0% grade. The treadmill speed was held constant at 3.0 mph throughout the test. However, the treadmill grade was elevated by 2.0% every 2 min until participants reached 70% HRR. In this method, resting heart rate was first subtracted from the age-estimated HRmax (220 – age (years)). This value was multiplied by percent intensity (e. g., 70%), and resting HR was added to this value to obtain a target HRR (Armstrong et al., 2006):

$$70\%\ \text{HRR} = [(220 - \text{age}) - \text{resting HR}] \times 70\% + \text{resting HR}$$

Resting HR and blood pressure (BP) were measured after participants quietly sat in a chair at least 5 min. During the submaximal exercise testing, HR was continuously monitored using a Quinton Q4500 12 lead electrocardiograph (Quinton Instruments, Bothell, WA), and BP was also measured in the last minute of each stage. In addition, ratings of perceived exertion (RPE) were monitored at the end of each stage using the 6-20 Borg's scale (Borg, 1982). The submaximal exercise test was terminated when participants reached 70% HRR or wished to voluntarily stop exercising before reaching 70% HRR. During the submaximal exercise testing, expired respiratory gases were continuously collected and analyzed using a Parvo Medics Truemax 2400® metabolic measurement system (Consentius Technologies, Sandy, UT) for the following metabolic

variables: VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$ and $L \cdot min^{-1}$), VCO_2 ($L \cdot min^{-1}$), fraction of expired O_2 (FeO_2, %) and CO_2 ($FeCO_2$, %), respiratory exchange ratio (RER), and minute ventilation (V_E, $L \cdot min^{-1}$). After exercise testing was terminated, participants recovered for approximately 5 min. During recovery, BP and HR were immediately measured post exercise, and every 3 min thereafter until the participants' HR and BP returned to resting values.

Study Design

There was no randomization in the order of niacin supplement conditions due to its potential flushing side effect. Thus, all participants were first assigned to a without-niacin (WON) condition. After the completion of the WON condition, all participants were assigned to the with-niacin (WN) condition. However, either a rest (R) or exercise (E) trial was randomly assigned during each WON or WN condition. During the E trial, all participants performed a single bout of aerobic exercise on the treadmill at 60% HRR until 400 kcal were expended. All R and E trials were conducted at the same time between 06:00 and 08:00 a.m. During the E trial, the speed of treadmill was held constant at 3.0 mph while the grade was elevated and adjusted to achieve the appropriate exercise intensity (60% HRR) based on the data obtained from submaximal exercise testing. During the E trial, BP was measured, and HR was also continuously monitored using a polar heart rate monitor (Polar Electro, Woodbury, NY). During the E trial, expired respiratory gases including RER were collected and analyzed at the initiation, mid, and last 15 min of exercise to determine 400 kcal of energy expenditure. The last 10 min of expired gases collected at each time point were averaged and used to calculate energy

expenditure. Estimation of 400 kcal of energy expenditure during exercise was calculated using a thermal equivalents table of O_2 for RER (McArdle et al., 1999). During the **E** trial, all participants had a 5-min short break at a half of the estimated total exercise time. During the R trial, each participant reported to the lab for blood collection but not exercise. Either the R or E trial was conducted at least 1 week apart to prevent any acute influence of exercise on blood profiles.

Niacin Supplementation

During the with-niacin (WN) condition, participants ingested an extended-release type of niacin, Niaspan (Kos Pharmaceuticals, Miami, FL). Participants ingested the niacin in tablet form with a low fat snack 1 or 2 hr before bedtime. If needed, participants ingested a 325 mg dose of aspirin or a 200 mg dose of ibuprofen 30 min prior to taking niacin to minimize the potential for flushing side effects (Whelan et al., 1992).

The final dose of niacin in this study was 1,000 mg per day taken for 4 weeks. To reach the final dose of 1,000 mg/day, participants started with a low dose of 250 mg/day during the first week of WN condition. During the second week, the dosage was increased up to 500 mg/day, and thereafter 1,000 mg/day for 4 weeks. This particular dosing schedule was designed to minimize the potential flushing side effect. During the 3rd week of 1,000 mg of niacin condition, all participants reported to the laboratory for either the R or E trial. Additionally, all participants continued to take 1,000 mg of niacin during the 4th week for either the R or E trial. Participants did not take any other nutritional or lipid altering supplementations other than niacin provided by the investigator as part of the treatment in this study.

Dietary and Physical Activity Considerations

Participants did not consume any beverage containing alcohol during the study period because alcohol intake may influence concentrations of TG and HDL-C (Converse & Skinner, 1992). Each participant completed a 3-day diet record from the day preceding the first blood draw to the day before the last blood collection to insure consistency in food intake. Based on the first 3-day diet record provided by each participant, each participant consumed the same dinner the night before each blood collection. All self reported dietary records were evaluated using Nutritionist Pro™ software (First Data Bank, Indianapolis, IN). In addition to the 3-day diet record, all participants provided a 5-day physical activity record from 3 days prior to the first blood draw to the day before the last blood collection.

Body Composition Assessment

Body composition was determined by a Lunar dual-energy x-ray absorptiometer (Lunar DPX-IQ). During the body composition test, participants lay supine, fully clothed, on a padded table for the scan. All x-ray scans were conducted by a licensed x-ray technician. A waist to hip ratio (WHR) was also determined from the minimum waist (at the narrowest part of the torso) and maximum hip (at the maximal circumference of the hip, just below the gluteal fold) circumference while the participant was in a standing position at the end of a normal breath. Each site was measured twice, and averaged if the difference in duplicate measurements was within 5 mm. If duplicate measurements were not within 5 mm, an additional measure was performed until the difference in duplicate measurements was within 5 mm (Tharrett, McInnis, & Peterson, 2006).

Blood Analyses

All participants reported to the laboratory between 06:00 and 08:00 a.m. with at least 10 hours of fasting. After 20 min of resting in a chair, approximately 20 ml [1 × 5.0 ml and 2 × 7.5 ml] venous blood samples were collected into vacutainer tubes. Blood samples were drawn immediately before (0 hour) and at 24 and 48 hours post exercise (or rest) during each trial (RWN, rest + with-niacin; EWN, exercise + with-niacin; RWON, rest + without-niacin: or EWON, exercise + without-niacin).

Following each blood draw, approximately 500 µl of whole blood from the vacutainer tube containing EDTA was immediately pippetted into a micro-centrifuge tube. Hematocrit was immediately analyzed while the remaining samples were frozen at -70 °C for the later hemoglobin analysis. Hematocrit was measured in duplicate using the standard microhematocrit method, and the hemoglobin concentration was analyzed in duplicate using the Drabkin and Austin (Drabkin & Austin, 1935) cyanmet-hemoglobin method (Kit# 271-73901, Wako, Richmond, VA). All lipid and lipoprotein concentrations were corrected for changes in post-exercise plasma volume, which was determined by changes in post-exercise hematocrit and hemoglobin values (Dill & Costill, 1974). All procedures of hematocrit and hemoglobin analyses are described in appendix H.

Immediately after the blood draws, blood samples remained at room temperature at least 15 min and then were centrifuged at 3000 rpm for 15 min to separate serum. Serum was then immediately frozen at -70 °C for later analyses. Serum samples in duplicate were used to analyze the concentrations of TG (Kit# 85460, Raichem, Columbia, MD), TC (Kit# 85430, Raichem, Columbia, MD), HDL-C (Kit# 82051, Raichem,

Columbia, MD), and HDL_3-C (Dextran sulfate precipitation method for HDL_3-C, see appendix H) using enzymatic measurements. All enzymatic measurements were performed using the PowerWave^{TM} XS microplate spectrophotometer (BioTek instruments, Winooski, VT), and the coefficient of variation (CV) for TG, TC, HDL-C, and HDL_3-C in the current study were 2.1, 1.8, 0.6, and 1.5%, respectively. Detailed procedures of all enzymatic measurements are described in appendix H. The concentration of HDL_2-C was calculated from the difference between HDL-C and HDL_3-C, and the concentration of LDL-C was estimated using the following Friedewald formula (Friedewald, Levy, & Fredrickson, 1972): LDL-C = TC – (HDL-C + TG/5) (units in mg/dl).

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences 11.0 (SPSS Inc, Chicago, IL). All data were reported as mean ± standard deviation. The changes in blood lipids and lipoproteins including TC, TG, LDL-C, HDL-C, HDL_2-C, HDL_3-C, and TC to HDL-C ratio were analyzed using a 2 (conditions; **With**O**u**t **N**iacin = WON or With Niacin = WN) × 2 (trials; Rest = R or Exercise = E) × 3 (times; 0, 24, and 48 hr) analysis of variance (ANOVA) with repeated measures. In addition, ANOVA with repeated measures was also employed to examine the differences in the average of total caloric intake and macronutrient contents including carbohydrate, fat, and protein for each trial (RWON, EWON, RWN, and EWN). When the *F*-ratio was significant, Bonferroni post-hoc was applied to determine the nature of the differences. The level of statistical significance was set at $p < .05$.

Sample Size

Appropriate sample sizes needed for power = .80 at $\alpha = .05$ in a single-group repeated measures (Stevens, 2002) were calculated using effect size (*ES*) obtained from previous research, which had similar study-settings to the current study. The formula for *ES* is presented below, and *ES* can be calculated by dividing the mean difference of the experimental ($\overline{X}_1$) and control ($\overline{X}_2$) groups by the standard deviation of the control (*SDcontrol*) group or the pooled variance of the treatment groups if there is no control group (Vincent, 1999).

$$ES = \frac{\overline{X}_1 - \overline{X}_2}{SD_{control}}$$

A reduction of TG and an increase in HDL-C are often observed after a single bout of exercise and niacin supplementation. Therefore, the sample size for this study was calculated based on *ES* of TG and HDL-C with either exercise or Niaspan reported in previous studies. Three studies related to the effects of 1,000 mg of extended-release niacin (Niaspan) on TG and HDL-C in the elderly (Table 5) and four studies examining the effects of exercise on TG and HDL-C in postmenopausal women (Table 6) were used to calculate *ES*. It should be noted that most of the previous studies investigating the effects of 1,000 mg of Niaspan on lipids and lipoproteins in older individuals did not clearly report the results according to gender. Some studies examined how long-term exercise training with or without hormonal therapy affects lipids and lipoproteins in postmenopausal women.

Table 5

Selective Studies (Related to Niaspan) Used to Calculate ES

Study (Author. year)	$(\overline{X}_1 - \overline{X}_2)$		$SD_{control}$		*ES*	
	TG	HDL-C	TG	HDL-C	TG	HDL-C
Goldberg, 2000	19.6	-7.1	36.2	15.5	0.54	0.46
Knopp et al., 1998	24.6	-8.3	68.8	8.6	0.36	0.97
Guyton et al., 1998	37.6	-12.8	68.0	10.0	0.55	1.28
Mean					0.48	0.90

Note. $(\overline{X}_1 - \overline{X}_2)$ = mean difference; $SD_{control}$ = Standard deviation of control group: *ES* = effect size; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol

However, the effect of a single bout of aerobic exercise on blood lipids and lipoproteins particularly in postmenopausal women has been rarely reported. Thus, the exercise training studies in postmenopausal women, except for Weise (2005), were used in this study to calculate *ES*. An average of *ES* calculated based on the previously published seven studies was .52. The minimum number of participants needed for power = .80 at α = .05 in a single-group repeated measures was calculated to be 15 participants (Stevens, 2002).

Table 6

Selective Studies (Related to Exercise) Used to Calculate ES

Study	$(\overline{X}_1 - \overline{X}_2)$		$SD_{control}$		*ES*	
(Author, year)	TG	HDL-C	TG	HDL-C	TG	HDL-C
Lindheim et al., 1994	16.3	-0.50	21.0	3.3	0.78	0.15
Wu et al., 2006	13.7	-0.70	41.8	13.6	0.33	0.05
Alhassan et al., 2006	18.0	-10.0	63.0	12.0	0.29	0.83
Weise et al., 2005	9.0	-3.0	51.4	16.9	0.18	0.18
Mean					0.40	0.30

Note. $(\overline{X}_1 - \overline{X}_2)$ = mean difference; $SD_{control}$ = Standard deviation of control group; *ES* = effect size; TG = triglyceride; HDL-C = high-density lipoprotein cholesterol.

CHAPTER IV

RESULTS

Participants

A total of 45 volunteers initially responded to advertisement for the study. After the initial screening interview, 25 participants who did not meet the criteria for participation were excluded due to the following reasons: currently taking some form of blood lipid altering medications (n = 5), regularly participating in some type of physical activities (n = 6), currently smoking cigarettes (n = 4), and not willing to participate due to conflict with a schedule (n = 10). A total of 20 participants signed written informed consent and completed medical history forms. However, 2 out of 20 participants dropped out due to the adverse reactions of niacin such as flushing, itching, or swelling with a dosage of 1,000 mg/day of niacin.

Four out of 18 participants who completed all the study procedures were on some type of medication; 2 on thyroid medication (Levothyroxine), 1 on antidepression medication (Sertraline), and 2 on hormone therapy (Estradiol patch or Prometrium). There were no statistical differences in any analyses when the data from the participants who were on medications were included. Therefore, all data were pooled together and used for further statistical analyses. The physiological characteristics of participants are presented in Table 7.

Table 7

Physiological Characteristics of Participants

	Mean ± SD	Minimum	Maximum
Age (yrs)	56.8 ± 6.5	46.0	71.0
Height (cm)	161.3 ± 6.7	147.0	171.0
Weight (kg)	75.8 ± 13.9	57.5.0	115.4
BMI (kg/m^2)	29.2 ± 5.3	21.1	39.3
% Fat	46.2 ± 6.6	34.6	55.6
WHR	0.82 ± 0.04	0.75	0.87
TG (mg/dl)	97.5 ± 36.7	37.5	101.1
TC (mg/dl)	226.8 ± 33.5	160.8	288.2
LDL-C (mg/dl)	164.1 ± 30.5	103.4	229.6
HDL-C (mg/dl)	43.1 ± 8.2	27.1	65.0
HDL_2-C (mg/dl)	10.5 ± 4.5	1.9	24.2
HDL_3-C (mg/dl)	32.7 ± 5.8	23.5	49.9
TC/HDL-C ratio	5.5 ± 1.5	3.3	9.0
HRmax (bpm)	164.0 ± 7.0	149.0	174.0
60% HRR (bpm)	134.0 ± 6.0	118.0	141.0
VO_2 (L/min) at 60% HRR	1.41 ± 0.25	1.00	2.01
VO_2 (ml/kg/min) at 60% HRR	18.7 ± 2.3	12.9	22.2
VCO_2 (L/min) at 60% HRR	1.17 ± 0.24	0.67	1.68
V_E (L/min) at 60% HRR	29.1 ± 5.7	19.8	40.0

	Mean ± SD	Minimum	Maximum
RER at 60% HRR	0.83 ± 0.06	0.71	0.93
Total exercise time for 400 kcal (min)	60.3 ± 10.5	37.0	80.0

Note. All values are expressed as means ± SD (standard deviation). BMI = body mass index, WHR = waist to hip ratio, TG = triglyceride, TC = total cholesterol, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, HDL_2-C = HDL-C subfraction 2, HDL_3-C = HDL-C subfraction 3, HRmax = age-estimated heart rate max (220 – age), HRR = heart rate reserve [(HRmax – HRrest) × intensity + HRrest], VO_2 = volume of oxygen, VCO_2 = volume of carbon dioxide, V_E = ventilation, RER = respiratory exchange ratio (VCO_2/VO_2).

Effects of Niacin on Blood Lipids and Lipoproteins

Effects of Niacin on TC, LDL-C, and TG

Four weeks of niacin supplement (1,000 mg/day) did not significantly change TC, LDL-C, or TG in postmenopausal women (Table 8). The concentrations of TC before and after the niacin supplement were 226.0 ± 31.8 and 217.4 ± 30.0 mg/dl, respectively. The concentration of LDL-C did not significantly change before (163.2 ± 29.2 mg/dl) and after (151.5 ± 30.2 mg/dl) the niacin supplement. The initial concentration of TG was 96.7 ± 45.5 mg/dl, and did not change (84.6 ± 33.1 mg/dl) after the niacin supplement. There was no significant difference in condition (with- or without-niacin) X time (0, 24, or 48 hr) interaction on TC, LDL-C, and TG.

Table 8

Changes in Blood Lipids and Lipoproteins Before And After Each Trial

	Niacin		Exercise	
	Before	After	Before	After
TC (mg/dl)	226.0 ± 31.8	217.4 ± 30.0	223.8 ± 32.6	219.5 ± 29.7
LDL-C (mg/dl)	163.2 ± 29.2	151.5 ± 30.2	159.7 ± 31.1	155.0 ± 29.2
TG (mg/dl)	96.7 ± 45.5	84.6 ± 33.1	88.8 ± 32.7	92.5 ± 46.5
HDL-C (mg/dl)	43.5 ± 8.4	*48.9 ± 7.6	46.3 ± 8.8	46.1 ± 8.1
HDL_2-C (mg/dl)	10.8 ± 4.8	*14.4 ± 6.5	12.6 ± 6.1	12.7 ± 5.9
HDL_3-C (mg/dl)	32.6 ± 5.7	34.5 ± 4.6	33.7 ± 5.3	33.4 ± 5.3
TC/HDL-C Ratio	5.4 ± 1.4	*4.5 ± 1.0	5.0 ± 1.3	5.0 ± 1.3

Note. All values are expressed as means ± SD (standard deviation). TG = triglyceride, TC = total cholesterol, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, HDL_2-C = HDL-C subfraction 2, HDL_3-C = HDL-C subfraction 3. * $p < .05$ – values are significantly different from the before niacin condition.

Effects of Niacin on HDL-C, HDL_2-C, HDL_3-C, and TC/HDL-C Ratio

The concentration of HDL-C significantly ($F(1, 204) = 23.898$, $p < .001$) increased after 4 weeks of the niacin supplement (1,000 mg/day) in postmenopausal women. The HDL-C concentration at baseline was 43.5 ± 8.4 mg/dl, and increased by 5.4 mg/dl or 12.4% (48.9 ± 7.6 mg/dl) with the niacin supplement (Table 8 and Figure 7). However, there was no significant difference in the condition X time interaction on HDL-C.

Niacin supplementation (1,000 mg/day) for 4 weeks also significantly (F (1, 204) = 20.299, $p < .001$) increased HDL_2-C in sedentary, postmenopausal women. The baseline HDL_2-C concentration was 10.8 ± 4.8 mg/dl, and increased by 3.6 mg/dl or 33.3% with the niacın supplement. However, the concentration of HDL_3-C did not significantly change. The concentrations of HDL_3-C before and after the niacin supplement were 32.6 ± 5.7 and 34.5 ± 4.6 mg/dl, respectively (Table 8 and Figure 7). There was no significant difference in the condition X time interaction on HDL_2-C and HDL_3-C.

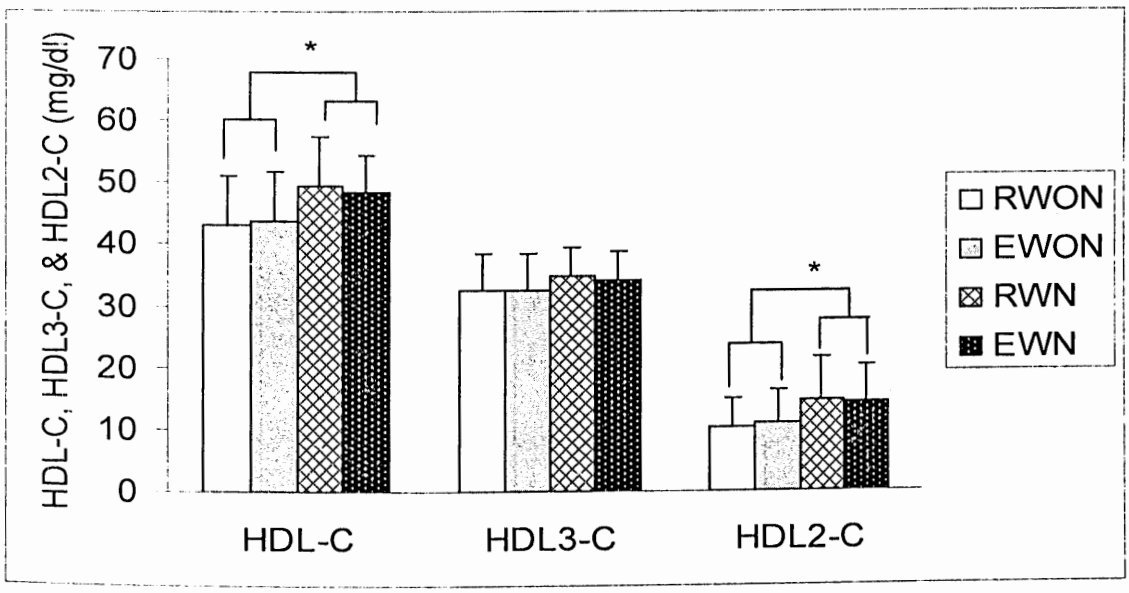

Figure 7. Main effects of exercise or niacin on HDL-C, HDL_3-C, and HDL_2-C.

Note. HDL-C = high-density lipoprotein, RWON = rest without niacin, EWON = exercise without niacin, RWN = rest with niacin, EWN = exercise with niacin. * $p < .05$ – values are significantly different from the without niacin conditions.

