THE EFFECTS OF AEROBIC EXERCISE AND EXTENDED-RELEASE NIACIN

ON FASTING AND POSTPRANDIAL BLOOD LIPIDS

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THE EFFECTS OF AEROBIC EXERCISE AND EXTENDED-RELEASE NIACIN ON FASTING AND POSTPRANDIAL BLOOD LIPIDS

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THE EFFECTS OF AEROBIC EXERCISE AND EXTENDED-RELEASE NIACIN

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Eric Paul Plaisance, son of Evans Plaisance and Linda Plaisance, was born on March 5, 1974, in Thibodaux, Louisiana. He graduated from Central Lafourche High School in 1992. He attended Nicholls State University in Thibodaux, LA and graduated with a Bachelor's of Science degree in Biology in 1997. He then attended the United States Sports Academy in Daphne, AL, in the Fall of 1997 and graduated with a Master's degree in Health Fitness Management and Exercise Science in 1998. In 2001, he married Jennifer Reynolds of Mobile, AL. After working as an exercise physiologist in the Department of Cardiology at Providence Hospital from 1998-2002 he entered the doctoral program in the Department of Health & Human Performance at Auburn University, Auburn, Alabama, in 2002. He would like to thank his wife for her patience, love and support.

DISSERTATION ABSTRACT

THE EFFECTS OF AEROBIC EXERCISE AND EXTENDED-RELEASE NIACIN ON FASTING AND POSTPRANDIAL BLOOD LIPIDS

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Doctor of Philosophy, December 15, 2006
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The primary purpose of this investigation was to compare the combined effects of aerobic exercise and extended-release niacin on fasting and postprandial lipemia. Fifteen men with the metabolic syndrome (Age = 46 ± 2; BMI = 34.0 ± 0.8 $kg \cdot m^{-2}$; Waist circumference = 107.9 ± 2.1 cm; HOMA score = 4.3 ± 0.5; Triglycerides = 286 ± 26; HDL-C = 40 ± 2; Systolic blood pressure = 130 ± 4; Diastolic blood pressure = 84 ± 2) underwent each of four conditions (control: high-fat meal only; exercise: exercise performed one hour prior to a high-fat meal; niacin: high-fat meal consumed after six weeks of extended-release niacin; niacin + exercise: high-fat meal consumed after six weeks of extended-release niacin and a single session of exercise) to determine the effects of niacin and exercise on postprandial lipemia. Blood samples were obtained on

each occasion at baseline and at two-hour intervals up to eight hours following the high-fat meal. Fasting blood samples were also obtained before and again at 24 and 48 hours post-exercise during the exercise and niacin + exercise conditions to determine the combined effects of niacin and exercise on fasting triglyceride and glucose metabolism. Blood samples were analyzed for triglyceride, glucose and insulin concentrations. Area under the curve was calculated for triglyceride and insulin during the postprandial period. Differences in blood variables of interest were determined by multiple repeated-measures ANOVAs ($p < 0.05$ for all). Niacin + exercise lowered the postprandial total triglyceride area under the curve and temporal responses to a greater extent than exercise alone. The incremental triglyceride area under the curve and temporal responses were similar to control in the niacin + exercise condition. Insulin concentrations in the niacin condition were increased by 54% compared to control at the two-hour postprandial timepoint and were reduced by 16% when exercise was combined with niacin. Baseline fasting triglycerides were correlated with the total triglyceride area under the curve for each condition. Fasting triglycerides were reduced by 15% and 27% twenty-four and 48 hours following exercise. Six weeks of niacin lowered fasting triglycerides by 37%; however, fasting triglycerides were not reduced further when an identical exercise session was performed immediately following the niacin intervention. These findings indicate an additive influence of niacin and exercise on postprandial lipemia that may be mediated in similar and distinctly different ways. Furthermore, niacin-mediated reductions in fasting triglycerides may attenuate the triglyceride lowering effect of exercise.

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CHAPTER I.

INTRODUCTION

Metabolic Syndrome and Cardiovascular Disease

The incidence of obesity among U.S. adults increased 50% in the past two decades and continues to rise.[1] Reductions in vocational and leisure-time physical activity appear to be responsible, at least in part, for the increasing prevalence of obesity.[2] While obesity independently increases the risk of cardiovascular disease (CVD), the relationship between abdominal obesity and CVD is particularly strong due to its association with insulin resistance, elevated levels of fasting and postprandial triglycerides, low levels of high-density lipoprotein-cholesterol (HDL-C) and hypertension.[3-5] The collective expression of these abnormalities with abdominal obesity is known as the metabolic syndrome.[3, 6] It is currently estimated that 25% of U.S. adults express three or more of these characteristics.[7] Accordingly, the National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III) recognizes the need for lifestyle and pharmacological interventions as part of a prevention strategy for reducing CVD risk in individuals with the metabolic syndrome.[6]

The association between abdominal obesity and hypertriglyceridemia may be explained largely by excess visceral and subcutaneous adipose tissue triglyceride hydrolysis.[5] An increase in non-esterified fatty acid (NEFA) availability increases the

hepatic synthesis of triglycerides and subsequent synthesis and secretion of VLDL-triglycerides. Therefore, in addition to exercise, individuals with abdominal obesity may benefit from pharmacologic reductions in adipose tissue triglyceride hydrolysis and hepatic VLDL-triglyceride secretion.

While fasting blood lipid and lipoprotein metabolism is highly predictive of future CVD, the magnitude and duration of postprandial lipid metabolism may provide additional information regarding CVD risk. For example, Wideman and colleagues [8] examined the effects of a high-fat meal in sedentary, normolipidemic males with abdominal obesity. Despite normal fasting triglyceride levels, males with abdominal obesity had a higher magnitude and total triglyceride response to a high-fat meal compared to normal weight controls. It has been proposed that an exaggerated postprandial rise and sustained elevations in serum triglycerides after a meal is atherogenic due to elevated levels of chylomicron remnants and the production of small, dense LDL particles.[9, 10]

Effects of Aerobic Exercise on Characteristics of the Metabolic Syndrome

Aerobic exercise training has been shown to independently improve triglyceride and HDL-C concentrations.[11, 12] However, many of the benefits of exercise on triglyceride and HDL-C metabolism are associated with acute metabolic changes produced by the most recent bout of exercise performed. Holloszy and colleagues [13] noted reductions in serum triglycerides shortly after exercise that persisted for up to 44 hours in a cohort of men participating in an endurance exercise intervention. A number of investigators have since examined the acute effects of exercise on lipid and lipoprotein metabolism. Delayed reductions in triglycerides [14-21] and increases in HDL-C [15-17,

19, 22-27] and its subfractions, HDL_2-C [15, 16, 18, 22] and HDL_3-C, [15, 18, 23, 26] have been reported 24 to 48 hours following exercise. In contrast, acute bouts of exercise appear to have little effect, if any, on total cholesterol and LDL-C. [14-16, 18, 21, 28-30]

The primary mechanisms responsible for the acute exercise induced changes in lipid and lipoprotein metabolism appear to be due to elevations in skeletal muscle LPL activity.[31] For example, LPL protein content in vastus lateralis was increased eight hours following a single bout of moderate-intensity aerobic exercise and remained elevated up to 22 hours. Likewise, elevated post-heparin LPL activity has been reported four to 24 hours following aerobic exercise.[16, 17, 23, 32, 33] While post-heparin LPL activity may reflect changes in adipose tissue and skeletal muscle tissue LPL activity, elevations in LPL activity have been noted in sedentary males 24 hours following a single bout of moderate-intensity exercise.[17, 34] Importantly, no changes in hepatic triglyceride lipase activity, cholesterol ester transfer protein activity, and lecithin:cholesterol ester transfer protein activity were reported [17, 34] providing further support that elevated LPL activity is primarily responsible for the observed changes in lipid and lipoprotein metabolism following a single session of exercise in sedentary males. Therefore, an acute bout of exercise appears to lower triglycerides and raise HDL-C levels primarily by increasing the clearance of triglyceride-rich lipoprotein particles via increases in skeletal muscle LPL activity.

An acute bout of exercise is associated with an insulin-independent increase in cellular glucose transport.[35-37] In addition, two to four hours following exercise, there is an increase in insulin stimulated glucose transport.[35] Insulin stimulated glucose disposal increases as much as 40% following moderate-intensity exercise and remains

elevated for 24 to 48 hours [38-40]. Therefore, single bouts of aerobic exercise may be a strategy to ameliorate the niacin-induced reductions in insulin sensitivity.

The acute metabolic effects of a single session of aerobic exercise have also been shown to attenuate postprandial lipemia. Moderate-intensity aerobic exercise durations of 30 to 90 minutes performed one to 16 hours prior to a high fat meal results in a 15 to 50% reduction in postprandial triglycerides [10, 41-43] and up to a 41% reduction in insulin concentrations.[44] Further, these changes may be partially attributed to the influence of insulin on adipose and skeletal muscle LPL. Following a meal, insulin increases adipose tissue LPL activity while decreasing skeletal muscle tissue LPL activity.[45] Since aerobic exercise can lower the insulin response to a meal, it is possible that less circulating insulin may permit greater activation of skeletal muscle LPL activity when a meal is preceded by exercise. Therefore, the increased hydrolysis of plasma triglycerides following a meal may be associated with increases in skeletal muscle LPL activity which is normally suppressed in the absence of previous exercise.[42]

Effects of Niacin on Characteristics of the Metabolic Syndrome

Due to the limited effects of traditionally prescribed statins on triglyceride and HDL-C metabolism, isolated or combined abnormalities in serum triglyceride and HDL-C concentrations may require alternative pharmacological strategies.[6, 46] Niacin (nicotinic acid or vitamin B_3) is a pharmacological agent first reported to influence lipid metabolism by Altschul and colleagues in 1955.[47] At therapeutic doses, niacin produces 16 to 35% reductions in triglycerides and 18 to 45% elevations in HDL-C with less dramatic changes in total cholesterol and LDL-C concentrations [46, 48-53]. Therefore, niacin may be an ideal agent for individuals with isolated or combined serum

triglyceride and HDL-C abnormalities. However, unlike statins and fibrates, the use of niacin has been limited due to adverse reactions such as cutaneous flushing, headaches, hepatotoxicity and gastrointestinal problems.[54-56] In the last decade, an extended-release formulation of niacin has become available by prescription that is associated with fewer side-effects and similar efficacy to immediate and sustained-release formulations of niacin.[50, 51, 57] Extended-release niacin is titrated over the course of three to four weeks from 500 to 1500 $mg \cdot day^{-1}$ and reaches maximal efficacy between four to eight weeks of administration.[51, 57]

The mechanisms for niacin mediated changes in blood lipid characteristics remain unclear. However, niacin has been shown to reduce adipose tissue lipolysis via indirect inhibition of hormone-sensitive lipase.[58] A concomitant reduction in adipose tissue lipolysis and fatty acid transport to the liver, along with niacin's apparent inhibition of hepatic diacylglycerol acyl transferase which is an important enzyme in the hepatic production of triglycerides, have been proposed to reduce the hepatic production of triglycerides and the secretion of triglyceride rich VLDL-triglycerides. Finally, niacin has been shown to increase adipose tissue lipoprotein lipase activity (LPL activity).[59, 60] Lipoprotein lipase is a serine hydrolase primarily bound to the vascular endothelium of adipose and muscle tissue capillaries and is responsible for the hydrolysis of serum triglycerides.

In addition to reductions in VLDL-triglyceride secretion and elevations in adipose tissue LPL activity, niacin also appears to have a direct effect on HDL metabolism. HDL particles are intricately involved in the removal of excess cholesterol from peripheral cells, including the vascular endothelium, and are inversely associated with CVD.[61]

Therefore, an increase in HDL-C levels would be expected to reduce CVD risk or progression. It has been proposed that niacin inhibits an HDL/apo-A1 catabolism receptor without affecting the hepatic scavenger receptor-B1 (SR-B1).[61, 62] Inhibition of catabolic receptors is thought to reduce the hepatic uptake of HDL particles but permit scavenger receptors to take up cholesterol esters associated with the lipoprotein.

The effects of extended-release niacin on postprandial lipemia have not been investigated to date. However, King et al. [48] found that 12 weeks of an immediate release form of niacin reduced the total triglyceride area under the curve (triglyceride AUC_T) following a high-fat meal by 41% in individuals with isolated low HDL-C. Similarly, O'Keefe and colleagues [63] found that 18 weeks of immediate-release niacin resulted in 32% reductions in the triglyceride AUC_T. The proposed mechanisms for changes in postprandial lipemia appear to be similar to those responsible for niacin's influence on fasting blood lipid and lipoprotein metabolism and include increases in adipose tissue LPL activity and reductions in postprandial VLDL secretion [48].

Although niacin and acute exercise are both associated with significant improvements in fasting and postprandial blood lipid characteristics, the pharmacological use of niacin remains low not only due to cutaneous flushing but also due to significant reductions in insulin sensitivity.[64] Extended-release niacin is associated with less severe reductions in insulin sensitivity; however, minor elevations in fasting blood glucose levels are still observed (5 to 7%).[57, 65] The mechanisms for the niacin-induced changes in insulin sensitivity are currently unclear. However, it has been proposed that as blood niacin levels wane in the hours after administration, non-esterified fatty acid (NEFA) concentrations "rebound". Since NEFAs influence insulin sensitivity,

insulin resistance associated with niacin may occur by mechanisms consistent with those of the glucose-fatty acid cycle [66, 67]. However, other investigators have found that insulin resistance occurred without significant elevations in NEFAs suggesting that the reduction in insulin sensitivity can occur by other pathways.[64]

Combined Effects of Aerobic Exercise and Niacin

The combined effects of aerobic exercise and extended-release niacin on blood lipid and glucose metabolism in the fasted and postprandial state have not been previously examined. However, the independent effects of niacin on adipose tissue lipolysis and LPL activity and reductions in hepatic VLDL-triglyceride secretion in combination with the acute effects of exercise on skeletal muscle LPL activity might be expected to provide additive reductions in triglycerides and elevations in HDL-C in the fasted and postprandial state. Since a single session of aerobic exercise upregulates both insulin-dependent and independent pathways of glucose transport, exercise may also ameliorate the reduction in insulin sensitivity associated with the use of niacin. The primary purpose of this investigation was to examine the combined effects of six weeks of extended-release niacin and a single session of moderate-intensity aerobic exercise on fasting blood lipids and postprandial lipemia. A secondary purpose was to determine the effects of a single session of aerobic exercise on insulin sensitivity following niacin administration. This study did not investigate the mechanisms by which niacin and exercise improve lipid and glucose metabolism.

Hypotheses and Rationale

Question

1. What are the effects of six weeks of niacin and a single session of moderate-intensity aerobic exercise on postprandial blood lipid, glucose and insulin responses in obese males exhibiting the metabolic syndrome?

Hypotheses

It was hypothesized that niacin and aerobic exercise would decrease postprandial triglycerides to a greater extent than exercise or niacin alone in the hours following a single exercise bout. An alternative hypothesis was that the expected reduction in fasting triglycerides produced by niacin would attenuate the triglyceride lowering effect of exercise on postprandial lipemia.

Rationale

Niacin-induced elevations in adipose tissue LPL activity and reductions in VLDL secretion along with exercise-induced elevations in skeletal muscle tissue LPL activity may provide an additive reduction in postprandial triglyceride concentrations. Aerobic exercise performed prior to a meal has been shown to lower postprandial insulin levels. Since higher insulin levels may play a permissive role in the regulation of LPL activity, it was possible that a reduction in insulin levels with exercise would increase skeletal muscle LPL activity which is normally suppressed following a meal.

Question

2. What are the effects of six weeks of niacin and a single session of moderate-intensity aerobic exercise on fasting blood lipid, glucose and insulin responses in obese males exhibiting the metabolic syndrome?

Hypotheses

It was hypothesized that the combined effects of short-term niacin and a single session of exercise would decrease fasting triglyceride concentrations to a greater extent than exercise or niacin alone in the days following exercise.

Rationale

Niacin is titrated over the course of three to four weeks from 500 $mg \cdot day^{-1}$ to a maximum dosage of 1500-2000 $mg \cdot day^{-1}$ and is associated with significant changes in triglyceride concentrations.[55] Single sessions of aerobic exercise at energy expenditures of 350 to 500 kcals are also associated with significant changes in triglyceride and HDL-C metabolism in sedentary males. Although each intervention independently affects triglyceride and HDL-C metabolism, the mechanisms responsible for these changes are thought to be unique to each. Niacin is thought to increase adipose tissue LPL activity and reduce adipose tissue triglyceride hydrolysis. An increase in adipose tissue LPL activity would result in an increase in the clearance of serum triglycerides and a concomitant increase in HDL-C levels. In addition, the reduction in adipose tissue triglyceride hydrolysis and hepatic triglyceride synthesis would reduce VLDL-triglyceride secretion. Therefore, these mechanisms would be expected to lower triglycerides and raise HDL-C.

Conversely, exercise appears to lower serum triglycerides by increasing skeletal muscle and adipose tissue LPL activity and the hydrolysis of triglyceride-rich particles in sedentary obese individuals. Therefore, it is possible that an acute bout of exercise may provide an additive reduction in triglycerides and an elevation in HDL-C following the administration of niacin.

While it may be argued that the absolute reduction in serum triglycerides induced by exercise may be blunted following the niacin intervention due to less triglyceride substrate, it is more likely that an additive effect on triglyceride and HDL-C concentrations would occur since the energy requirements of the cell following exercise remain the same even in the presence of niacin. Therefore, despite lower fasting levels of triglycerides and HDL-C after the administration of niacin, the energy requirements of cellular metabolism following exercise would be expected to provide an additive lowering of serum triglycerides and an elevation in HDL-C.

Assumptions

1. Middle-aged individuals with the metabolic syndrome sampled from the Auburn-Opelika community represent the population response to niacin and acute exercise interventions.
2. Participants followed all instructions provided throughout the study protocol.
3. The exercise intervention was practical for use by middle-aged adults.

Delimitations

1. Only males with the metabolic syndrome were recruited for this study.
2. Apparently healthy individuals who had no known metabolic or pulmonary diseases were used.
3. A single aerobic exercise session at an intensity of 70% $\dot{V}O_{2max}$ was used to expend 500 kcals.
4. Extended-release niacin administered at 1500 $mg \cdot day^{-1}$ was the only medication and dosage used to test the hypotheses.

Limitations

1. Participants were only recruited from the Auburn-Opelika community.
2. Outside physical activity and dietary intake were quantified using self-reported questionnaires.
3. A single baseline blood sample may not account for daily variations in lipid and lipoprotein metabolism.

Significance of the Study

Although niacin and exercise are popular strategies to improve blood lipid metabolism, there have been no investigations to date which have combined niacin and exercise to examine the unique effects of each intervention on blood lipids. Therefore, this study is the first to provide data on the combined effects of niacin and an acute session of aerobic exercise on fasting and postprandial blood lipids. It is likely that individuals with the metabolic syndrome may benefit the most from this combined strategy due to the typically high triglyceride and low HDL-C levels associated with abdominal obesity, insulin resistance and a sedentary lifestyle. Finally, exercise may be identified as a useful intervention to improve niacin-mediated insulin resistance which may permit individuals with insulin resistance or type 2 diabetes with elevated triglycerides to take niacin without compromising glucose regulation.

CHAPTER II.

REVIEW OF LITERATURE

Metabolic Syndrome

The National Cholesterol Education Program (NCEP) identified the metabolic syndrome as a target for CVD risk reduction in its most recent Adult Treatment Panel recommendations.[6] The metabolic syndrome is a group of interrelated risk factors which include abdominal obesity, insulin resistance, low HDL-C, elevated triglycerides and hypertension.[68] It has been estimated that over 25% of the U.S. population meet criteria for the syndrome.[7] Therefore, lifestyle and pharmacological interventions designed to reduce individual risk factors associated with the metabolic syndrome may be an effective strategy to reduce rates of CVD.

Hypertriglyceridemia is a common feature of the metabolic syndrome and may be characterized by elevated triglyceride concentrations in the fasted and postprandial state. The mechanisms responsible for hypertriglyceridemia in individuals with abdominal obesity and the metabolic syndrome are not completely understood but appear to be associated with adipose and hepatic tissue insulin resistance.[69] Indeed, insulin resistance was associated with higher fasting and postprandial triglycerides in individuals with the hypertriglyceridemic waist phenotype when compared to individuals without abdominal obesity.[70]

The strategy recommended by NCEP to lower plasma triglycerides begins with therapeutic lifestyle changes such as exercise, diet and weight-loss.[6] Aerobic exercise training in the presence or absence of weight-loss has been shown to reduce both fasting and postprandial triglycerides.[71] However, many of the health benefits attributed to aerobic exercise training are associated with the metabolic effects of the most recent bout of exercise performed. Single sessions of aerobic exercise have been shown to reduce fasting triglyceride concentrations by 14 to 50%.[72] Reductions in fasting triglyceride concentrations may also explain the observed reduction in postprandial triglyceride concentrations when aerobic exercise is performed prior to a meal.[73] The mechanisms responsible for exercise-mediated changes in fasting and postprandial triglycerides appear to be due to increases in skeletal muscle LPL activity [31] and/or reductions in hepatic VLDL-triglyceride secretion.[74, 75]

Despite the effects of aerobic exercise on plasma triglyceride concentrations, many individuals with hypertriglyceridemia require pharmacological agents to achieve blood lipid goals. Niacin is one of the most effective pharmacological agents for lowering triglyceride and raising HDL-C concentrations.[76] Reductions of 20 to 50% for triglycerides and increases of 15 to 35% for HDL-C have been reported with niacin at dosages of 1000 to 2000 $mg \cdot day^{-1}$.[77] Niacin reduces triglyceride concentrations presumably by reducing adipocyte triglyceride hydrolysis and hepatic triglyceride synthesis.[78] Despite the significant benefits of niacin on plasma triglyceride concentrations in individuals with hypertriglyceridemia, the clinical use of niacin remains relatively low in comparison to statins and fibrates due to adverse reactions such as cutaneous flushing, reductions in insulin sensitivity and fatigue.[53]

Aerobic exercise and niacin are known to improve triglyceride and HDL-C concentrations, however, there are currently no published reports which have examined the combined effects of aerobic exercise and niacin on blood lipid metabolism in individuals at high risk for CVD. Since the mechanisms by which niacin and exercise improve triglyceride concentrations may be complementary, it is possible that the combination of these strategies may provide additive improvements in both fasting and postprandial triglyceride concentrations. Since exaggerated postprandial triglyceride concentrations have been identified as a risk factor for the metabolic syndrome and CVD [4], this investigation will provide valuable information regarding the combined impact of aerobic exercise and niacin on postprandial lipemia.