The TC to HDL-C ratio significantly ($F(1, 204) = 24.239$, $p < .001$) decreased with the niacin supplement in the current study. The TC to HDL-C ratio at baseline was 5.4 ± 1.4, and decreased by 14.8% (4.5 ± 1.0) after ingesting 1,000 mg/day of niacin for 4 weeks (Table 8). However, there was no significant difference in the condition X time interaction on the TC/HDL-C ratio.

Effects of Exercise on Blood Lipids and Lipoproteins

Effects of Exercise on TC, LDL-C, and TG

A single bout of exercise requiring 400 kcal of energy expenditure did not significantly change TC, LDL-C, or TG. The concentration of TC before and after a single bout of exercise was 223.8 ± 32.6 and 219.5 ± 29.7 mg/dl, respectively. The initial concentration of LDL-C (159.7 ± 31 mg/dl) did not change after a single bout of exercise (155.0 ± 29.2 mg/dl). Moreover, the concentration of TG was not altered by a single bout of exercise (from 88.8 ± 32.7 to 92.5 ± 46.5 mg/dl). There was no significant difference in trial (rest or exercise) X time interaction on TC, LDL-C, and TG.

Effects of Exercise on HDL-C, HDL_2-C, HDL_3-C, and TC/HDL-C Ratio

Changes in HDL-C, HDL_2-C, and HDL_3-C before and after a single bout of exercise are presented in Table 8. Unlike niacin, a single bout of exercise (400 kcal) did not significantly increase HDL-C, HDL_2-C, or HDL_3-C in sedentary, postmenopausal women. The baseline HDL-C concentration was 46.3 ± 8.8 mg/dl, and was unchanged (46.1 ± 8.1 mg/dl) after a single bout of exercise. The concentrations of HDL_2-C before and after a single bout of exercise were 12.6 ± 6.1 and 12.7 ± 5.9 mg/dl, respectively. A single bout of exercise did not significantly change the concentration of HDL_3-C. The

HDL_3-C concentration at baseline was 33.7 ± 5.3 mg/dl, and remained unchanged (33.4 ± 5.3 mg/dl) after exercise. In addition, the TC to HDL-C ratio did not significantly change (5.0 ± 1.3 and 5.0 ± 1.3) after a single bout of exercise. There was no significant difference in the trial X time interaction on HDL-C, HDL_2-C, HDL_3-C, and TC/HDL-C Ratio.

Effects of Niacin and Exercise on Blood Lipids and Lipoproteins

Effects of Niacin and Exercise on TC, LDL-C, and TG

Niacin supplementation (1,000 mg/day) combined with a single bout of exercise (400 kcal) did not significantly change TC, LDL-C, or TG at any time period (0, 24, and 48 hr) for any trials. There were no significant differences in both the condition X trial and condition X trial X time interactions on TC, LDL-C, and TG.

Effects of Niacin and Exercise on HDL-C, HDL_2-C, HDL_3-C, and TC/HDL-C Ratio

Changes in HDL-C at each time period (0, 24, and 48 hr) for each trial are depicted in Figure 8. The concentration of HDL-C at all the time periods (0, 24, and 48 hr) during the with-niacin (RWN and EWN) conditions was significantly higher ($F(11, 187) = 16.101$, $p < .001$) than the without-niacin (RWON and EWON) conditions. An average concentration of HDL-C for the with- or without-niacin condition was 48.9 ± 7.6 and 43.5 ± 8.4 mg/dl, respectively. As described in Figure 8, a single bout of exercise during the with-niacin condition did not alter HDL-C at any time periods (0, 24, and 48 hr). There were no significant differences in both the condition X trial and condition X trial X time interactions on HDL-C.

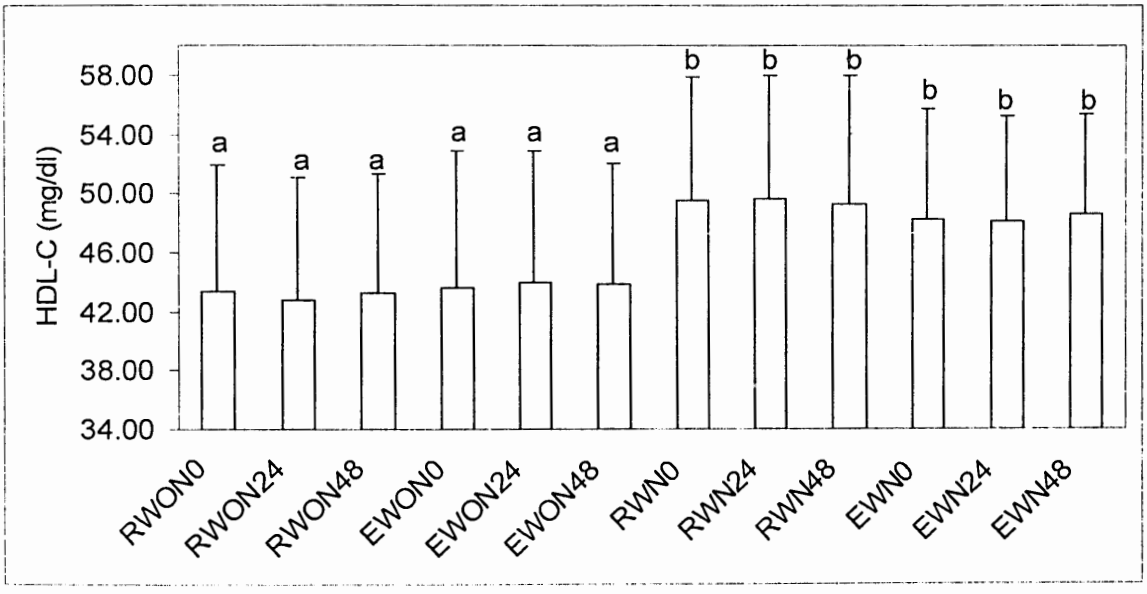

Figure 8. Effects of exercise and niacin on changes in HDL-C during each trial.

Note. HDL-C = high-density lipoprotein, RWON 0 = rest without niacin at 0 hr, RWON 24 = rest without niacin at 24 hr, RWON 48 = rest without niacin at 48 hr, EWON 0 = exercise without niacin at 0 hr, EWON 24 = exercise without niacin at 24 hr, EWON 48 = exercise without niacin at 48 hr, RWN 0 = rest with niacin at 0, RWN 24 = rest with niacin at 24, RWN 48 = rest with niacin at 48, EWN 0 = exercise with niacin at 0 hr, EWN 24 = exercise with niacin at 24 hr, EWN 48 = exercise with niacin at 48 hr. Different superscripts are significantly different from each other ($p < .05$).

Similar to the HDL-C responses to niacin and a single bout of exercise, the concentration of HDL_2-C at all the time periods (0, 24, and 48 hr) during the with-niacin (RWN and EWN) conditions were significantly higher ($F(11, 187) = 14.322$, $p < .001$) than the without-niacin (RWON and EWON) conditions. An average concentration of HDL_2-C for the with- or without-niacin condition was 14.4 ± 6.5 and 10.8 ± 4.8 mg/dl,

respectively. However, there was no additive effect of a single bout of exercise on HDL_2-C at any time periods (0, 24, and 48 hr) during the with-niacin condition (Figure 9). There were no significant differences in both the condition X trial and condition X trial X time interactions on HDL_2-C.

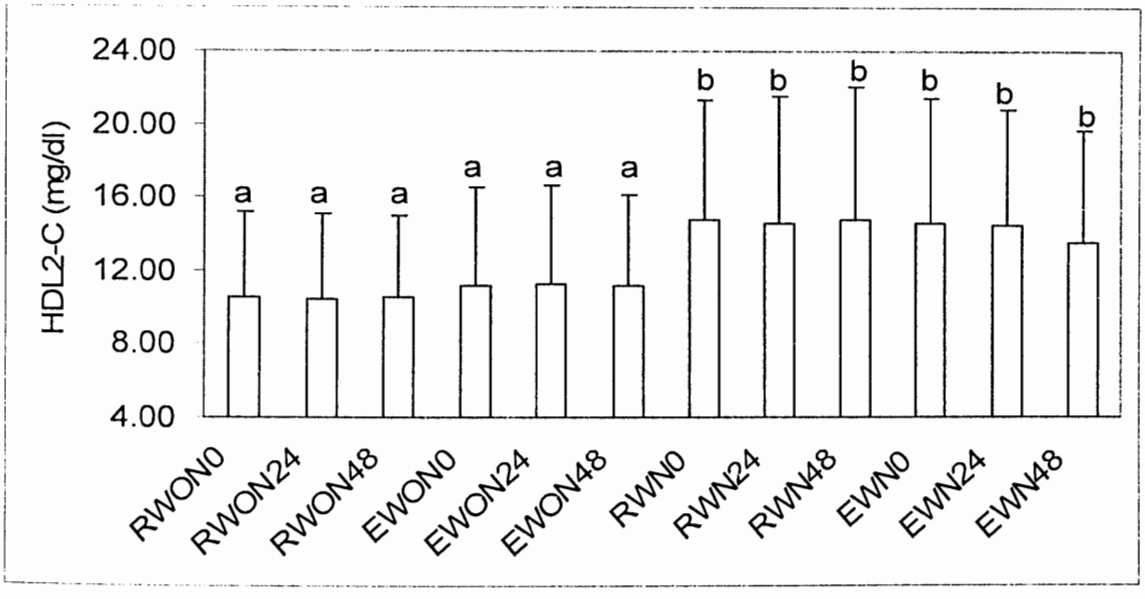

Figure 9. Effects of exercise and niacin on changes in HDL_2-C during each trial.

Note. HDL_2-C = high-density lipoprotein subfraction 2, RWON 0 = rest without niacin at 0 hr, RWON 24 = rest without niacin at 24 hr, RWON 48 = rest without niacin at 48 hr, EWON 0 = exercise without niacin at 0 hr, EWON 24 = exercise without niacin at 24 hr, EWON 48 = exercise without niacin at 48 hr, RWN 0 = rest with niacin at 0, RWN 24 = rest with niacin at 24, RWN 48 = rest with niacin at 48, EWN 0 = exercise with niacin at 0 hr, EWN 24 = exercise with niacin at 24 hr, EWN 48 = exercise with niacin at 48 hr. Different superscripts are significantly different from each other ($p < .05$).

The concentration of HDL_3-C was not significantly changed with the niacin supplementation (1,000 mg/day) combined with a single bout of exercise (400 kcal). There were no significant differences in both the condition X trial and condition X trial X time interactions on HDL_3-C.

Changes in TC to HDL-C ratio at each time period (0, 24, and 48 hr) for each trial are presented in Figure 10. According to the repeated measures ANOVA, the ratio of TC to HDL-C at all the time periods (0, 24, and 48 hr) during the with-niacin (RWN and EWN) conditions was significantly lower ($p < .05$) than the without-niacin (RWON and EWON) conditions. However, a single bout of exercise did not significantly affect the TC to HDL-C ratio at any time periods (0, 24, and 48 hr) during the with-niacin condition. There were no significant differences in both the condition X trial and condition X trial X time interactions on TC/HDL-C Ratio.

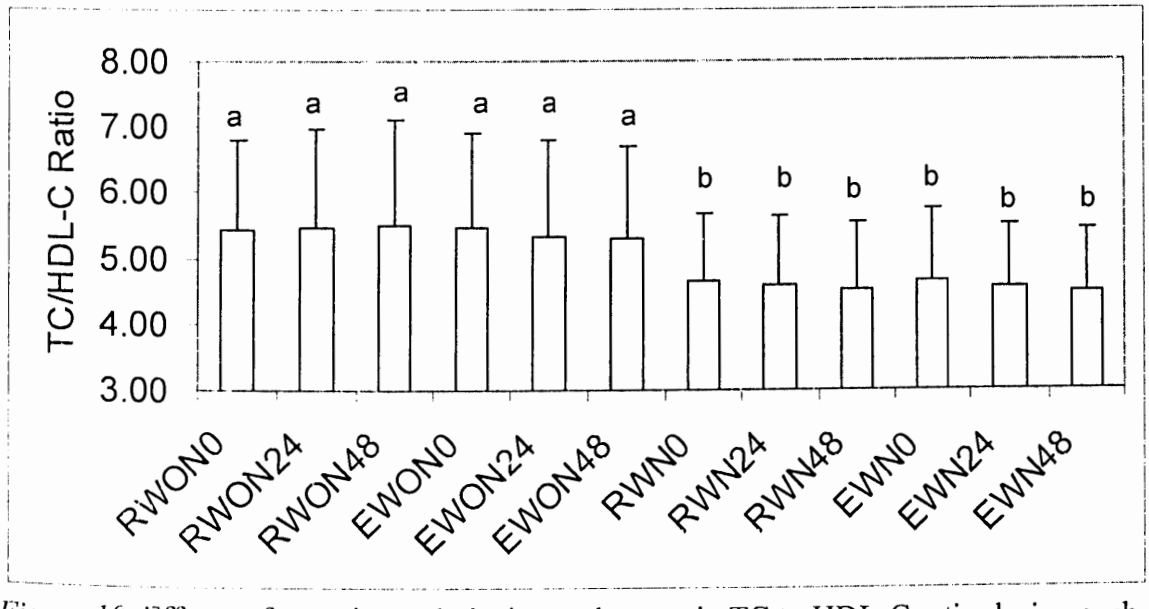

Figure 10. Effects of exercise and niacin on changes in TC to HDL-C ratio during each trial.

Note. TC = total cholesterol, HDL-C = high-density lipoprotein, RWON 0 = rest without niacin at 0 hr, RWON 24 = rest without niacin at 24 hr, RWON 48 = rest without niacin at 48 hr, EWON 0 = exercise without niacin at 0 hr, EWON 24 = exercise without niacin at 24 hr, EWON 48 = exercise without niacin at 48 hr, RWN 0 = rest with niacin at 0, RWN 24 = rest with niacin at 24, RWN 48 = rest with niacin at 48, EWN 0 = exercise with niacin at 0 hr, EWN 24 = exercise with niacin at 24 hr, EWN 48 = exercise with niacin at 48 hr. Different superscripts are significantly different from each other ($p < .05$).

The changes in Hb and Hct at 0, 24, and 48 hr after each trial are reported in Table 9. There was no significant difference in Hct or Hb at any time period for any trial. Plasma volume changes are presented in Table 10, and were calculated using the method of Dill and Costill (1974). Plasma volume was not significantly changed at any time period compared with baseline. Therefore, the concentrations of blood lipids and lipoproteins in this study were reported with plasma volume unadjusted concentrations.

Table 9

Changes in Hct and Hb at 0, 24, and 48 hr After Each Trial

		RWON	EWON	RWN	EWN
Hct (%)	0 hr	39.9 ± 1.8	39.1 ± 2.1	39.3 ± 2.1	39.1 ± 1.8
	24 hr	39.5 ± 1.9	38.8 ± 1.6	39.0 ± 2.0	38.8 ± 1.9
	48 hr	39.8 ± 2.1	38.6 ± 1.9	38.9 ± 1.8	38.5 ± 2.2
Hb (mg/dl)	0 hr	14.6 ± 0.8	14.3 ± 0.7	14.3 ± 0.8	14.0 ± 0.8
	24 hr	14.4 ± 0.8	14.4 ± 0.8	14.4 ± 0.8	14.2 ± 0.7
	48 hr	14.3 ± 0.8	14.6 ± 0.8	14.2 ± 0.9	14.3 ± 0.8

Note. All values are expressed as mean ± SD (standard deviation). Hct = hematocrit, Hb = hemoglobin, RWON = rest without niacin, EWON = exercise without niacin, RWN = rest with niacin, EWN = exercise with niacin.

Table 10

Changes in Plasma Volume at 24 and 48 hr After Each Trial

	24 hr	48 hr
RWON	-0.1 ± 5.0	-0.3 ± 5.0
EWON	-1.3 ± 3.2	-3.1 ± 3.2
RWN	-1.2 ± 3.4	-0.1 ± 4.9
EWN	-1.9 ± 3.1	-2.8 ± 3.4

Note. All values are expressed as mean ± SD (standard deviation). Plasma volume changes (%) for each trial were calculated as compared to baseline plasma volume. RWON = rest without niacin, EWON = exercise without niacin, RWN = rest with niacin, EWN = exercise with niacin.

An average of 3-day caloric intake and macronutrient contents including carbohydrate, fat, and protein for each trial are presented in Table 11. The average caloric intake for RWON, EWON, RWN, and EWN were 1541.1 ± 399.9, 1624.2 ± 628.6, 1509.6 ± 520.1, and 1515.7 ± 354.7 kcal, respectively. Carbohydrate, fat, and protein contents for each trial were also similar. Repeated measures ANOVA revealed that there were no significant differences in total caloric intake, carbohydrate, fat, and protein contents for each trial.

Table 11

Average of 3-day Dietary Consumption for Each Trial

	Total kcals	CHO (%)	Fat (%)	Protein (%)
RWON	1541.1 ± 399.9	47.5 ± 9.2	35.7 ± 8.3	16.8 ± 5.9
EWON	1624.2 ± 628.6	46.8 ± 6.0	37.8 ± 6.2	15.0 ± 2.5
RWN	1509.6 ± 520.1	46.8 ± 13.1	36.0 ± 10.6	17.4 ± 5.1
EWN	1515.7 ± 354.7	51.2 ± 13.1	29.6 ± 9.4	18.3 ± 2.7

Note. All values are expressed as mean ± SD (standard deviation). RWON = rest without niacin, EWON = exercise without niacin, RWN = rest with niacin, EWN = exercise with niacin, CHO = carbohydrate.

CHAPTER V

DISCUSSION AND SUMMARY

It has been well documented that physical activity (Durstine et al., 2000; Lamarche et al., 1997) and niacin (Guyton, 2004; Pieper, 2003; Piepho, 2000) independently play an important role in reducing the risk factors for CVD by favorably modifying blood lipids and lipoproteins. According to the previously published studies, a single bout of exercise decreases TG and increases HDL-C (Crouse et al., 1995; Ferguson et al., 1998; Gordon et al., 1998; Grandjean et al., 2000; Kantor et al., 1987). It has been also reported that niacin increases HDL-C, HDL_2-C, and apo A, and decreases TC, VLDL-C, LDL-C, TG, apo B, Lp(a), and the TC to HDL-C ratio (Goldberg, 1998; Grundy et al., 1981; Knopp et al., 1998; Knopp et al., 1985; Squires et al., 1992; Wang et al., 2000).

Despite the aforementioned beneficial effects of exercise and niacin, no study to date has investigated the independent and combined effects of a single bout of exercise and niacin on blood lipids and lipoproteins particularly in postmenopausal women. Therefore, the present study examined the effects of 4-weeks of niacin supplementation (1,000 mg/day) and a single bout of exercise at 60% HRR (400 kcal) on blood lipids (TC and TG) and lipoproteins (LDL-C, HDL-C, HDL_2-C, and HDL_3-C) in postmenopausal women.

The main research questions were twofold: a) does niacin and a single bout of exercise independently influence blood lipids and lipoproteins, and b) does the combination of niacin and a single bout of exercise improve blood lipids and lipoproteins significantly more than either niacin or a single bout of exercise alone.

Effects of Niacin on TC, LDL-C, and TG

Niaspan, an extended-release type of niacin, has been widely recommended to treat dyslipidemia because Niaspan not only positively changes blood lipids and lipoproteins, but also minimizes adverse effects such as flushing, itching, redness, and hepatotoxicity (Knopp et al., 1998; McKenney, 2003). The recommended minimum and maximum dosage of Niaspan is 500 and 2,000 mg/day, respectively since doses greater than 2,000 mg/day may plateau the antilipidemic effects of niacin. It has been reported that Niaspan (~ 2,000 mg/day) can lower TC, LDL-C and TG up to 10.0, 25.0, and 50.0%, respectively (Abourjaily, 2001; Morgan et al., 1998). In the present study, 1,000 mg of Niaspan was used for 4 weeks to examine the effects of niacin on blood lipid and lipoprotein metabolism.

Despite niacin's reported lipid and lipoprotein lowering effects, 4-weeks of 1,000 mg/day of niacin in the current study did not significantly decrease TC, LDL-C, or TG in sedentary, postmenopausal women. Previous studies have reported that niacin lowered the concentrations of TC, LDL-C, and TG in healthy individuals (Wang et al., 2001) and individuals with hypercholesterolemia (Knopp et al., 1998), type 2 diabetes (Garg & Grundy, 1990; Kane et al., 2001; Pan et al., 2002), dyslipidemia (Goldberg, 2004; Goldberg et al., 2000; Grundy et al., 1981; Morgan et al., 1998; Sakai et al., 2001), and

CAD (Alderman et al., 1989; Capuzzi et al., 1998; Guyton et al., 1998).

For example, Knopp and colleagues reported reductions in TC (8.0%), TG (16.0%), and LDL-C (12.0%) in both men and women with hypercholesterolemia after the niacin supplement (1,500 mg/day) for 8 weeks (Knopp et al., 1998). Sakai and colleagues also reported reductions in TC (6.5 mg/dl or 3.2%) and TG (35.4 mg/dl or 18.0%) from baseline in 139 dyslipidemic patients after the 2,000 mg/day of niacin supplement for 19 weeks (Sakai et al., 2001). Likewise, long-term niacin therapy (average dose of 2,000 mg/day for almost 2 years) for patients with CAD decreased TC, LDL-C and TG by 10.0, 20.0 and 28.0%, respectively (Capuzzi et al., 1998; Guyton et al., 1998).

Participants in the current study were sedentary, postmenopausal women whose initial concentrations of TC, LDL-C, and TG were 226.0, 163.2, and 96.7 mg/dl, respectively. In contrast to the results of aforementioned studies (Capuzzi et al., 1998; Guyton et al., 1998; Knopp et al., 1998; Sakai et al., 2001), the niacin supplement in the current study did not significantly decrease TC, LDL-C, and TG in hypercholesterolemic, postmenopausal women. One of the possible explanations for no changes in TC, LDL-C, and TG with the niacin supplement may be a different study protocol used in the current study. The duration (4 weeks) and dosage (1,000 mg/day) of niacin used in the current study were relatively shorter and lower as compared to other studies (Capuzzi et al., 1998; Guyton et al., 1998; Knopp et al., 1998; Sakai et al., 2001) that reported the significant reductions in TC, LDL-C, and TG. Although Goldberg (1998) suggested that as low as 500 mg/day of niacin may alter blood lipids and lipoproteins in women, there

may be a minimal dosage and duration required to significantly decrease TC, LDL-C, and TG for postmenopausal women who have initially higher TC and LDL-C but normal TG.

The mechanism by which niacin positively influences blood lipids and lipoproteins is not fully understood. However, it is known that when niacin is bound to HM 74A (Mahboubi et al., 2005; Zhang et al., 2005), the activity of cAMP in adipose tissue is inhibited by a G_i-protein-mediated inhibition of adenylyl cyclase (Benyo et al., 2005; Zhang et al., 2005). The inhibition of cAMP by niacin eventually leads to a decrease in adipose lipolysis, resulting in a decrease in mobilization of plasma FFA (Carlson, 2005; Piepho, 2000; Zhang et al., 2005). Niacin directly and indirectly reduces synthesis of TG in the liver. For instance, a decreased mobilization of plasma FFA, which is induced by a reduction of adipose lipolysis, contributes to a decrease in uptake of FFA by the liver, and consequently reduces the synthesis of TG and VLDL in the liver (Karpe & Frayn, 2004). A reduced hepatic synthesis of TG is considered a secondary effect of niacin in the liver. In addition, niacin directly decreases the hepatic synthesis of TG by inhibiting diacylglycerol acyltransferease 2, the rate limiting enzyme for TG synthesis. Niacin also decreases the formation of fatty acyl CoA, a substrate for TG, by directly inhibiting acetyl CoA in the liver (Ganji et al., 2004). A niacin-induced reduction in hepatic TG synthesis leads to the secretion of a fewer number of VLDL and smaller VLDL particles, which contain less TG. Thus, a reduction in the number of VLDL particles available for catabolism may contribute to a reduction in LDL particles in the blood stream (Drood et al., 1991).

Effects of Niacin on HDL-C, HDL_2-C, HDL_3-C, and TC/HDL-C Ratio

It has been reported that niacin increases total HDL-C, HDL_2-C, and HDL_3-C, and decreases the TC to HDL-C ratio (Alderman et al., 1989; Garg & Grundy, 1990; Goldberg et al., 2000; Knopp et al., 1998; Morgan et al., 2003; Pan et al., 2002; Sakai et al., 2001; Sprecher, 2000). According to the previously published studies, niacin (1,000 – 4,000 mg/day) increased HDL-C and HDL_2-C by up to 35.0 and 70.0%, and decreased the ratio of TC to HDL-C by 35.0% from baseline (Goldberg, 1998; Goldberg et al., 2000; Guyton et al., 1998; Kane et al., 2001; Knopp et al., 1998; Morgan et al., 1998; Pan et al., 2002; Sakai et al., 2001).

After 4-weeks of niacin supplement (1,000 mg/dl) in the present study, the baseline concentrations of HDL-C (43.5 mg/dl) and HDL_2-C (10.8 mg/dl) were significantly increased by 12.4 and 33.3%, respectively. Niacin also decreased the TC to HDL-C ratio from 5.4 to 4.5 (14.8%); however, the concentration of HDL_3-C was not significantly changed after the niacin supplement although HDL_3-C increased from 32.6 mg/dl to 34.5 mg/dl (5.8%).

Similar to the current study, the concentration of HDL-C increased 36.0% from 42.0 to 57.0 mg/dl, and HDL_2-C also increased 50.0% from 34.0 to 51.0 mg/dl in diabetic patients after 16-weeks of niacin supplementation (1,000 – 4,000 mg/day) (Pan et al., 2002). Squires and colleagues (1992) also reported an 18.0% increase (6.0 mg/dl) in HDL-C and a 25.0% decrease (from 6.8 to 5.1) in the ratio of TC to HDL-C with the niacin supplement (mean dosage, 1,297 mg/day) in individuals with initially lower concentrations of HDL-C (mean of 34.0 mg/dl) (Squires et al., 1992). Patients with

dyslipidemia increased HDL-C by 24.8% (from 30.7 to 38.3 mg/dl) and decreased the TC to HDL-C ratio by 21.9% (from 6.4 to 5.0) after 2,000 mg/day of niacin for 19 weeks (Sakai et al., 2001). In addition, both hypercholesterolemic men and women increased HDL-C (20.0%), HDL_2-C (37.0%), and HDL_3-C (17.0%) from baseline after 8-weeks of 1,500 mg/day of niacin (Knopp et al., 1998).

Unlike the responses of TC, LDL-C, and TG to relatively short and low dosage of niacin used in the current study, HDL-C and HDL_2-C significantly increased and the TC to HDL-C ratio was reduced after 4-weeks of 1,000 mg/day of niacin. However, the magnitude of changes in HDL-C (12.4%), HDL_2-C (33.3%), and the TC/HDL-C ratio (14.8%) observed in the present study were smaller than other studies that have reported an increase in HDL-C (up to 30%) and HDL_2-C (up to 72%) and a decrease in the TC/HDL-C ratio (up to 35%) (Goldberg et al., 2000; Guyton & Capuzzi, 1998; Knopp et al., 1998; Pan et al., 2002; Sakai et al., 2001).

According to the niacin dose response study in individuals with primary hyperlipoproteinemia, the concentration of HDL-C at the dosages of 1,000 and 3,000 mg/day increased 15 and 30% from baseline, respectively. In addition, HDL_2-C at the dosage of 1,000 and 3,000 mg/day increased by 38 and 72% from baseline, respectively, and the TC/HDL-C ratio at 1,000 and 3,000 mg/day of niacin decreased by 17 and 35% from baseline, respectively (Goldberg et al., 2000). The magnitude of changes in HDL-C, HDL_2-C, and the TC/HDL-C ratio with 1,000 mg/day of niacin observed in Goldberg and colleagues' study was very similar to the current study, suggesting that the responses of HDL-C, HDL_2-C, and the TC/HDL-C ratio may be more associated with a dosage but not

with the duration of niacin ingestion.

Although it is well documented that niacin positively influences HDL-C metabolism, the exact mechanism is not clearly understood. It has been proposed that a niacin-induced increase in HDL-C may result from the increased activity of selective cholesterol uptake, which selectively removes cholesterol from HDL-C, and blocks hepatic catabolism of HDL particles containing apo A-I (Ganji et al., 2003; Jin et al., 1997; Sprecher, 2000). Thus, the increased activity of selective cholesterol uptake augments the RCT pathway, which also promotes an overall increase in HDL_3-C (Converse & Skinner, 1992; Lewis & Rader, 2005).

Although the present study did not measure the concentration of apo A-I, it has been previously reported that niacin at various dosages increased apo A-I (Goldberg et al., 2000; Guyton, 2004; Jin et al., 1997; Knopp et al., 1998; Sakai et al., 2001). For example, apo A-I increased from 105.1 to 115.9 mg/dl (10.3%) in patients with dyslipidemia after 2,000 mg/day of niacin supplementation for 19 weeks (Sakai et al., 2001), and hypercholesterolemic men and women also increased apo A-I by 8.0% from baseline after 1,500 mg/day of niacin ingestion for 16 weeks (Knopp et al., 1998). Goldberg and colleagues also reported that apo A-I increased approximately 12.0% from baseline after the niacin supplement (3,000 mg/day) in 131 individuals with dyslipidemia (Goldberg et al., 2000).

There is an inverse relationship between the concentrations of HDL-C and plasma TG. A niacin-induced decrease in plasma TG may lead to an increase in HDL-C, which is mediated by the activity of CETP. The main role of CETP is to transfer TG from TG-rich

VLDL and LDL particles to HDL particles in exchange for cholesterol ester (Champe et al., 2005; Kwiterovich, 1998). In other words, an increased activity of CETP depletes cholesterol esters from HDL-C and stores more TG in HDL particles, which consequently enhances the removal process of TG-rich HDL-C via a holoparticle HDL-C uptake in the kidney (Kashyap, 1998). Unfortunately, no study to date has investigated the effects of niacin on CETP activity. Therefore, it is difficult to conclude whether or not niacin directly affected CETP activity.

Effects of Exercise on TC, LDL-C, and TG

Although the effects of a single bout of exercise on TC, LDL, and TG are not consistent (Bermingham et al., 2004; Ferguson et al., 2003; Ferguson et al., 1998; Grandjean et al., 2000; Vuorimaa et al., 2005), it has been documented that a single bout of exercise may not decrease TC and LDL-C, but may decrease TG (Bermingham et al., 2004; Crouse et al., 1995; Durstine et al., 2000; Grandjean et al., 2000; Kelley et al., 2006; Sgouraki et al., 2004; Weise et al., 2005). For instance, the concentration of TC in sedentary men was reduced by 3.0% from 217.0 mg/dl immediately following a single bout of exercise at 70% VO_2max until 500 kcal were expended. The concentration of TG also decreased by 16.0 mg/dl from baseline (144.0 mg/dl) after 24 and 48 hr of exercise (Grandjean et al., 2000). In addition, Ferguson and colleagues reported that moderately trained men decreased TC (from 170.0 to 156.0 mg/dl) and LDL-C (from 105.0 to 86.0 mg/dl) in response to a single bout of exercise requiring more than 1,000 kcal. However, the concentration of TG did not change after a single bout of exercise (Ferguson et al., 2003).

In the present study, a single bout of exercise at 60% HRR (until 400 kcal) did not significantly alter TC, LDL-C, and TG in sedentary, postmenopausal women. The results of the current study were consistent with previously published studies (Bermingham et al., 2004; Biggerstaff, 2000; Kushnick, 2003). For example, a single bout of exercise at low (300 – 350 kcal) and high (600 – 700 kcal) volumes did not change TC and LDL-C in men (Biggerstaff, 2000; Kushnick, 2003). Bermingham and colleagues also reported that patients with CHD did not significantly decrease TC, LDL-C, or TG after arm ergometry exercise at 65 – 75% HRmax (Bermingham et al., 2004). In addition, Weise and colleagues found that postmenopausal women did not significantly change TC and LDL-C after performing a single bout of exercise at 70% VO_2peak until 400 kcal were expended. However, the concentration of TG 24 hr following exercise was significantly reduced from 127 to 118 mg/dl (8.5%), but returned to 122 mg/dl 48 hr after exercise (Weise et al., 2005). Although the exercise intensity and volume for the current study were very similar to Weise and colleagues' study (2005), the concentration of TG in the current study did not change after a single bout of exercise. One of the main differences between the current study and Weise et al. (2005) is a different concentration of TG at baseline. In the current study, the concentration of TG before exercise was 88.8 mg/dl while the initial concentration of TG in the Weise and colleagues' study was 127.0 mg/dl. It has been reported that the magnitude of changes in TG are dependent upon the baseline level of TG (Lamarche et al., 1997; Thompson et al., 1997), suggesting that individuals with higher initial TG concentrations may have a greater or significant reduction in TG after exercise (Thompson et al., 1997). Lastly, it has been reported that

TC and LDL-C may not be altered in response to a single bout of exercise but may be changed by diet and weight loss (Durstine et al., 2000).

The present study did not measure LPL activity, but several studies have reported that a single bout of exercise may increase LPL activity (Ferguson et al., 1998; Grandjean & Crouse, 2001; Visich et al., 1996; Weise et al., 2005; Zhang et al., 2002), and thus lower TG. The activity of LPL may increase after a single bout of exercise, and the peak point may be reached approximately 24 hr following exercise (Grandjean & Crouse, 2001). It has also been reported that muscle LPL and mRNA activity were enhanced as early as 4 hr following exercise (Seip, Mair, Cole, & Semenkovich, 1997) or 14 to 24 hr after exercise (Grandjean et al., 2000; Perreault, Lavely, Kittelson, & Horton, 2004).

Although it has been reported that LPL activity in men may increase for up to 48 hr following exercise in conjunction with a decrease in plasma TG (Grandjean et al., 2000), Perreault et al., (2004) suggested that the acute response of LPL activity following exercise is gender specific. For example, LPL activity increased in men but not in premenopausal women after cycling exercise at 85% of lactate threshold for 90 min (Perreault et al., 2004). In contrast, Weise and colleagues reported that LPL activity actually decreased following exercise in hypercholesterolemic, postmenopausal women. The inconsistent results of LPL responses to exercise in women suggest that TG may be modulated by factors other than LPL in postmenopausal women (Weise et al., 2005).

Effects of Exercise on HDL-C, HDL_2-C, HDL_3-C, and TC/HDL-C Ratio

Previous studies often reported an increase in HDL-C in response to a single bout of exercise (Bermingham et al., 2004; Ferguson et al., 2003; Ferguson et al., 1998;

Grandjean et al., 2000; Sgouraki et al., 2004), and it is well documented that the exercise-induced increase in HDL-C is one of the well-known effects of exercise on blood lipids and lipoproteins (Durstine et al., 2001; Kelley, Kelley, & Vu Tran, 2005).

In general, a single bout of exercise may increase HDL-C up to 34.0%, and the exercise-induced elevation of HDL-C may last for several days following exercise (Grandjean & Crouse, 2001). Sedentary men with lower initial HDL-C significantly increased the concentration of HDL-C by 16.7 and 25.0% following low (350 kcal) and high (700 kcal) volumes of a single bout of exercise at 60% VO_2max, respectively (Biggerstaff, 2000). The concentration of HDL-C increased from 46.0 to 50.0 mg/dl 24 hr following a single bout of exercise at 65% VO_2max (600 kcal), but the increased HDL-C returned to baseline 72 hr post-exercise in men (Kushnick, 2003). Although the concentration of HDL-C did not change in response to low intensity (60% VO_2max) exercise, high intensity exercise (75% VO_2max) increased HDL-C 24 hr following exercise in recreational runners (Gordon et al., 1994). It has also been reported that HDL-C increased (up to 6.0 mg/dl) 48 hr after a single bout of exercise in trained women (Gordon et al., 1998) and in both normo- and hypercholesterolemic men (Grandjean et al., 2000).

The concentration of HDL-C in the current study, however, did not significantly increase in response to a single bout of exercise. The baseline HDL-C concentration was 46.3 ± 8.8 mg/dl, and remained unchanged (46.1 ± 8.1 mg/dl) after a single bout of exercise. Weise and colleagues (2005) reported that the concentration of HDL-C after 24 hr of a single bout of exercise significantly increased (3.0 mg/dl or 4.8%) from

immediately post-exercise (62.0 mg/dl). However, the exercise-induced increase in HDL-C was not significant anymore after 48 hr post-exercise. It has to be noted in Weise and colleagues' study that the concentration of HDL-C at baseline was 65.0 mg/dl, decreased to 62.0 mg/dl immediately post-exercise, and significantly increased up to 65.0 mg/dl from immediately post-exercise after 24 hr of exercise. It has been suggested that changes in lipids and lipoproteins including HDL-C immediately after exercise may be associated with a change in plasma volume (Kushnick, 2003), but Weise et al. (2005) did not measure or control for the plasma volume change. Therefore, it is difficult to determine if the significant increase in HDL-C immediately following exercise was actually induced by exercise or plasma volume change. One of the main differences between the current study and Weise et al. (2005) is the different initial HDL-C concentrations. The HDL-C concentration at baseline (43.1 mg/dl) in the current study was relatively lower than that (65.0 mg/dl) in Weise et al. (2005). Therefore, if the significant increase in HDL-C 24 hr following exercise was actually caused by a single bout of exercise, the initial HDL-C concentration may play an important role in altering HDL-C in postmenopausal women

In addition, factors associated with an increase in HDL-C include weight loss, exercise, high-fat diets, and female gender (Kashyap, 1998). It has been also suggested that a minimal exercise threshold may be required to significantly increase HDL-C in different individuals (Durstine et al., 2001; Ferguson et al., 1998). A single bout of exercise at 60 – 70% VO_2max (350 – 1400 kcal) significantly increased HDL-C (up to 21% from baseline) in men (Biggerstaff, 2000; Grandjean et al., 2000; Kushnick, 2003). Biggerstaff (2000) reported that an 16.7% increase in HDL-C from baseline (35.8 mg/dl)

after a relatively low volume (350 kcal) of a single bout of exercise in men. However, the similar exercise intensity (60% HRR or 70% VO_2peak) and volume (400 kcal) used in the current study and Weise et al. (2005) did not observe any overall exercised-induced changes in HDL-C in postmenopausal women. This suggests that the exercise volume greater than 400 kcal may be required to significantly alter HDL-C in postmenopausal women.

The responses of HDL-C subfractions and the TC to HDL-C ratio to a single bout of exercise are equivocal (Angelopoulos et al., 1993; Biggerstaff, 2000; Ferguson et al., 1998; Park & Ransone, 2003; Sgouraki et al., 2001). In the present study, a single bout of exercise (60% HRR requiring 400 kcal) did not significantly alter HDL_2-C (12.6 vs. 12.7 mg/dl), HDL_3-C (33.7 vs. 33.4 mg/dl), or TC to HDL-C ratio (5.0 vs. 5.0). Following a high volume (1,500 kcal) of a single bout of exercise, trained men increased HDL_2-C and HDL_3-C by 43.0% (from 14.0 to 20.0 mg/dl) and 25.0% (from 28.0 to 35.0 mg/dl), respectively (Ferguson et al., 1998).

Similar to the current study, both HDL_2-C and HDL_3-C did not change in response to a single bout of exercise in young (Imamura et al., 2000) and postmenopausal (Weise et al., 2005) women or normo- and hyperlipidemic men (Zhang et al., 2002). It is known that HDL subfraction metabolism is associated with LCAT activity, which promotes conversion of HDL_3-C to HDL_2-C (Durstine et al., 2000). The LCAT activity plays an important role in the maturation of pre β-1 HDL (Lewis & Rader, 2005; Smolin & Grosvenor, 2002), which consequently promotes the initiation of the RCT pathway (Lewis & Rader, 2005; von Eckardstein et al., 2001). Increased LCAT activity promotes

conversion of small, dense HDL_3-C to large, less dense HDL_2-C by progressively converting and storing cholesterol esters in the core of HDL-C (Kwiterovich, 1998; Kwiterovich, 2000; Lewis & Rader, 2005). Although several studies have investigated the effects of exercise training on LCAT activity, only limited investigations have previously examined the effects of a single bout of exercise on LCAT activity (Grandjean et al., 2000; Weise et al., 2005). For example, Weise et al. (2005) reported an approximate 7.1% increase in LCAT activity (from 4.78 to 5.12 μmol cholesterol ester/L/h) only in normocholesterolemic, postmenopausal women, but not in hypercholesterolemic, postmenopausal women, 24 hr following moderate intensity (70% VO_2peak) of a single bout of exercise (400 kcal). The exercise-induced increase in LCAT activity remained for 48 hr after exercise (Weise et al., 2005). In contrast, the LCAT activity in both normo-and hypercholesterolemic men did not change following a single bout of exercise at 70% VO_2max requiring 500 kcal (Grandjean et al., 2000). Therefore, it is difficult to conclude how a single bout of exercise affects LCAT activity in different populations. However, based on the results of Weise et al. (2005), it can be speculated that LCAT activity in hypercholesterolemic, postmenopausal women in the current study may not be influenced by a single bout of exercise, leading to no change in HDL-C metabolism.

Effects of Niacin and Exercise on Blood Lipids and Lipoproteins

Niacin and exercise independently influence blood lipids and lipoproteins via different mechanisms. Thus, it was hypothesized in the current study that when a single bout of exercise is combined with niacin, there may be additive effects of exercise on changes in blood lipids and lipoproteins. However, the results revealed that the

combination of niacin and a single bout of exercise did not significantly improve TC, LDL-C, and TG at any time period (0, 24, and 48 hr) as compared with niacin or exercise alone. Likewise, there was no additive effect of a single bout of exercise on HDL-C, HDL_2-C, HDL_3-C, and TC to HDL-C ratio at any time period during the niacin condition.

Due to the lack of information available, it is difficult to mechanistically explain why a single bout of exercise when combined with niacin could not significantly improve blood lipids and lipoproteins more than niacin and exercise alone. However, it could be speculated that a niacin-induced reduction in TG (12.5%) in the present study might reduce the TG substrate available for skeletal muscle LPL. In addition, the mean concentration of TG in the current study was 97.5 mg/dl at baseline, and the lowest and highest concentration of TG was 37.5 and 101.1 mg/dl, respectively, indicating that most participants had normal concentrations of TG. It has been reported that the magnitude of changes in TG following exercise is dependent upon the baseline TG concentration. Individuals with higher initial TG concentrations showed a greater reduction in TG after exercise (Durstine et al., 2000; Thompson et al., 1997).