The following sections provide a review of the epidemiological evidence for blood lipids as risk factors for CVD and the mechanisms by which niacin and exercise influence lipid and lipoprotein metabolism. The impact of niacin on CVD morbidity and mortality and its effects on fasting and postprandial blood lipid metabolism will then be discussed to provide a rationale for using niacin in individuals with hypertriglyceridemia. Finally, empirical evidence will be presented for exercise as an independent strategy to improve blood lipid metabolism and ultimately CVD risk.

Blood Lipids and Cardiovascular Disease

Fasting Blood Lipids

Epidemiological investigations provide convincing evidence that total cholesterol and LDL-C are CVD risk factors.[79-81] The risk of CVD is two to five fold higher when total cholesterol levels are greater than 220 $mg \cdot dL^{-1}$ when compared to levels less than 220 $mg \cdot dL^{-1}$.[79] The results of a recent meta-analysis of population based studies

suggests a linear relationship between the absolute reduction in LDL-C and the incidence of coronary and other major cardiovascular events.[82] Indeed, for every 1% reduction in LDL-C concentrations, a 1% reduction in the incidence of CVD events was observed.[83] The strong association between LDL-C and CVD and the high incidence of elevated cholesterol in the population has prompted the inclusion of LDL-C as a primary target for interventional strategies to reduce CVD risk, especially in high-risk individuals.[6]

Despite the association between LDL-C and CVD, the risk of CVD varies widely depending on other blood lipid characteristics and the number and severity of additional risk factors.[80] The contribution of other risk factors to overall CVD risk is evidenced by the fact that CVD remains one of the leading causes of death and disability in the world despite effective risk reduction strategies.[6] Data from the Framingham Study [84] demonstrate an inverse relationship between HDL-C and cardiovascular morbidity and mortality independent of LDL-C concentrations. In fact, the incidence of CVD was eight-fold higher in individuals with HDL-C concentrations less than 35 $mg \cdot dL^{-1}$ compared to those with HDL-C concentrations greater than 65 $mg \cdot dL^{-1}$.[85] Furthermore, a meta-analysis of four clinical trials suggests that for every one $mg \cdot dL^{-1}$ decrease in plasma HDL-C, there is a two to three percent increase in CVD risk independent of LDL-C and other risk factors.[86] Efforts to raise HDL-C in high-risk middle-aged males with CVD and isolated low HDL-C concentrations provide evidence that increases in HDL-C reduce CVD mortality and nonfatal myocardial infarction.[87]

A higher incidence of elevated triglycerides in patients with CVD suggests that triglycerides may also be atherogenic.[88, 89] However, the association between

triglycerides and CVD is often reduced after statistically controlling for HDL-C and total cholesterol concentrations.[90] Others have shown that triglyceride remains an important predictor of CVD risk even after controlling for HDL-C concentrations in middle-aged men.[91] Although the evidence is debatable, hypertriglyceridemia may place men at an increased risk of CVD regardless of HDL-C or LDL-C concentrations. Therefore, NCEP identified hypertriglyceridemia as a secondary target for CVD risk reduction.[6]

Postprandial Lipemia

Postprandial lipemia refers to the increase in plasma triglyceride concentrations in the hours after a meal. Postprandial triglycerides generally peak at four hours and may remain elevated for up to eight hours in sedentary obese individuals.[92] Zilversmit [9] was one of the first to propose that a greater magnitude and duration of postprandial lipemia may increase the risk of CVD by increasing the infiltration of VLDL and chylomicron remnants into the vascular endothelium or indirectly by lowering HDL-C concentrations. Patsch and co-workers [93] also suggest that the negative association between HDL-C concentrations and CVD originates in part from a positive relationship between CVD and plasma triglyceride concentrations in the postprandial state. Furthermore, postprandial but not fasting triglyceride concentrations exhibited a positive relationship with CVD that was stronger than fasting HDL-C.[94] Finally, Wideman and colleagues [8] found that abdominally obese males had significantly higher postprandial triglyceride concentrations compared to normal weight controls despite both groups exhibiting normal fasting blood lipid concentrations. Since individuals spend as much as two-thirds of the day in a postprandial state, postprandial lipemia may represent a more

valid marker of blood lipid metabolism and the risk of CVD compared to fasting blood lipid parameters.

Methods Used to Evaluate Postprandial Lipemia

Several methods have been used to report the postprandial response to a meal under experimental conditions. Unlike fasting blood lipid concentrations where a single value is reported and compared following the administration of an intervention, postprandial triglyceride concentrations are typically measured over the course of six to eight hours.[75]

Blood samples in the postprandial state are generally obtained at one to two hour intervals over the course of six to eight hours. The peak triglyceride response is generally observed three to four hours after meal ingestion and can be influenced by exercise and pharmacological interventions.[41, 48] The rate of triglyceride clearance from the blood may also be determined by observing the duration of postprandial lipemia.[95] Furthermore, many investigations examine the magnitude of postprandial lipemia at pre-defined timepoints to compare differences between experimental interventions designed to reduce postprandial lipemia.

Two of the most consistently used methods to report postprandial lipemia is the total triglyceride area under the curve (triglyceride AUC_T) and the triglyceride incremental area under the curve (triglyceride AUC_I). The triglyceride AUC_T is calculated using the trapezoidal rule [96] and determines the total area under the six to eight hour curve resulting from the rise in triglycerides following a meal. Alternatively, the triglyceride AUC_I uses the trapezoidal rule, but subtracts baseline triglyceride concentrations from triglyceride concentrations obtained over the course of the

postprandial period (In other words, the AUC is relative to baseline triglyceride concentrations). Since the initial fasting triglyceride concentrations influences the postprandial response to a meal, this method allows comparison between individuals with differences in fasting triglyceride concentrations and within an individual on different occasions, after different meals, and before and after exercise or pharmacological interventions.

The meals used to determine postprandial lipemia range from high-fat meals to meals containing a mixture of macronutrients. The majority of investigations have prepared high-fat meals containing whipping cream and ice cream or whipping cream and a variety of cereals and nuts to obtain the high-fat content.[43, 44, 97, 98] Other investigations have employed a more balanced mixture of macronutrients that may be found in a typical Western diet.[99] Since the triglyceride content of a meal appears to influence the magnitude of postprandial lipemia [100], differences in the triglyceride content of meals make it difficult to compare the postprandial response in investigations conducted to date. Although the assessment of postprandial lipemia remains experimental, postprandial lipemia may be used in the future, similar to oral glucose tolerance testing, to identify individuals at risk for chronic disease such as diabetes and CVD. Therefore, it may become necessary to standardize the content of meals to provide normative data for postprandial triglyceride responses in a variety of populations.

Lipid and Lipoprotein Transport and Metabolism

Forward Lipid Transport

Forward lipid transport refers to the transport of dietary and endogenously-produced lipids in the blood.[101] Following a meal, triglycerides enter the small

intestine which in turn stimulates the secretion of lipase and bile acids from the pancreas and gallbladder. Bile acids emulsify the large triglyceride droplets and increase the efficiency of triglyceride hydrolysis by pancreatic lipase. Fatty acids, bile acids and phospholipids then combine to form amphipathic structures known as micelles which permit the uptake of fatty acids at the unstirred water layer of the intestinal duodenum. Finally, triglycerides produced by the reesterification of fatty acids and cholesterol esters combine with apolipoprotein B-48 and apolipoprotein A-1 to form triglyceride-rich chylomicrons.[72] Chylomicrons are then secreted into the mesenteric lymph and ultimately enter the vascular circulation. Apolipoprotein A-1 is then transferred spontaneously to HDL particles as the chylomicron enters the circulation and occurs independently of triglyceride hydrolysis.[102] Simultaneously, apolipoprotein E and C-2 associated with the HDL particle are transferred to the surface of chylomicrons. The transfer of apolipoprotein C-2 from HDL is critical since this apolipoprotein is required for the activation of lipoprotein lipase (LPL) [103, 104] while apolipoprotein E is required for receptor-mediated uptake and degradation of chylomicron remnants.

Lipoprotein lipase is a serine hydrolase found predominantly on the vascular endothelium of adipose tissue and skeletal muscle capillaries and is bound by a heparin-like glycosaminoglycan.[31] In the postprandial state, LPL activity is increased in adipose tissue while LPL activity in skeletal muscle tissue is essentially unchanged.[103] Adipose tissue LPL activity increases with increases in insulin that occur in the postprandial state. An elevated LPL activity in adipocytes increases triglyceride hydrolysis and adipose tissue uptake and storage of NEFAs following a meal. As insulin

levels subside in the postabsorptive state, skeletal muscle LPL activity may increase to allow for the uptake of NEFAs.[31]

VLDL secreted by the liver are also involved in the forward transport of lipids, particularly during the postabsorptive state. VLDL is secreted from the liver with its primary apolipoprotein, apolipoprotein B-100. The hydrolysis of triglycerides associated with VLDL particles results in the formation of smaller, more dense, intermediate and low-density lipoproteins. The increasing density of this molecule reflects the loss of triglyceride and phospholipids. The resulting LDL particle consists primarily of cholesterol and is the primary carrier of cholesterol to peripheral tissues and the liver.

Reverse Cholesterol Transport

The accumulation of cholesterol in peripheral tissues is regulated in part by the entero-hepatic production of HDL. By virtue of their molecular structure, HDL particles provide for the removal of cholesterol from peripheral tissues. HDL are produced as components of chylomicrons, nascent VLDL and from intestinal and hepatic origin. Some HDL may also be secreted as lipid poor HDL. Apolipoprotein A-1 binding sites on HDL particles bind free cholesterol and phospholipids on its surface. Lecithin cholesterol acyl transferase then catalyzes the transfer of fatty acids primarily from phosphatidylcholine in the HDL molecule which esterifies and internalizes the cholesterol. Cholesterol esters and triglycerides may then be transferred between HDL and VLDL and LDL particles by cholesterol ester transfer protein.[102]

Niacin: Mechanisms of Action

The effects of niacin on lipid and lipoprotein metabolism are currently unclear.[46] However, at least four mechanisms have been proposed which may include

1) indirect inhibition of hormone sensitive lipase in adipose tissue 2) activation of adipose tissue LPL 3) inhibition of the synthesis and secretion of VLDL by the liver and 4) the selective uptake of cholesterol esters from HDL by the hepatic scavenger receptor-B1.

Intracellular adipose tissue triglyceride hydrolysis is thought to be inhibited by niacin via the c-AMP pathway.[54, 55] Niacin has been shown to inhibit adenylate cyclase activity which ultimately leads to a reduction in adipose tissue lipolysis by hormone sensitive lipase and a subsequent decrease in the mobilization of fatty acids from adipose tissue. Fatty acids mobilized from adipose tissue are a significant substrate for the production of triglycerides in the liver. Although *de novo* synthesis of fatty acids occurs in the liver, a reduction in adipose tissue-derived fatty acids mediated by niacin is thought to reduce the substrate available for the synthesis of triglycerides and subsequent assembly of VLDL in the liver.

Increases in adipose tissue LPL activity have also been reported following the administration of niacin [60] while others report no changes.[105] Although the results are equivocal, it is possible that niacin functions similarly to insulin in adipose tissue to raise LPL activity and inhibit lipolysis.

The hepatic processing of apolipoprotein B-100 is a central component in the regulation of VLDL secretion.[58] The major regulatory processes in intracellular apolipoprotein B-100 processing and VLDL secretion include: localization of newly synthesized apolipoprotein B-100 as it translocates across the endoplasmic reticular membrane, post-translational apolipoprotein B degradation, and the synthesis and addition of core lipids to the nascent VLDL particle.[106, 107] Evidence to date suggests

that much of the apolipoprotein B-100 synthesized *de novo* is not secreted but is instead post-translationally degraded in the liver. Apolipoprotein B-100 is synthesized on the rough endoplasmic reticulum and is translocated from the endoplasmic reticular membrane to the lumen. It has been proposed that the amount of time the apolipoprotein remains associated with the reticular membrane determines the magnitude of degradation. For example, a prolonged association with the membrane targets apolipoprotein B-100 for degradation while the rapid translocation of apolipoprotein B-100 across the reticular membrane facilitates apolipoprotein B-100 secretion as VLDL. This process is mediated by protease degradation, the synthesis and availability of lipids, and the transfer of lipids by microsomal triglyceride transfer protein.[58] Therefore, an increase in the synthesis or availability of fatty acids would reduce the rate of apolipoprotein B-100 degradation as a result of rapidly providing the required triglyceride to the apolipoprotein core. It might also be expected that a reduction in triglyceride availability would increase the time required for lumenal translocation, thereby increasing the possibility of protease mediated destruction. Dixon et al. [108] found that oleic acid increased the synthesis of triglyceride and reduced the degradation of apolipoprotein B-100 resulting in an increase in VLDL secretion. Further confirmation that apolipoprotein B-100 secretion as VLDL relies on the association of triglyceride was revealed by inhibiting fatty acid and triglyceride synthesis in hepatocytes.[109]

Niacin has been shown to decrease the synthesis of hepatic triglycerides and increase the degradation of apolipoprotein B-100.[110, 111] Grundy and colleagues [110] observed a 21% reduction in the synthetic rate of VLDL in hyperlipidemic males following five weeks of niacin. Furthermore, niacin increased the intracellular

degradation of and subsequent secretion of apolipoprotein B-100 in human HepG2 cell lines but did not affect the expression of apolipoprotein B-100 or microsomal triglyceride transfer protein.[111] Niacin also inhibited fatty acid synthesis and the enzyme diacylglycerol acyl transferase.

The primary mechanism by which niacin lowers serum triglycerides appears to be due to reductions in adipose tissue-derived fatty acids as substrate for the subsequent synthesis of hepatic triglycerides.[78] Furthermore, it has been proposed that the observed reduction in the activity of the rate-limiting enzyme for hepatic triglyceride synthesis, diacylglycerol acyl transferase, may qualify niacin as a class of diacylglycerol acyl transferase inhibitors.[77]

Niacin is currently the most potent agent for increasing HDL-C levels.[46] The mechanisms responsible for these changes appear to be related to a decrease in the rate of HDL and apolipoprotein A-1 catabolism in the liver [62, 112] with no effect on hepatic apolipoprotein A-1 synthesis. [113, 114] In agreement with these observations, an increase in apolipoprotein A-1 levels were noted after the administration of niacin.[115] Jin and colleagues [114] found that niacin selectively inhibited the uptake of apolipoprotein A-1 but not HDL-cholesterol esters suggesting that niacin inhibits the removal of HDL-apolipoprotein A-1 at the level of a putative HDL catabolism receptor or pathway, but not the selective uptake of cholesterol ester by the SR-B1 receptor.[61]

Aerobic Exercise: Mechanisms of Action

The mechanisms responsible for reductions in postprandial lipemia following aerobic exercise are not completely understood. However, aerobic exercise performed one to 16 hours prior to the ingestion of a high-fat meal has been shown to lower

postprandial lipemia by 18 to 51%.[45, 116] The most likely explanation for these reductions is an increase in skeletal muscle and/or adipose tissue LPL activity. Previous investigations suggest that LPL activity is increased four to 24 hours following acute aerobic exercise in skeletal muscle.[117, 118]

Although LPL is the most likely candidate to explain the reductions in postprandial lipemia following exercise, direct assessment of triglyceride clearance and measurements of post-heparin and skeletal muscle LPL activity have not corroborated an increase in LPL activity suggesting that other factors may be associated with the reduction in postprandial lipemia. Therefore, it is possible that other factors, including reductions in VLDL-triglyceride secretion and reductions in the absorption of triglycerides from the gut may also lower triglyceride concentrations observed in the postprandial state following aerobic exercise.

Triglyceride Clearance

Increases in skeletal muscle LPL activity [119] and post-heparin LPL activity have been observed following acute [17, 18, 34] and chronic exercise [120, 121] in both sedentary and physically active populations. Studies which have examined the mechanisms responsible for these changes suggest that local changes in metabolism following skeletal muscle contraction are the most important physiological stimulus for LPL regulation.[122] Indeed, hindlimb-unloaded rats had lower triglyceride uptake and reduced LPL activity which was reversed following four hours of hindlimb reloading and slow walking on a treadmill.[123] LaDu and colleagues [124] found that red and white vastus skeletal muscle showed 30% increases in total LPL activity immediately post-exercise, falling to less than 20% of baseline by 24 hours. Furthermore, LPL mRNA

was 65 to 100% higher immediately following exercise but was not different from baseline 24 hours later. In addition, Seip et al [119] found that LPL mRNA increased immediately following exercise, peaked at four hours, began to fall by eight hours and returned to baseline levels 20 hours after exercise. Conversely, Bey and Hamilton [122] found that LPL mRNA concentration remained unchanged after acute and prolonged intermittent treadmill activity suggesting that post-translational processes are responsible for the upregulation of LPL activity following exercise.

The mechanisms responsible for the upregulation of skeletal muscle LPL following aerobic exercise are poorly understood. A number of factors including insulin, catecholemines and skeletal muscle contraction have been proposed to increase skeletal muscle LPL activity following aerobic exercise.[31] Reductions in insulin have been reported following a single session of exercise [38, 125] and appear to be associated with reductions in postprandial lipemia.[126] Therefore, reductions in insulin levels following aerobic exercise may permit skeletal muscle lipoprotein lipase activation during the postprandial period which is normally suppressed by insulin.

Since the upregulation of LPL activity in locally contracting muscle appears to be a metabolic event, it is possible that reductions in the adenosine triphosphate (ATP): adenosine monophosphate (AMP) ratio following exercise may upregulate AMP-activated protein kinase (AMPK) activity.[119] An increase in AMPK activity has been previously shown to upregulate luminal LPL activity in cardiomyocytes without upregulating LPL mRNA. Therefore, it is possible that AMPK serves as a post-translational mediator of LPL activity.[127] While the mechanisms for the regulation of

LPL by AMPK remain unclear, it is possible that AMPK increases the vesicular trafficking of pre-formed LPL from the cell to the capillary lumen.

VLDL-triglyceride Secretion

Intrahepatic stores of fatty acids derived from excess macronutrient intake and from adipose tissue hydrolysis increase the production of triglyceride and subsequent secretion of VLDL-triglyceride by the liver. Following a meal, insulin inhibits the secretion of VLDL-triglyceride from the liver. Therefore, individuals with normal hepatic insulin sensitivity would be expected to have a minimal increase in VLDL-triglyceride secretion following a meal. Conversely, hepatic insulin resistance associated with obesity would increase the secretion of VLDL-triglyceride in the postprandial period. [128-130] A simultaneous efflux of VLDL-triglyceride and postprandial elevations in chylomicrons would be expected to increase the magnitude and duration of postprandial lipemia.[131] Therefore, interventions which decrease fatty acid transport to the liver and/or decrease hepatic triglyceride secretion would be expected to lower both fasting and postprandial plasma triglyceride levels.

Empirical evidence to support the hypothesized regulation of VLDL-triglyceride secretion by exercise is limited. Indirect evidence in both animal and human models suggests that prior exercise may reduce postprandial VLDL-triglyceride secretion.[132, 133] Mondon and colleagues [132] were interested in the relationship between serum triglycerides and VLDL-triglyceride secretion. The investigators found that exercise training lowered the secretion of pre-labeled VLDL-triglyceride in rats following 70 to 85 days of self-selected running. The proposed mechanisms for the reduction in VLDL-triglyceride secretion was an observed reduction in serum insulin concentrations

indicating an increase in hepatic insulin sensitivity and a reduction in free fatty acid substrate availability for VLDL synthesis.

Four weeks of voluntary running reduced hepatic triglyceride secretion in rats.[133] The reduction in triglyceride secretion was accompanied by an increase in hepatic ketone body production suggesting that exercise may increase fatty acid oxidation and reduce the re-esterification of free fatty acids in the liver. Similarly, prior exercise increased postprandial serum ketones and reduced insulin and free fatty acid levels providing further support in humans that exercise may increase free fatty acid oxidation in the liver thereby reducing VLDL-triglyceride secretion and ultimately plasma triglyceride concentrations.[134]

Intestinal Absorption

A reduced rate of chylomicron appearance into the circulation has been suggested as a possible mechanism by which prior exercise lowers postprandial lipemia.[135] However, the majority of evidence suggests that exercise has little effect on intestinal absorption. The gastric emptying of intestinal triglycerides was not delayed following aerobic exercise in both human and animal models.[45, 74] Furthermore, exercise performed immediately following a high-fat meal did not impair fat absorption from the intestine.[136] Therefore, it seems unlikely that aerobic exercise would reduce the triglyceride rate of appearance from the intestine.

Effects of Nicotinic Acid on CVD Risk

Prospective studies provide convincing evidence that niacin reduces CVD risk. The Coronary Drug Project [137, 138] was a nationwide, double-blind, placebo-controlled study designed to evaluate the long-term effects of niacin and other lipid-

lowering agents on the primary endpoint of all-cause mortality in men with previous myocardial infarction. Three grams of niacin per day reduced total cholesterol by 10% and triglyceride by 26% during the six-year follow-up period. These changes were associated with reductions in non-fatal MI and cerebrovascular accidents by 26% and 24% compared to those treated with placebo.

The Familial Atherosclerosis Treatment Study [139] compared the independent and combined effects of niacin and colestipol and dietary therapy versus dietary counseling in patients with CVD. Niacin and colestipol increased HDL-C by 43% and decreased LDL-C compared to the diet only group. The combination of niacin and colestipol produced a significant reduction in at least one out of nine proximal atherosclerotic lesions compared to individuals receiving conventional dietary treatment. A 73% reduction in mortality, MI, and revascularization rates were observed following the 2.5 year treatment.