Summary

The present study examined the independent and combined effects of 4-weeks of niacin (1,000 mg/day) and a single bout of exercise at 60% HRR (400 kcal) on the blood lipid and lipoprotein profiles in postmenopausal women. Although not significant, the concentrations of TC, LDL-C, and TG decreased after the niacin supplement. The niacin treatment without the exercise intervention significantly increased HDL-C (5.4 mg/dl or 12.4 %) and HDL_2-C (3.6 mg/dl or 33.3 %) from baseline. Therefore, it is suggested that 4-

weeks of the niacin supplement (1,000 mg/day) can favorably increase HDL-C, predominantly HDL_2-C.

Recommendations for Future Study

The current study is one of the first studies that have examined the effects of niacin (1,000 mg/day for 4 weeks) and a single bout of exercise (at 60% HRR until 400 kcal) on blood lipids and lipoproteins in postmenopausal women. The following are recommendations for future studies related to this line of inquiry:

1. A similar study should focus on identifying the optimal amount of exercise needed to modify blood lipid and lipoprotein profiles in sedentary, postmenopausal women.
2. A similar study should focus on identifying the appropriate dosage of niacin required to significantly decrease TC, LDL-C, and TG in sedentary, postmenopausal women with the normal concentration of TG.
3. A similar study should focus on examining the responses of enzymes and proteins such as LPL, LCAT, CETP, and HL to the niacin supplement at various dosages since no study has reported the effects of niacin on these enzymes and proteins. Examining these enzymes and proteins, which are associated with lipid and lipoprotein metabolism, will help promote a better understanding of lipids and lipoproteins metabolism in response to exercise and niacin.
4. A similar study should be conducted in different study populations, especially individuals with dyslipidemia.

REFERENCES

Abourjaily, M. L. (2001). A review of Niaspan, an extended-release niacin. *Nutrition in Clinical Care, 4*, 250-255.

Acton, S., Rigotti, A., Landschulz, K. T., Xu, S., Hobbs, H. H., & Krieger, M. (1996). Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. *Science, 271*(5248), 518-520.

Aiello, R. J., Brees, D., Bourassa, P. A., Royer, L., Linsey, S., Coskran, T., et al. (2002). Increased atherosclerosis in hyperlipidemic mice with inactivation of ABCA 1 in macrophages. *Arteriosclerosis, Thrombosis, and Vascular Biology, 22*, 630-637.

Alderman, J. D., Pasternak, R. C., Sacks, F. M., Smith, H. S., Monrad, S. E., & Grossman, W. (1989). Effect of a modified, well-tolerated niacin regimen on serum total cholesterol, high density lipoprotein cholesterol and the cholesterol to high density lipoprotein ratio. *The American Journal of Cardiology, 64*, 725-729.

Alhassan, S., Reese, K. A., Mahurin, J., Plaisance, E. P., Hilson, B. D., Garner, J. C., et al. (2006). Blood lipid responses to plant stanol ester supplementation and aerobic exercise training. *Metabolism Clinical and Experimental, 55*, 541-549.

Altena, T. S., Michaelson, J. L., Ball, S. D., Guilford, B. L., & Thomas, T. R. (2006). Lipoprotein subfraction changes after continuous or intermittent exercise training. *Medicine and Science in Sports and Exercise, 38*(2), 367-372.

Altschul, R., Hoffer, A., & Stephen, J. D. (1955). Influence of nicotinic acid on serum cholesterol in man. *Archives of Biochemistry, 54*(2), 558-559.

American Heart Association. (2006). *Heart Disease and Stroke Statistics - 2006 Update.* Dallas, TX: American Heart Association.

Andersen, R. E., Wadden, T. A., Bartlett, S. J., Zemel, B., Verde, T. J., & Franckowiak, S. C. (1999). Effects of lifestyle activity vs structured aerobic exercise in obese women: a randomized trial. *The Journal of the American Medical Association, 281*, 335-340.

Angelopoulos, T. J., Robertson, R. J., Goss, F. L., Metz, K. F., & LaPorte, R. E. (1993). Effect of repeated exercise bouts on high density lipoprotein-cholesterol and its subfractions HDL2-C and HDL3-C. *International Journal of Sports Medicine, 14*, 196-201.

Armstrong, L., Balady, G. J., Berry, M. J., Davis, S. E., Davy, B. M., Davy, K. P., et al. (2006). *ACSM's guidelines for exercise testing and prescription* (7th ed.). Baltimore, MD: Lippincott Williams & Wilkins.

Asikainen, T. M., Kukkonen-Harjula, K., & Miilunpalo, S. (2004). Exercise for health for early postmenopausal women: a systematic review of randomized controlled trials. *Sports Medicine, 34*(11), 753-778.

Attie, A. D., Kastelein, J. P., & Hayden, M. R. (2001). Pivotal role of ABCA1 in reverse cholesterol transport influencing HDL levels and susceptibility to atherosclerosis. *Journal of Lipid Research, 42*(11), 1717-1726.

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, 82*, 495-506.

Benyo, Z., Gille, A., Kero, J., Csiky, M., Suchankova, M. C., Nusing, R. M., et al. (2005). GPR109A (PUMA-G/HM74A) mediates nicotinic acid-induced flushing. *The Journal of Clinical Investigation, 115*(12), 3634-3640.

Berg, A., Frey, I., Baumstark, M. W., Halle, M., & Keul, J. (1994). Physical activity and lipoprotein lipid disorders. *Sports Medicine, 17*, 6-21.

Berg, K. (1994). Lp(a) Lipoprotein: an overview. *Chemistry and Physics of Lipids, 68*, 9-16.

Berg, V. H. (1997). Bioavailability of niacin. *European Journal of Clinical Nutrition, 51*, S64-S65.

Bermingham, M. A., Mahajan, D., & Neaverson, M. A. (2004). Blood lipids of cardiac patients after acute exercise on land and in water. *Archives of Physical Medicine and Rehabilitation, 85*(3), 509-511.

Biggerstaff, K. D. (2000). *Caloric expenditure on acute lipoprotein responses to aerobic exercise.* Unpublished doctoral dissertation, The Florida State University, Tallahassee.

Binder, E. F., Birge, S. J., & Kohrt, W. M. (1996). Effects of endurance exercise and hormone replacement therapy on serum lipids in older women. *Journal of the American Geriatrics Society, 44*, 231-236.

Blumenthal, J. A., Matthews, K., Fredrikson, M., Rifai, N., Schniebolk, S., German, D., et al. (1991). Effects of exercise training on cardiovascular function and plasma lipid, lipoprotein, and apolipoprotein concentrations in premenopausal and postmenopausal women. *Arteriosclerosis and Thrombosis, 11*, 912-917.

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.

Borg, G. (1982). Ratings of perceived exertion and heart rates during short-term cycle exercise and their use in a new cycling strength test. *International Journal of Sports Medicine, 3*, 153-158.

Boutcher, S. H., Meyer, B. J., Craig, G. A., & Astheimer, L. (2003). Plasma lipid and fibrinogen levels in aerobically trained and untrained postmenopausal women. *The Journal of sports medicine and physical fitness, 43*(2), 231-235.

Brewer, H. B. J. (2004). Focus on high-density lipoproteins in reducing cardiovascular risk. *American Heart Journal, 148*, S14-18.

Brites, F., Verona, J., De Geitere, C., Fruchart, J. C., Castro, G., & Wikinski, R. (2004). Enhanced cholesterol efflux promotion in well-trained soccer players. *Metabolism, 53*(10), 1262-1267.

Brousseau, M. E., Santamarina-Fojo, S., Vaisman, B. L., Applebaum-Bowden, D., Berard, A. M., Talley, G. D., et al. (1997). Overexpression of human lecithin: cholesterol acyltransferase in cholesterol-fed rabbits: LDL metabolism and HDL metabolism are affected in a gene dose-dependent manner. *Journal of Lipid Research, 38*(12), 2537-2547.

Brown, B. G., Zambon, A., Poulin, D., Rocha, A., Maher, V. M., Davis, J. W., et al. (1998). Use of niacin, statins, and resins in patients with combined hyperlipidemia. *The American Journal of Cardiology, 81*(4A), 52B-59B.

Capuzzi, D. M., Guyton, J. R., Morgan, J. M., Goldberg, A. C., Kreisberg, R. A., Brusco, O. A., et al. (1998). Efficacy and safety of an extended-release niacin (Niaspan): a long-term study. *The American Journal of Cardiology, 82*(12(A)), 74U-81U.

Carlson, L. A. (2005). Nicotinic acid: the broad-spectrum lipid drug. A 50th anniversary review. *Journal of Internal Medicine, 258*, 94-114.

Castelli, W. P., Garrison, R. J., Wilson, P. W., Abbott, R. D., Kalousdian, S., & Kannel, W. B. (1986). Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. *The Journal of the American Medical Association, 256*, 2835-2838.

Cervantes-Laurean, N. D., McElvaney, G., & Moss, J. (1998). Niacin. In E. M. Shills, Olson, A. J., Shike, M., & Ross, A. C. (Ed.), *Modern Nutrition in Health and Disease* (9th ed.). Baltimore, MD: Lippincott Williams & Wilkins.

Champe, P. C., Harvey, R. A., & Ferrier, D. R. (2005). *Lippincott's Illustrated Reviews: Biochemistry* (3rd ed.). Philadelphia, PA: Lippincott Williams & Wilkins.

Christison, J. K., Rye, K. A., & Stocker, R. (1995). Exchange of oxidized choletreryl linolcate between LDL and HDL mediated by cholesteryl ester transfer protein. *Journal of Lipid Research, 36*, 2017-2026.

Converse, C. A., & Skinner, E. R. (1992). *Lipoprotein analysis; a practical approach.* Oxford, NY: Oxford University Press.

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: evidence from men of the Health, Risk Factors, Exercise Training and Genetics (HERITAGE) Family Study. *Arteriosclerosis, Thrombosis, and Vascular Biology, 21*, 1226-1232.

Crouse, J. R. (1996). New developments in the use of niacin for treatment of hyperlipidemia: new considerations in the use of an old drug. *Coronary artery disease, 7*(4), 321-326.

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 single session of exercise on lipids and apolipoproteins in hypercholesterolemic men. *Journal of Applied Physiology, 83*, 2019-2028.

Crouse, S. F., O'Brien, B. C., Grandjean, P. W., Lowe, R. C., Rohack, J. J., Green, J. S., et al. (1997). 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., 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.

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.

Deeb, S. S., Zambon, A., Carr, M. C., Ayyobi, A. F., & Brunzell, J. D. (2003). Hepatic lipase and dyslipidemia: interactions among genetic variants, obesity, gender, and diet. *Journal of Lipid Research, 44*, 1279-1286.

Despres, J. P., Ferland, M., Moorjani, S., Nadeau, A., Tremblay, A., Lupien, P. J., et al. (1989). Role of hepatic-triglyceride lipase activity in the association between intra-abdominal fat and plasma HDL-cholesterol in obese women. *Arteriosclerosis, 9*(4), 485-492.

Dill, D. B., & Costill, D. L. (1974). Calculation of percentage changes in volumes of blood, plasma, and red cells in dehydration. *Journal of Applied Physiology, 37*, 247-248.

Dowling, E. A. (2001). How exercise affects lipid profiles in women; what to recommend for patients. *The Physician and Sports Medicine, 29*(9), 45-52.

Drabkin, O. L., & Austin, J. H. (1935). Spectrophotometric studies II. Preparation from washed cells; nitric oxide, hemoglobin, and sulfhemoglobin. *The Journal of Biological Chemistry, 112*, 51-55.

Drood, M. J., Zimetbaum, J. P., & Frishman, H. W. (1991). Nicotinic acid for the treatment of hyperlipoproteinemia. *Journal of Clinical Pharmacology, 31*, 641-650.

Durstine, J. L., Crouse, S. F., & Moffatt, R. J. (2000). Lipids in exercise and sports. In J. A. Driskell & I. Wolinsky (Eds.), *Energy yielding macronutrients and energy metabolism in sports nutrition* (pp. 87-117). FL: CRC press.

Durstine, J. L., Davis, P. G., Ferguson, M. A., Alderson, N. L., & Trost, S. G. (2001). Effects of short-duration and long-duration exercise on lipoprotein(a). *Medicine and Science in Sports and Exercise, 33*, 1511-1516.

Durstine, J. L., Ferguson, M. A., Szymanski, L. M., Davis, P. G., Alderson, N. L., Trost, S. G., et al. (1996). Effect of a single session of exercise on lipoprotein(a). *Medicine and Science in Sports and Exercise, 28*, 1277-1281.

Durstine, J. L., Grandjean, P. W., Cox, C. A., & Thompson, P. D. (2002). Lipids, lipoproteins, and exercise. *Journal of Cardiopulmonary Rehabilitation, 22*(6), 385-398.

Fahlman, M. M., Boardley, D., Lambert, C. P., & Flynn, M. G. (2002). Effects of endurance training and resistance training on plasma lipoprotein profiles in elderly women. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 57*, B54-B60.

Ferguson, M. A., Alderson, N. L., Trost, S. G., Davis, P. G., Mosher, P. E., & Durstine, J. L. (2003). Plasma lipid and lipoprotein responses during exercise. *Scandinavian Journal of Clinical and Laboratory Investigation, 63*, 73-80.

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*(3), 1169-1174.

Fielding, C. J., & Fielding, P. E. (1995). Molecular physiology of reverse cholesterol transport. *Journal of Lipid Research, 36*, 211-228.

Fletcher, B., Berra, K., Ades, P., Braun, L. T., Burke, L. E., Durstine, J. L., et al. (2005). Managing abnormal blood lipids: a collaborative approach. *Circulation, 112*, 3184-3209.

Foger, B., Wohlfarter, T., Ritsch, A., Lechleitner, M., Miller, C. H., Dienstl, A., et al. (1994). Kinetics of lipids, apolipoproteins, and cholesteryl ester transfer protein in plasma after a bicycle marathon. *Metabolism, 43*(5), 633-639.

Fonong, T., Toth, M. J., Ades, P. A., Katzel, L. I., Calles-Escandon, J., & Poehlman, E. T. (1996). Relationship between physical activity and HDL-cholesterol in healthy older men and women: a cross-sectional and exercise intervention study. *Atherosclerosis, 127*, 177-183.

Ford, S. E., Giles, H. W., & Dietz, H. W. (2002). Prevalence of the metabolic syndrome among US adults: findings from the third national health and nutrition examination survey. *The Journal of the American Medical Association, 287*, 356-359.

Friedewald, W. T., Levy, R. I., & Fredrickson, D. S. (1972). Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clinical Chemistry, 18*, 499-502.

Ganji, S. H., Kamanna, V. S., & Kashyap, M. L. (2003). Niacin and cholesterol: role in cardiovascular disease (review). *The Journal of Nutritional Biochemistry, 14*, 298-305.

Ganji, S. H., Tavintharan, S., Zhu, D., Xing, Y., Kamanna, V. S., & Kashyap, M. L. (2004). Niacin noncompetitively inhibits DGAT2 but not DGAT1 activity in HepG2 cells. *Journal of Lipid Research, 45*, 1835-1845.

Garg, A., & Grundy, M. S. (1990). Nicotinic acid as therapy for dyslipidemia in non-insulin-dependent diabetes mellitus. *Journal of American Medicine Association, 264*, 723-726.

Goldberg, A. C. (1998). Clinical trial experience with extended-release niacin (Niaspan): dose-escalation study. *The American Journal of Cardiology, 82*, 35U-38U.

Goldberg, A. C. (2004). A meta-analysis of randomized controlled studies on the effects of extended-release niacin in women. *The American Journal of Cardiology, 94*, 121-124.

Goldberg, A. C., Alagona, P. J., Capuzzi, D. M., Guyton, J., Morgan, J. M., Rodgers, J., et al. (2000). Multiple-dose efficacy and safety of an extended-release form of niacin in the management of hyperlipidemia. *The American Journal of Cardiology, 85*, 1100-1105.

Goodyear, L. J., Van Houten, D. R., Fronsoe, M. S., Rocchio, 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*, 588-592.

Gordon, D. J., Probstfield, J. L., Garrison, R. J., Neaton, J. D., Castelli, W. P., Knoke, J. D., et al. (1989). High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. *Circulation, 79*, 8-15.

Gordon, P. M., Fowler, S., Warty, V., Danduran, M., Visich, P., & Keteyian, S. (1998). Effects of acute exercise on high density lipoprotein cholesterol and high density lipoprotein subfractions in moderately trained females. *British Journal of Sports Medicine, 32*(1), 63-67.

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

Grandjean, P. W., & Crouse, S. F. (2001). Lipids and Lipoprotein Disorders. In S. von Duvillard, and Limura, L. (Ed.), *Clinical Exercise Physiology: Application and Physiological Principles*. Philadelphia, PA: Lippincott, Williams & Wilkins.

Grandjean, P. W., Crouse, S. F., O'Brien, B. C., Rohack, J. J., & Brown, J. A. (1998). The effects of menopausal status and exercise training on serum lipids and the activities of intravascular enzymes related to lipid transport. *Metabolism, 47*, 377-383.

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*(2), 472-480.

Grandjean, P. W., Oden, G. L., Crouse, S. F., Brown, J. A., & Green, J. S. (1996). Lipid and lipoprotein changes in women following 6 months of exercise training in a worksite fitness program. *The Journal of Sports Medicine and Physical Fitness, 36*, 54-59.

Grundy, S. M., Mok, H. Y., Zech, L., & Berman, M. (1981). Influence of nicotinic acid on metabolism of cholesterol and triglycerides in man. *Journal of Lipid Research, 22*(1), 24-36.

Guyton, J. R. (2004). Extended-release niacin for modifying the lipoprotein profile. *Expert Opinion on Pharmacotherapy, 5*(6), 1385-1398.

Guyton, J. R., & Capuzzi, D. M. (1998). Treatment of hyperlipidemia with combined niacin-statin regimens. *The American Journal of Cardiology, 82*(12A), 82U-84U.

Guyton, J. R., Goldberg, A. C., Kreisberg, R. A., Sprecher, D. L., Robert Superko, H., & O'Connor, C. M. (1998). Effectiveness of once-nightly dosing of extended-release niacin alone and in combination for hypercholesterolemia. *The American Journal of Cardiology, 82*, 737-743.

Haddock, B. L., Marshak, H. P., Mason, J. J., & Blix, G. (2000). The effect of hormone replacement therapy and exercise on cardiovascular disease risk factors in postmenopausal women. *Sports Medicine, 29*, 39-49.

Hageman, G. J., & Stierum, R. H. (2001). Niacin, poly(ADP-ribose) polymerase-1 and genomic stability. *Mutation Research, 475*, 45-56.

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-density lipoprotein subfractions in obese men with type 2 diabetes. *Metabolism, 48*, 641-644.

Hammad, S. M., Stefansson, S., Twal, W. O., Drake, C. J., Fleming, P., Remaley, A., et al. (1999). Cubilin, the endocytic receptor for intrinsic factor-vitamin B(12) complex, mediates high-density lipoprotein holoparticle endocytosis. *Proceedings of the National Academy of Sciences of the United States of America, 96*(18), 10158-10163.

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.

Houmard, J. A., Bruno, N. J., Bruner, R. K., McCammon, M. R., Israel, R. G., & Barakat, H. A. (1994). Effects of exercise training on the chemical composition of plasma LDL. *Arteriosclerosis, Thrombosis, and Vascular Biology, 14*, 325-330.

Imamura, H., Katagiri, S., Uchid, K., Miyamoto, N., Nakano, H., & Shirota, T. (2000). Acute effects of moderate exercise on serum lipids, lipoproteins and apolipoproteins in sedentary young women. *Clinical and Experimental Pharmacology & Physiology, 27*(12), 975-979.

Inazu, A., Jiang, X. C., Haraki, T., Yagi, K., Kamon, N., Koizumi, J., et al. (1994). Genetic cholesteryl ester transfer protein deficiency caused by two prevalent mutations as a major determinant of increased levels of high density lipoprotein cholesterol. *The Journal of Clinical Investigation, 94*(5), 1872-1882.

Ito, K. M. (2002). Niacin-based therapy for dyslipidemia: Past evidence and future advances. *American Journal of Managed Care, 8*, S315-S322.

Jafari, M., Leaf, D. A., Macrae, H., Kasem, J., O'conner, P., Pullinger, C., et al. (2003). The effects of physical exercise on plasma prebeta-1 high-density lipoprotein. *Metabolism, 52*(4), 437-442.

Jin, F. Y., Kamanna, V. S., & Kashyap, M. L. (1997). Niacin decreases removal of high-density lipoprotein apolipoprotein A-I but not cholesterol ester by Hep G2 cells. Implication for reverse cholesterol transport. *Arteriosclerosis, Thrombosis, and Vascular Biology, 17*(10), 2020-2028.

Jonas, A., von Eckardstein, A., Kezdy, K. E., Steinmetz, A., & Assmann, G. (1991). Structural and functional properties of reconstituted high density lipoprotein discs prepared with six apolipoprotein A-I variants. *Journal of Lipid Research, 32*(1), 97-106.

Kahn, S. E., Beard, J. C., Schwartz, M. W., Ward, W. K., Ding, H. L., Bergman, R. N., et al. (1989). Increased beta-cell secretory capacity as mechanism for islet adaptation to nicotinic acid-induced insulin resistance. *Diabetes, 38*, 562-568.

Kane, P. M., Hamilton, A. R., Addesse, E., Busch, S. R., & Bakst, G. (2001). Cholesterol and glycemic effects of Niaspan in patients with type 2 diabetes. *Pharmacotherapy, 21*(12), 1473-1478.

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*(2), 188-192.

Karpe, F., & Frayn, N. K. (2004). The nicotinic acid receptor-a new mechanism for an old drug. *The Lancet, 363*, 1892-1894.

Kashyap, M. L. (1998). Mechanistic studies of high-density lipoproteins. *The American Journal of Cardiology, 82*, 42U-48U.

Kelley, G. A., & Kelley, K. S. (2006). Aerobic exercise and HDL2-C: a meta-analysis of randomized controlled trials. *Atherosclerosis, 184*, 207-215.

Kelley, G. A., Kelley, K. S., & Franklin, B. (2006). Aerobic exercise and lipids and lipoproteins in patients with cardiovascular disease: a meta-analysis of randomized controlled trials. *Journal of Cardiopulmonary Rehabilitation, 26*, 131-139.

Kelley, G. A., Kelley, K. S., & Tran, Z. V. (2004). Aerobic exercise and lipids and lipoproteins in women: a meta-analysis of randomized controlled trials. *Journal of Women's Health, 13*, 1148-1164.

Kelley, G. A., Kelley, K. S., & Vu Tran, Z. (2005). Aerobic exercise, lipids and lipoproteins in overweight and obese adults: a meta-analysis of randomized controlled trials. *International Journal of Obesity, 29*, 881-893.

Knopp, R. H., Alagona, P., Davidson, M., Goldgerg, A. C., Kafonek, S. D., Kashyap, M., et al. (1998). Equivalent efficacy of a time-release form of niacin (Niaspan) given once-a-night versus plain niacin in the management of hyperlipidemia. *Metabolism, 47*(9), 1097-1104.

Knopp, R. H., Ginsberg, J., Albers, J. J., Hoff, C., Ogilvie, J. T., Warnick, G. R., et al. (1985). Contrasting effects of unmodified and time-release forms of niacin on lipoproteins in hyperlipidemic subjects: clues to mechanism of action of niacin. *Metabolism, 34*(7), 642-650.

Knowles, H. J., Te Poele, R. H., Workman, P., & Harris, A. L. (2006). Niacin induces PPARgamma expression and transcriptional activation in macrophages via HM74 and HM74a-mediated induction of prostaglandin synthesis pathways. *Biochemical Pharmacology, 71*, 646-656.

Kota, B. P., Huang, T. H., & Roufogalis, B. D. (2005). An overview on biological mechanisms of PPARs. *Pharmacological Research, 51*, 85-94.

Kozarsky, K. F., Donahee, M. H., Rigotti, A., Iqbal, S. N., Edelman, E. R., & Krieger, M. (1997). Overexpression of the HDL receptor SR-BI alters plasma HDL and bile cholesterol levels. *Nature, 387*, 414-417.

Kunitake, S. T., La, K. J., & Kane, J. P. (1985). Apolipoprotein A-I containing lipoproteins with pre-beta electrophoretic mobility. *Journal of Lipid Research, 26*, 549-555.

Kushnick, R. M. (2003). *Lipid and lipoprotein metabolism in response to treadmill walking at two levels of caloric expenditure: a comparison of black and white American men.* Unpublished doctoral dissertation, The Florida State University, Tallahassee.

Kuvin, J. T., Ramet, M. E., Patel, A. R., Pandian, N. G., Mendelsohn, M. E., & Karas, R. H. (2002). A novel mechanism for the beneficial vascular effects of high-density lipoprotein cholesterol: enhanced vasorelaxation and increased endothelial nitric oxide synthase expression. *American Heart Journal, 144*(1), 165-172.

Kwiterovich, P. O. J. (1998). The antiatherogenic role of high-density lipoprotein cholesterol. *The American Journal of Cardiology, 82*, 13Q-21Q.

Kwiterovich, P. O. J. (2000). The metabolic pathways of high-density lipoprotein, low-density lipoprotein, and triglycerides: a current review. *The American Journal of Cardiology, 86 (suppl)*, 5L-10L.

Lamarche, B., Tchernof, A., Moorjani, S., Cantin, B., Dagenais, G. R., Lupien, P. J., et al. (1997). Small, dense low-density lipoprotein particles as a predictor of the risk of ischemic heart disease in men. Prospective results from the Quebec Cardiovascular Study. *Circulation, 95*(1), 69-75.

Lehmann, R., Engler, H., Honegger, R., Riesen, W., & Spinas, G. A. (2001). Alterations of lipolytic enzymes and high-density lipoprotein subfractions induced by physical activity in type 2 diabetes mellitus. *European Journal of Clinical Investigation, 31*, 37-44.

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*(4), 513-520.

Lewis, F. G., & Rader, J. D. (2005). New insights into the regulation of HDL metabolism and reverse cholesterol transport. *Circulation Research, 96*, 1221-1232.

Lippi, G., Schena, F., Salvagno, G. L., Montagnana, M., Ballestrieri, F., & Guidi, G. C. (2006). Comparison of the lipid profile and lipoprotein(a) between sedentary and highly trained subjects. *Clinical Chemistry and Laboratory Medicine, 44*(3), 322-326.

Lloyd-Jones, D. M., Larson, M. G., Beiser, A., & Levy, D. (1999). Lifetime risk of developing coronary heart disease. *The lancet, 353*(9147), 89-91.

Lokey, E. A., & Tran, Z. V. (1989). Effects of exercise training on serum lipid and lipoprotein concentrations in women: a meta-analysis. *International Journal of Sports Medicine, 10*(6), 424-429.

Lokey, E. A., & Tran, Z. V. (1989). Effects of exercise training on serum lipid and lipoprotein concentrations in women: a meta-analysis. *International Journal of Sports Medicine, 10*(6), 424-429.

Lorenzen, A., Stannek, C., Lang, H., Andrianov, V., Kalvinsh, I., & Schwabe, U. (2001). Characterization of a G protein-coupled receptor for nicotinic acid. *Molecular Pharmacology, 59*(2), 349-357.

Maclean, P. S., Tanner, C. J., Houmard, J. A., & Barakat, H. A. (2001). Plasma cholesteryl ester transfer protein activity is not linked to insulin sensitivity. *Metabolism, 50*(7), 783-788.

Mahboubi, K., Witman-Jones, T., Adamus, J. E., Letsinger, J. T., Whitehouse, D., Moorman, A. R., et al. (2005). Triglyceride modulation by acifran analogs: activity towards the niacin high and low affinity G protein-coupled receptors HM74A and HM74. *Biochemical and Biophysical Research Communications, 340*, 482-490.

Marcil, M., Brooks-Wilson, A., Clee, S. M., Roomp, K., Zhang, L. H., Yu, L., et al. (1999). Mutations in the ABC1 gene in familial HDL deficiency with defective cholesterol efflux. *Lancet, 354*(9187), 1341-3146.

Matthews, K. A., Mellahn, E., Kuller, L. H., Kelsey, S. F., Caggiula, A. W., & Wing, R. R. (1989). Menopause and risk factors for coronary heart disease. *New England Journal of Medicine, 321*(10), 641-646.

McArdle, W. D.. Katch, F. I., & Katch, V. L. (1999). *Sports & exercise nutrition.* Baltimore, MD: Lippincott Williams & Wilkins.

McKenney, J. (2003). Niacin for dyslipidemia: Considerations in product selection. *American Journal of Health-System Pharmacy, 60*(10), 995-1005.

Meyers, C. D., Kamanna, V. S., & Kashyap, M. L. (2004). Niacin therapy in atherosclerosis. *Current Opinion in Lipidology, 15*, 659-665.

Morgan, J. M., Capuzzi, D. M., Baksh, R. I., Intenzo, C., Carey, C. M., Reese, D., et al. (2003). Effects of extended-release niacin on lipoprotein subclass distribution. *The American Journal of Cardiology, 91*, 1432-1436.

Morgan, J. M., Capuzzi, D. M., & Guyton, J. R. (1998). A new extended-release niacin (Niaspan): efficacy, tolerability, and safety in hypercholesterolemic patients. *The American Journal of Cardiology, 82*, 29U-34U.

Morgan, J. M., Carey, C. M., Lincoff, A., & Capuzzi, D. M. (2004). The effects of niacin on lipoprotein subclass distribution. *Preventive Cardiology, 7*, 182-187.

Murray, R. K., Granner, D. K., Mayes, P. A., & Rodewell, V. W. (2000). *Harper's biochemistry* (25th ed.). Stamford, CT: Appleton & Lange.

National Cholesterol Education Program. (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 (Adult Treatment Panel III). *The Journal of the American Medical Association, 285*(19), 2486-2497.

Pan, J., Van, J. T., Chan, E., Kesala, R. L., Lin, M., & Charles, A. M. (2002). Extended-release niacin treatment of the atherogenic lipid profile and lipoprotein(a) in diabetes. *Metabolism, 51*(9), 1120-1127.

Park, D. H., & Ransone, J. W. (2003). Effects of submaximal exercise on high-density lipoprotein-cholesterol subfractions. *International Journal of Sports Medicine, 24*, 245-251.

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.

Pieper, J. A. (2003). Overview of niacin formulations: Differences in pharmacokinetics, efficacy, and safety. *American Journal of Health-System Pharmacists, 60*, S9-S14.

Piepho, R. W. (2000). The pharmacokinetics and pharmacodynamics of agents proven to raise high-density lipoprotein cholesterol. *The American Journal of Cardiology, 86*(12A), 35L-40L.

Poynten, A. M., Gan, S. K., Kriketos, A. D., O'Sullivan, A., Kelly, J. J., Ellis, B. A., et al. (2003). Nicotinic acid-induced insulin resistance is related to increased circulating fatty acids and fat oxidation but not muscle lipid content. *Metabolism, 52*(6), 699-704.

Puchois, P., Kandoussi, A., Fievet, P., Fourrier, J. L., Bertrand, M., Koren, E., et al. (1987). Apolipoprotein A-I containing lipoproteins in coronary artery disease. *Atherosclerosis, 68*, 35-40.

Rader, D. J., Ikewaki, K., Duverger, N., Schmidt, H., Pritchard, H., Frohlich, J., et al. (1994). Markedly accelerated catabolism of apolipoprotein A-II (apo-II) and high density lipoproteins containing apo A-II in classic lecithin: cholesterol acyl-transferase deficiency and fish-eye disease. *The Journal of Clinical Investigation, 93*, 321-330.

Rainwater, D. L. (1998). Electrophoretic separation of LDL and HDL subclasses. In J. M. Ordovas (Ed.), *Lipoprotein Protocols*. Totowa, NJ: Humana Press Inc.

Rainwater, D. L., Mitchell, B. D., Comuzzie, A. G., & Haffner, S. M. (1999). Relationship of low density lipoprotein particle size and measures of adiposity. *International Journal of Obesity, 23*, 180-189.

Ramet, M. E., Ramet, M., Lu, Q., Nickerson, M., Savolainen, M. J., Malzone, A., et al. (2003). High-density lipoprotein increases the abundance of eNOS protein in human vascular endothelial cells by increasing its half-life. *Journal of the American College of Cardiology, 41*, 2288-2297.

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.

Ready, A. E., Naimark, B., Ducas, J., Sawatzky, J. V., Boreskie, S. L., Drinkwater, D. T., et al. (1996). Influence of walking volume on health benefits in women post-menopause. *Medicine and Science in Sports and Exercise, 28*, 1097-1105.

Riemens, S., van Tol, A., Sluiter, W., & Dullaart, R. (1998). Elevated plasma cholesteryl ester transfer in NIDDM: relationships with apolipoprotein B-containing lipoproteins and phospholipid transfer protein. *Atherosclerosis, 140*(1), 71-79.

Rinninger, F., Kaiser, T., Windler, E., Greten, H., Fruchart, J. C., & Castro, G. (1998). Selective uptake of cholesteryl esters from high-density lipoprotein-derived LpA-I and LpA-I: A-II particles by hepatic cells in culture. *Biochimica et Biophysica Acta, 1393*, 277-291.

Ross, R. (1986). The pathogenesis of atherosclerosis - an update. *New England Journal of Medicine, 314*, 488-500.

Rubic, T., Trottmann, M., & Lorenz, R. L. (2004). Stimulation of CD36 and the key effector of reverse cholesterol transport ATP-binding cassette A1 in monocytoid cells by niacin. *Biochemical Pharmacology, 67*, 411-419.

Rubin, E. M., Krauss, R. M., Spangler, E. A., Verstuyft, J. G., & Clift, S. M. (1991). Inhibition of early atherogenesis in transgenic mice by human apolipoprotein A-I. *Nature, 353*, 256-267.

Rust, S., Rosier, M., Funke, H., Real, J., Amoura, Z., Piette, J. C., et al. (1999). Tangier disease is caused by mutations in the gene encoding ATP-binding cassette transporter 1. *Nature Genetics, 22*(4), 352-355.

Sakai, T., Kamanna, V. S., & Kashyap, M. L. (2001). Niacin, but not gemfibrozil, selectively increases LP-AI, a cardioprotective subfraction of HDL, in patients with low HDL cholesterol. *Arteriosclerosis, Thrombosis, and Vascular Biology, 21*, 1783-1789.

Savage, P. D., Brochu, M., & Ades, P. A. (2004). Gender alters the high-density lipoprotein cholesterol response to cardiac rehabilitation. *Journal of Cardiopulmonary Rehabilitation, 24*, 248-254.

Schaefer, E. J., Heaton, W. H., Wetzel, M. G., & Brewer, H. B. (1982). Plasma apolipoprotein A-1 absence associated with a marked reduction of high density lipoproteins and premature coronary artery disease. *Arteriosclerosis, 2*, 16-26.

Seip, R. L., Mair, K., Cole, T. G., & Semenkovich, C. F. (1997). Induction of human skeletal muscle lipoprotein lipase gene expression by short-term exercise is transient. *The American Journal of Physiology, 272*, E255-261.

Seip, R. L., Moulin, P., Cocke, T., Tall, A., Kohrt, W. M., Mankowitz, K., et al. (1993). Exercise training decreases plasma cholesteryl ester transfer protein. *Arteriosclerosis and Thrombosis, 13*, 1359-1367.

Sgouraki, E., Tsopanakis, A., Kioussis, A., & Tsopanakis, C. (2004). Acute effects of short duration maximal endurance exercise on lipid, phospholipid and lipoprotein levels. *The Journal of Sports Medicine and Physical Fitness, 44*(4), 444-450.

Sgouraki, E., Tsopanakis, A., & Tsopanakis, C. (2001). Acute exercise: response of HDL-C, LDL-C lipoproteins and HDL-C subfractions levels in selected sport disciplines. *The Journal of Sports Medicine and Physical Fitness, 41*, 386-391.

Shepherd, J. (1992). Lipoprotein metabolism: an overview. *Annales Academic Medicine Singapore, 21*(1), 106-113.

Shepherd, J., Betteridge, J., & Gaal, V. L. (2005). Nicotinic acid in the management of dyslipidaemia associated with diabetes and metabolic syndrome: a position paper developed by a European Consensus Panel. *Current Medical Research and Opinion, 21*(5), 665-682.

Shlipak, M. G., Simon, J. A., Vittinghoff, E., Lin, F., Barrett-Connor, E., Knopp, R. H., et al. (2000). Estrogen and progestin, lipoprotein(a), and the risk of recurrent coronary heart disease events after menopause. *The Journal of the American Medical Association, 283*, 1845-1852.

Singh, A. T., Rainwater, D. L., Haffner, S. M., VandeBerg, J. L., Shelledy, W. R., Moore, P. H., et al. (1995). Effect of diabetes on lipoprotein size. *Arteriosclerosis, Thrombosis, and Vascular Biology, 15*, 1805-1811.

Smolin, L. A., & Grosvenor, M. B. (2002). *Nutrition: Science & Applications* (3rd ed.). New York, NY: John Wiley & Sons, Inc.

Snyder, S. (1990). Comparison of cholesterol-lowering regimens. *American Family Physician, 42*(3), 761-768.

Sowers, M. R., & La Pietra, M. T. (1995). Menopause: its epidemiology and potential association with chronic disease. *Epidemiology Review, 17*, 287-302.

Spieker, L. E., Hurlimann, D., Ruschitzka, F., Corti, R., Enseleit, F., Shaw, S., et al. (2002). Mental stress induces prolonged endothelial dysfunction via endothelin-A receptors. *Circulation, 105*(24), 2817-2820.

Sprecher, D. L. (2000). Raising high-density lipoprotein cholesterol with niacin and fibrates: a comparative review. *The American Journal of Cardiology, 86(suppl)*, 46L-50L.

Squires, R. W., Allison, T. G., Gau, G. T., Miller, T. D., & Kottke, B. A. (1992). Low-dose, time-release nicotinic acid: effects in selected patients with low concentrations of high-density lipoprotein cholesterol. *Mayo Clinic Proceedings, 67*, 885-860.

Steinmetz, A., & Utermann, G. (1985). Activation of lecithin: cholesterol acyltransferase by human apolipoprotein A-IV. *The Journal of Biological Chemistry, 260, 42258-42264.*

Stevens, J. P. (2002). *Applied multivariate statistics for the social sciences* (4th ed.). Mahwah, NJ: Lawrence Erlbaum Associates, Inc.

Sunami, Y., Motoyama, M., Kinoshita, F., Mizooka, Y., Sueta, K., Matsunaga, A., et al. (1999). Effects of low-intensity aerobic training on the high-density lipoprotein cholesterol concentration in healthy elderly subjects. *Metabolism, 48*, 984-988.

Superko, H. R., & Hecht, H. S. (2001). Metabolic disorders contribute to subclinical coronary atherosclerosis in patients with coronary calcification. *The American Journal of Cardiology, 88*, 260-264.

Svendsen, O. L., Hassager, C., & Christiansen, C. (1994). Six months' follow-up on exercise added to a short-term diet in overweight postmenopausal women--effects on body composition, resting metabolic rate, cardiovascular risk factors and bone. *International Journal of Obesity, 18*, 692-698.

Szmedra, L., LeMura, L. M., & Shearn, W. M. (1998). Exercise tolerance, body composition and blood lipids in obese African-American women following short-term training. *The Journal of Sports Medicine and Physical Fitness, 38*, 59-65.

Tharrett, S. J., McInnis, K. J., & Peterson, J. A. (2006). *ACSM's health fitness facility standards and guidelines* (3rd ed.). Champaign, IL: Human Kinetics.

Thomas, T. R., Smith, B. K., Donahue, O. M., Altena, T. S., James-Kracke, M., & Sun, G. Y. (2004). Effects of omega-3 fatty acid supplementation and exercise on low-density lipoprotein and high-density lipoprotein subfractions. *Metabolism, 53*, 749-754.

Thompson, P. D., Crouse, S. F., Goodpaster, B., Kelley, D., Moyna, N., & Pescatello, L. (2001). The acute versus the chronic response to exercise. *Medicine and Science in Sports and Exercise, 33*(Suppl), S438-445.

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, 46*, 217-223.

Tunaru, S., Kero, J., Schaub, A., Wufka, C., Blaukat, A., Pfeffer, K., et al. (2003). PUMA-G and HM74 are receptors for nicotinic acid and mediate its anti-lipolytic effect. *Nature Medicine, 9*(3), 352-355.

Ueda, Y., Royer, L., Gong, E., Zhang, J., Cooper, P. N., Francone, O., et al. (1999). Lower plasma levels and accelerated clearance of high density lipoprotein (HDL) and non-HDL cholesterol in scavenger receptor class B type I transgenic mice. *The Journal of Biological Chemistry, 274*, 7165-7171.

Vaisman, B. L., Lambert, G., Amar, M., Joyce, C., Ito, T., Shamburek, R. D., et al. (2001). ABCA 1 overexpression leads to hyperalphalipoproteinemia and increased biliary cholesterol excretion in transgenic mice. *The Journal of Clinical Investigation, 108*, 303-309.

Vincent, W. J. (1999). *Statistics in Kinesiology* (2nd ed.). Champaign, IL: Human Kinetics.

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 and Occupational Physiology, 72*(3), 242-248.

von Eckardstein, A., Nofer, J. R., & Assmann, G. (2001). High density lipoproteins and arteriosclerosis. Role of cholesterol efflux and reverse cholesterol transport. *Arteriosclerosis, Thrombosis, and Vascular Biology, 21*(1), 13-27.

Vuorimaa, T., Ahotupa, M., Irjala, K., & Vasankari, T. (2005). Acute prolonged exercise reduces moderately oxidized LDL in healthy men. *International Journal of Sports Medicine, 26*, 420-425.

Wang, M., & Briggs, M. R. (2004). HDL: The mechanism, function, and therapeutic importance. *Chemical Reviews, 104*, 119-137.

Wang, W., Basinger, A., & Neese, R. A. (2000). Effects of nicotinic acid on fatty acid kinetics, fuel selection, and pathways of glucose production in women. *American Journal of Physiology, Endocrinology, and Metabolism, 279*, E50-E59.

Wang, W., Basinger, A., Neese, R. A., Shane, B., Myong, S., Christiansen, M., et al. (2001). Effect of nicotinic acid administration on hepatic very low density lipoprotein-triglyceride production. *American Journal of Physiology, Endocrinology, and Metabolism, 43*, E540-E547.