Similarly, males with previous coronary bypass surgery and hypercholesterolemia were treated with a colestipol and niacin regimen to determine if raising HDL-C and lowering LDL-C would reverse the progression of atherosclerotic lesions.[140] Angiography performed on each participant prior to and after receiving the treatment regimen revealed that 61% of the treatment group had reductions or no change in lesion progression during the two year follow-up period.

Finally, the Stockholm Ischemic Heart Disease Secondary Prevention Study compared all-cause mortality in survivors of myocardial infarction using niacin and clofibrate.[141] Total mortality was decreased by 26% with the greatest benefit

occurring in patients with baseline triglyceride concentrations greater than 135 $mg \cdot dL^{-1}$ regardless of baseline concentrations of LDL-C.

Time-Course and Dose Response

Investigations conducted to date which have examined the impact of niacin on blood lipids range in duration from one day to as long as 96 weeks at dosages that range from 100 to 3000 $mg \cdot dL^{-1}$. Carlson and colleagues [142] found that a single dose of niacin (1000 mg) provided to hyperlipidemic patients lowered plasma triglyceride concentrations by eight percent, four to six hours following its administration. Similar reductions in total cholesterol concentrations were reported 24 hours following the administration of a single dose of niacin (1000 mg) in healthy participants and in patients with CVD.[47]

Despite the effects of a single dose of niacin on triglyceride and total cholesterol concentrations, there have been no other investigations conducted to date which have examined the effects of a single dose or lower doses of niacin on other components of the blood lipid profile including LDL-C and HDL-C.

The time-course of blood lipid changes appears to be influenced by the dosage of niacin used. For example, niacin was titrated by 500 mg every four weeks to a maximum dose of 3000 $mg \cdot day^{-1}$ to determine the effects of niacin on blood lipid characteristics.[52] Despite the findings that total cholesterol, LDL-C and triglycerides were reduced and HDL-C elevated in a dose-dependent fashion from 500 to 2500 $mg \cdot day^{-1}$, this study was limited in that it did not determine the effects of each dosage for longer than four weeks.

The Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial overcame some of these limitations by examining the effects of two dosages of niacin over 16 weeks.[57] Hyperlipidemic, overweight, type 2 diabetics with triglycerides greater than 200 $mg \cdot dL^{-1}$ and HDL-C less than 40 $mg \cdot dL^{-1}$ were used to evaluate the effects of extended-release niacin on blood lipids. Participants were randomized to placebo or extended-release niacin at 1000 $mg \cdot day^{-1}$ or 1500 $mg \cdot day^{-1}$. Changes in blood lipids were significantly greater with the administration of 1500 $mg \cdot day^{-1}$ compared to 1000 $mg \cdot day^{-1}$ after four weeks of administration. The effects of niacin on triglyceride and HDL-C concentrations were similar at four weeks for both dosages. However, the maximal efficacy of niacin on triglyceride and HDL-C concentrations was reached between four and eight weeks and remained different between the two dosages for up to 16 weeks. Therefore, higher doses (1500 $mg \cdot day^{-1}$) of niacin appear to affect blood lipids to a greater extent beyond four weeks while lower dosages (1000 $mg \cdot day^{-1}$) of niacin appear to plateau within four weeks. Finally, triglyceride and HDL-C levels plateaued beyond eight weeks at both dosages. Similarly, Knopp and colleagues [51] found that there were no changes in blood lipids beyond 8 weeks in an overweight middle-aged population with and without CVD at a dosage of 1500 $mg \cdot day^{-1}$ over 16 weeks.

Morgan and colleagues [143] examined the effects of extended-release niacin at doses of 1000 $mg \cdot day^{-1}$ and 2000 $mg \cdot day^{-1}$ compared to placebo in individuals at high risk for or with known CVD. As expected, the 12-week treatment with niacin (2000 $mg \cdot day^{-1}$) reduced triglycerides and increased HDL-C more than the group receiving

1000 mg·day^{-1}. In a continuation of the same trial, blood lipids were measured at 48 and 96 weeks to determine the long-term safety and efficacy of niacin.[144] HDL-C and triglyceride concentrations were similar at 12 weeks compared to 48 and 96 weeks, while significantly greater reductions were observed in total cholesterol and LDL-C beyond 12 weeks. These results suggest that all components of the blood lipid profile are affected by niacin relatively rapidly but that the effects of niacin on total cholesterol and LDL-C may take a longer period of time compared to triglyceride and HDL-C concentrations.

Effects of Niacin on Postprandial Lipemia

Despite evidence that niacin lowers fasting blood lipids and decreases the risk of CVD, there have been only two published reports which have examined the effects of niacin on postprandial metabolism. King and colleagues [48] evaluated the effects of 12 weeks of immediate-release niacin on the postprandial triglyceride response to a high-fat meal. The dosage of niacin used ranged from 1500 to 3000 mg·day^{-1} depending on the tolerance of the participant. Each participant was overweight and had isolated low HDL-C (< 35 mg·dL^{-1}) as their primary blood lipid abnormality. The triglyceride AUC_T and triglyceride AUC_I responses to the fatty meal fell by 41% and 45%, respectively. The triglyceride AUC_T and AUC_I were both correlated with fasting triglyceride concentrations.

Individuals with low HDL-C (< 40 mg·dL^{-1}) and high triglyceride (> 150 mg·dL^{-1}) concentrations were administered immediate-release niacin for 18 weeks (3000 mg·day^{-1}).[63] Individuals treated with pravastatin had no reductions in postprandial lipemia while the administration of niacin in combination with pravastatin lowered the triglyceride AUC_T by 32%.

There are currently no published reports on the effects of different forms of niacin on postprandial blood lipids. While the high dosages of niacin (3000 mg·day^{-1}) used in previous studies clearly demonstrate that niacin lowers postprandial lipids, there are also no reports on the effects of more commonly used dosages (1000 to 2000 mg·day^{-1}) on postprandial triglycerides.

Forms of Niacin

Niacin may be obtained over the counter or by prescription. Over the counter versions of niacin are sold as immediate-release or sustained-release. Immediate-release niacin formulations generally reach peak absorption within one hour of ingestion and have a metabolic half-life of approximately one hour.[46] They are marketed as "immediate-release", "crystalline" or "plain" niacin. To date, only one immediate-release niacin product has been approved by the FDA for lipid-altering therapy (Niacor, Upsher-Smith, Minneapolis, MN).

Sustained release formulations are produced by a variety of absorption-delaying techniques that increase dissolution times to more than 12 hours. Sustained-release niacin is marketed as "controlled-release," "no flush" or time-release". Immediate-release and sustained-release formulations of niacin are similar in cost and range from $1.48 to $14.99 per month at a dosage of 2000 mg·day^{-1}. No-flush preparations are slightly more expensive and range from $13.64 to $31.20 per month at a dosage of 2000 mg·day^{-1}.

The only long-acting niacin formulation approved by the FDA for the treatment of dyslipidemia is the prescription only extended-release form of niacin known as Niaspan produced by Kos Pharmaceuticals. Niaspan is absorbed over eight to 12 hours which

makes it suitable for once-a-day bedtime dosing. In contrast, immediate-release and sustained-release formulations are generally taken multiple times per day with meals. The release characteristics of each of the niacin formulations are important because they determine how niacin is metabolized which in turn influences the adverse reactions associated with its use. The average cost for Niaspan is $60 per month at a dosage of 1500 $mg \cdot day^{-1}$.

Metabolism and Adverse Reactions

Niacin is easily absorbed in the gastrointestinal tract with peak blood levels (one to three μg/mL) observed within four to five hours following administration.[54] Niacin is metabolized by two different pathways in the liver that generally determine the primary types of adverse reactions experienced: 1) the conjugation or nicotinuric acid pathway and 2) the nicotinamide pathway. The conjugation pathway results in the formation of nicotinuric acid produced by the conjugation of niacin and glycine. Nicotinuric acid is a potent mediator of prostaglandin secretion. Prostaglandins are potent vasodilators which increase peripheral blood flow. The nicotinamide pathway involves a series of oxidation-reduction reactions that ultimately results in the production of nicotinamide and pyramidine metabolites which in high concentration may induce hepatotoxicity. The nicotinamide pathway is a high-affinity, low-capacity pathway.[46, 145] Therefore, immediate-release formulations of niacin rapidly saturate the nicotinamide pathway and are predominantly metabolized through the high-capacity nicotinuric pathway. The production of excess prostaglandins then increases vasodilation which is thought to be responsible for cutaneous flushing.

In contrast, longer-acting niacin preparations are absorbed more slowly which allow them to be metabolized in the nicotinamide pathway resulting in less severe flushing. Although sustained release formulations produce fewer episodes of flushing, the consequence of slower absorption is an increased risk of hepatotoxicity reflected by typical increases in the liver enzymes alanine transferase (ALT) and aspartate transferase (AST) concentrations.[46] Extended-release niacin has an intermediate absorption rate which allows it to be more evenly metabolized between the nicotinuric acid and nicotinamide pathways resulting in less severe adverse reactions compared to immediate or sustained-release formulations.[46]

The adverse reactions associated with the use of extended-release niacin are equivalent to those produced by other forms of niacin, however, the frequency and severity of cases tend to be far reduced.[53, 65] Extended-release niacin, like other forms of niacin, is associated with cutaneous flushing (defined as redness, warmth, tingling or itching), nausea, loss of appetite, increases in glucose and uric acid levels, and increases in hepatic enzymes such as AST and ALT. Visible skin flushing generally lasts only one to two minutes but may be experienced for greater than 30 minutes.[54]

Extended-Release Niacin Administration

Extended-release niacin is obtained by prescription only. Extended-release niacin is available in 500 mg and 1000 mg tablets. It is typically titrated as follows: 500 $mg \cdot day^{-1}$ for one to four weeks followed by an increase to 1000 $mg \cdot day^{-1}$ for one to four weeks. Titrations up to 2000 $mg \cdot day^{-1}$ can be carried out thereafter. The benefits of extended-release niacin increase up to a dosage of 2000 $mg \cdot day^{-1}$ and then level off.[65]

To combat the adverse reactions associated with niacin, several strategies have been implemented such as taking extended-release niacin once-daily after a meal or snack prior to bedtime, consuming oatmeal to reduce the absorption rate of niacin, avoiding hot fluids and taking a 325 mg aspirin 30 to 60 minutes prior to taking the niacin to reduce prostaglandin synthesis. In a study that compared extended-release niacin versus plain niacin, extended-release niacin taken at bedtime affected flushing in only a few patients but was not sufficient to discontinue the medication.[51] Therefore, extended-release niacin is currently the safest form of niacin available and has similar effects on blood lipids to immediate-release and sustained-release formulations of niacin.

Aerobic Exercise and Fasting Blood Lipids

Cross-sectional investigations provide evidence that individuals who accumulate a greater volume of exercise have a more favorable blood lipid profile compared to individuals who accumulate less exercise.[146] The most consistent blood lipid differences observed in individuals of contrasting physical activity and fitness are triglyceride and HDL-C concentrations. Triglycerides are 19-50% lower and HDL-C 19-50% higher when comparing individuals of contrasting physical activity and fitness status.[147].

Total cholesterol and LDL-C are generally lower in physically active individuals compared to their sedentary counterparts.[148-150] However, many of the investigations which have examined differences in total cholesterol and LDL-C among individuals of contrasting physical activity status fail to control for several confounding variables which may reduce the differences between these groups. For example, Hagan and colleagues [146] found that runners and weight-matched controls had similar total cholesterol and

LDL-C concentrations despite significant differences in triglyceride and HDL-C concentrations. Therefore, higher levels of physical activity appear to be independently associated with differences in triglyceride and HDL-C concentrations and to a lesser extent total cholesterol and LDL-C.

Exercise training interventions suggest that plasma lipid changes occur most frequently following eight to 14 weeks of aerobic exercise at an energy expenditure greater than 1200 kcals·week^{-1}.[147] Triglycerides and HDL-C are the most consistently observed components of the lipid profile changed following exercise training interventions. Reductions in triglyceride concentrations of seven to 33% and elevations in HDL-C of 10 to 18% have been reported.[120, 151-154] Conversely, exercise training infrequently results in reductions in total cholesterol and LDL-C unless changes in diet and/or body weight or composition accompany exercise training. Indeed, total cholesterol and LDL-C was reduced in sedentary males with the addition of an American Heart Association Phase I diet to an aerobic exercise program [155] while exercise induced weight-loss lowered total cholesterol and LDL-C by four and 10%, respectively.[152]

While the cumulative effects of aerobic exercise training are associated with characteristic changes in triglyceride and HDL-C metabolism, at least part of the benefits of aerobic exercise are the results of the most recent bout of exercise performed. In fact, Holloszy and colleagues [13] provided direct evidence that reductions in serum triglycerides are an acute effect that appear shortly after exercise and persist for several hours. Since then, a number of investigations have provided further support that the metabolic effects of a single aerobic exercise session produce quantitatively similar

changes in triglyceride and HDL-C concentrations to cumulative exercise that may last for up to 72 hours.

The majority of studies conducted to date have examined the acute effects of long-duration and high-intensity exercise such as marathon running on blood lipids in healthy and physically active individuals. In contrast, fewer investigations have been conducted that employ sedentary individuals with isolated or combined impairments in blood lipid concentrations or those performing moderate-intensity and duration exercise.

Crouse and colleagues [27] were one of the first groups to simultaneously examine the acute effects of moderate and high-intensity aerobic exercise on blood lipid and apolipoprotein concentrations in sedentary hypercholesterolemic males. The purpose of this investigation was to determine the effects of different exercise intensities (50 and 85% of $\dot{V}O_{2max}$) at similar caloric expenditure (350 kcal). Triglyceride concentrations were reduced by 18% at 24-hours post-exercise and remained below baseline up to 48 hours. Interestingly, HDL-C and HDL_3-C were increased by approximately 9% while HDL_2-C increased 27% but did not meet criteria for significance. Results from this study support the contention that the volume of exercise, quantified by caloric expenditure, may be more important than the intensity of exercise for mediating changes in blood lipids. These results provided evidence that a lower threshold may exist for lowering blood lipid concentrations in individuals who are initially sedentary and/or with elevated initial total cholesterol concentrations compared to individuals of higher fitness.

In a follow-up publication, Crouse et al. [156] were interested in differentiating the transient effects of exercise and the extent to which the transient changes in blood lipids are affected by exercise training in sedentary, hypercholesterolemic males.

Therefore, participants were asked to exercise three days per week at 350 kcals·day^{-1} at 50% or 85% of measured $\dot{V}O_{2max}$ for 24 weeks. Blood samples were obtained 60 to 72 hours following exercise at eight, 16 and 24 weeks. Triglyceride, LDL-C, and HDL-C were not changed in either group while HDL_2-C increased 79% when the high and moderate-intensity groups were combined. These findings provide further evidence that exercise intensity has little influence as compared to exercise caloric expenditure (exercise volume) on blood lipid concentrations suggesting that higher intensity exercise may not be necessary to change blood lipids in sedentary hypercholesterolemic individuals. In addition, the absence of observed changes in blood lipids following a 24-week aerobic exercise program provide further support that at least part of the effects of exercise training may only be as good as the last bout of exercise performed.

Grandjean and colleagues [17] compared the blood lipid and lipoprotein enzyme activities following exercise in sedentary normo- and hypercholesterolemic males to determine if baseline total cholesterol concentrations influence the blood lipid response to exercise. Twenty-eight males with cholesterol concentrations less than 200 mg·dL^{-1} and those with total cholesterol concentrations greater than 240 mg·dL^{-1} were asked to expend 500 kcals at an intensity of 70% $\dot{V}O_{2max}$. Triglyceride concentrations were reduced by approximately 10% in both groups while HDL-C was increased due to an increase of HDL_3-C. A delayed increase in post-heparin LPL activity was observed up to 48 hours following the exercise session while no changes were observed in hepatic triglyceride lipase activity, cholesterol ester transfer protein activity or lecithin cholesterol ester transferase activity providing further support for the contention that reductions in triglyceride concentrations following exercise are due to increases in LPL activity.

The results of acute exercise investigations suggest that total cholesterol and triglyceride status are unlikely to influence the response to an acute bout of exercise. Instead, it is thought that the amount of exercise performed (quantified as energy expenditure) may have the most important influence on blood lipid responses regardless of cholesterol or triglyceride status.

Effects of a Single Bout of Aerobic Exercise on Postprandial Lipemia

There is clear evidence from cross-sectional investigations comparing endurance-trained and untrained men that regular exercise is associated with low concentrations of postprandial lipemia.[157-160] However, it is difficult to interpret these findings because participants were not asked to refrain from exercise 12 to 36 hours prior to the high-fat meal. Studies which have specifically examined the chronic versus acute effects of aerobic exercise on postprandial lipemia suggest that lower postprandial triglycerides associated with regular exercise are instead due to the most recent bout of exercise performed. Indeed, no differences in postprandial lipemia were observed when the most recent bout of exercise occurred more than 60 hours before a high-fat meal in endurance-trained and untrained individuals.[161, 162]

Longitudinal investigations also provide evidence that the effects of exercise training on postprandial lipemia may be due to acute metabolic changes associated with the most recent bout of exercise performed. Post-training assessments of fat tolerance were made within 36 hours following the last exercise session in several studies [121, 163] while those comparing the training response more than 48 hours following a meal observed no effects on postprandial lipemia.[164, 165]

Further evidence that exercise training *per se* may not influence postprandial triglyceride concentrations in the absence of recent exercise comes from detraining studies. Endurance-trained individuals who stopped training for more than 60 hours had triglyceride levels in the postprandial state that were 35% higher than levels compared 15 hours following the last exercise training session.[166] Herd and colleagues [167] found that 13 weeks of training followed by nine days of detraining increased postprandial lipemia by 37% within 60 hours following detraining and 46% by nine days of detraining. Therefore, the beneficial effects of exercise training are rapidly reversed in the absence of recent exercise suggesting that aerobic exercise sessions performed in the hours prior to a high-fat meal are responsible for the reductions in postprandial lipemia and are consistent with transient changes in fasting blood lipids observed after a single session of exercise.

Similar to fasting blood lipid concentrations, the acute effects of exercise on postprandial lipemia appear to be determined by the volume as opposed to intensity of exercise performed.[168] However, a greater part of the literature has focused on the effects of exercise in relatively fit and lean normolipidemic males performing 60 minutes or more of high-intensity exercise.[95] Since it appears that a lower energy expenditure is required to reduce fasting triglyceride concentrations in sedentary obese individuals as compared to fit individuals, it is probable that lower amounts of exercise are required to lower postprandial lipemia when compared to physically active and lean individuals.

Influence of Obesity on Postprandial Lipemia

Sedentary individuals with abdominal obesity are five times more likely to have elevations in fasting and postprandial triglyceride concentrations.[169] Indeed, Mamo

and colleagues [169] examined the effects of a postprandial fat challenge in obese sedentary males (BMI 35.8, Waist:Hip ratio 1.02) with average triglyceride concentrations of 150 $mg \cdot dL^{-1}$ compared to 80 $mg \cdot dL^{-1}$ in a lean control group. Following the high-fat meal, obese individuals had a 68% higher triglyceride AUC_T. The investigators found that the apolipoprotein B-48 AUC was significantly greater in obese individuals compared to controls. In addition, LDL particle binding to mononuclear LDL receptors was 50% lower compared to lean controls. The LDL receptor is considered to be a primary route of remnant clearance; therefore any compromise will lead to remnant accumulation in other nonobese dyslipidemic phenotypes. Since insulin stimulates LDL-receptor activity[101], the insulin resistance of obese participants may reduce LDL receptor activity and thereby increase the concentration of remnant particles in circulation.

Mekki and colleagues [92] found that women with abdominal obesity had a higher triglyceride AUC_T compared to women who were lean or those with gynoid obesity. Interestingly, the mean triglyceride response was higher in women with abdominal obesity and fasting hypertriglyceridimia compared to abdominally obese individuals with normotriglyceridemia. The results of this investigation provide evidence that abdominal obesity independently increases postprandial lipemia but may be exacerbated by fasting hypertriglyceridemia. Furthermore, intestinally-derived triglyceride-rich lipoproteins accumulated more markedly in the serum of both groups with abdominal obesity. In contrast, postprandial triglyceride-rich lipoprotein accumulation was not different between gynoid obese and normal-weight controls.

Lewis and colleagues,[170] found that obese individuals with normal triglyceride levels had a higher total lipemic response to a high-fat meal compared to normal weight and normotriglyceridemic controls. Furthermore, abdominally obese males had higher levels of postprandial lipemia than men without abdominal obesity.[8]

Despite evidence that obese individuals with or without elevated triglyceride levels have exaggerated postprandial lipemia, Zhang and colleagues [71] are the only investigators which have examined the effects of prior exercise on postprandial lipemia in obese individuals.[71] Participants were exercised at 60% of $\dot{V}O_{2max}$ for one hour and it was found that the triglyceride AUC_T was 37% lower than a non-exercising control group suggesting that individuals who are obese and hypertriglyceridemic respond similarly to normal weight and normolipidemic populations. Additional work will be required to determine the optimal energy expenditure required to lower postprandial lipemia in obese individuals with hypertriglyceridemia.

Influence of Isolated Low HDL-C on Postprandial Lipemia

While fasting hypertriglyceridemia is commonly associated with low HDL-C concentrations and higher postprandial lipemia, isolated low concentrations of fasting HDL-C and normal triglyceride concentrations were not associated with a higher level of postprandial lipemia compared to individuals with higher concentrations of HDL-C.[171] The authors suggest that since apolipoprotein A-1 is required for the synthesis of chylomicrons that it is possible that low apolipoprotein A-1 allows triglycerides to remain low in individuals with low HDL-C.

Patsch and colleagues [172] examined the association between high and low concentrations of HDL_2-C on postprandial lipid metabolism. Twenty-eight young to

middle-aged normolipidemic male and females were asked to consume a meal consisting of approximately 1300 kcals. Individuals with higher HDL_2-C and normolipidemia catabolized chylomicrons at a greater rate than individuals with normal fasting lipids and low HDL_2-C concentrations.