Weise, S. D., Grandjean, P. W., James, R., 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.

Whelan, A. M., Price, S. O., Fowler, S. F., & Hainer, B. L. (1992). The effect of aspirin on niacin-induced cutaneous reactions. *The Journal of Family Practice, 34*, 165-168.

Williams, P. T. (1993). High density lipoproteins and lipase activity in runners. *Atherosclerosis, 98*(2), 251-254.

Williams, P. T. (1996). High-density lipoprotein cholesterol and other risk factors for coronary heart disease in female runners. *The New England Journal of Medicine, 334*(20), 1298-1303.

Wilson, P. W. (1990). High-density lipoprotein, low-density lipoprotein and coronary artery disease. *The American Journal of Cardiology, 66*(6), 7A-10A.

Wilund, K. R., Ferrell, R. E., Phares, D. A., Goldberg, A. P., & Hagberg, J. M. (2002). Changes in high-density lipoprotein-cholesterol subfractions with exercise training may be dependent on cholesteryl ester transfer protein (CETP) genotype. *Metabolism, 51*, 774-778.

Zambon, A., Austin, M. A., Brown, B. G., Hokanson, J. E., & Brunzell, J. D. (1993). Effect of hepatic lipase on LDL in normal men and those with coronary artery disease. *Arteriosclerosis and Thrombosis, 13*(2), 147-153.

Zambon, A., Deeb, S. S., Bensadoun, A., Foster, K. E., & Brunzell, J. D. (2000). In vivo evidence of a role for hepatic lipase in human apoB-containing lipoprotein metabolism, independent of its lipolytic activity. *Journal of Lipid Research, 41*, 2094-2099.

Zhang, J. Q., Smith, B., Langdon, M. M., Messimer, H. L., Sun, G. Y., Cox, R. H., et al. (2002). Changes in LPLa and reverse cholesterol transport variables during 24-h postexercise period. *American Journal of Physiology. Endocrinology and Metabolism, 283*, E267-274.

Zhang, Y., Schmidt, R. J., Foxworthy, P., Emkey, R., Oler, J. K., Large, T. H., et al. (2005). Niacin mediates lipolysis in adipose tissue through its G-protein coupled receptor HM74A. *Biochemical and Biophysical Research Communications, 334*, 729-732.

APPENDIX A

Research Flyer

IF YOU ARE OR KNOW:

- A WOMAN
- 40 TO 80 YEARS OLD
- NON-SMOKER
- NON-EXERCISER
- NO KNOWN METABOLIC DISEASE

Purpose of Study:

To investigate the effects of niacin and a single bout of moderate-intensity exercise expending 400 calories of energy on blood lipid and lipoprotein profiles in postmenopausal women.

$100 + More!

Free Cholesterol Analysis!

Free Bone Mineral Density!

Free Fitness Assessment!

Free Dietary Analysis!

Research Participants Needed!!!!

Call the TWU Exercise Physiology Laboratory at 940-898-2340.

Blood Samples and Exercise will be required.

Earn **$100** for completion of ALL procedures!!!

APPENDIX B

Medical History Form

MEDICAL HISTORY FORM

Name _____
Street _____
City _____ State_____ Zip_____
Age _____ Sex _____ Current Weight _____lbs Email _____
Telephone (Day) (_____)_____-_____ Night (_____)_____-_____
Personal Physician Name and Address _____
_____

Directions: Please answer the following questions to the best of your knowledge about yourself. Check below any medical condition, treatment, or problems that concern you.

I. Heart and Circulatory:
___ Heart attack
___ Stroke
___ Valve problems
___ Heart murmur
___ Enlarged heart
___ Irregular heart beat
___ Atherosclerosis
___ High blood pressure (Controlled)
___ High blood pressure (Uncontrolled)
___ Rheumatic fever
___ Cardiac surgery
___ Coronary bypass
___ High triglyceride levels
___ High cholesterol levels
___ Varicose veins
___ Anemia
___ Hemophilia
___ Diabetes (Controlled)
___ Diabetes (Uncontrolled)
___ Phlebitis, emboli
___ Other, Specify: _____

II. Respiratory:
___ Emphysema
___ Bronchitis
___ Pneumonia
___ Asthma
___ Lung disease
___ Other, Specify: _____

III. Other Disease or Ailments:
___ Back injuries
___ Epilepsy
___ Allergies
___ Liver disease
___ Kidney disease
___ Arthritis

___ Orthopedic (joint or bone) leg or arm problems
___ Other, Specify: _____

Please explain any conditions you checked YES in I-III above: _____
_____

IV. Have You Recently Had:
___ Chest pain
___ Shortness of breathe upon exertion
___ Heart palpitations (racing heart)
___ Cough on exertion
___ Cough-up blood
___ Swollen, still or painful joints
___ Dizziness
___ Lightheadedness
___ Back problems

Please explain any conditions you checked YES in IV above: _____
_____

V. Family Medical History (Immediate Relatives):
___ Heart attack
___ Stroke
___ Atherosclerosis
___ High blood pressure
___ Diabetes
___ Lung disease
___ Respiratory problems
___ Heart surgery or
___ Heart-related surgery
___ Other, Specify: _____

VI. Tobacco:
Do you currently smoke? ___ Yes ___ No
If yes, how long? _____
Amount smoked per day? _____
If you do not currently smoke, have you ever used it? ___ Yes ___ No
If yes, how long? _____
How long ago did you quit? _____

VII. Exercise:
Do you exercise? ___ Yes ___ No
If yes, what kind of exercise do you presently engage in? _____
Is your level of effort: ___ Minimal ___ Moderate ___ High
How often/long do you exercise? ___ Days per week ___ Minutes per day

Please list current medications, prescriptions, supplements or over-the-counter drugs taken and why:
_____
_____

Please describe your present medical condition and anything we should be aware of concerning your health: _____
_____

Date of last physical examination? _____

Results: _____
Date of last ECG? _____
Results: _____

I certify that my responses to the foregoing questionnaire are true, accurate, and complete.

Signature _____ Date_____

APPENDIX C

Informed Consent Form

TEXAS WOMAN'S UNIVERSITY
CONSENT TO PARTICIPATE IN RESEARCH

Title: The Effects of Niacin and a Single Bout of Exercise on Blood Lipid and Lipoprotein Profiles in Postmenopausal Women.

Investigator: Yunsuk Koh, MS.....(940) 898-2340
Advisor: Vic Ben-Ezra, Ph.D.....(940) 898-2597

Explanation and Purpose of the Research

PLEASE NOTE THAT YOU MUST CONSENT TO PARTICIPATE BEFORE ANY PROCEDURES PERFORMED.

You are being considered as a participant because you are apparently healthy, do not smoke, do not have diabetes (either juvenile [Type 1] or maturity onset [Type 2]), cardiovascular disease, and are not pregnant. We will verify this information from medical history forms which will be completed by you as a part of this study. The purpose of the current study is to investigate the effects of niacin and a single bout of exercise on blood lipid and lipoprotein profiles in postmenopausal women. This study involves participating in exercise on a treadmill, drawing blood, and taking a dietary supplement, Niaspan (extended-release niacin, a B vitamin). Prior to participating in the study you will fill out a medical history form, and this questionnaire will provide information about your health and disease risk factors. You will be paid $100.00 when you complete the research study.

Research Procedures

Submaximal Oxygen Consumption (VO_2) Test

You will perform a submaximal exercise test on a motor-driven treadmill. Your data obtained from submaximal exercise testing will be used to predict your maximal oxygen consumption (VO_2max), the maximal volume of oxygen that you can consume during exercise. After three minutes of warm-up at a speed of 2.0 mph with 0 % grade, the treadmill walking exercise protocol will start at 3.0 mph with 0 % grade. The treadmill speed will be held constant at 3.0 mph throughout the test. However, the treadmill grade will be elevated by 2.0 % every three minutes until you reach 70% heart rate reserve. To calculate heart rate reserve your resting heart rate is first subtracted from the age-estimated heart rate max (220 – age (yrs)). This value will be multiplied by percent intensity (e. g., 70% in this study), and resting heart rate will be added to this value to obtain a target heart rate reserve. Resting heart rate and blood pressure will be measured after you quietly sit in a chair at least five minutes. During submaximal exercise testing heart rate will be continuously monitored using a 12-lead electrocardiograph (ECG), and blood pressure will also be measured in the last minute of each stage. In addition, ratings of perceived exertion will be monitored at the end of each stage. The submaximal exercise test will be terminated when you reach 70% heart rate reserve or wish to stop exercise testing. During submaximal exercise testing expired respiratory gases will be continuously collected and analyzed using an oxygen uptake system.

After exercise testing is terminated, you will cool down for approximately five minutes. During recovery, blood pressure and heart rate will be immediately measured post exercise, and every minute thereafter until your heart rate and blood pressure return to resting values.

Study Design

There will be no randomization in the order of niacin supplement conditions due to its potential side effect such as flushing. Thus, you will first be assigned to a without-niacin (WON) condition. After the completion of the WON condition, you will be assigned to the with-niacin (WN) condition. Either a rest or exercise trial will be randomly assigned within each WON or WN condition. During the exercise trial you will perform a single bout of aerobic exercise on the treadmill at 70% of estimated VO_2max until 500 kcal are expended. All rest and exercise trials will be conducted at the same time between 06:00 and 08:00 AM at the Exercise Physiology Lab (Pioneer Hall 114). During the exercise trial the speed of treadmill will be held constant at 3.0 mph while the grade will be elevated and adjusted to achieve the appropriate exercise intensity (70% VO_2max). During the exercise trial, heart rate will be continuously monitored using a portable heart rate monitor, and blood pressure will also be monitored. During the exercise trial expired respiratory gases will be collected and analyzed at the initiation, mid, and last 15 minutes of exercise to determine 500 kcal of energy expenditure. During the rest trial you will report to the lab for blood collection but not exercise. Either the rest or exercise trial will be conducted at least one week apart to prevent any acute influence of exercise in blood lipid and lipoprotein profiles.

Niacin Supplementation

You will ingest an extended-release type of niacin, Niaspan, during the with-niacin (WN) condition. You will take the niacin with a low fat snack one or two hours before bedtime. If needed, you will ingest a 325 mg dose of aspirin or ibuprofen (200 mg) 30 minutes prior to taking niacin to minimize the potential for flushing side effects (your skins turn red). The final dose of niacin in this study will be 1,000 mg per day taken for 4 weeks. To reach the final dose of 1,000 mg, you will start with a low dose of 250 mg per day during the first week of WN condition. During the second week the dosage will be increased up to 500 mg per day, and thereafter 1,000 mg per day for 4 weeks. This particular dosing schedule is designed to minimize the potential flushing side effect. During the 3rd week of 1,000 mg of niacin condition, you will report to the laboratory for either the rest or exercise trial. Additionally, you will continue to take 1,000 mg of niacin during the 4th week for either rest or exercise trial. You will not take any other nutritional or lipid modification supplementations other than niacin provided by the investigator as part of the treatment in this study.

Dietary and Physical Activity Considerations

You will not consume any alcohol containing beverage throughout the study because it may influence blood lipids levels. You will complete a detailed 3-day diet record from the day preceding the first blood draw to the day before the last blood collection to insure consistency in food intake. Based on the first 3-day diet record provided by you, you will consume the same dinner the night before each blood collection. In addition to the 3-day diet record, you will provide a 5-day physical activity record from three days prior to the first blood draw to the day before the last blood draw.

Body Composition Assessment

The waist-to-hip ratio will be determined from your minimum waist and maximum hip circumference while you are in a standing position, and at the end of a normal breath. An additional waist circumference measure will be taken to approximate central (intra-abdominal) fat mass. Body composition: skin-fold measures will be taken at 3 sites including back of your upper

arm, top of your hip, and thigh. All skin-fold measures will be made on the right side of the body, and each site will be measured twice. Female lab assistants will be taking all the body composition measurements.

In addition, body composition will also be determined by using a FDA-approved dual energy x-ray absorptiometer, the Lunar DEXA. You will be asked to lie face up, fully clothed, on a padded table for the scan. A registered technician will perform all x-ray scan measurements.

Blood Analyses

You will report to the laboratory between 06:00 and 08:00 AM with at least 10 hours of fasting. After 20 minutes of resting in a chair, approximately 20 mL (1 × 5.0 mL and 2 × 7.5 mL) venous blood samples will be collected. Blood samples will be drawn immediately before (0 hour) and at 24 and 48 hours post exercise (or rest) during each treatment (**RWN**; rest + with-niacin, **EWN**; exercise + with-niacin, **RWON**; rest + without-niacin, or **EWON**; exercise + without-niacin). All blood lipids, lipoproteins, glucose, insulin, and C-peptide will be analyzed all together once data collection is completed.

Exercise Considerations

During the 6 weeks of participation in the study you will not be exercising on your own except to perform normal daily living activities.

The procedures outlined above have been explained to you by Yunsuk Koh, MS or other project personnel _____, and that you can contact them during office hours at 940-898-2340 if any questions arise.

Maximum total time commitment

The estimated total amount of time involved with all procedures in the study will be 17 hours. You will complete the informed consent and medical history forms and an orientation to the study (approximately 1 hour). The submaximal exercise test (including ECG preparation; 1.5 hours) and body composition assessments (30 minutes) require approximately 2 hours. During the exercise and rest trials you will spend a total of 6 hours (3 hours per trial). These two trials will be conducted with with-niacin (WN) and without-niacin (WON) conditions. Therefore, a total amount of time commitment for all experimental procedures in the lab is approximately 12 hours. You will also complete a 3-day diet record and a 5-day physical activity record form on your own time (approximately 2 hours). You will be involved with the study for 8 weeks (including 2 weeks of the without-niacin condition and 6 weeks of the with-niacin condition).

Potential Risks

A possible risk of cardiac or cardiovascular event (heart attack) may occur during the testing or training sessions. There is less risk to you since you are a non-smoker and have been screened via medical history questionnaire for cardiovascular risk factors and any other metabolic abnormalities (e.g. diabetes) that would preclude you from the study. To reduce the risk you will be monitored carefully throughout the testing and training, and all additional persons involved with the exercise portion of the study will be CPR trained. In addition, blood pressure will be checked periodically to assure normal responses.

There is a risk of tripping or falling off the treadmill. There will be at least two trained lab technicians next to the treadmill at all times to assist if you should need help.

A risk of hematoma (bruise) may result from the blood collection procedure. To reduce the potential risks of discomfort, trained medical personnel will draw all the blood samples. In addition there is a risk of contamination from blood products. To reduce this risk all personnel handling tubes associated with any blood products will be wearing latex or vinyl gloves. In addition, all needles and syringes will be disposed of in sharps container. All table tops will be covered with a non-porous, absorbent disposable pad.

You may experience a risk of muscle soreness for a period of up to three or four days following the submaximal exercise test or possibly after a single bout of exercise on the treadmill during exercise trials. This soreness is common with individuals who are not accustomed to regular exercise, and is temporary. You will likely experience muscle fatigue from the testing and training. The fatigue will last a few hours from the testing procedures and your muscles will feel normal again. You will be instructed on proper stretching procedures and allowed to warm-up before beginning any treadmill exercise.

In case of a medical emergency, the fire department's Emergency Medical Team will be alerted. Telephones are available in the testing labs.

You may experience a risk of side effects to niacin. These side effects are usually short-lived and reversible when niacin is discontinued. You should be aware that the 1,000 mg of niacin may cause some of the following side effects/adverse reactions: skin flushing (color of skin turns red) or itching (most common), emesis (vomiting), gastrointestinal disturbance (diarrhea), blood glucose instability (elevation of blood sugar), or elevation of liver enzymes; it should be noted that these effects are associated with doses in the 1,500-4,000 mg/day range. The flushing is associated with the vasodilatation (dilation of a blood vessel) effects of niacin which can be reduced or prevented by ingesting a child's dose of aspirin (325 mg) or ibuprofen (200 mg) 30-60 minutes prior to taking the niacin.

To reduce the possibility of improper disclosure your name will be kept confidential and will never be associated with the data in any presentation of results. All responses to the written questionnaires will only be viewed by the research team. Your data will be kept on file for a maximum of 5 years after the data are published. All data files will be kept in a locked cabinet and access to the files will be limited to Yunsuk Koh, MS. All data will be destroyed after the five year period (paper will be shredded, computer data erased). It is anticipated that the results of this study will be published in a research publication. No names or other identifying information will be included in any publication.

During body composition assessment with the x-ray scan, there will be a small amount of radiation exposure to each participant. The total amount of radiation that each participant will receive during the study is 0.4 mrem (lumbar spine), 0.13 mrem (femur), 0.005 mrem (forearm) and 0.26 mrem (whole body) using the Lunar DEXA 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.

Confidentiality will be protected to the extent that is allowed by law.

An additional risk factor is the possibility of embarrassment from having waist to hip ratio and skin fold measures taken and ECG electrodes applied. To minimize this risk, all measurements will be taken by female lab assistants as the participant and the procedures will be done behind closed doors without any others present. In addition ECG electrode placement will

be done behind closed doors with a female lab assistant.

The risks of side effects caused by aspirin or ibuprofen include heart burn, diarrhea, stomach upset, vomiting, faint ringing in the ear, black, bloody, tarry stools, or blurred vision. If you experience any side effects, you will immediately stop taking aspirin or ibuprofen. The side effects will be reversible once aspirin or ibuprofen is stopped. There is a possible risk that you may be allergic to aspirin or ibuprofen. If you are, you are not required to take aspirin or ibuprofen prior to niacin ingestion.

The researchers will try to prevent any problem that could happen because of this research. You should let the researchers know at once if there is a problem and they will help you. However, TWU does not provide medical services or financial assistance for injuries that might happen because you are taking part in this research.

Participation and Benefits

Your participation in this study is completely voluntary and you may discontinue your participation in the study at any time without penalty. The results of this study will help answer questions regarding the effect of exercise and niacin on blood lipid and lipoprotein profiles. The information is useful so that a better understanding of how niacin and exercise, either independently or together may reduce risk factors associated with cardiovascular disease. Each participant who completes the study will receive $100.00; free information about their fitness level, and risk factors related to diabetes and cardiovascular disease. An abstract of the study will be provided to you at the end of the study if you desire to receive it.

Questions Regarding the Study

You will be given a copy of this signed and dated consent form to keep. If you have any questions about the research study you should ask the researcher: their phone numbers are at the top of this form. If you have questions about your rights as a participant in this research or the way this study has been conducted, you may contact the Texas Woman's University Office of Research and Sponsored Programs at 940-898-3375 or via e-mail at IRB@twu.edu.

Your participation in this study is completely voluntary. You have read this form, and the test procedures that you will perform and the risks and discomforts. Knowing these risks and discomforts, and having had an opportunity to ask questions that have been answered to your satisfaction, you consent to participate in this test.

Check here if you would like to receive a summary of the results of this study and list below the address to which this summary should be sent.

☐ _____

_____

---------- ----------

Participant's Signature **Date**

APPENDIX D

Initial Screening Form

Niacin Exercise Women (NEW) Screening Form

Today's Date: _____

Check only one: ○ **eligible** ○ **washout** ○ **ineligible**

NAME

First Name:_____ Last Name:_____

PERSONAL INFORMATION

What is your gender? ○ male ○ female

What is your date of birth? _____

How old are you? _____

When was your last period? _____

What is your ethnic identity?

○ American Indian ○ Asian-American/Pacific Islander ○ African-American
○ Latina/Hispanic ○ Caucasian ○ Other

MEDICAL HISTORY

Has your physician ever told you that you have high blood pressure?	○ yes	○ no
Has your physician ever told you that your cholesterol level was high?	○ yes	○ no
Have you lost more than 20 lbs in the past 6 months?	○ yes	○ no
If yes, was this weight loss deliberate?	○ yes	○ no
Have you ever had a heart attack?	○ yes	○ no
If yes, was this within the past 6 months?	○ yes	○ no
Have you ever had a stroke?	○ yes	○ no
If yes, was this within the past 6 months?	○ yes	○ no

Do you have diabetes? o yes o no

Do you suffer from liver, kidney, or heart problems? o yes o no

Do you have any known drug allergies? o yes o no

Do you have any serious medical condition that might keep you from exercising? o yes o no

Do you currently take any prescription medications? o yes o no

If yes, what medications? _____

Have you taken any vitamins, supplements, or omega-3 during the past 6 weeks? o yes o no

If yes, what supplements and how long? _____

Do you currently take niacin or other lipid lowering medications? o yes o no

If yes, what lipid lowering medications and how long? _____

PERSONAL HABITS

Do you regularly participate in any physical activity such as walking, running, aerobic dance, swimming or playing sports at least three times per week, 20 minutes or longer each time? o yes o no

If yes, how long and what activity? _____

Do you smoke? o yes o no If yes, how many cigarettes per day? _____

How many alcoholic drinks do you consume per week? _____ (if < 1 per week, enter 0)

CONTACT INFORMATION

Number and Street Address: _____

_____

City: _____ State: _____ Zip Code: _____

What is your daytime telephone number? _____

What is your evening telephone number? _____

What is your cellular number? _____

What is your email address? _____

ADDITIONAL INFORMATION

You will be given $100 and free BMD, body composition, blood analysis (TC, TG, LDL, HDL, Glucose, Insulin, C-peptide, etc), nutritional counseling, fitness assessment, and more when you complete the all study procedures.

If accepted into this study, are you willing to maintain your current diet, exercise, and supplement routine approximately for 3 months without changing any of these factors?

○ yes ○ no

During this study, a total of 12 blood draws will be necessary. These are fasting blood draws, meaning that you will not be able to eat for at least 10 hours prior to the blood draw. You will be required to give blood 3 consecutive days in a row on 4 separate occasions. After the first 2 weeks of blood draws, you will be asked to take a Niacin (Niaspan) supplement for a total of 6 weeks. During the study, you will also be asked to complete a 3-day diet record and a 5-day physical activity record form.

Are you still willing to take part in this study? ○ yes ○ no

APPENDIX E

3-day Diet Record Form

INSTRUCTIONS FOR RECORDING DIET RECORD

1. Record your 3-day food intake during each trial (rest or exercise with or without niacin) from **the day before your first blood draw to the night before your last blood draw**. For example, if your 3-day blood draws are scheduled on Tuesday (0 hr), Wednesday (24 hrs), and Thursday (48 hrs), you record your diet from Monday morning to Wednesday night.

2. Record **all foods and liquids** that are consumed. List **EVERYTHING** that you eat or drink (including water). Be sure to record anything eaten or drank between meals (even if it is just a piece of candy).

3. Indicate the location of the meal or snack (home, cafeteria, restaurant, etc). If it is a restaurant, give the name (McDonald's, Pizza Hut, Chile's, etc).

4. Describe your food thoroughly:

   - Indicate as closely as possible the correct quantity (weight, size, ounces, and portion) of the food or beverage consumed. Hints: a piece of meat the size of your hand is approximately 3-4 ounces. Compare the size of your meat with a fast food 1/4 pound (4 oz.) hamburger. Give relative size of fruit – medium banana, small apple.

   - Whenever possible indicate brand names (Kellogg's Rice Krispies, Campbell's chicken noodle soup, etc).

   - Indicate the method of cooking (boiled, baked, fried, grilled, etc) and if anything was added while cooking (microwaved corn with 1 teaspoon of butter).

   - Include processing information (fresh, canned, frozen, dehydrated, etc).

   - Describe the components of combination foods: sandwich – 2 slices of whole wheat bread, 2 ounces of ham, 1 slice of American cheese, 1 slice of tomato, 1 teaspoon of mayonnaise; or casserole: beef, egg noodles, tomato sauce, carrots.

   - Be as specific as possible. Examples: list 2% low-fat milk, not just "milk"; list Jello Brand instant vanilla pudding, not just "pudding."

5. If you have no idea how to record a food you eat, just do the best you can.

6. Try to record what you eat immediately after you ate it. It is amazing how easy it is to forget what you ate for breakfast by lunchtime.

3-DAY DIET RECORD

ID: NEW _____ Name _____ Today's Date ____/____/____

Your Trial (check only one): □Rest+No niacin □Exercise+No niacin □Rest+Niacin □Exercise+Niacin

Please use one sheet for each day's food intake. Use one line for each food item. If you remember to record the food as you eat it, things will go much easier.

Food	Amount	Location

*** If you need more space, please write on the back of this sheet.**

APPENDIX F

5-day Physical Activity Record Form

5-DAY PHYSICAL ACTIVITY RECORD FORM

ID: NEW_____

Name: _____ Date: from ___/___/___ to ___/___/___

Your Trial (check only one): ☐Rest+No niacin ☐Exercise+No niacin ☐Rest+Niacin ☐Exercise+Niacin

This form should be filled out to the best of your knowledge for any physical activities that you participated in during the week of each trial. Record any physical activities from 3 days prior to the first blood draw to the day before the last blood draw. For example, if your 3-day blood draws are scheduled on Tuesday (0 hr), Wednesday (24 hrs), and Thursday (48 hrs), you record your physical activity from Saturday (previous week) to the day before the last blood draw day, which is Wednesday.

Please check any of the following that you participated in during the past week;

	Which day(s)	How long (min)	How hard (light, moderate, or heavy)
Jogging			
Swimming			
Cycling			
Walking			
Tennis			
Basketball			
Soccer			
Volleyball			
Weight training			
Aerobic Dance			
Aqua Aerobics			
Step Aerobics			
Stairmaster			
Others?			

Please do not interpret this as our wish that you become regularly active during the study. We just want to make sure that you are not doing anything that will influence your/our results.

APPENDIX G

Permission Letter for Primary Care Physician

Permission to Participate in a Research Study
SPRING-SUMMER 2007

Research title: The Effects of Niacin and A Single Bout of Exercise on Blood Lipid and Lipoprotein Profiles in Postmenopausal Women

Researchers: Vic Ben-Ezra, PhD
Kyle Biggerstaff, PhD
Yunsuk Koh, PhD candidate

Dear Physician:

A patient of yours, _____, is interested in participating in a research study involving exercise and niacin supplementation. The exercise will consist of walking on a treadmill at a moderate walking intensity for approximately one hour. During this walk the participant will have heart rate and blood pressure monitored. The treadmill walk will occur on two separate occasions, one time under normal dietary conditions, and a second time after six (6) weeks of niacin supplementation. The niacin supplement will be Niaspan, the extended release form of niacin. Each participant will follow this dosing schedule: week 1-250mg/day for 7 days; week 2- 500mg/day for 7 days; and weeks 3-6 – 1000mg/day for 7 days. All participants will be made aware of the possible side-effects of taking niacin which include: skin flushing, rash, itching, possible allergic reaction, and elevation of liver enzymes. In an effort to reduce some of these effects it will be recommended to take one-two 81 mg "baby" aspirins or one 200 mg ibuprofen tablet 30 minutes before the Niaspan. The Niaspan will be taken 30-60 minutes before bedtime. We will be checking liver enzymes after one week on the 1000mg/day regimen. Prior to participation each participant will be made aware of all the details of the study and a consent form will be reviewed and signed. The study has been approved by the Texas Woman's University Institutional Review Board.

Please let us and/or your patient,_____, know if you would not recommend that she participate.

Please check only one: Recommend ( ) Not Recommend ( )

If not, please briefly explain why _____

Sincerely,

Vic Ben-Ezra, PhD
Professor
Office: (940) 898-2597; FAX (940) 898-2581

APPENDIX H

Procedures for Blood Analyses

Procedures of Hematocrit Analysis

1. Fill the two capillary tubes two-thirds full with well-mixed venous blood.
2. Seal one end of the capillary tube with clay.
3. Place the tube in the microhematocrit centrifuge, with the plugged end away from the center of the centrifuge.
4. Centrifuge at a speed of 10,000 to 12,000 rpm for 2 minutes.
5. Place the tube in the microhematocrit reader and read % of hematocrit.

Procedures of Hemoglobin Analysis (Wako Hemoglobin B Kit# 271-73901)

1. Prepare four different standards (5, 10, 15, and 29.9 g/dL) using standard solution.
2. Label all tubes in duplicate including 'blank' 'standard' 'sample' and 'control' tubes.
3. Add 200 µL of whole blood samples to appropriate tubes.
4. Add 5.0 mL of the color working solution to all test tubes.
5. Mix all tubes well and allow standing for 3 minutes at room temperature.
6. Read absorbance using the PowerWave™ XS microplate spectrophotometer (set the wavelength at 540 nm).
7. Determine total hemoglobin concentration (mg/dL).

Procedures of triglycerides (TG) using Raichem Kit# 85460

1. Bring the TG reagent and samples to room temperature before performing the assay.
2. Label blank, standard, control and sample tubes in duplicate.
3. Add 1.0 mL of reagent to all test tubes.
4. Add 10 µL of samples to appropriate samples tubes.
5. Mix well.
6. Incubate all tubes at 37 °C for 5 minutes.
7. Set the PowerWave™ XS microplate spectrophotometer at 540 nm wavelength.
8. Read absorbance and determine the concentration of TG in mg/dL.

Procedures of total cholesterol (TC) using Raichem Kit# 80037

1. Bring the TC reagent and samples to room temperature before performing the assay.
2. Label blank, standard, control and sample tubes in duplicate.
3. Add 1.0 mL of reagent to all test tubes.
4. Add 10 µL of samples to appropriate samples tubes.
5. Mix well.
6. Incubate all tubes at 37 °C for 15 minutes.
7. Set the PowerWave™ XS microplate spectrophotometer at 500 nm wavelength.
8. Read absorbance and determine the concentration of TC in mg/dL.

Procedures of high-density lipoprotein (HDL-C) using Raichem Kit# 82051

1. Bring the HDL-C precipitating reagent, controls, and samples to room temperature before performing the assay.
2. Label blank (water), control, and sample tubes in duplicate.
3. Pipette 500 µL of water, controls, and samples into appropriately labeled tubes.
4. Add 50 µL of HDL-C precipitating reagent to all test tubes.
5. Mix well for approximately 5 seconds in a vortex type mixer.
6. Let stand for 5 minutes at room temperature.
7. Centrifuge for 15 minutes at 2500 rpm.
8. Carefully take supernatant out from each tube and use as HDL-C samples.
9. The cholesterol standard is used without treatment with precipitating reagent.
10. Perform a total cholesterol assay described above using Raichem Kit# 80037.

Procedures of Dextran Sulfate Precipitating Solution for HDL_3-C

1. Measure 70 ml of dH_2O in a graduated cylinder. Add the dH_2O to a beaker with a magnetic stir bar. Place the beaker on the magnetic stirrer and begin stirring.
2. Weigh-out 1.91 g of dextran sulfate (Dextralip 50), 39.74 g of $MgCl_2 \cdot 6H_2O$, and 50 mg of NaN_3.
3. Slowly mix dextran sulfate, $MgCl_2 \cdot 6H_2O$, and NaN_3 (add in small incremens to prevent clumping) into the dH_2O (70 ml) and continue stirring until mixture is completely dissolved.
4. It is not advisable to adjust pH, as fluctuations in ionic strength resulting from pH adjustment seem to contribute to more variablility than the slight batch-to-batch differences in pH.
5. Transfer quantitatively to a graduated cylinder and adjust the final volume to 100 ml to give a concentration of 20 g/L
6. The final working reagent contains 19.1 mg/ml dextran sulfate, 1.95 mol/L $MgCl_2$, and 0.05 % NaN_3.
7. Store at 4-8 °C. Dextran sulfate stock solution can have a shelf life of 2 – 3 months at 4 °C.

Procedures of high-density lipoprotein 3 (HDL_3-C)

1. Bring the HDL_3-C precipitating reagent, controls, and samples to room temperature before performing the assay.
2. Label blank (water), control, and sample tubes in duplicate.
3. Pipette 500 µL of water, controls, and samples into appropriately labeled tubes.
4. Add 50 µL of HDL-C precipitating reagent to all test tubes.
5. Mix well for approximately 5 seconds in a vortex type mixer.
6. Let stand for 15 – 20 minutes at room temperature.
7. Centrifuge at 3000 rpm for 15 minutes at 4 °C.
8. Carefully take supernatant out from each tube and use as HDL_3-C samples.
9. Perform a total cholesterol assay described above using Raichem Kit# 80037.

APPENDIX I

Participants' TG Data

Participants' TG Data (mg/dl)

N	RWON0	RWON24	RWON48	EWON0	EWON24	EWON48	RWN0	RWN24	RWN48	EWN0	EWN24	EWN48
1	95.36	119.37	147.17	146.74	105.63	106.63	129.18	106.49	108.20	139.46	133.89	103.06
2	87.22	96.21	85.08	116.77	69.66	87.22	97.93	66.67	115.05	109.06	127.90	104.78
3	94.50	76.09	76.94	89.79	61.96	75.23	105.20	74.80	58.10	79.51	64.10	60.67
4	150.59	142.03	133.47	139.03	100.92	94.50	70.95	73.52	87.65	90.65	76.94	101.78
5	71.36	74.80	67.95	66.67	56.40	48.68	76.94	63.24	85.51	88.08	55.96	72.23
7	204.55	197.69	160.01	234.10	293.61	310.31	95.78	100.49	109.49	123.62	128.33	122.33
8	51.68	39.69	47.40	39.69	40.98	37.50	58.53	39.26	48.89	70.09	37.50	43.12
9	88.93	95.36	97.07	69.66	68.38	76.52	84.65	86.36	76.52	94.07	90.65	70.09
11	101.35	99.64	83.79	95.36	63.24	86.36	106.49	83.79	94.93	89.36	63.24	67.10
12	121.48	184.85	153.17	174.14	152.73	174.57	108.20	168.58	172.00	211.83	209.68	209.68
13	78.67	72.23	85.08	84.65	74.80	54.25	60.67	52.96	52.54	85.94	65.38	71.81
14	121.05	117.62	94.07	124.47	101.78	106.49	108.63	107.77	94.07	104.35	109.91	137.75
15	61.10	51.68	68.38	65.38	57.68	72.66	73.52	52.11	59.39	59.39	56.82	54.25
16	84.66	88.08	81.23	62.39	91.07	105.20	63.67	68.81	80.37	70.10	94.50	97.93
17	65.81	69.66	63.67	69.66	57.25	66.24	61.96	57.68	53.39	47.40	56.39	53.82
18	58.53	68.81	61.53	70.52	55.53	67.95	55.53	41.83	38.83	52.11	48.68	51.25
19	69.24	82.51	87.22	85.51	78.66	99.63	75.23	49.11	55.11	75.23	58.10	69.24
20	130.04	132.61	127.47	85.08	67.52	89.36	75.23	61.10	68.81	78.66	71.38	103.92

Note. TG = triglyceride, N = participant's id number, RWON 0 = rest without niacin at 0 hr, RWON 24 = rest without niacin at 24 hr, RWON 48 = rest without niacin at 48 hr, EWON 0 = exercise without niacin at 0 hr, EWON 24 = exercise without niacin at 24 hr, EWON 48 = exercise without niacin at 48 hr, RWN 0 = rest with niacin at 0, RWN 24 = rest with niacin at 24, RWN 48 = rest with niacin at 48, EWN 0 = exercise with niacin at 0 hr, EWN 24 = exercise with niacin at 24 hr, EWN 48 = exercise with niacin at 48 hr.

APPENDIX J

Participants' TC Data

Participants' TC Data (mg/dl)

N	RWON0	RWON24	RWON48	EWON0	EWON24	EWON48	RWN0	RWN24	RWN48	EWN0	EWN24	EWN48
1	241.45	248.31	265.65	246.70	246.29	262.83	260.81	263.23	269.28	249.52	248.31	245.01
2	239.43	247.01	228.95	236.20	230.56	224.92	254.76	246.70	233.79	240.65	243.87	245.49
3	279.47	287.03	288.24	283.40	286.22	272.91	286.22	286.22	295.90	269.28	276.14	245.89
4	238.22	219.27	229.76	235.81	222.10	221.69	218.86	213.22	199.91	244.28	212.41	230.16
5	183.37	178.93	171.67	194.26	197.08	198.70	158.77	157.56	157.15	164.82	168.45	176.92
7	263.23	271.70	272.51	245.89	260.41	243.47	215.23	215.23	212.41	221.28	204.34	200.71
8	196.68	199.10	201.12	193.05	187.40	178.13	207.57	207.97	207.77	174.10	161.19	174.90
9	197.08	198.30	195.47	197.08	206.36	197.49	238.63	226.13	208.78	191.03	201.52	199.91
11	232.58	227.34	231.77	247.10	232.58	207.97	266.06	255.17	215.23	242.66	230.97	221.29
12	272.11	274.12	273.72	277.75	271.70	269.69	218.86	216.44	212.41	218.86	222.50	213.22
13	213.62	220.07	222.09	206.76	204.34	207.97	217.25	203.94	201.52	211.20	212.81	220.07
14	222.90	234.60	239.84	233.39	220.48	220.48	256.78	257.99	230.19	240.65	232.58	231.77
15	249.92	242.66	240.65	245.08	240.24	248.31	245.08	249.12	239.44	238.63	235.40	225.32
16	212.01	210.39	210.39	203.94	203.94	213.62	205.15	185.79	206.76	192.24	189.42	194.66
17	245.89	234.60	245.89	249.92	250.73	271.70	222.50	235.40	230.97	215.23	214.43	228.14
18	174.90	173.29	181.35	187.00	181.76	187.81	176.92	165.62	172.48	168.45	168.85	169.25
19	174.90	160.78	170.46	172.88	173.29	167.24	185.39	192.65	187.00	189.82	191.44	177.72
20	231.37	231.37	247.50	241.05	224.72	226.13	216.04	203.94	209.99	225.32	214.43	222.90

Note. TC = total cholesterol, N = participant's id number, RWON 0 = rest without niacin at 0 hr, RWON 24 = rest without niacin at 24 hr, RWON 48 = rest without niacin at 48 hr, EWON 0 = exercise without niacin at 0 hr, EWON 24 = exercise without niacin at 24 hr, EWON 48 = exercise without niacin at 48 hr, RWN 0 = rest with niacin at 0, RWN 24 = rest with niacin at 24, RWN 48 = rest with niacin at 48, EWN 0 = exercise with niacin at 0 hr, EWN 24 = exercise with niacin at 24 hr, EWN 48 = exercise with niacin at 48 hr.

APPENDIX K

Participants' LDL-C Data

Participants' LDL -C Data (mg/dl)

N	RWON0	RWON24	RWON48	EWON0	EWON24	EWON48	RWN0	RWN24	RWN48	EWN0	EWN24	EWN48
1	185.91	190.74	201.17	186.74	192.94	207.54	196.89	202.76	205.06	181.36	180.30	184.00
2	174.64	180.42	165.03	167.30	170.18	162.06	187.24	184.28	164.46	171.43	171.46	176.60
3	217.28	228.07	229.62	222.86	228.41	213.15	214.23	220.18	229.78	201.40	207.09	182.03
4	178.91	162.83	176.00	177.52	171.12	169.93	166.08	159.73	146.17	186.78	159.07	169.73
5	132.18	125.05	119.16	142.92	145.28	147.21	103.56	104.00	98.43	104.62	113.26	115.89
7	191.20	202.07	210.35	169.23	172.75	153.57	158.12	157.44	156.04	161.06	145.29	142.09
8	132.29	136.92	136.76	131.71	127.47	116.52	135.12	141.76	138.44	110.73	99.13	113.20
9	127.05	127.31	124.78	126.72	133.29	126.86	161.86	150.69	136.41	115.02	127.67	127.21
11	171.01	167.66	170.56	185.19	177.47	149.34	194.45	187.91	144.51	177.44	169.30	158.65
12	185.65	178.86	188.08	177.93	179.44	174.04	135.32	125.33	122.10	116.46	123.10	117.81
13	159.17	164.71	165.12	147.57	148.40	154.66	160.22	148.00	147.01	148.40	156.11	160.03
14	156.49	168.88	176.58	167.65	158.95	156.08	183.39	187.42	163.13	170.50	159.58	154.81
15	183.01	180.08	173.18	178.53	175.94	182.63	179.36	185.75	176.41	175.47	173.92	159.72
16	149.47	144.33	144.15	144.37	136.58	143.30	132.77	109.42	129.82	123.14	119.11	119.48
17	187.23	176.28	188.00	190.83	193.73	214.32	160.06	174.19	170.62	153.89	153.74	167.58
18	123.57	118.62	128.90	130.57	129.74	131.25	115.24	103.46	111.82	108.49	108.67	108.82
19	116.53	103.37	111.21	112.94	114.46	105.63	112.43	120.54	112.66	115.32	123.97	107.51
20	170.37	170.25	185.86	186.85	173.66	171.86	160.47	153.90	159.18	174.86	163.10	163.40

Note. LDL-C = low-density lipoprotein cholesterol, N = participant's id number, RWON 0 = rest without niacin at 0 hr, RWON 24 = rest without niacin at 24 hr, RWON 48 = rest without niacin at 48 hr, EWON 0 = exercise without niacin at 0 hr, EWON 24 = exercise without niacin at 24 hr, EWON 48 = exercise without niacin at 48 hr, RWN 0 = rest with niacin at 0, RWN 24 = rest with niacin at 24, RWN 48 = rest with niacin at 48, EWN 0 = exercise with niacin at 0 hr, EWN 24 = exercise with niacin at 24 hr, EWN 48 = exercise with niacin at 48 hr.