Exercise Timing

The timing of exercise prior to a high-fat meal has been shown to influence the magnitude of postprandial lipemia. For example, Zhang and colleagues [116] examined the effects of exercise timing on postprandial lipemia in young trained males with normolipidemia. The investigators measured triglyceride concentrations for eight hours following a high-fat meal and found that the triglyceride AUC_T was 51% lower when exercise was performed 12 hours prior to the meal while exercise performed one hour prior reduced the triglyceride AUC_T by 38%. However, there were no statistically significant differences between the 12-hour and one-hour pre-meal exercise interventions.

Since exercise has been shown to increase LPL activity for as much as 24 hours [17], Zhang and colleagues [71] were interested in the effects of exercise on postprandial lipemia performed 12 and 24 hours before a high-fat meal. The single session of exercise lowered the triglyceride AUC_T by 37% and 33% compared to the control and 24 hour pre-exercise trials which indicate that the effect of this intervention lasts about 12 hours but is not observed 24 hours later. The absence of an effect at 24 hours also suggests that VLDL-triglyceride secretion may have played a role in these findings since triglyceride clearance should be elevated as a result of increased LPL activity by 24 hours post-exercise.

To date there have been no studies which have examined the effects of a single session of aerobic exercise on postprandial lipemia in a group of abdominally obese sedentary older males performed one hour before a high-fat meal. This information is important from a practical perspective since the reduction in postprandial lipemia associated with exercise performed one to two hours before a high-fat meal is a tangible recommendation that may increase public awareness about the acute effects of a single session of aerobic exercise.

Summary

Rates of obesity in the United States have increased by more than two-fold over the last 25 years and continue to rise. While obesity is highly associated with CVD, excess abdominal adiposity increases the risk of insulin resistance and is thought to be a primary etiological factor in the development of the metabolic syndrome. It has been estimated that over 25% of U.S. adults meet criteria for the metabolic syndrome as defined by NCEP which includes abdominal obesity, insulin resistance, low HDL-C, elevated triglycerides, and hypertension.

Treatment of individual risk factors including blood lipids is an integral component of CVD risk reduction strategies. NCEP recommends physical activity and weight-loss as initial strategies to reduce lipid and non-lipid risk factors. The metabolic effects of a single session of aerobic exercise appear to improve triglyceride and HDL-C levels similarly to exercise training suggesting that even individual exercise sessions may improve blood lipid characteristics in obese individuals with hypertriglyceridemia. The mechanisms responsible for these changes appear to be associated with an improved

clearance of plasma triglycerides as a result of increases in LPL activity and possibly by reductions in VLDL-triglyceride secretion.

Niacin is one of the most effective pharmacological agents for the reduction of triglycerides and increases in HDL-C. The mechanisms responsible for these changes appear to be influenced by reductions in adipose tissue lipolysis and VLDL-triglyceride secretion and inhibition of the HDL catabolic receptor.

While both niacin and exercise produce significant changes in fasting and postprandial triglyceride concentrations, there have been no investigations to date which have examined the effects of combining each intervention on fasting or postprandial blood lipids. Since niacin is thought to reduce VLDL-triglyceride secretion and may increase adipose tissue LPL activity while exercise is thought to increase triglyceride clearance by increasing skeletal muscle LPL activity and secondarily by reducing VLDL-triglyceride secretion, it is possible that short-term niacin and acute exercise may provide additive or synergistic effects on both fasting and postprandial triglyceride concentrations. Reductions in VLDL-triglyceride secretion associated with niacin would be expected to reduce VLDL-triglyceride secretion following a high-fat meal.

CHAPTER III.

METHODS

Overview

Fifteen participants performed each of four conditions to determine the combined effects of a single session of moderate-intensity aerobic exercise and six weeks of niacin on fasting and postprandial triglycerides. Each participant was pre-screened for the study by Exercise Technology Laboratory personnel and an attending physician. Participants were asked to ingest a high-fat meal followed by blood sampling at two-hour intervals for up to eight hours. The next day, participants were asked to return to the lab where they walked on a treadmill at 60 to 70% $\dot{V}O_{2max}$ until approximately 500 kcals were expended. Participants were then provided an identical high-fat meal as the previous day one hour following the exercise session with blood sampling again over eight hours. Next, participants were asked to return 24 and 48 hours later to determine the effects of exercise on fasting blood lipids and insulin sensitivity. Participants then started a six week treatment period with niacin. Following this period, all participants followed the same previously described protocol in order to determine postprandial lipemia and fasting blood lipids.

Participants

Recruitment of Volunteers

Fifteen males were recruited for this study by newspaper advertisements, posted flyers, presentations, departmental mailouts and by word of mouth at Auburn University and in the Auburn-Opelika community (Appendix A). Volunteers who met the following criteria were admitted into the study: 1) males between the ages of 30 and 65 2) previously sedentary – defined as no regular leisure time physical activity or strenuous vocational activity for the last six months as defined by the U.S. Surgeon General [173] 3) obese (body mass index (BMI) > 30 $kg \cdot m^{-2}$, waist girth > 88 cm) 4) triglycerides ≥ 150 $mg \cdot dL^{-1}$ 5) non-smokers. These criteria were used for the selection of participants because epidemiological evidence suggests that individuals who meet these criteria are at an increased risk of CVD due to their age, sedentary lifestyle, abdominal distribution of excess body fat and elevated triglycerides and may benefit from both exercise and niacin interventions.[3] Other exclusion criteria included medications known to influence lipid, lipoprotein, or glucose metabolism, and a history of or active gout, peptic ulcer disease or liver disease.

Preliminary Experimental Procedures

Screening

Volunteers were initially screened by informal face-to-face or telephone interview (Appendix B). Volunteers who met the initial criteria by interview were invited to the Exercise Technology Laboratory for additional preliminary screening. At the preliminary screening, volunteers were fully informed about the nature of the study and asked to complete an institutionally approved informed consent (Appendix C). Volunteers were

then asked to complete a health history and exercise questionnaire (Appendix D and E, respectively). Height, weight, and waist circumference measurements were then obtained to screen for BMI and waist circumference criteria. Next, a venous blood sample was obtained and sent to a CDC certified laboratory (Laboratory Corporation of America, Birmingham, AL) to determine baseline blood lipid and glucose concentrations. Individuals who met these criteria were asked to return for a second visit to the laboratory for further testing.

Physiological Assessment

During the second visit to the laboratory, anthropometric measurements such as height, weight, BMI, waist and hip circumferences and other physiological measures were obtained. Height was measured to the nearest 0.25 inch using a stadiometer while weight was determined using a balance scale to the nearest 0.25 pounds. Body mass index was calculated as body mass (kg) / height (m^2). All waist and hip circumferences were measured to the nearest 0.5 cm. Waist was defined as the narrowest portion of the torso between the umbilicus and the xiphoid process while measurements of the hip were obtained as the maximal thickness of the hips or buttocks. Body composition was determined using Dual Energy X-ray Absorptiometry (DXA) according to the manufacturer's instructions (Lunar Prodigy, General Electric, Fairfield, CT).

Each participant then received a physical examination by a physician. Following the physical exam, participants who were permitted to exercise performed a graded exercise test using a standard Bruce protocol [174] performed on a motor driven treadmill to determine cardiorespiratory fitness. Twelve-lead electrocardiography was monitored throughout the treadmill test to evaluate the cardiovascular response to exercise. Blood

pressure was obtained manually during the last minute of each stage and as needed using a mercury sphygmomanometer. Breath-by-breath analysis of O_2 consumption and CO_2 production was averaged over 30-second intervals using an automated system (Ultima Exercise Stress Testing System, Medical Graphics, Minneapolis, MN). $\dot{V}O_{2max}$ was defined as the highest observed O_2 uptake. An exercise test was considered maximal if at least two of the following criteria were met: 1) respiratory exchange ratio ≥ 1.15 2) heart rate within 10 beats·min^{-1} of age predicted max 3) rating of perceived exertion ≥ 18. Individuals who were cleared to exercise by the attending physician and Exercise Technology Lab personnel and who met all study criteria were asked to continue in the study and were provided instructions on completion of the project at a general participant meeting.

Dietary Analysis

Volunteers who met all criteria for the study were provided a dietary (Appendix F) and daily physical activity record (Appendix G) to be completed three days prior to and during all blood sampling periods. The purpose of the dietary record was to determine the type and quantity of foods each participant consumed during a typical week. Other than requesting that participants maintain similar caloric and nutrient intake during the blood sampling period, there was no attempt to modify dietary composition.

Participants were given instructions to complete the food log three days prior to and throughout each experimental intervention and blood sampling period. They were then asked to return the food log for analysis. Food logs were analyzed using a commercially available software package (Food Processor for Windows, Version 7.40,

ESHA Research, Salem, OR). Total caloric intake and the amount of protein, fat, and carbohydrate (g) were estimated from the food log.

Physical activity records were used to determine average caloric expenditure prior to and during the blood sampling period. Participants were asked to record the time spent performing a comprehensive category of activities. Metabolic equivalents were assigned to each type of activity and caloric expenditure estimated by the type and duration of activity. Combined with dietary records, physical activity records were used to account for background physical activity or dietary changes that can potentially influence changes in triglycerides, insulin, or glucose observed under experimental conditions.

Experimental Procedures

Participants who agreed to exercise and met all criteria were asked to record all food and drink consumed three days prior to additional testing. In addition, they were asked to avoid any planned leisure time physical activity or strenuous vocational activity three days prior to the control condition. Participants then returned to the lab where a baseline blood sample was obtained followed by the administration of a high fat meal (control condition). Blood samples were then obtained two, four, six and eight hours later. The following day each participant returned to the lab and another baseline blood sample was obtained (exercise condition). Following the baseline blood sample, participants were asked to walk on a treadmill at 70% of $\dot{V}O_{2max}$ obtained from the treadmill test until 500 kcals of energy was expended. Participants were then asked to consume an identical test meal consumed the day before and blood was sampled again at two, four, six and eight hours. Next, participants were asked to return 24 and 48 hours later for additional blood sampling.

Following the 48-hour blood sampling period, the attending physician wrote a six-week prescription for extended-release niacin. Niacin was titrated over the course of two weeks up to a maintenance dose of 1500 mg·day^{-1} for four weeks. After the niacin treatment period, participants were asked to return to the lab where each participant completed the identical postprandial and fasting blood sampling periods at the control and exercise conditions (Fig. 1).

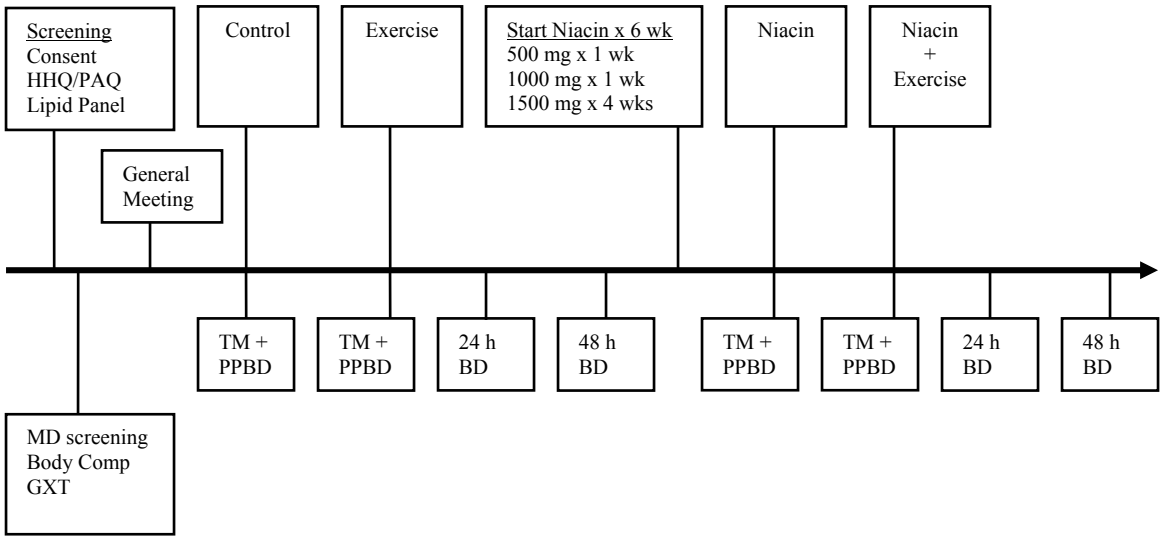

Fig. 1. Study schematic. Volunteers who met all criteria for the study underwent each of four conditions to determine the effects of niacin and exercise on postprandial lipemia. Each condition required the participant to consume a high-fat meal with temporal blood sampling at two hour intervals for eight hours. Control consisted of consuming a high-fat test meal (TM = Test meal; PPBD = Postprandial blood sampling); Exercise consisted of a single session of aerobic exercise performed one hour prior to an identical high-fat meal. The niacin condition examined the effects of six weeks of niacin on the postprandial response to an identical high fat meal. Niacin + exercise consisted of an identical session of aerobic exercise as performed previously combined with six weeks of niacin to examine the combined effects of these interventions on postprandial lipemia. Fasting blood samples were obtained at 24 and 48 hours following the exercise and niacin + exercise conditions. HHQ = Health History Questionnaire; PAQ = Physical Activity Questionnaire; BD = Blood Draw.

High Fat Meals

The high fat meal consisted of approximately 270 mL of whipping cream and 65 g of ice cream provided at the control, exercise, niacin and niacin + exercise conditions. The meal contained approximately 1000 kcals and consisted of approximately 100 g fat, 17 g carbohydrate, and 3 g protein.[116] Each meal was identical in total caloric content and composition. Participants were required to drink the high-fat meal within 15 minutes. Blood samples were then obtained at two, four, six and eight hours.

Acute Exercise Intervention

All participants completed an aerobic exercise session on two occasions (after the control and just before beginning the six week niacin condition and just after completing the niacin intervention). On each occasion, treadmill walking was completed one hour prior to ingesting a high-fat meal at the exercise and niacin + exercise conditions (Fig. 1). A standard kcal equivalent of 5 kcal·L^{-1} of O_2 and $\dot{V}O_{2max}$ ($L \cdot min^{-1}$) obtained from a graded exercise test was used to estimate the intensity and duration of exercise needed to elicit an energy expenditure of 500 kcal prior to the experimental exercise session. The rate of energy expenditure was calculated by multiplying the kcal equivalent by the corresponding $\dot{V}O_2$ ($L \cdot min^{-1}$). The duration of exercise was estimated by dividing 500 kcal by the calculated rate of energy expenditure.

Participants were asked to warm-up at 2.5 mph with a 2% incline on the treadmill for three minutes. Following the warm-up, the treadmill speed and grade were increased to approximately 70% of $\dot{V}O_{2max}$ for each participant. Respiratory gas analysis and heart rates were obtained initially and at approximately 15-minute intervals to verify energy

expenditure and intensity. Adjustments to the speed or incline of the treadmill were made to maintain exercise intensity.

Niacin Intervention

The attending physician, Jack Mahurin, D.O., provided a six-week prescription for niacin following the 48-hour blood draw of the exercise condition. The Auburn University Student Pharmacy filled the prescription for one week and the participant was required to return to the pharmacy each week for refills. Refills of niacin were only dispensed by the pharmacy after participants completed a questionnaire regarding any adverse effects of niacin at the Exercise Technology Laboratory. If the participant wished to continue in the study, they were provided a notice to take to the pharmacy verifying that they wished to continue in the study.

Titrations of niacin occurred as follows: Week One: 500 $mg \cdot day^{-1}$; Week Two: 1000 $mg \cdot day^{-1}$; Weeks Three to Six: 1500 $mg \cdot day^{-1}$.[55] Prior to the exercise condition and on weekly intervals thereafter, blood samples were obtained to determine blood lipid and liver enzymes to monitor the possible effects of niacin on hepatotoxicity.

Experimental Blood Sampling

For each blood sampling period, participants were asked to report to the laboratory following an eight to twelve hour fast at approximately the same time of day. Bodyweight was determined prior to the initial blood draw for each condition. Participants were asked to sit for five minutes where they completed a pre-blood draw questionnaire (Appendix H). Blood pressure was obtained after five minutes of rest. Prior to each meal, an intravenous catheter (Ethicon Endo-Surgery, Inc., Cincinatti, OH, 20G 1.25 inch cathlon clear) was inserted into an antecubital vein capped by an

intermittent injection port (Kawasumi Laboratories, Inc., Tampa, FL). Blood was then drawn into two 7.0 mL serum vacutainer tubes for the assessment of baseline measures (Becton Dickinson Vacutainer, Franklin Lakes, NJ, 13 x 100 mm). Following the high fat meal, serum blood samples were obtained at two, four, six and eight hours. Sodium heparin lock (Abbott Laboratories, North Chicago, IL, 10 USP U/mL) was used as needed to maintain catheter patency throughout the blood sampling period.

Immediately following each blood collection, a small portion of the whole blood sample was used to determine hemoglobin and hematocrit content while the remainder of the sample was allowed to clot. Whole blood from the serum tubes was centrifuged at 1500 X g for 20 minutes to isolate serum. Aliquots of serum were stored and isolated in 2.0 mL ultracentrifuge tubes for later analyses. A 2.0 mL aliquot of serum was isolated from baseline at each condition and 24 and 48 hours post-exercise for HDL-C separations. All aliquots were stored at -70 °C for future analyses. Participants returned to the lab and serum was obtained from blood samples drawn under fasting conditions at 24 and 48 hours following the exercise sessions (Fig. 1).

Two 7.0 mL serum tubes were obtained at baseline for each condition and during the 24 and 48 hour post-exercise period following the niacin and niacin + exercise conditions for a total of 112 mL of blood throughout the study. One 7.0 mL serum tube was obtained during each of the baseline, two, four, six and eight hour postprandial timepoints for a total blood volume of 140 mL of blood throughout the study. Therefore, a total blood volume of approximately 250 mL was obtained throughout the study. A minimum of eight needle sticks over the entire investigation was required to obtain all

blood samples. Each participant was asked to report to the lab a total of 17 times for a total time commitment of approximately 40 hours.

Analysis of Dependent Variables

Whole blood sampled from serum vacutainer tubes was used to determine hemoglobin and hematocrit concentrations to estimate possible shifts in plasma volume associated with each condition.[175] HDL subfractions were separated according to the procedures of Warnick and Albers [176] and Gidez et al.[177] Serum triglycerides were analyzed using an enzymatic triglyceride reagent (Raichem, San Diego, CA, Kit # 85424). Blood lipid concentrations, glucose and all hepatic and metabolic markers reported for the weekly changes produced by niacin were determined by a CDC certified laboratory. LDL-C was calculated using the formula by Freidewald et al.[178] Glucose concentrations were analyzed using the glucose oxidase and modified Trinder color reaction (Raichem, San Diego, CA, Kit # 80039). Insulin concentrations were analyzed using a microplate ELISA technique (LINCO Research, St. Charles, MO, Kit # EZHI-14K). Insulin resistance was assessed using the glucose to insulin ratio and by calculation of the homeostasis model assessment (HOMA) score, defined as the product of fasting insulin concentration ($\mu U \cdot mL^{-1}$) and fasting glucose concentration ($mg \cdot dL^{-1}$)) divided by 22.5.[169, 179] Determinations of insulin resistance were made at baseline before each condition and at 24 and 48 hours following exercise and the niacin + exercise conditions to determine 1) if niacin increased insulin resistance and 2) if exercise was able to ameliorate niacin induced increases in insulin resistance. The intra-assay and inter-assay coefficients of variation for triglycerides were 1.1% and 2.7%. The intra-assay and inter-assay coefficients of variation for glucose were 0.5% and 1.3%. Insulin

concentrations were determined for all timepoints collected on a participant during a single analysis. The intra-assay coefficient of variation was 3.3% for insulin.

Statistical Procedures

Postprandial triglyceride and insulin concentrations were quantified using the 1) mean triglyceride and insulin response from baseline, two, four, six and eight hours 2) and the total and incremental triglyceride and insulin area under the curve [96] calculated as:

$$PPL\ (mg \cdot dL^{-1} \cdot 8h) = n_B + 2[n_2 + n_4 + n_6] + n_8 \quad (Total)$$

$$PPL\ (mg \cdot dL^{-1} \cdot 8h) = 2[n_2 + n_4 + n_6] + n_8 - 7n_B \quad (Incremental)$$

Where n_B represents the baseline plasma triglyceride value and n_2 to n_8 represent triglyceride values from two to eight hours after the test meal. The same procedure was used to quantify postprandial insulin AUC in $\mu U \cdot mL^{-1} \cdot 8h$.

The design used to address the purpose of this study was a within subjects design using participants as their own control. A one (cohort) x four (condition) ANOVA with repeated measures on condition was used to compare the postprandial triglyceride and insulin AUC_T, AUC_I and peak responses. The temporal responses over the eight hour postprandial period were analyzed with a four (condition) x 5 (time) repeated measures ANOVA. A 2 (condition) x 3 (time) repeated measures ANOVA was used to compare fasting responses. Relationships between physiological characteristics and changes in the dependent variables were determined by using Pearson product-moment correlation

coefficients. All data were analyzed using the Statistical Analysis System (SAS for Windows, version 9.1, SAS Institute, Cary, NC).

The independent variables in this study included condition (control, exercise, niacin, niacin + exercise) and blood sampling points (baseline, two, four, six, eight, 24 and 48 hours post-exercise). The dependent variables in the study included: anthropometric measures (height, weight, waist circumference, percentage body fat and BMI) and concentrations of total cholesterol, triglycerides, HDL-C, LDL-C, insulin and glucose. The glucose to insulin ratio and HOMA score were also dependent variables of interest. Significant differences observed between groups were followed-up using Duncan's New Multiple Range Test. Significance was accepted at the $p < 0.05$ level.

CHAPTER IV.

RESULTS

Participant Selection

Sixty-one volunteers responded to advertisements for the study. A total of 18 volunteers were excluded during an initial screening by telephone or personal interview. Ten volunteers did not meet body composition or blood lipid criteria for entry into the study. A total of 33 volunteers met all inclusion criteria. Eighteen volunteers met entry criteria for the study but decided not to participate due to personal time constraints. A total of 15 participants started and completed all phases of the study (Fig. 2). Eleven out of 15 participants that completed the study were Caucasian while four individuals were of African-American, Asian or Hispanic descent.

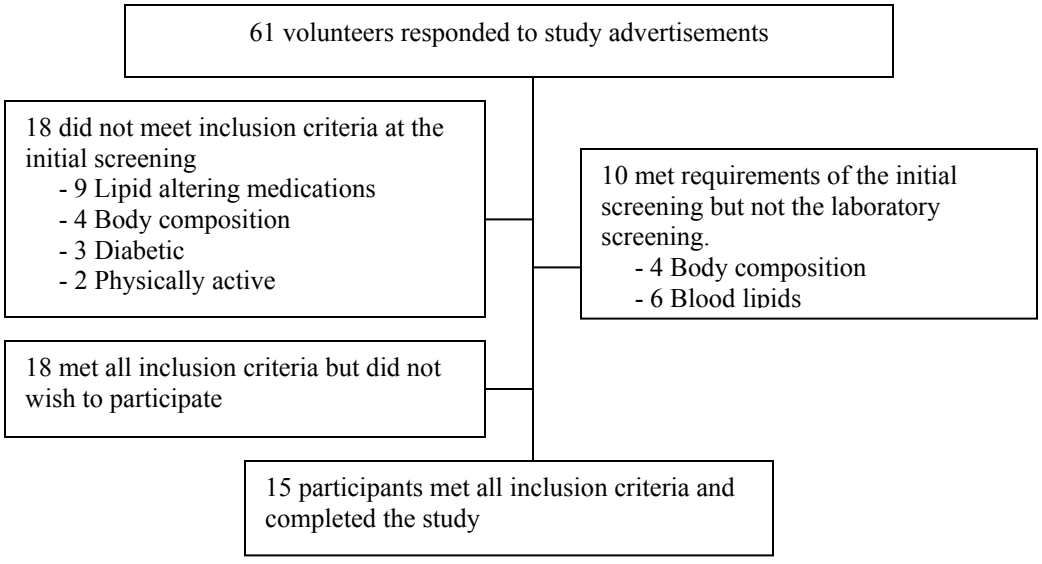

Fig. 2. Participant selection

Baseline Physiological Characteristics

All participants in the study met at least three of the five criteria for the metabolic syndrome as defined by NCEP.[6] Participants ranged in age from 32 to 57 years. The cohort could be classified as "high risk" for CVD based on the average BMI (34.0 ± 0.8) and waist circumference (107.9 ± 2.1 cm).[180] Body fat percentage was below the 10^{th} percentile for men 40 to 60 years of age.[181] Six participants were characterized as hypertensive based on blood pressure assessment in the laboratory or by prior clinical diagnosis. Nine participants had elevated fasting insulin concentrations and were considered insulin resistant based on the homeostasis model (HOMA) score and blood glucose concentrations.[179, 182] All participants exhibited elevated triglyceride concentrations with baseline triglycerides ranging from 156 to 512 $mg \cdot dL^{-1}$. Seven participants were classified as hyperlipidemic with total cholesterol concentrations greater than 240 $mg \cdot dL^{-1}$ and triglyceride concentrations greater than 200 $mg \cdot dL^{-1}$. The remaining individuals had primary hypertriglyceridemia and only mildly elevated total cholesterol concentrations. Two participants had known CVD with prior cardiovascular interventions but were not taking any medications known to influence lipid or glucose metabolism and were cleared by their primary-care physician to participate in the study. One participant experienced ventricular tachycardia during the graded exercise test in the presence of the attending physician at our laboratory. The participant was referred to their primary-care physician for follow-up by the attending physician and was provided written clearance to participate in the study. Participants self-reported less than two days per week of physical activity for approximately 20 minutes per session. Relative $\dot{V}O_{2max}$

was 27.7 ± 5.1 mL·kg·min^{-1} placing the group at the 10th percentile for fitness.[181] The baseline physiological characteristics of the participants are provided in Table 1.

Table 1. Baseline physiological characteristics

	Mean ± SE			Minimum	Maximum
Age	46	±	2	32	57
Height (cm)	175.5	±	2.4	161.3	195.6
Weight (kg)	105.3	±	4.6	85.7	146.4
BMI (kg·m^{-2})	34.0	±	0.8	28.9	39.3
% fat	35	±	5	23	43
Waist girth (cm)	107.9	±	2.1	95.3	123.8
Hip girth (cm)	113.8	±	2.0	104.1	132.1
SBP (mmHg)	130	±	4	108	154
DBP (mmHg)	84	±	2	66	102
Insulin (μU·mL^{-1})	15.6	±	3.1	5.1	52.1
HOMA score	3.9	±	0.7	1.2	12.4
Glucose (mg·dL^{-1})	103	±	7	88	193
G/I ratio	8.0	±	1.3	1.8	25.7
Triglyceride (mg·dL^{-1})	286	±	26	156	512
Total cholesterol (mg·dL^{-1})	226	±	8	172	264
LDL-C (mg·dL^{-1})	135	±	9	87	190
HDL-C (mg·dL^{-1})	40	±	2	25	58
$\dot{V}O_{2max}$ (L·min^{-1})	2.9	±	0.7	1.8	3.9
$\dot{V}O_{2max}$ (mL·kg·min^{-1})	27.7	±	5.1	18.2	36.2

Values are presented as means ± standard error along with minimum and maximum values in range. HOMA score = Homeostasis model score; G/I ratio = Glucose to insulin ratio; SBP = Systolic blood pressure; DBP = Diastolic blood pressure.

Effects of Niacin Over Six Weeks

Blood Lipids

Six weeks of niacin reduced baseline triglyceride concentrations by 37% from an average of 293 ± 37 mg·dL^{-1} to 185 ± 17 mg·dL^{-1} ($p < 0.0001$; $F_{1,5} = 5.82$) (Fig. 3). Twelve out of 15 participants demonstrated reductions in triglyceride concentrations with niacin which ranged from 20 to 408 mg·dL^{-1}. Reductions in triglyceride concentrations

occurred by the fourth week of the intervention ($p < 0.0001$; $F_{1,5} = 5.82$) and an additional 13% reduction occurred between weeks four and six. The percent decrease in total cholesterol and LDL-C was not significant; however, HDL-C concentrations were increased by 15% at week six compared to control ($p < 0.0001$; $F_{1,5} = 5.97$) (Table 2). The total cholesterol to HDL-C ratio was reduced from 5.8 ± 0.2 to 4.6 ± 0.2 after six weeks of niacin ($p < 0.0001$; $F_{1,5} = 7.54$). Body weight was not significantly changed from baseline at any time throughout the study.

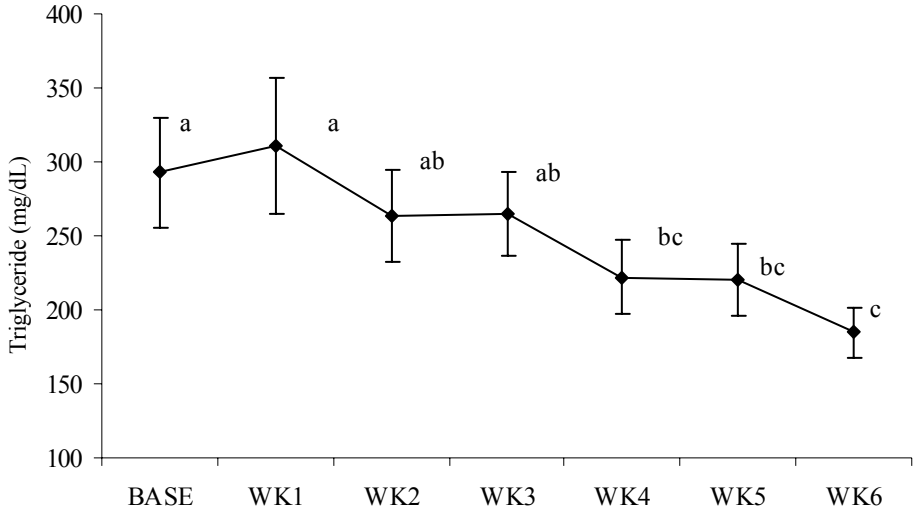

Fig. 3. Effects of six weeks of extended-release niacin on serum triglyceride levels by week. All values are means ± standard error. The dosage of niacin used was: WK1: 500 mg·day^{-1}; WK2: 1000 mg·day^{-1}; WK3 to WK6: 1500 mg·day^{-1}. Means with the same superscript are similar ($p > 0.05$).

Table 2. Weekly blood chemistry changes with the six-week niacin intervention

	BASE	WK1	WK2	WK3	WK4	WK5	WK6
TG	293 ± 37^{a}	311 ± 46^{a}	$263 \pm 31^{a,b}$	$265 \pm 28^{a,b}$	$222 \pm 25^{b,c}$	$220 \pm 24^{b,c}$	185 ± 17^{c}
TC	226 ± 8^{a}	217 ± 12^{a}	216 ± 10^{a}	215 ± 11^{a}	215 ± 11^{a}	208 ± 11^{a}	210 ± 9^{a}
LDL-C	135 ± 9^{a}	120 ± 12^{a}	130 ± 9^{a}	119 ± 11^{a}	127 ± 9^{a}	121 ± 10^{a}	126 ± 8^{a}
HDL-C	$40 \pm 2^{a,b}$	39 ± 2^{a}	$41 \pm 3^{a,b}$	$41 \pm 2^{a,b}$	$43 \pm 3^{a,d}$	$45 \pm 3^{c,d}$	46 ± 2^{c}
GLU	96 ± 2^{a}	$96 \pm 4^{a,b}$	$104 \pm 5^{a,b,c}$	$103 \pm 3^{a,b,c}$	$107 \pm 4^{d,b,c}$	112 ± 5^{d}	$109 \pm 4^{d,c}$
ALT	33 ± 3^{a}	28 ± 3^{b}	25 ± 3^{b}	27 ± 2^{b}	27 ± 3^{b}	25 ± 2^{b}	27 ± 2^{b}
AST	23 ± 1^{a}	21 ± 0^{a}	21 ± 2^{a}	23 ± 1^{a}	23 ± 2^{a}	23 ± 1^{a}	24 ± 1^{a}
GGT	47 ± 9^{a}	$45 \pm 8^{a,b}$	$38 \pm 6^{c,b}$	$38 \pm 6^{c,b}$	36 ± 5^{c}	35 ± 6^{c}	35 ± 6^{c}
UA	7.2 ± 0.3^{a}	7.2 ± 0.4^{a}	7.3 ± 0.3^{a}	7.6 ± 0.3^{a}	7.6 ± 0.4^{a}	7.7 ± 0.5^{a}	7.5 ± 0.3^{a}
Ca	9.6 ± 0.1^{a}	9.5 ± 0.1^{a}	9.6 ± 0.1^{a}	9.6 ± 0.1^{a}	9.5 ± 0.1^{a}	9.5 ± 0.1^{a}	9.4 ± 0.1^{a}
Phos	$3.3 \pm 0.1^{a,b,c}$	$3.4 \pm 0.1^{a,b}$	3.5 ± 0.1^{a}	3.5 ± 0.1^{a}	$3.4 \pm 0.1^{a,b,c}$	$3.1 \pm 0.2^{b,c}$	3.1 ± 0.1^{c}

All values are means ± standard error. TG = Triglycerides; TC = Total cholesterol; LDL-C = Low density lipoprotein cholesterol; HDL-C = High-density lipoprotein cholesterol; GLU = blood glucose (Values are $mg \cdot dL^{-1}$). ALT = Alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transpeptidase (Values are $IU \cdot L^{-1}$). Ca = Calcium; Phos = Phosphorus; UA = Uric acid (Values are $mg \cdot dL^{-1}$). Means with the same superscript are similar ($p > 0.05$).

Adverse Reactions

Fasting insulin concentrations and the homeostasis model (HOMA) score were not increased by niacin despite a 12% increase in glucose concentrations ($p = 0.003$; $F_{1,5} = 3.66$) (Table 2). Alanine aminotransferase and GGT levels were lower following the intervention while AST levels remained unchanged. Uric acid levels remained unchanged throughout the study period (Table 2).

Nine out of 15 participants reported mild to moderate flushing at some point during the intervention. Participants described the event in most cases as cutaneous redness, itching or tingling. Despite the rapid titration used in this investigation, there

was no relationship between the weekly titrations of niacin and adverse reactions. Flushing events occurred randomly throughout the study but did not last more than two or three hours per event and usually did not occur on consecutive days. Only two individuals reported more than one episode of flushing. Fatigue was the second most common adverse reaction reported. A total of three individuals reported fatigue that continued throughout the study.

Effects of Niacin and Exercise in the Postprandial State

Triglycerides

Plasma volume was not changed in the hours after a meal for any of the conditions (Table 3). Therefore, blood triglyceride, insulin, glucose and AUC calculations were made using plasma volume unadjusted concentrations. As compared to the control condition, the triglyceride AUC_T was 13% and 23% lower in the exercise and niacin conditions compared to control ($p < 0.0001$; $F_{1,3} = 11.83$) (Fig. 4A). The addition of exercise to the six-week niacin intervention reduced the triglyceride AUC_T by 27% from the control condition ($p < 0.0001$; $F_{1,3} = 11.83$) but was not different from the reduction in the AUC_T observed in the niacin condition. Triglyceride AUC_I was reduced by 32% in the exercise condition ($p = 0.02$; $F_{1,3} = 3.50$) (Fig 4B); however, the triglyceride AUC_I for the niacin and niacin + exercise conditions were not different from control. Peak triglyceride concentrations were reduced similarly from 490 ± 35 $mg \cdot dL^{-1}$ to 404 ± 35 $mg \cdot dL^{-1}$ and 400 ± 35 $mg \cdot dL^{-1}$ by the exercise and niacin conditions ($p < 0.0001$; $F_{1,3} = 11.83$). However, the peak triglyceride concentration in the niacin + exercise condition (360 ± 34 $mg \cdot dL^{-1}$) was not significantly lower than the exercise or

niacin conditions. The length of time required for triglycerides to peak was between two and four hours and was not influenced by any of the conditions.

Table 3. Changes in plasma volume during the postprandial blood sampling period

	HR 2	HR 4	HR 6	HR 8
CON	0.1 ± 1.9	-0.6 ± 1.3	1.1 ± 1.4	-0.2 ± 1.1
EX	-0.7 ± 0.8	-1.1 ± 0.9	-0.4 ± 1.6	-2.5 ± 1.1
NIA	-1.3 ± 1.1	-2.0 ± 0.6	-1.8 ± 1.0	-0.2 ± 1.0
NIEX	-0.8 ± 0.8	-1.5 ± 1.1	-0.7 ± 0.9	-2.5 ± 1.1

All values are expressed as percentage change relative to baseline plasma volume ± standard error. CON = Control; EX = Exercise; NIA = Niacin; NIEX = Niacin + Exercise. Plasma volume did not significantly change during the postprandial blood sampling period ($p > 0.05$).

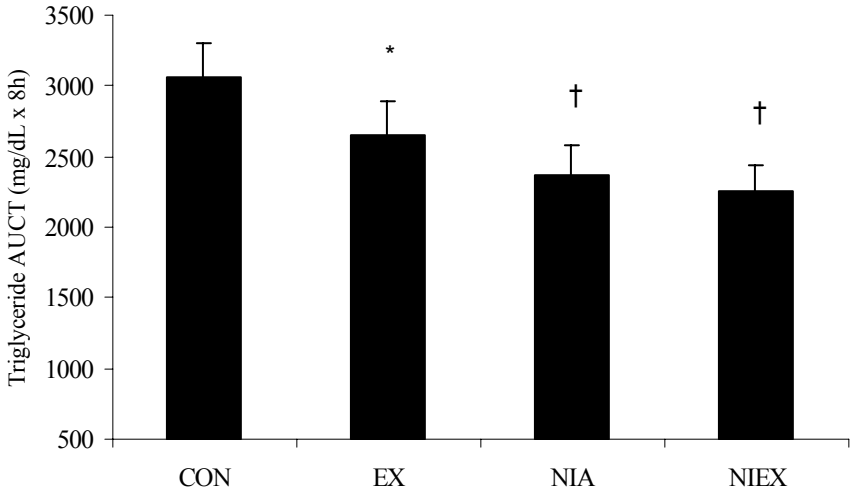

Fig. 4A. Triglyceride area under the curve total (AUC_T). AUC_T was calculated as $n_B + 2 (n_2 + n_4 + n_6) + n_8$ where n_B represents baseline and n_2 to n_8 represents the triglyceride response two, four, six and eight hours following the meal for each condition.[96] All values are means ± standard error. * = Significant difference from control; † = Significant difference from control and exercise ($p < 0.05$). CON = Control; EX = Exercise; NIA = Niacin; NIEX = Niacin + Exercise.

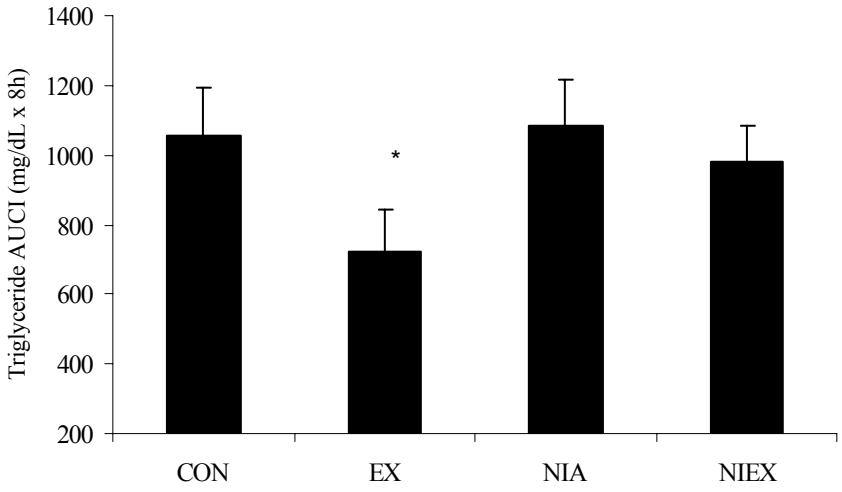

Fig. 4B. Triglyceride area under the curve incremental (AUC_I). AUC_I was calculated as $2(n_2 + n_4 + n_6) + n_8 - 7n_B$ where n_B represents baseline and n_2 to n_8 represents the triglyceride response two, four, six and eight hours following the meal for each condition. All values are means ± standard error. * = significant difference from control ($p < 0.05$). CON = Control; EX = Exercise; NIA = Niacin; NIEX = Niacin + Exercise.

Mean triglyceride responses for each condition over eight hours are presented in Fig. 4C. Baseline triglyceride concentrations were lower for the niacin and niacin + exercise conditions compared to the baseline values for the control or exercise conditions ($p < 0.05$; $F_{4,210} = 342.00$). Postprandial triglyceride concentrations were lower at two ($p < 0.05$; $F_{4,210} = 225.00$), four ($p < 0.05$; $F_{4,210} = 15.05$) and six hours ($p < 0.05$; $F_{4,210} = 7.50$) in the exercise condition compared to control. Niacin reduced postprandial lipemia to a greater extent than exercise at two ($p < 0.05$; $F_{4,210} = 225.00$), four ($p < 0.05$; $F_{4,210} = 15.05$) and eight hours ($p < 0.05$; $F_{4,210} = 6.20$) following the meal. Exercise + niacin reduced postprandial triglycerides more effectively than exercise or niacin alone at two ($p < 0.05$; $F_{4,210} = 225.00$), six ($p < 0.05$; $F_{4,210} = 7.50$) and eight hours ($p < 0.05$; $F_{4,210} = 6.20$) following the meal.

Exercise lowered the incremental triglyceride response ($p = 0.009$; $F_{3,4} = 4.38$) while the relative change in the postprandial triglyceride response for the niacin and niacin + exercise conditions were not different than control (Fig. 4D).

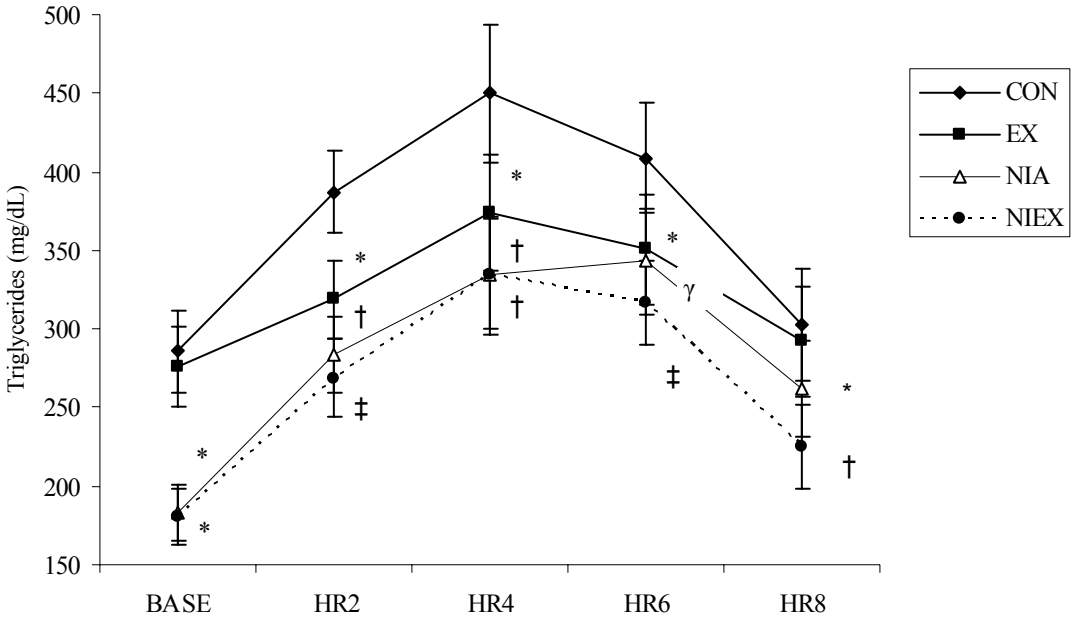

Fig. 4C. Postprandial triglyceride responses over time. All values are means ± standard error. * = Significant difference from control; † = Significant difference from control and exercise; ‡ = Significant difference from control, exercise and niacin; γ = Significant difference from exercise ($p < 0.05$). CON = Control; EX = Exercise; NIA = Niacin; NIEX = Niacin + Exercise.