APPENDIX L

Participants' HDL-C Data

Participants' HDL-C Data (mg/dl)

N	RWON0	RWON24	RWON48	EWON0	EWON24	EWON48	RWN0	RWN24	RWN48	EWN0	EWN24	EWN48
1	36.47	33.70	35.05	30.61	32.22	33.96	38.08	39.17	42.58	40.27	41.23	40.40
2	47.35	47.35	46.90	45.55	46.45	45.42	47.93	49.09	46.32	47.41	46.83	47.93
3	43.29	43.74	43.23	42.58	45.42	44.71	50.95	51.08	54.50	51.98	56.23	51.73
4	29.19	28.03	27.07	30.48	30.80	32.86	38.59	38.79	36.21	39.37	37.95	40.07
5	36.92	38.92	38.92	38.01	40.52	41.75	39.82	40.91	41.62	42.58	44.00	46.58
7	31.12	30.09	30.16	29.84	28.94	27.84	37.95	37.69	34.47	35.50	33.38	34.15
8	54.05	54.24	54.88	53.40	51.73	54.11	60.74	58.36	59.55	49.35	54.56	53.08
9	52.24	51.92	51.28	56.43	59.39	55.33	59.84	58.17	57.07	57.20	55.72	58.68
11	41.30	39.75	44.45	42.84	42.46	41.36	50.31	50.50	51.73	47.35	49.02	49.22
12	62.16	58.29	55.01	64.99	61.71	60.74	61.90	57.39	55.91	60.03	57.46	53.47
13	38.72	40.91	39.95	42.26	40.98	42.46	44.90	45.35	44.00	45.61	43.62	45.68
14	42.20	42.20	44.45	40.85	41.17	43.10	51.66	49.02	48.25	49.28	51.02	49.41
15	54.69	52.24	53.79	53.47	52.76	51.15	51.02	52.95	51.15	51.28	50.12	54.75
16	45.61	48.44	49.99	47.09	49.15	49.28	59.65	62.61	60.87	55.08	51.41	55.59
17	45.50	44.39	45.16	45.16	45.55	44.13	50.05	49.67	49.67	51.86	49.41	49.80
18	39.62	40.91	40.14	42.33	40.91	42.97	50.57	53.79	52.89	49.54	50.44	50.18
19	44.52	40.91	41.81	42.84	43.10	41.68	57.91	62.29	63.32	59.45	55.85	56.36
20	34.99	34.60	36.15	37.18	37.56	36.40	40.52	37.82	37.05	34.73	37.05	38.72

Note. HDL-C = high-density lipoprotein cholesterol, N = participant's id number, RWON 0 = rest without niacin at 0 hr, RWON 24 = rest without niacin at 24 hr, RWON 48 = rest without niacin at 48 hr, EWON 0 = exercise without niacin at 0 hr, EWON 24 = exercise without niacin at 24 hr, EWON 48 = exercise without niacin at 48 hr, RWN 0 = rest with niacin at 0. RWN 24 = rest with niacin at 24, RWN 48 = rest with niacin at 48, EWN 0 = exercise with niacin at 0 hr, EWN 24 = exercise with niacin at 24 hr, EWN 48 = exercise with niacin at 48 hr.

APPENDIX M

Participants' HDL_2-C Data

Participants' HDL_2-C Data (mg/dl)

N	RWON0	RWON24	RWON48	EWON0	EWON24	EWON48	RWN0	RWN24	RWN48	EWN0	EWN24	EWN48
1	5.27	4.06	4.50	2.78	3.87	4.19	4.68	5.31	5.80	5.89	6.33	6.15
2	8.76	14.27	10.25	8.71	8.57	9.03	10.44	10.11	10.39	9.98	9.34	8.95
3	5.67	4.63	4.38	5.61	6.38	6.64	8.98	8.40	10.07	10.34	9.53	10.28
4	3.70	3.38	3.33	1.94	3.88	4.32	6.61	7.20	5.72	4.80	6.88	4.52
5	6.95	8.56	9.93	7.33	9.64	10.94	11.21	11.01	10.36	12.03	12.61	13.43
7	3.42	4.01	3.27	4.55	5.14	4.30	6.69	6.88	6.32	7.42	5.42	5.10
8	16.76	15.72	17.00	17.08	16.19	17.86	22.28	21.46	21.87	17.77	21.16	18.58
9	18.97	20.21	16.26	21.99	24.24	21.99	21.32	19.58	23.41	24.45	21.41	21.26
11	10.04	8.75	11.96	12.10	11.14	8.87	14.32	15.02	16.90	12.26	16.14	12.06
12	12.28	11.92	10.84	15.31	16.38	15.73	18.06	14.78	15.31	18.20	13.62	10.21
13	8.76	7.90	8.30	9.57	9.27	8.87	12.15	10.78	12.16	11.11	11.32	10.92
14	9.19	9.32	9.88	10.17	8.81	10.54	15.02	12.25	13.23	15.62	15.61	14.32
15	12.40	12.29	13.90	12.09	9.70	9.97	10.94	11.51	12.56	13.66	14.00	13.57
16	11.43	11.02	13.61	12.59	12.64	13.35	21.00	21.10	20.01	17.14	16.26	16.87
17	15.60	14.17	15.20	14.74	16.89	14.75	19.89	19.19	19.32	21.77	20.03	19.19
18	13.87	12.76	13.03	15.09	14.77	15.21	22.94	26.62	22.54	22.69	22.88	22.75
19	17.35	16.01	15.03	18.13	16.58	14.57	27.30	29.86	32.32	29.36	28.22	25.81
20	8.27	7.88	8.46	10.33	9.15	9.81	11.47	11.23	8.13	6.84	9.62	9.54

Note. HDL_2-C = high-density lipoprotein cholesterol subfraction 2, N = participant's id number, RWON 0 = rest without niacin at 0 hr, RWON 24 = rest without niacin at 24 hr, RWON 48 = rest without niacin at 48 hr, EWON 0 = exercise without niacin at 0 hr, EWON 24 = exercise without niacin at 24 hr, EWON 48 = exercise without niacin at 48 hr, RWN 0 = rest with niacin at 0, RWN 24 = rest with niacin at 24, RWN 48 = rest with niacin at 48, EWN 0 = exercise with niacin at 0 hr, EWN 24 = exercise with niacin at 24 hr, EWN 48 = exercise with niacin at 48 hr.

APPENDIX N

Participants' HDL_3-C Data

Participants' HDL_3-C Data (mg/dl)

N	RWON0	RWON24	RWON48	EWON0	EWON24	EWON48	RWN0	RWN24	RWN48	EWN0	EWN24	EWN48
1	31.20	29.64	30.55	27.83	28.35	29.77	33.40	33.86	36.78	34.38	34.90	34.25
2	38.59	33.08	36.65	36.84	37.88	36.39	37.49	38.98	35.93	37.43	37.49	38.98
3	37.62	39.11	38.85	36.97	39.04	38.07	41.97	42.68	44.43	41.64	46.70	41.45
4	25.49	24.65	23.74	28.54	26.92	28.54	31.98	31.59	30.49	34.57	31.07	35.55
5	29.97	30.36	28.99	30.68	30.88	30.81	28.61	29.90	31.26	30.55	31.39	33.15
7	27.70	26.08	26.89	25.29	23.80	23.54	31.26	30.81	28.15	28.08	27.96	29.05
8	37.29	38.52	37.88	36.32	35.54	36.25	38.46	36.90	37.68	31.58	33.40	34.50
9	33.27	31.71	35.02	34.44	35.15	33.34	38.52	38.59	33.66	32.75	34.31	37.42
11	31.26	31.00	32.49	30.74	31.32	32.49	35.99	35.48	34.83	35.09	32.88	37.16
12	49.88	46.37	44.17	49.68	45.33	45.01	43.84	42.61	40.60	41.83	43.84	43.26
13	29.96	33.01	31.65	32.69	31.71	33.59	32.75	34.57	31.84	34.50	32.30	34.76
14	33.01	32.88	34.57	30.68	32.36	32.56	36.64	36.77	35.02	33.66	35.41	35.09
15	42.29	39.95	39.89	41.38	43.06	41.18	40.08	41.44	38.59	37.62	36.12	41.18
16	34.18	37.42	36.38	34.50	36.51	35.93	38.65	41.51	40.86	37.94	35.15	38.72
17	29.90	30.22	29.96	30.42	28.66	29.38	30.16	30.48	30.35	30.09	29.38	30.61
18	25.75	28.15	27.11	27.24	26.14	27.76	27.63	27.17	30.35	26.85	27.56	27.43
19	27.17	24.90	26.78	24.71	26.52	27.11	30.61	32.43	31.00	30.09	27.63	30.55
20	26.72	26.72	27.69	26.85	28.41	26.59	29.05	26.59	28.92	27.89	27.43	29.18

Note. HDL_3-C = high-density lipoprotein cholesterol subfraction 3, N = participant's id number, RWON 0 = rest without niacin at 0 hr, RWON 24 = rest without niacin at 24 hr, RWON 48 = rest without niacin at 48 hr, EWON 0 = exercise without niacin at 0 hr, EWON 24 = exercise without niacin at 24 hr, EWON 48 = exercise without niacin at 48 hr, RWN 0 = rest with niacin at 0, RWN 24 = rest with niacin at 24, RWN 48 = rest with niacin at 48, EWN 0 = exercise with niacin at 0 hr, EWN 24 = exercise with niacin at 24 hr, EWN 48 = exercise with niacin at 48 hr.

APPENDIX O

Participants' TC to HDL-C Ratio Data

Participants' TC to HDL-C Ratio Data

N	RWON0	RWON24	RWON48	EWON0	EWON24	EWON48	RWN0	RWN24	RWN48	EWN0	EWN24	EWN48
1	6.62	7.37	7.58	8.06	7.64	7.74	6.85	6.72	6.32	6.20	6.02	6.06
2	5.06	5.22	4.88	5.19	4.96	4.95	5.32	5.03	5.05	5.08	5.21	5.12
3	6.46	6.56	6.67	6.66	6.30	6.10	5.62	5.60	5.43	5.18	4.91	4.75
4	8.16	7.82	8.49	7.74	7.21	6.75	5.67	5.50	5.52	6.20	5.60	5.74
5	4.97	4.60	4.41	5.11	4.86	4.76	3.99	3.85	3.78	3.87	3.83	3.80
7	8.46	9.03	9.04	8.24	9.00	8.75	5.67	5.71	6.16	6.23	6.12	5.88
8	3.64	3.67	3.66	3.62	3.62	3.29	3.42	3.56	3.49	3.53	2.95	3.30
9	3.77	3.82	3.81	3.49	3.47	3.57	3.99	3.89	3.66	3.34	3.62	3.41
11	5.63	5.72	5.21	5.77	5.48	5.03	5.29	5.05	4.16	5.12	4.71	4.50
12	4.38	4.70	4.98	4.27	4.40	4.44	3.54	3.77	3.80	3.65	3.87	3.99
13	5.52	5.38	5.56	4.89	4.99	4.90	4.84	4.50	4.58	4.63	4.88	4.82
14	5.28	5.56	5.40	5.71	5.36	5.12	4.97	5.26	4.77	4.88	4.56	4.69
15	4.57	4.65	4.47	4.58	4.55	4.85	4.80	4.70	4.68	4.65	4.70	4.12
16	4.65	4.34	4.21	4.33	4.15	4.33	3.44	2.97	3.40	3.49	3.68	3.50
17	5.40	5.28	5.44	5.53	5.50	6.16	4.45	4.74	4.65	4.15	4.34	4.58
18	4.41	4.24	4.52	4.42	4.44	4.37	3.50	3.08	3.26	3.40	3.35	3.37
19	3.93	3.93	4.08	4.04	4.02	4.01	3.20	3.09	2.95	3.19	3.43	3.15
20	6.61	6.69	6.85	6.48	5.98	6.21	5.33	5.39	5.67	6.49	5.79	5.76

Note. TC = total cholesterol, HDL-C = high-density lipoprotein cholesterol, N = participant's id number, RWON 0 = rest without niacin at 0 hr, RWON 24 = rest without niacin at 24 hr, RWON 48 = rest without niacin at 48 hr, EWON 0 = exercise without niacin at 0 hr, EWON 24 = exercise without niacin at 24 hr, EWON 48 = exercise without niacin at 48 hr, RWN 0 = rest with niacin at 0, RWN 24 = rest with niacin at 24, RWN 48 = rest with niacin at 48, EWN 0 = exercise with niacin at 0 hr, EWN 24 = exercise with niacin at 24 hr, EWN 48 = exercise with niacin at 48 hr.

APPENDIX P

Participants' Hb Data

Participants' Hb Data (mg/dl)

N	RWON0	RWON24	RWON48	EWON0	EWON24	EWON48	RWN0	RWN24	RWN48	EWN0	EWN24	EWN48
1	14.7	13.5	15.3	13.9	14.2	14.1	13.4	13.9	14.2	13.7	14.1	14.0
2	14.2	14.3	14.0	14.4	14.1	13.9	14.7	14.6	13.3	13.9	14.2	14.1
3	14.7	14.4	15.0	14.1	14.6	14.4	13.6	14.0	14.5	14.5	14.6	13.8
4	13.7	14.1	14.1	13.8	13.6	13.7	14.3	13.7	13.0	12.6	13.8	13.2
5	15.5	14.9	15.2	16.0	16.1	15.5	14.6	15.1	14.2	15.4	15.0	14.7
7	14.9	13.9	14.9	14.7	15.1	15.0	14.5	14.3	14.0	14.3	14.4	14.4
8	14.6	14.5	14.7	14.4	13.7	14.4	14.7	14.4	14.5	13.9	13.6	13.8
9	14.1	15.0	15.3	13.8	13.9	13.7	15.0	15.4	15.7	14.2	14.9	14.6
11	14.2	13.9	13.8	15.0	14.6	14.5	14.5	14.1	14.5	14.6	13.8	15.0
12	14.7	14.6	14.8	14.5	15.0	15.2	13.8	14.2	13.9	13.8	14.4	14.5
13	13.7	14.3	14.7	14.6	14.1	15.1	14.5	14.6	14.0	14.2	14.3	14.9
14	16.8	16.6	16.5	15.0	15.7	15.8	16.2	16.8	16.5	16.0	15.7	16.3
15	13.4	13.5	13.5	13.9	13.9	13.7	13.2	13.6	14.1	12.9	13.6	13.0
16	14.4	13.7	12.9	13.8	14.6	15.4	14.8	14.3	14.1	13.8	14.3	14.1
17	14.1	14.0	13.8	13.7	14.1	14.4	15.2	14.2	13.7	13.7	13.4	14.2
18	14.8	14.8	14.1	13.5	13.4	14.5	13.7	14.3	14.6	13.2	13.5	14.3
19	14.5	14.3	14.2	13.2	13.2	13.8	12.7	13.3	12.5	13.2	12.8	13.1
20	15.0	15.5	15.2	15.1	14.8	15.3	14.2	14.4	14.2	14.9	15.0	14.7

Note. Hb = hemoglobin, N = participant's id number, RWON 0 = rest without niacin at 0 hr, RWON 24 = rest without niacin at 24 hr, RWON 48 = rest without niacin at 48 hr, EWON 0 = exercise without niacin at 0 hr, EWON 24 = exercise without niacin at 24 hr, EWON 48 = exercise without niacin at 48 hr, RWN 0 = rest with niacin at 0, RWN 24 = rest with niacin at 24, RWN 48 = rest with niacin at 48, EWN 0 = exercise with niacin at 0 hr, EWN 24 = exercise with niacin at 24 hr, EWN 48 = exercise with niacin at 48 hr.

APPENDIX Q

Participants' Het Data

Participants' Hct Data (%)

N	RWON0	RWON24	RWON48	EWON0	EWON24	EWON48	RWN0	RWN24	RWN48	EWN0	EWN24	EWN48
1	38.5	40.0	42.0	38.5	38.5	38.5	39.0	38.0	40.0	39.0	39.0	38.5
2	39.0	38.5	37.0	38.0	37.0	36.5	39.0	39.0	38.0	38.0	38.0	38.0
3	42.0	40.0	42.5	40.0	40.0	39.0	40.5	39.5	40.0	40.0	40.5	39.0
4	38.5	38.0	37.0	38.0	37.5	38.0	37.0	36.0	35.0	38.5	38.0	37.0
5	41.5	40.5	40.0	42.5	40.0	41.0	40.5	41.0	39.5	40.0	39.0	39.0
7	41.0	41.0	41.0	39.0	39.5	38.5	39.5	39.0	39.0	40.5	40.5	39.5
8	39.0	39.0	40.0	39.0	37.0	39.0	41.0	39.0	40.0	37.0	37.0	38.0
9	38.5	38.5	39.5	35.0	36.0	35.0	38.5	38.5	38.0	37.0	38.0	37.0
11	38.5	37.0	39.0	40.0	39.0	38.0	39.0	38.0	39.0	38.5	37.0	37.0
12	38.5	38.0	38.0	38.0	39.5	38.5	38.0	39.0	39.0	39.0	39.0	39.0
13	40.0	39.0	39.0	39.5	39.5	39.0	40.0	39.5	39.0	39.0	38.5	39.0
14	44.5	45.0	45.0	44.0	42.0	43.0	45.0	45.0	45.0	43.5	44.0	45.0
15	39.0	37.5	38.0	37.5	38.0	37.5	37.0	37.0	37.0	37.0	38.0	36.0
16	39.5	39.5	39.0	39.0	39.0	40.0	39.5	40.0	40.5	40.0	40.0	40.0
17	39.0	39.0	39.0	39.5	39.0	38.0	39.0	39.0	38.0	39.0	38.0	38.0
18	39.0	39.5	39.5	39.0	38.5	39.0	39.0	39.0	38.5	39.0	38.0	39.0
19	40.0	38.5	38.0	36.0	36.5	36.0	35.0	36.0	35.0	36.5	35.0	34.5
20	43.0	42.0	42.0	42.0	41.0	41.0	41.0	40.0	40.0	42.0	40.0	40.0

Note. Hct = hematocrit, N = participant's id number, RWON 0 = rest without niacin at 0 hr, RWON 24 = rest without niacin at 24 hr, RWON 48 = rest without niacin at 48 hr, EWON 0 = exercise without niacin at 0 hr, EWON 24 = exercise without niacin at 24 hr, EWON 48 = exercise without niacin at 48 hr, RWN 0 = rest with niacin at 0, RWN 24 = rest with niacin at 24, RWN 48 = rest with niacin at 48, EWN 0 = exercise with niacin at 0 hr, EWN 24 = exercise with niacin at 24 hr, EWN 48 = exercise with niacin at 48 hr.

APPENDIX R

Participants' Anthropometric Data

Participants' Anthropometric Data

N	Age (year)	Height (cm)	Weight (kg)	BMI (kg m^{-2})	BF (%)	WHR	HRmax (bpm)	HRrest (bpm)	60% HRR (bpm)	ExTime (min)
1	60	159.6	66.8	26.2	34.1	.82	160	96	134	57
2	46	151.0	70.4	30.9	48.4	.87	174	60	128	59
3	58	152.6	63.9	27.4	46.9	.83	162	68	124	56
4	71	166.0	90.9	33.0	46.4	.83	149	72	118	57
5	58	163.8	89.8	33.5	51.5	.78	157	70	136	69
7	67	160.0	75.9	29.7	43.4	.82	162	91	141	45
8	50	168.7	60.8	21.4	35.8	.83	163	76	137	65
9	54	162.0	80.7	30.8	53.1	.78	163	65	134	58
11	63	171.4	115.4	39.3	53.3	.87	153	68	128	75
12	50	165.1	57.5	21.1	40.1	.81	170	70	140	64
13	56	161.0	81.2	31.3	55.6	.79	166	64	135	46
14	59	157.2	73.5	29.7	46.2	.87	157	65	130	37
15	54	147.0	78.0	36.1	54.4	.82	170	68	140	65
16	60	159.6	66.8	26.2	48.4	.82	164	71	136	61
17	46	151.0	70.4	30.9	46.9	.87	161	78	136	80
18	58	152.6	63.9	27.4	46.4	.83	170	70	140	70
19	71	166.0	90.9	33.0	51.5	.83	169	62	137	63
20	58	163.8	89.8	33.5	43.4	.78	166	62	135	58

Note. N = participant's id number, BMI = body mass index, BF = body fat, WHR = waist to hip ratio, HR = heart rate, HRR = heart rate reserve, ExTime = total exercise time to expend 400 kcal.

APPENDIX S

Participants' Plasma Volume Change Data

Participants' Plasma Volume Change Data (%)

N	RWON24	RWON48	EWON24	EWON48	RWN24	RWN48	EWN24	EWN48
1	3.24	5.05	-2.11	-1.42	-6.13	-3.15	-2.84	-3.43
2	-2.01	-3.91	-0.63	-.60	.68	7.62	-2.11	-1.42
3	-2.90	-0.80	-3.42	-4.59	-5.32	-7.39	.59	2.38
4	-4.13	-6.72	.10	0.73	1.48	3.89	-9.91	-8.36
5	2.73	-0.58	-6.61	-0.51	-2.09	.21	.03	2.08
7	7.19	0	-1.37	-3.29	.08	2.23	-.69	-3.21
8	.69	1.93	-0.42	0	-3.02	-1.16	2.21	3.52
9	-6.00	-5.39	2.20	.73	-2.60	-5.73	-2.05	-2.74
11	-1.93	4.27	.11	-1.86	.13	0	1.57	-6.56
12	-0.66	-2.00	0.59	-3.32	-.19	1.96	-4.17	-4.83
13	-6.65	-9.19	3.55	-4.57	-1.96	.92	-2.01	-4.70
14	2.37	2.99	-8.90	-7.27	-3.57	-1.82	3.11	1.62
15	-4.66	-3.35	1.37	1.46	-2.94	-6.38	-2.51	-3.53
16	5.11	10.18	-5.48	-8.03	4.84	7.69	-3.50	-2.13
17	.71	2.17	-4.10	-8.57	7.04	8.03	-.45	-6.06
18	1.32	6.35	-.58	-6.90	-4.20	-7.40	-4.80	-7.69
19	-2.50	-3.12	1.43	-4.35	-1.70	1.60	-1.23	-3.49
20	-3.23	-3.67	-.46	-3.71	-3.85	-2.50	-5.51	-3.58

Note. N = participant's id number, RWON 24 = rest without niacin at 24 hr, RWON 48 = rest without niacin at 48 hr, EWON 24 = exercise without niacin at 24 hr, EWON 48 = exercise without niacin at 48 hr, RWN 24 = rest with niacin at 24, RWN 48 = rest with niacin at 48, EWN 24 = exercise with niacin at 24 hr, EWN 48 = exercise with niacin at 48 hr.