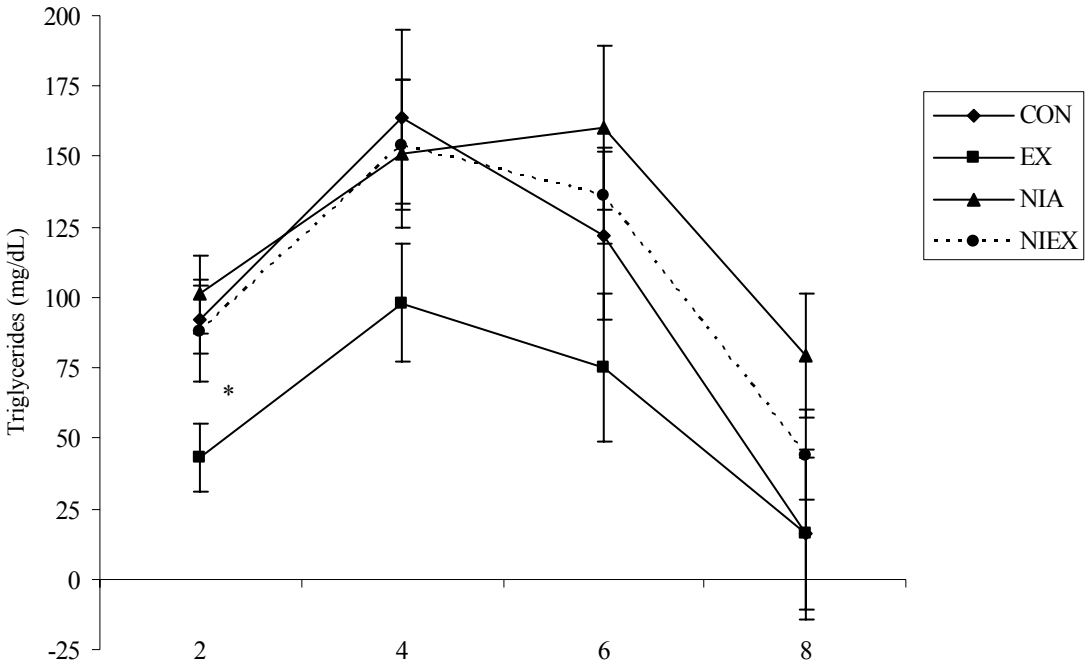

Fig. 4D. Triglyceride responses by condition. All triglyceride concentrations were corrected for baseline triglyceride values (triglycerides at each hour – baseline triglycerides). All values are means ± standard error. * = Significant difference between conditions ($p < 0.05$). CON = Control; EX = Exercise; NIA = Niacin; NIEX = Niacin + Exercise.

Insulin

Niacin increased the insulin AUC_T by 37% from control ($p = 0.001$; $F_{1,3} = 6.33$) (Fig. 5A) The insulin AUC_T was not different for exercise or niacin + exercise and control. The insulin AUC_I and peak insulin response was significantly greater after six weeks of niacin compared to control ($p < 0.0001$; $F_{1,4} = 9.73$ (Fig. 5A) Exercise reduced the insulin AUC_I ($p < 0.0001$; $F_{1,3} = 9.73$) but had no effect on the peak insulin response compared to control. Niacin + exercise reduced the insulin AUC_I compared to control ($p < 0.001$; $F_{1,3} = 9.73$) (Fig. 5B).

The two-hour postprandial insulin response was 54% higher for the niacin condition compared to control ($p < 0.05$; $F_{4,208} = 21.05$). Insulin concentrations were

lower two and four hours after the meal in the exercise condition compared to control (Fig. 6). The two-hour postprandial insulin response was 16% lower in the niacin + exercise condition compared to niacin but remained higher than the exercise or control conditions ($p < 0.05$; $F_{4,208} = 7.18$). Insulin concentrations at the four-hour time point in the niacin + exercise condition were similar to control but remained higher than exercise ($p < 0.05$; $F_{4,208} = 7.18$).

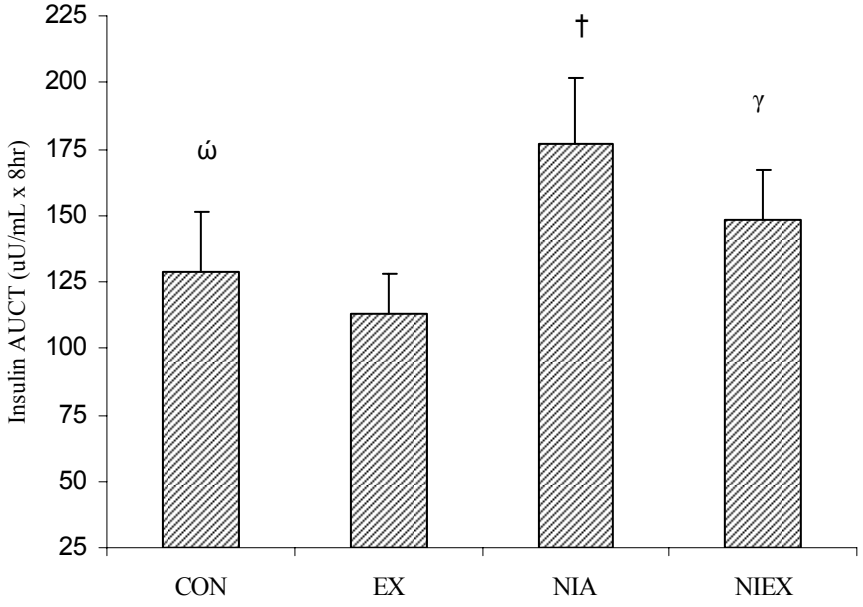

Fig. 5A. Insulin area under the curve total (AUC_T). AUC_T was calculated as $n_B + 2 (n_2 + n_4 + n_6) + n_8$ where n_B represents baseline and n_2 to n_8 represents the insulin response two, four, six and eight hours following the meal for each condition. All values are means ± standard error. † = Significant difference from control and exercise; γ = Significant difference from exercise; ώ = No significant difference with NIEX. CON = Control; EX = Exercise; NIA = Niacin; NIEX = Niacin + Exercise.

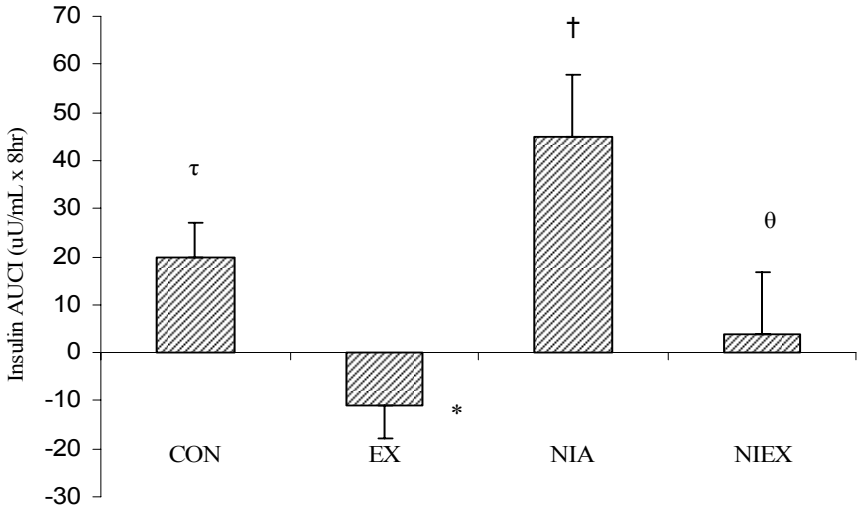

Fig. 5B. Insulin area under the curve incremental (AUC_I). AUC_I was calculated as 2 ($n_2 + n_4 + n_6$) + n_8 - $7n_B$ where n_B represents baseline and n_2 to n_8 represents the insulin response two, four, six and eight hours following the meal for each condition. All values are means ± standard error. * = Significant difference from control; † = Significant difference from control and exercise; θ = Significant difference from niacin; τ = No significant difference from NIEX. CON = Control; EX = Exercise; NIA = Niacin; NIEX = Niacin + Exercise.

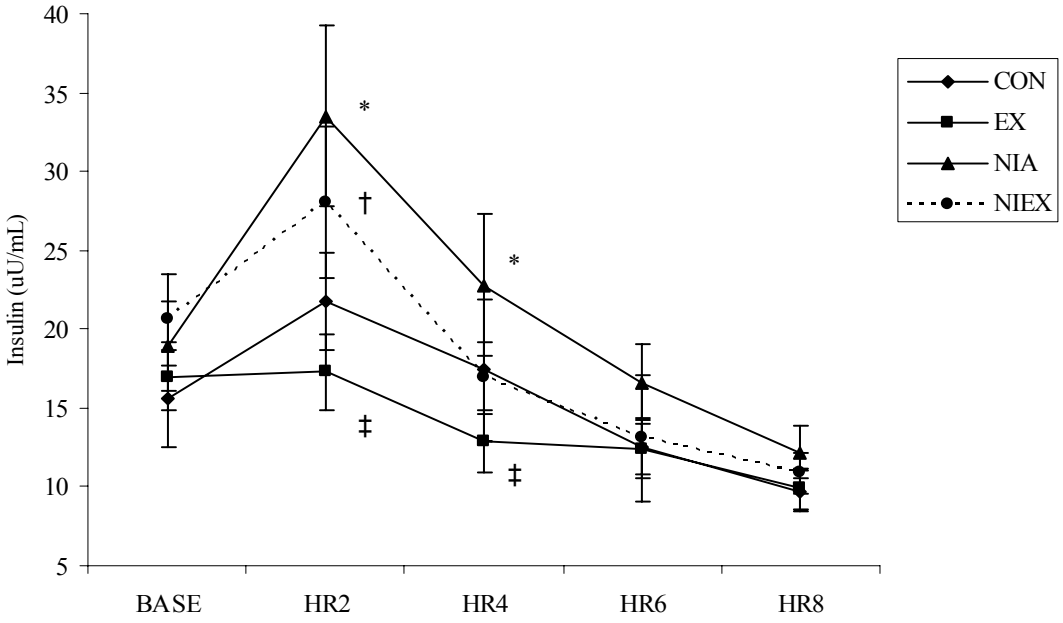

Fig. 6. Postprandial insulin responses over time. All values are means ± standard error. * = Significant difference from control, exercise and niacin + exercise; † = Significant difference from control, exercise and niacin; ‡ = Significant difference from control, niacin and niacin + exercise ($p < 0.05$). CON = Control; EX = Exercise; NIA = Niacin; NIEX = Niacin + Exercise.

Glucose

Glucose concentrations were significantly lower at the six and eight-hour postprandial timepoints compared to the two and four-hour postprandial timepoints for all conditions ($p = 0.0006$; $F_{1,4} = 5.72$).

Fasting Responses to Niacin and Exercise

Triglycerides

Triglyceride concentrations were reduced by 15% and 27% at 24 and 48 hours following the exercise condition ($p < 0.05$; $F_{2,37} = 17.56$) (Fig. 7). Triglyceride concentrations were not lower than baseline at 24 and 48 hours in the niacin + exercise condition.

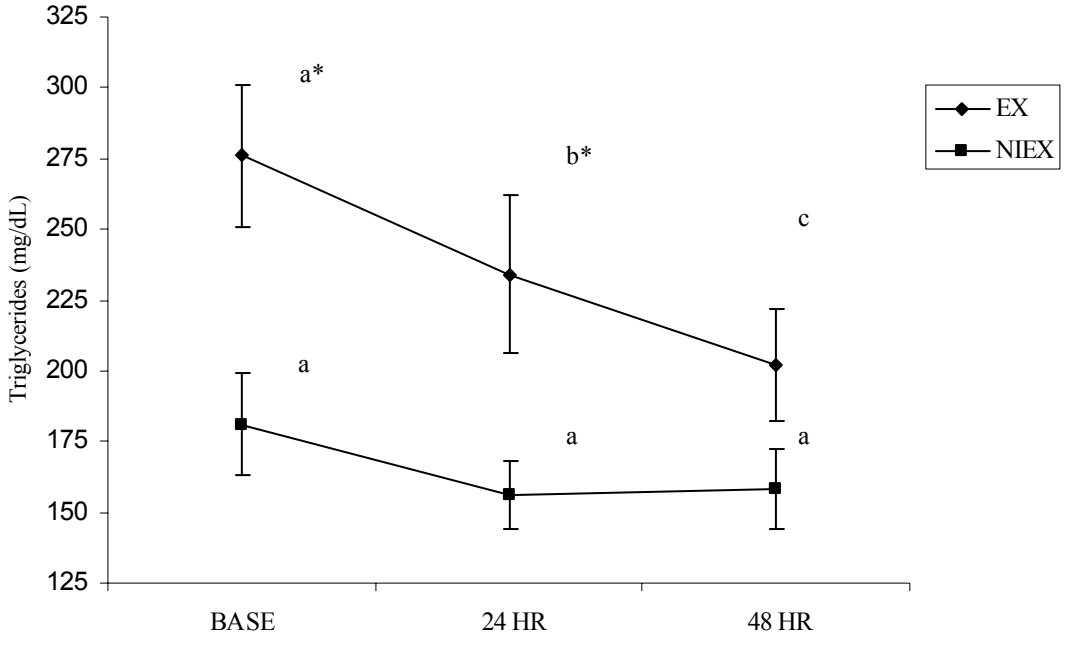

Fig. 7. Fasting triglyceride responses. All values are means ± standard error. Means with the same superscript are similar ($p > 0.05$). * Indicates a significant difference between conditions.

Insulin

Insulin concentrations were significantly higher in the niacin + exercise condition (20.8 $\mu U \cdot mL^{-1}$) compared to the exercise condition (15.8 $\mu U \cdot mL^{-1}$) ($p = 0.01$; $F_{1,2} = 7.78$). However, fasting insulin concentrations did not change after exercise either before or after six weeks of niacin (Table 4).

Glucose

Glucose concentrations did not change with exercise but were significantly increased from baseline at 24 and 48 hours after exercise and six weeks of niacin (Fig. 8). Glucose concentrations were not different between the exercise or niacin + exercise conditions

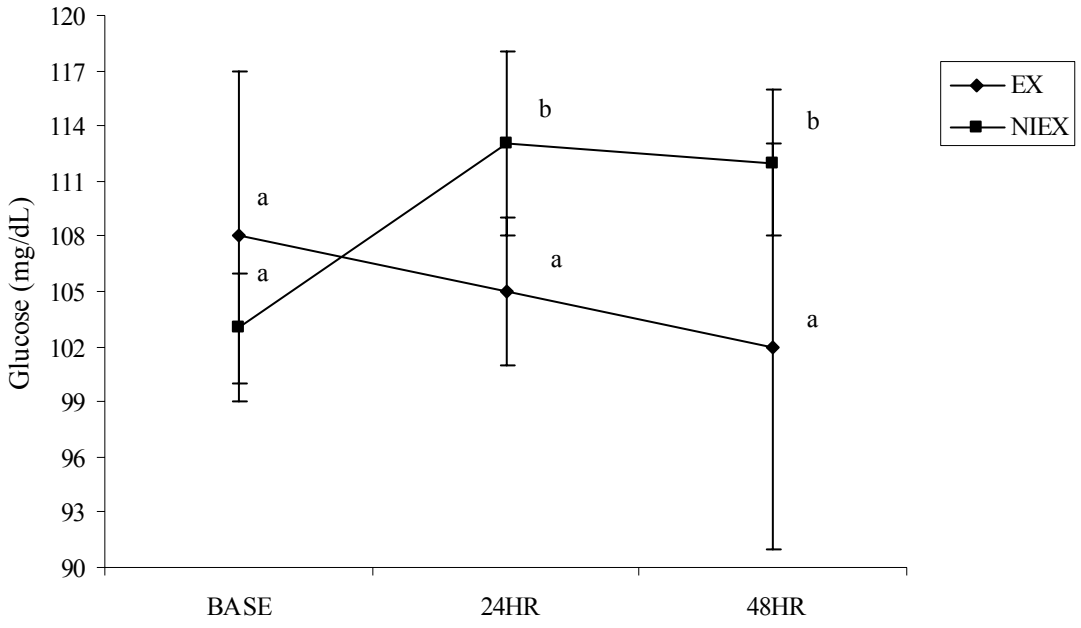

Fig. 8. Fasting glucose responses. All values are means ± standard error. Means with the same superscript are similar ($p > 0.05$). No significant differences between EX and NIEX conditions ($p > 0.05$).

Insulin Resistance

HOMA was higher ($p = 0.009$; $F_{4,1} = 8.64$) and GIR lower ($p = 0.03$; $F_{4,1} = 6.22$) in the niacin + exercise condition compared to the exercise condition.

Table 4. Fasting insulin and clinical indices of insulin sensitivity

	BASELINE	24 HR	48 HR
EX			
Insulin ($\mu U \cdot mL^{-1}$)	17.0 ± 2.2	14.9 ± 2.6	15.4 ± 2.9
HOMA score	4.3 ± 0.5	3.7 ± 0.6	3.9 ± 0.9
G/I ratio	8.0 ± 1.3	9.1 ± 1.6	9.3 ± 1.9
NIEX			
Insulin ($\mu U \cdot mL^{-1}$)*	20.6 ± 2.9	21.7 ± 3.3	20.0 ± 2.5
HOMA score*	5.3 ± 0.8	6.3 ± 1.1	5.5 ± 0.7
G/I ratio*	6.3 ± 0.7	6.7 ± 0.9	6.5 ± 0.7

Values are means ± standard error. 24 HR = 24 hours post-exercise; 48 HR = 48 hours post-exercise; G/I ratio = Glucose to insulin ratio; HOMA score = Homeostasis model score calculated as [fasting insulin (uU/mL) * fasting glucose (mmol/L)] / 22.5.[179] * = Significant differences between conditions. All values were similar within each condition ($p > 0.05$).

Correlational Analysis

Weekly Changes in Blood Chemistry With Niacin

Waist circumference was positively associated with baseline blood glucose concentrations ($r = 0.52$; $p = 0.05$) and remained associated with blood glucose throughout the six-week period. Correlations between other physiological characteristics and weekly changes in blood chemistries were not observed.

Postprandial Responses and Physiological Characteristics

Baseline fasting triglyceride concentrations were correlated with the triglyceride AUC_T (Control: $r = 0.82$; $p = 0.0002$, Exercise: $r = 0.87$; $p = 0.0041$, Niacin: $r = 0.81$; $p = 0.0002$, Niacin + Exercise: $r = 0.89$; $p < 0.0001$) and peak triglyceride responses for each condition. Baseline fasting triglycerides were not correlated with the triglyceride AUC_I for any of the conditions. Waist circumference was positively associated with the insulin AUC_I for the niacin ($p = 0.03$; $r = 0.55$) and exercise ($p = 0.02$; $r = 0.02$) conditions.

Diet and Physical Activity

Caloric intake, carbohydrate and protein intake were not different before the control condition and throughout the 24 and 48 hour blood sampling periods associated with the exercise and niacin + exercise conditions (Table 5).

Average daily energy expenditure was estimated from daily physical activity records. The average daily energy expenditure was 1655 ± 466 kcals·day^{-1} during the pre-niacin interventions and 1732 ± 401 kcals·day^{-1} during the post-niacin intervention without accounting for the energy expenditure accumulated during the days exercise was performed in the study.

Table 5. Daily energy and macronutrient intake

Day	Total Kcals	Fat (g)	CHO (g)	PRO (g)	P/S ratio
Pre-Niacin Intervention					
1	2548 ± 244	103 ± 19	312 ± 15	85 ± 11	0.7 ± 0.2
2	2227 ± 85	82 ± 9	263 ± 21	79 ± 8	0.8 ± 0.4
3	2024 ± 81	73 ± 5	277 ± 15	65 ± 5	0.9 ± 0.5
4	2332 ± 189	117 ± 15	274 ± 19	80 ± 14	0.6 ± 0.2
5	2502 ± 175	122 ± 12	289 ± 37	78 ± 7	0.7 ± 0.6
6	2429 ± 228	93 ± 9	321 ± 57	82 ± 7	0.8 ± 0.3
Post-Niacin Intervention					
1	2250 ± 89	91 ± 10	264 ± 21	86 ± 9	0.9 ± 0.3
2	2184 ± 190	89 ± 10	307 ± 33	118 ± 50	0.7 ± 0.2
3	2240 ± 142	92 ± 9	269 ± 25	78 ± 10	0.6 ± 0.4
4	2598 ± 136	158 ± 19	259 ± 17	65 ± 5	0.5 ± 0.3
5	2497 ± 117	138 ± 13	257 ± 18	70 ± 9	0.8 ± 0.3
6	2200 ± 140	81 ± 4	281 ± 29	78 ± 6	0.8 ± 0.2

All values are means ± standard error. Pre-Niacin Intervention = Daily energy and macronutrient intake 3 days before and throughout the control and exercise conditions. Post-Niacin Intervention = Daily energy and macronutrient intake 3 days before and throughout the niacin and niacin + exercise conditions. There were no significant differences in caloric or macronutrient intake within or between conditions.

CHAPTER V.

DISCUSSION

The primary purpose of this investigation was to compare the combined effects of a single session of aerobic exercise and six weeks of extended-release niacin on postprandial lipemia in individuals with the metabolic syndrome. It was hypothesized that exercise and niacin would additively reduce postprandial lipemia due to differences in the proposed mechanisms by which each intervention works. Alternatively, it was proposed that combining exercise and niacin might reduce the influence of each intervention on postprandial lipemia. The results indicate that exercise and niacin have an additive influence and that each intervention attenuates postprandial lipemia in similar and distinctly different ways. We found that aerobic exercise performed one hour prior to a meal reduced the triglyceride AUC_T compared to control. Furthermore, when pre-existing (baseline) triglycerides were subtracted from the temporal responses, the triglyceride AUC_I and temporal responses remained significantly lower than control indicating that exercise has an influence on postprandial lipemia other than by decreasing fasting triglyceride concentrations.

The triglyceride AUC_I and temporal responses following niacin were not different from control despite a 23% reduction in the triglyceride AUC_T. Therefore, it appears that niacin decreases the triglyceride AUC_T primarily by lowering fasting triglyceride

concentrations. These results confirm previous reports that reductions in fasting triglycerides are significantly correlated with the postprandial triglyceride AUC_T.[183]

Although exercise and niacin appear to work differently to blunt the rise in triglycerides after a meal, the combined influence reduced the triglyceride AUC_I – but not significantly from control – indicating that the influence of niacin may alter the influence of exercise on postprandial lipemia.

Effects of Exercise on Postprandial Lipemia

A single session of aerobic exercise completed in the hours preceding a meal can reduce postprandial lipemia by 18 to 51%.[75] The majority of studies conducted to date have examined the effects of exercise on postprandial lipemia in physically fit individuals. There is little information regarding the influence of aerobic exercise on postprandial lipemia in individuals at high risk for CVD. Furthermore, the effects of an exercise session performed one hour prior to a meal, which is a typical time to engage in exercise, have not been investigated in this population. In the current investigation, a single session of moderate-intensity aerobic exercise performed one hour prior to a high-fat meal lowered the triglyceride AUC_I by 32% and the peak triglyceride response by 18% compared to individuals with the metabolic syndrome.

Zhang and colleagues [71] found that the triglyceride AUC_I was reduced by 32% when exercise was performed twelve hours prior to a high-fat meal in obese hypertriglyceridemic males. Furthermore, the peak triglyceride levels for the control condition and the magnitude of reduction by exercise were similar to the present investigation (~17%). These results provide evidence that moderate-intensity aerobic exercise performed one hour before a high-fat meal reduces postprandial lipemia to the

same extent as exercise performed twelve hours prior to a high-fat meal in obese sedentary men with hypertriglyceridemia.

Similar changes in postprandial lipemia have been observed when exercise was performed one to twelve hours before a high-fat meal in physically active and lean normotriglyceridemic men.[168] Sixty-minutes of aerobic exercise performed one hour prior to a high-fat meal reduced the triglyceride AUC_I by 38% compared to a non-exercise condition in physically fit normolipidemic males.[71] Likewise, moderate-intensity aerobic exercise lowered the triglyceride AUC_I by 39% when performed one hour before a high-fat meal.[44] Aerobic exercise performed sixteen hours before a high-fat meal in middle-aged males with normolipidemia reduced the triglyceride AUC_I by 18%.[45] Therefore, the magnitude of reduction observed in postprandial lipemia with moderate-intensity aerobic exercise appears to be similar between individuals of contrasting fitness, body composition and baseline triglyceride status.

Many investigations have examined the influence of exercise on postprandial lipemia using moderate-intensity aerobic exercise at caloric expenditures of greater than 800 kcals in physically active populations.[95, 168] The exercise session in the present investigation was performed at 70% of $\dot{V}O_{2max}$ at an energy expenditure of 500 kcals. Therefore, this study suggests that lower amounts of exercise may be required to reduce postprandial lipemia in sedentary men compared to those who are physically active.

The mechanisms by which aerobic exercise lowers postprandial lipemia are not completely understood, but are thought to be primarily associated with delayed elevations in skeletal muscle LPL activity.[166] It has also been proposed that aerobic exercise may reduce hepatic VLDL-triglyceride secretion.[75] Although it is likely that exercise

mediated increases in LPL activity are responsible for the reductions in postprandial lipemia, reductions in VLDL-triglyceride secretion may also contribute to these reductions. Since skeletal muscle LPL activity would be expected to increase following exercise, but not niacin, it might be hypothesized that a similar reduction in postprandial triglycerides would occur when exercise is combined with niacin. Our data support the contention that VLDL-triglyceride secretion contributes to the reduction in postprandial lipemia with exercise since exercise performed after the niacin intervention produced only an additional 4% reduction in the triglyceride AUC_T from the niacin condition.

Increases in skeletal muscle [119] and post-heparin LPL activity have been observed following acute [17, 18, 34] and chronic exercise [120, 121] in both sedentary and physically active populations. Exercise increases LPL activity in skeletal muscle in a number of ways: 1) increases in LPL mRNA [119] 2) increased activity of luminal LPL [184] 3) Increased LPL mobilization to the endothelial surface via β-adrenergic stimulation and/or skeletal muscle contractile activity.[31]

Insulin have been proposed to play a permissive role in the regulation of skeletal muscle LPL activity following aerobic exercise.[31] During the postprandial state, insulin has been shown to upregulate adipose tissue LPL activity with essentially no changes in skeletal muscle LPL activity. Therefore, the upregulation of adipose tissue LPL activity following a meal would be expected to increase hydrolysis of triglycerides in adipose tissue and may contribute to increases in postheparin LPL activity observed after exercise in sedentary and obese individuals. It is possible that the well known reductions in postprandial insulin concentrations observed when exercise is performed before a meal may lower the attenuating effect of insulin on skeletal muscle LPL

activity.[71, 126] An increase in skeletal muscle LPL activity during the postprandial state would be expected to enhance triglyceride clearance and facilitate cellular NEFA uptake when exercise is performed before a meal.

We found that insulin concentrations in the exercise condition were similar to baseline following a high-fat meal whereas insulin concentrations increased by over 40% during the control condition two hours following a meal. Similarly, Aldred and colleagues [41] found that insulin concentrations were 22% lower than control when aerobic exercise was performed sixteen hours before a meal. In combination, these results provide evidence that the rise in insulin after a meal is attenuated when exercise precedes a meal.[71] Although we can only speculate from the results of the current investigation, a dampened insulin response to a meal after exercise provides a permissive condition that allows LPL activity to increase uninhibited by a normal insulin response.

Although empirical evidence to support the hypothesized regulation of VLDL-triglyceride secretion by exercise is limited, indirect evidence in both animal and human models suggests that prior exercise may reduce postprandial VLDL-triglyceride secretion.[132, 133] Mondon and colleagues [132] found that exercise training lowered the secretion of pre-labeled VLDL-triglyceride in rats following 70 to 85 days of self-selected running. The proposed mechanisms for the reduction in VLDL-triglyceride secretion was a reduction in serum insulin concentrations indicating an increase in hepatic insulin sensitivity and a reduction in free fatty acid substrate availability for VLDL synthesis. Prior exercise increased postprandial insulin and NEFA concentrations in humans providing further support that exercise may increase NEFA oxidation in the

liver thereby reducing VLDL-triglyceride secretion and ultimately plasma triglyceride concentrations in the postprandial state.[134]

Reductions in postprandial insulin concentrations observed during the exercise condition of the current investigation may indicate an improvement in insulin sensitivity. The suggestion that insulin sensitivity improved during the exercise condition is limited in that we did not directly measure insulin sensitivity. However, the lower insulin concentrations during the postprandial state of the exercise condition compared to control with no changes in blood glucose suggests that insulin sensitivity was improved in the exercise condition. Increased insulin sensitivity has been associated with lower hepatic VLDL-triglyceride secretion.[4] Therefore, a reduction in VLDL secretion may also contribute to a lower postprandial lipemic response after exercise.

It remains unclear as to whether skeletal muscle LPL activity or VLDL-triglyceride secretion play primary or supporting roles in the reduction of postprandial lipemia following exercise. Since an increase in skeletal muscle LPL activity is unexpected with niacin and due to the absence of a reduction in the triglyceride AUC_I with niacin, it appears that reductions in VLDL-triglyceride secretion play a significant role in the reduction of postprandial lipemia with aerobic exercise. Additional work will be required to determine the role of skeletal muscle LPL activity and VLDL-triglyceride secretion in obese, insulin resistant individuals with elevated triglycerides when exercise is performed one hour before a meal.

Effects of Niacin on Postprandial Lipemia

This is the first study to examine the effects of extended-release niacin on postprandial lipemia. The results of the present investigation provide evidence for the

first time that extended-release niacin reduces postprandial lipemia and the reduction in postprandial lipemia is similar to what has been previously reported for other forms of niacin. We found that niacin reduced the triglyceride AUC_T to a greater extent than exercise alone. However, it appears that the niacin-mediated reductions in the triglyceride AUC_T are primarily due to reductions in fasting triglyceride concentrations as evidenced by the absence of change in the triglyceride AUC_I.

Previous investigations have used immediate-release forms of niacin [48] or high dosages to quantify the effects of niacin on postprandial lipemia.[63] King and colleagues [48] found that 12 weeks of niacin at 2000 $mg \cdot day^{-1}$ reduced the triglyceride AUC_T by 41% and the triglyceride AUC_I by 45% in patients with hypertriglyceridemia and low HDL-C concentrations. In the current investigation, six weeks of extended-release niacin reduced the triglyceride AUC_T by 23% and the peak triglyceride response by 18%. However, the triglyceride AUC_I was not changed by niacin suggesting that although niacin reduced fasting triglycerides and the absolute triglyceride concentrations following a meal, that the increase in postprandial triglycerides relative to baseline was similar to control. The conflicting results for the triglyceride AUC_I in the current investigation and those by King and colleagues [48] may be explained by differences in the method used to calculate the incremental AUC. King and colleagues [48] used baseline triglyceride concentrations before the niacin intervention to calculate the triglyceride AUC_I instead of the fasting triglyceride concentrations following the niacin intervention. In the present investigation, the triglyceride AUC_I was calculated using the baseline fasting triglyceride concentrations following the six-week niacin intervention.

O'Keefe and colleagues [63] found that high dosages of niacin (3000 $mg \cdot day^{-1}$) and pravastatin (20 $mg \cdot day^{-1}$) for 18 weeks reduced postprandial lipemia in older men and postmenopausal women with hyperlipidemia. Pravastatin + niacin reduced the triglyceride AUC_T by 32% compared to pravastatin alone while the triglyceride AUC_I was unreported. These results suggest that niacin had the primary influence on postprandial lipemia.

The mechanisms by which niacin reduces both fasting and postprandial triglycerides are unclear. However, niacin may elicit direct or indirect inhibition of adipose tissue adenylate cyclase activity.[58] Reductions in adenylate cyclase activity reduce the activation of hormone sensitive lipase and ultimately reduces plasma NEFA concentrations. Since adipocyte-derived fatty acids are an important substrate for the synthesis of triglycerides in the liver and since triglycerides are required for the synthesis and secretion of VLDL particles, a reduction in plasma NEFA concentrations might reduce the secretion of VLDL-triglycerides by the liver ultimately reducing plasma triglyceride levels.

The temporal changes observed with niacin were primarily due to the reduction in fasting triglyceride concentrations in the present investigation. Therefore, the reduction in postprandial lipemia with niacin may be due to a reduction in fasting VLDL-triglyceride levels as opposed to an increase in the clearance of chylomicron and VLDL particles. A reduction in fasting VLDL-triglyceride concentrations would provide a reduction in the relative number of triglyceride-rich lipoproteins associated with LPL and enhance triglyceride clearance following a meal.

Interactive Mechanisms

It was hypothesized that since the proposed mechanisms by which niacin and exercise lower postprandial lipemia are different, that combining the interventions could result in an additive influence or reduce the influence of one over the other. Exercise reduced postprandial lipemia by decreasing triglycerides relative to baseline while niacin appears to lower postprandial lipemia primarily by reducing fasting triglyceride concentrations. When exercise and niacin were combined, the influence of exercise on postprandial lipemia was attenuated as evidenced by the absence of change in the triglyceride AUC_I indicating that at least part of the effect of exercise is similar to that of niacin and may reflect a decrease in hepatic VLDL secretion. It is also possible that the 37% reduction in the fasting triglyceride concentrations that occurred with the niacin intervention decreased available substrate. On the other hand, since the decreased insulin response to a meal after exercise was not observed after niacin, it is possible that niacin-mediated reductions in insulin sensitivity allow for continued suppression of VLDL-triglyceride secretion not observed when insulin sensitivity is increased after exercise.

Effects of Exercise on Fasting Triglyceride Concentrations

A secondary purpose of this investigation was to examine the effects of six weeks of niacin on the fasting triglyceride responses in the days following a single session of aerobic exercise. Aerobic exercise reduced fasting triglyceride concentrations by up to 27% forty-eight hours post-exercise in the present investigation. These findings are consistent with those from previous investigations.[20, 21, 151, 185-187] A single session of aerobic exercise designed to expend 350 kcals at 50% and 85% of $\dot{V}O_{2max}$ lowered fasting triglycerides by approximately 15% forty-eight hours after exercise in a

group of sedentary, hypercholesterolemic males.[27] Grandjean and colleagues [17] found that fasting triglyceride concentrations were reduced by 12% forty-eight hours following a single session of moderate-intensity exercise designed to expend 500 kcals. Ferguson and colleagues [16] observed a stepwise reduction in triglycerides with single sessions of moderate-intensity aerobic exercise designed to expend 800, 1100, 1300 and 1500 kcals in a group of exercise-trained males. Triglyceride reductions ranged from 26% at the 800 kcal exercise bout to 36% at the 1500 kcal exercise bout. The authors found that post-heparin LPL activity was increased up to 24-hours following the 1100 kcal exercise bout. Therefore, it appears that energy expenditures of 350 to 500 kcals may be required to reduce fasting triglycerides following a single session of aerobic exercise in sedentary males.

Effects of Niacin + Exercise on Fasting Triglyceride Concentrations

The results of this investigation suggest that combining niacin with a single session of aerobic exercise attenuates the triglyceride lowering effect of exercise in individuals with the metabolic syndrome. The most logical explanation for these findings is that the significant reduction in fasting triglycerides observed after six weeks of niacin reduced the triglyceride substrate available for skeletal muscle LPL. For example, a meta-analysis of blood lipid changes with exercise suggests that reductions in fasting triglycerides occur less frequently when initial triglyceride concentrations are low.[188]

Alternatively, it is possible that the higher insulin concentrations and insulin resistance observed in the niacin + exercise condition compared to exercise alone may have contributed to the absence of a reduction in fasting triglyceride levels 24 and 48 hours following exercise in the niacin + exercise condition. For example, Maheux and

colleagues [189] found that insulin resistance was associated with low post-heparin and adipose tissue LPL activity. Although the contribution of adipose tissue LPL activity to changes in fasting triglyceride concentrations is thought to be limited with exercise [31], it is possible that the chronic effect of insulin resistance on adipose tissue LPL activity may have contributed to the attenuation of the triglyceride lowering effect of exercise in the present study.

Likewise, chronic elevations in insulin concentrations have been shown to reduce the activation of skeletal muscle LPL.[33] A high carbohydrate diet was associated with elevated plasma concentrations of insulin and 55% reductions in LPL activity in skeletal muscle when compared to a mixed control diet. [190] Therefore, it is plausible that the niacin mediated increase in insulin levels reduced both adipose tissue and skeletal muscle lipoprotein lipase activity and may be responsible for attenuating the reduction in triglycerides associated with exercise.

Effects of Niacin on Blood Parameters by Week

Niacin lowered baseline triglycerides by 37% and raised HDL-C concentrations by 15% at the completion of the study. The most significant reduction in triglyceride concentrations occurred during the fourth week of the intervention and appeared to plateau by week six while HDL-C did not increase until the fifth week of the intervention. Our findings are consistent with the well-known reductions in triglycerides and increases in HDL-C following the administration of all forms of niacin at 1500 to 2000 $mg \cdot day^{-1}$ [48, 51, 52, 144, 191].

For example, Grundy and colleagues [57] reported that eight weeks of niacin at 1500 $mg \cdot day^{-1}$ reduced triglyceride concentrations by 35% in diabetic individuals with

hypertriglyceridemia. Triglyceride concentrations were not reduced beyond eight weeks. Similar reductions in triglyceride concentrations were observed in hyperlipidemic individuals taking niacin for up to 96 weeks.[51, 144] The results of the current investigation and those of previous investigations suggest that the greatest reduction in triglycerides occur between four and eight weeks with extended-release niacin.

Adverse Reactions

Despite the efficacy of niacin on blood lipid metabolism, the use of niacin in clinical practice has remained limited due to a number of adverse reactions. The most common adverse reactions associated with niacin are flushing, nausea, loss of appetite and increases in glucose concentrations.[54, 60, 77] We found that cutaneous flushing was reported at some point during the investigation in 60% of the participants. However, the event was generally isolated, was not associated with the rapid titration or dosage used in the study and was similar to the number of events reported in previous investigations.[51, 65]

Niacin increased fasting blood glucose concentrations in the current investigation by 12% but did not increase insulin concentrations or the HOMA score. Westphal and colleagues [192] observed an 11% elevation in blood glucose concentrations after eight weeks of niacin in a similar cohort. In contrast to the present investigation, fasting insulin concentrations and the HOMA score were significantly increased with niacin administration. Differences in our cohort's baseline insulin sensitivity and the size of the cohort used may be responsible for the absence of an increase in insulin concentrations or the HOMA score in the present investigation. Baseline insulin concentrations were 60% higher and the HOMA score 18% higher in the present investigation compared to

Westphal and colleagues.[192] It is possible that a more severe state of insulin resistance at baseline reduced the magnitude of change in insulin resistance relative to baseline in the present investigation.

Other investigations which have studied the effects of extended-release niacin on blood glucose concentrations demonstrate that niacin increases blood glucose by approximately 5%.[50, 51, 65] However, each of these investigations was conducted for more than eight weeks and did not measure insulin concentrations or changes in insulin sensitivity. The duration of the investigation may be important since Goldberg and colleagues [65] found that 12 weeks of extended-release niacin increased blood glucose concentrations by 5.4% at dosages of 500 to 1500 $mg \cdot day^{-1}$ while blood glucose concentrations were lower than baseline at 24 weeks despite a significant increase in the niacin dosage (3000 $mg \cdot day^{-1}$). Additional work will be required to determine the long-term effects of extended-release niacin on blood glucose metabolism.

Outside Influences on These Findings

Factors that may have influenced the results of this investigation include diet, physical activity, and changes in body weight. Participants were advised throughout the investigation not to make significant changes in their diet. Participants recorded all food and drink consumed three days before the control/exercise conditions and the exercise/niacin + exercise conditions and throughout all blood sampling points. Total caloric intake and macronutrient composition were not significantly different within or between conditions suggesting that diet did not have an appreciable effect on the results of this investigation. During the six week period, participants were also asked to avoid regular continuous physical activity as much as possible. Most of the participants had

relatively sedentary jobs and were capable of maintaining their physical activity to typical activities of daily living. All refrained from any formal exercise. Our participant's average body weight did not change throughout the study suggesting that no major changes in dietary consumption or physical activity occurred or were an appreciable influence on the magnitude or direction of blood variable changes observed with exercise or niacin administration.

Overall Findings

The results of this investigation provide evidence that exercise and niacin are effective strategies to reduce postprandial lipemia. Niacin reduced the triglyceride AUC_T by 23% compared to control. However, there were no differences in the triglyceride AUC_I suggesting that the effects of niacin on postprandial lipemia are mediated through reductions in fasting triglyceride concentrations. Exercise reduced the triglyceride AUC_T and AUC_I suggesting that exercise lowers postprandial lipemia without the influence of changes in fasting triglyceride concentrations. Exercise was also associated with an additive reduction in both the triglyceride AUC_T and the triglyceride response when exercise was combined with niacin suggesting that niacin and exercise are potentially complementary interventions to reduce postprandial lipemia.

Fasting triglycerides were reduced up to 27% by forty-eight hours in the exercise condition. Following the administration of six weeks of niacin, the triglyceride lowering effect of exercise was attenuated suggesting that a combination of lower fasting triglycerides and an increase in insulin resistance observed after the niacin intervention may be responsible for these changes.

While the relationship between fasting triglycerides and CVD remain controversial, the relationship between postprandial lipemia and CVD are strong.[93] Since postprandial lipemia considers the extent and duration of triglyceride elevations after a meal and may be viewed as a marker for triglyceride metabolism, the results of this investigation may be beneficial for practitioners prescribing niacin and exercise to patients with elevated triglyceride levels and the metabolic syndrome. Niacin + exercise may be a more effective strategy to reduce fasting triglycerides and the triglyceride AUC_T following a meal than either intervention alone. The triglyceride AUC_T is what would be observed and physiologically is what the total triglyceride load is in the vascular space.

The reductions in postprandial lipemia observed when exercise was performed one hour before a high-fat meal is a tangible recommendation that may increase public awareness about the acute effect of a single session of aerobic exercise alone or combined with pharmacological agents such as niacin. It is important to note that this reduction in postprandial lipemia was achieved with a single session of exercise without weight-loss. Furthermore, exercise seems to provide a complementary attenuation of increases in insulin levels following niacin suggesting that exercise may improve insulin sensitivity after a meal. Regular physical activity of a quantity that may be inadequate for weight reduction may still impart health benefits including transient improvements in metabolic health that are correlated with CVD risk reduction.

Finally, the results of this investigation provide evidence that extended-release niacin is a safe and practical pharmacological option for lowering triglycerides in individuals with the metabolic syndrome. This was evidenced by the absence of changes

in liver enzymes, uric acid, and phosphorus or calcium concentrations. Only mild cases of flushing were reported in this investigation despite the rapid titration used.

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APPENDICES

Appendix A

RESEARCH STUDY
Cholesterol and Exercise

We are seeking male volunteers between the ages of 30 and 65 to participate in a study to examine the effects of exercise and niacin on cholesterol, triglycerides, insulin and blood sugar following a meal
If you meet the criteria for the study you will receive:

1. Niacin (Niaspan)
2. Maximal graded exercise test to evaluate your fitness
3. Blood pressure assessment at rest and during exercise
4. Body fat and bone mineral density assessment performed by DEXA scan
5. Blood lipid and glucose profile at rest and following meals

If you are interested in participating in this study please contact:

Eric Plaisance
Exercise Technology Laboratory
Department of Health & Human Performance
Auburn University
(334) 844-1482
plaisep@auburn.edu

Appendix B

Telephone Interview Questionnaire

1. Name _____ Age _____

2. Phone Number (Hm) _____ (Wk) _____ (Cell) _____

3. E-mail _____

4. Have you participated in any form of physical activity in the past 6 months? If yes,

    Type _____

    Frequency _____

    Duration _____

5. Do you have a history of heart disease, lung disease, lung disease, or diabetes? Please describe _____

6. Do you know your TC or TG level? _____

7. Do you currently take any medications? If so, please describe.
_____
_____

8. Do you currently smoke? _____

9. Do you have a history of peptic ulcer disease, gout, dysrhythmia, or liver disease?
_____

10. Do you have any orthopedic problems? _____

Appendix C

A Copy of the INFORMED CONSENT used FOR THE RESEARCH STUDY ENTITLED:

"The Effects of Extended-Release Niacin and a Single Session of Aerobic Exercise on Fasting and Postprandial Blood Lipids"

Principal Investigator:	Eric P. Plaisance, M.S.
Co-Investigator:	Peter W. Grandjean, Ph.D., FACSM
Address of Investigators:	Department of Health and Human Performance 2050 Beard-Eaves Memorial Coliesum Auburn University Auburn, AL 36849-5323
Phone Numbers:	Exercise Technology Laboratory: 334-844-1482 Dr. Grandjean's Office: 334-844-1462 Dr. Grandjean's Cell: 334-444-4641
E-mail:	Eric Plaisance plaisep@auburn.edu Dr. Grandjean grandpw@auburn.edu

1. Study Purpose

You have been invited to participate in research that is being conducted to evaluate the combined effects of six weeks of extended-release niacin (Niaspan) and a single session of aerobic exercise on blood lipids. Niacin has been shown to improve all components of the blood lipid profile including total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) ("bad" cholesterol), high-density lipoprotein cholesterol (HDL-C) ("good cholesterol") and triglycerides (TG) (fats in the blood produced by the body or eaten). However, niacin has been shown to have its greatest impact on TG and HDL-C levels.

A single session of aerobic exercise has also been shown to have short-term effects on how the body breaks down TG in the blood and often results in increases in HDL-C levels with little to no effect on TC and LDL-C. Although niacin and exercise have similar effects on TG and HDL-C levels, the method by which each intervention works is thought to be different. Therefore, we are interested in determining if 6 weeks of niacin combined with a single session of exercise will decrease TG and increase HDL-C levels to a greater extent than niacin or exercise alone.

A physically inactive lifestyle and being overweight are also associated with higher levels and durations of TG levels in the hours following a meal. When you consider that we eat as many as 3-4 meals per day, as much as two-thirds of the day may be spent trying to clear and breakdown TG in the blood. Niacin and exercise have both been shown to lower TG levels after a meal. Since the method by which niacin and exercise lower TG is different, it is possible that the combination of each of these strategies may lower TG more than either alone. Ultimately, the effects of niacin and exercise on blood triglyceride and HDL-C levels may reduce overall cardiovascular disease risk and provides the basis for our interest in the effect of each of these strategies to improve blood lipid levels. You have been asked to participate in this study because you are a male between the ages of 30-65 with no physical condition or medical indications that would preclude a reliable assessment of the effects of niacin and exercise on your blood lipid profile.

2. Procedures Used to Address the Purpose

After you volunteer and provide your informed consent to be a participant in this study, you will be given a health history questionnaire and physical activity questionnaire to complete. Your are encouraged to answer the questionnaires to the best of your knowledge to ensure your safety as a participant. Subsequently, we will measure your height and weight and waist girth. Next, we will obtain a small sample of blood from your finger tip to determine your fasting TC, HDL-C, LDL-C, TG, and glucose (blood sugar). Finally, we will provide an overview of the study protocol and answer any questions that you may have as a participant. The inclusion criteria for the study include: Age 30-65, physically inactive lifestyle, overweight, TG levels > 150 mg/dl, non-smoker. **If you have any history of gout, peptic ulcers, heart rhythm problems, diabetes or liver disease you should not participate in this study. You MUST make us aware of any of these conditions before we draw your blood by truthfully informing us verbally and by answering the questions on the health and lifestyle history questionnaire.**

If you meet all criteria for the study you will be asked to return to the Exercise Technology Lab to undergo a physical exam by a physician. Following the physical exam, you will have a body composition assessment done using a total body X-ray (DEXA) scan to determine body fat levels. You will then be asked to perform an endurance exercise test to determine your cardiovascular fitness. To perform this test, a 12-lead electrocardiogram will be performed at rest and throughout the exercise test. Blood pressure will be obtained periodically throughout the test by a trained technician. This type of test is used to determine your fitness level and is sometimes called a VO_{2max} test. The treadmill will begin at a comfortable walking pace and progressively increase in speed and elevation. You may discontinue the test at any point due to exhaustion or other reasons. Throughout the course of the test, you will breath through a mouthpiece that is connected to a computer so that your oxygen uptake and carbon dioxide production can be measured. Heart rate and ratings of perceived exertion will be monitored throughout the test. Please report any unusual symptoms such as

lightheadedness, dizziness, faintness, chest pain or other signs or symptoms during the course of the testing procedures.

If you are selected to continue, you will then be scheduled for a third visit to the lab to provide you with instructions detailing the particular aspects of the study. During this meeting we will provide you with a physical activity record and a dietary record designed to record all physical activity and all food and drink consumed, respectively. You will be shown how to record the information requested on each form. The physical activity record will be used to determine the amount of outside physical activity you perform. You will be asked to limit outside strenuous physical exertion, excluding the exercise intervention. The dietary record you complete will be used to encourage you to eat similar foods throughout all blood sampling periods but is not intended to change your diet. The dietary record will help us to make sure that the results of the study are not due to changes in your diet and to help maintain your body weight throughout the study. We will provide you with a determination of the caloric intake and nutritional composition of your diet at the end of the study. Following the instructional meeting, we will try to determine a schedule for you to return for the additional requirements of the study.

After 3 days on a standardized diet and 8-12 hour fast, you will be asked to return to the laboratory (visit 4) to have your blood drawn. You will also be asked to refrain from any moderate or strenuous physical activity for 72 hours (3 days) prior to blood sampling. A blood sample, equal to about 1 tbsp (14 ml), will be obtained by inserting a small catheter with a needle into the most prominent vein site in your lower are. Following the blood sample, you will be asked to drink a "milkshake" consisting of whipping cream (20 tbsp) and ice cream (1/2 cup) within 15 minutes. The meal is designed to be high in fat and contains approximately 1000 Calories, 100 g fat, 17 g carbohydrate, and 3 g protein. Immediately after you drink the meal, we will ask you to remain at the lab to measure blood samples at 2 hour intervals up to 8 hours for a total of 5 blood samples and 6 tbsps of blood (including the baseline blood sample). Approximately 0.5 tablespoon of blood (7 mL) will be drawn at each of the two hour intervals. You will be asked to remain in the lab over the 8 hour period but will be allowed to perform light activities such as reading, watching television, paperwork, computing, etc. We will remove the catheter from your vein immediately following the last blood sample at 8 hours.

You will be asked to return to the lab the following day again after an 8-12 hour fast. Upon arrival, we will obtain your body weight and allow you to sit for 5 minutes before inserting a venous catheter. Following a baseline blood sample, you will be asked to perform an exercise session on a motor driven treadmill. The goal of the exercise session is to burn 500 Calories in a single session. During each test you will be asked to walk on a treadmill at an intensity of 60-70% of your VO_{2max} for a length of time required to burn 500 total Calories (50-90 minutes). This submaximal exercise bout will be personalized so that you will exercise on a treadmill at a level that is most comfortable for you. One hour following the exercise session, we will ask you to drink an identical milkshake as the day prior. We will again obtain blood samples (0.5 tbsp) at 2 hour intervals for 8 hours for a total of 3 tbsps including baseline. The following day we will ask you to

return to the lab following an 8-12 hour fast. A single venous blood blood draw will be obtained totaling 1 tbsp of blood. The next day you will be asked to return to the lab again following an 8-12 hour fast for a single venous blood draw. Following the blood draw, you will be provided a 6-week prescription for niacin (Niaspan) by Dr. Jack Mahurin, D.O., to be filled at the Auburn University Pharmacy. You will be asked to take 1 niacin tablet (500 mg) per day before bedtime with a snack or meal and avoid hot liquids or meals. Within the first week of taking niacin, symptoms such as redness, tingling, or itching of the skin are observed in some individuals. Dr. Mahurin will advise you to take niacin in the evening with a meal or snack before bedtime to reduce the likelihood and/or severity of these symptoms. If you experience any adverse reactions please contact Dr. Grandjean immediately and he will contact Dr. Mahurin to determine if medical treatment or follow-up is necessary. You will be asked to return to the lab the following week to complete an adverse reaction questionnaire and to verify that you wish to continue you with the study. If you decide that you wish to continue, you will be provided a note to take to the AU pharmacy to have the second week of Niaspan filled. The dose will be 1000mg/day (taken in a single dose in the evening). The dose will be increased to 1500 mg per day for week 3 and maintained for 4 weeks for a total of 6 weeks of niacin administration. Each week you will be asked to complete a questionnaire detailing any side-effects you may experience and we will provide a note for you to take to the pharmacist to have the subsequent week's prescription filled. You will be excused from the study if at any point you experience side-effects that are not tolerated.

The day after completing the niacin intervention, we will ask you to return to the lab where the identical procedures will be performed for the high fat meals. In short, you will return to the lab following a 12 hour fast. A blood sample will be obtained again followed by the consumption of another milkshake. Blood samples will then be measured at 2-hour intervals for 8 hours. These blood samples will be used to determine the effects of niacin alone on blood lipid levels. The following day you will again be asked to return after an 8-12 hour fast where a fasting blood sample will be obtained followed by an identical exercise session as discussed above. Blood samples will then be sampled at 2 hour intervals for up to 8 hours. The blood samples obtained during this phase of the study will be to determine the combined effects of niacin and exercise on blood lipid levels. Fasting blood samples will then be obtained again 24 and 48 hours following the final high fat meal. The total time commitment for this study will be approximately 40 hours over 8 weeks.

3. <u>Discomforts or Risks to be Reasonably Expected</u>
The following few paragraphs provide information about the potential risks and discomforts that you may experience as a participant in this study.

The risks associated with the graded exercise test are comparable to those you face when you perform hard exercise, which causes you to sweat and breath heavily. These include occasional abnormal blood pressure responses, the possibility of fainting, potentially abnormal heartbeats, heavy and difficult breathing, and in rare instances, heart attack, or death. In addition, there is a risk of falling on the treadmill that could cause cuts, scrapes

or bruises. You could also suffer orthopedic injuries, such as ankle, knee, hip or muscle strains and sprains, or rarely fracture bones. Studies have shown that your risk of death during this type of test is about 0.5 in 10,000 and your risk of harmful effects is about 5 to 8 in 10,000. We will make every effort to minimize these risks by carefully reviewing your health and physical examination. All of these procedures will be done before you are allowed to exercise. If we find physical problems that in our judgment, make exercise risky, we will not allow you to exercise in the study. During the graded exercise test, we will ask you to wear a mouthpiece so that we can measure the amount of oxygen you consume and the amount of carbon dioxide you produce. The primary risk involved is contamination of the mouthpiece. The risk will be minimized by using mouthpieces that will be cleansed with each use and using anti-bacterial, germ-killing solutions to sterilize other equipment between uses.

Ten electrodes will be placed on your skin to measure the electrical activity of your heart during a procedure called an electrocardiogram (ECG). Each electrode's site will be prepared by rubbing the skin with an abrasive material and then cleansed with an alcohol pad. These procedures may cause some irritation and a mild stinging sensation. There is a slight possibility that you will be allergic to the gel used in the electrodes. This may cause some itching and redness of the area that might last for several days. All equipment used meets all safety specifications to minimize any risk of electrical shock. The procedures are performed with strict adherence to guidelines by the American College of Sports Medicine.

Venous blood sampling requires the introduction of a small gauge syringe to a forearm vein to acquire the blood sample. Risks of the procedure are minimal and rare, but may result in moderate bruising and stiffness around the affected site. In addition, as with any similar procedure disrupting the skin barrier, there is a risk of contracting an infection. The risk to you and the technician will be minimized through the use of accepted sterile procedures which include: (1) latex surgical gloves by the technician; (2) antiseptic cleansing (70% alcohol) of the involved site prior to the puncture; (3) use of sterile equipment and instruments for each sample; and (4) proper dressing of the wound with antiseptic and bandage following sample collection.

Dual Energy X-Ray Absorptiometry measures expose you to X-rays which would be equivalent to that obtained from an airline flight from Atlanta to Dallas or like being outside on a clear sunny day for 2 hours.

Individuals taking extended-release niacin (Niaspan) in prescription form experience fewer side effects compared to over-the-counter forms of niacin. However, it is common during the first two weeks of taking niacin to experience side-effects including flushing (defined as redness, tingling, or itching of the skin), gastrointestinal distress such as bloating or diarrhea, increases in blood glucose levels, and elevations in liver enzymes due to the breakdown of niacin in the body.

4. Precautions and available medical treatment

We will make every effort to minimize all of the risks listed above by carefully reviewing your health and medical history questionnaire, evaluating your risk factors for cardiovascular disease and undergoing a physical exam by a physician. All of these procedures will be done before you are allowed to exercise or are prescribed niacin. If we find physical problems that, in our judgement, make exercise or the use of niacin risky, for your own protection we will not allow you to exercise in this study. Compensation for participating in the study will not be provided and will not include medical costs for physical injury or adverse effects. The participant is responsible for the cost of medical care needed as a result of participating in the study. Eric Plaisance and other trained graduate students will be in charge of conducting all of the lab and exercise measurements. Dr. Grandjean will supervise all of the exercise testing procedures and will be available in the event of an emergency. Dr. Grandjean and all individuals involved with the testing procedures are trained in CPR. Dr. Jack Mahurin, D.O., will provide medical supervision for all graded exercise tests and medical oversight for the niacin intervention. The emergency equipment and emergency plans for the Exercise Technology Laboratory meets standards that are recommended by the American College of Sports Medicine for non-medical exercise testing facilities.

All investigators will closely follow the emergency plans and procedures that have been previously established for the laboratory. The 7th edition of the American College of Sports Medicine's Guidelines for Exercise Testing and Prescription (2005) will be observed throughout all body composition assessment and graded exercise test procedures.

5. Benefits of participation

You will receive a physician exam and maximal graded exercise test with 12-lead electrocardiography. Body composition measurements such as waist measurements and the DEXA scan will also provide valuable information regarding your percentage fat and body weight distribution. You will also receive 6 weeks of Niaspan and blood lipid levels before and following the niacin intervention both fasting and following a meal. Finally, you will receive a report detailing your personal results from the study.

6. Right to privacy

All individual information obtained in this study will remain confidential and your right to privacy will be maintained. Data collected will be used for research purposes only and will be limited to access by the investigators of this study. Only data reported as group means or responses will be presented in scientific meetings and published in scientific journals. Confidential data will be destroyed following the project.

7. Consent

Participation is entirely voluntary. The decision to participate or not will not jeopardize your relationship with the Department of Health and Human Performance or Auburn University. Refusal to participate involves no penalty. You may withdraw your consent

and discontinue participation at any time for any reason. **We also reserve the right to withdraw you from the treatment regimen if we see any condition brought on by research adversely affecting your health.**

8. Questions concerning the research and the procedures

As investigators, it is our obligation to explain all of the procedures to you. We want to make sure that you understand what is required of you and what you can expect from us in order to complete this research project.

Please do not hesitate to inquire about the research, rights and responsibilities of the participant and the investigator now or at any time throughout the study.

9. Additional information regarding your rights as a research participant

For more information regarding your rights as a research participant, you may contact the Auburn University Office of Human Subjects Research or the Institutional Review Board by phone (334)-844-5966.

I HAVE READ AND UNDERSTAND THE EXPLANATIONS PROVIDED TO ME AND VOLUNTARILY AGREE TO PARTICIPATE IN THIS STUDY. I UNDERSTAND THAT I WILL BE GIVEN A COPY OF THE ENTIRE INFORMED CONSENT FOR MY OWN RECORDS.

_____ _____

Participant Signature Date

_____ _____

Investigator Obtaining Consent Date

Appendix D

HEALTH & LIFESTYLE HISTORY QUESTIONNAIRE

Please complete this form as accurately and completely as possible. The information you provide will be used to evaluate your health by the principle investigators who will oversee the conductance of this study. All information will be treated as privileged and confidential.

NOTE: This information is being collected for use in the study entitled, "The Effects of Extended-Release Niacin and a Single Session of Aerobic Exercise on Fasting and Postprandial Blood Lipids. All information obtained in this document will be destroyed upon completion of the study.

1. IDENTIFICATION & GENERAL INFORMATION

Name			Today's Date		
			/ / 06		
Age	**Date of Birth**	**Gender**	**Occupation**		
	/ /				
Home Address			**City**	**State**	**ZIP**
Home Phone	**Work Phone**		**e-mail**		
Emergency Contact		**Phone**	**Physician**		**Phone**

Please check the box that applies to you:

Race or Ethnic Background

☐ White, not of Hispanic origin ☐ American Indian / Alaskan native ☐ Asian

☐ Black, not of Hispanic origin ☐ Pacific Islander ☐ Hispanic

2. ILLNESS & MEDICAL HISTORY

Check all of the conditions or diseases for which **you** have been diagnosed and/or treated. Also give the date of occurrence or diagnosis. If you suspect that you may suffer from one of the conditions, please indicate this in the right hand margin after the date.

Medical Condition	Check if Applicable	Date Diagnosed (M / Yr)	Current?
AIDS			
Allergies			
Arthritis			
Osteoarthritis			
Rheumatoid			

Medical Condition	Check if Applicable	Date Diagnosed (M / Yr)	Current?
Asthma			
Bronchitis (chronic)			
Bone Fracture			
Cancer of any kind			
Cataracts			
Cirrhosis (liver)			
Colitis (ulcerative)			
Depression			
Eating Disorders (anorexia, bulimia)			
Emphysema			
Epilepsy			
Frequent Bleeding			
Gallstones / Gallbladder Disease			
Glaucoma			
Gout			
Hearing Loss			
High Anxiety / Phobias			
Hepatitis / Other liver problems			
Hysterectomy			
Menstruation Problems			
Osteoporosis			
Pneumonia			
Tuberculosis			
Renal / Kidney Problems			
Sleeping Problems			
Stomach / Duodenal Ulcer			
Substance Abuse Problems			
Rectal Growth or Bleeding			
Metabolic Problems Diagnosed	**Check if Applicable**	**Date Diagnosed (M / Yr)**	**Current?**
Thyroid Problems			
Diabetes			
Other			
Cardiovascular Problems Diagnosed	**Check if Applicable**	**Date Diagnosed (M / Yr)**	**Current?**
Angina			
Anemia (low iron)			
Coronary Disease			
Disease of the Arteries			
Enlarged Heart			
Heart Attack			
Heart Murmur			
Heart Rhythm Problem			

Heart Valve Problem			
Heart Problem (other)			
Heart Problem (other)			
High Blood Pressure (controlled)			
High Blood Pressure (uncontrolled)			
Medical Condition	**Check if Applicable**	**Date Diagnosed (M / Yr)**	**Current?**
Peripheral Vascular Disease			
Phlebitis or Emboli			
Rheumatic Fever			
Rheumatic Heart Disease			
Pulmonary Emboli			
Other Health Problems			
Any other health problems (please specify and include information on any recent illnesses, hospitalizations, or surgical procedures			
Have you ever had:	**Check if Applicable**	**Date Diagnosed (M / Yr)**	
An abnormal chest x-ray?			
An abnormal electrocardiogram (ECG)?			
An exercise stress test?			
An abnormal exercise stress test?			
Orthopedic Problems	**Check if Applicable**	**Date Diagnosed (M / Yr)**	**Current?**
Low Back Pain			
Shoulder Pain			
Elbow Pain			
Wrist or Hand Pain			
Hip Problems			
Knee Problems			
Ankle or Foot Problems			
Is your work or any other activity limited by a current orthopedic problem? If so, please specify:			
Other Orthopedic Problems			
Any other orthopedic problems (please specify and include information on any recent illnesses, hospitalizations, or surgical procedures			

3. SYMPTOMS or SIGNS SUGGESTIVE of DISEASE

Do you presently have or recently had (Check if Applicable):

Yes	Description	Yes	Description
	Have you experienced unusual pain or discomfort in your chest, neck, jaw, arms other areas that may be due to heart problems?		Do you suffer from swelling of the ankles (ankle edema)?
	Have you experienced unusual fatigue or shortness of breath at rest		Have you ever experienced an unusual and rapid throbbing or fluttering of the heart?
	Have you had any problems with dizziness or fainting?		Have you ever experienced severe pain in your leg muscles during walking?
	When you stand up, or sometimes during the night while you are sleeping, do you have difficulty breathing?		Has your doctor told you that you have a heart murmur?
	Have you ever experienced a seizure?		Have you ever had unexpected weight loss of 10 lbs or more?

3. Symptoms or Signs Suggestive of Disease

Do you presently have or recently had (Check if Applicable):

Yes	Description	Yes	Description
	Are you a male over 45 years of age, or a female over 55 years of age who has		Is your total serum cholesterol greater than 200 mg/dL
	Has your father or brother had a heart attack, cardiac revascularization surgery, or died suddenly of heart disease		Is your HDL cholesterol low (< 40 mg/dL for males, < 50 mg/dL for females), or has your doctor ever told you that your HDL cholesterol is low
	Are you a current cigarette smoker?		Are your triglyceride levels > 200 mg/dL, or has your doctor ever told you that your triglycerides are high?
	Has a doctor told you that you have high blood pressure (more than 140 / 90 mmHg)		Are you physically inactive and sedentary (little physical activity on the job
	Do you have diabetes mellitus?		Do you weigh more than 20 lbs more than you should?

Additional Family History Information

Check all of the conditions or diseases for which **any member of your immediate family, including grandparents**, have been diagnosed and/or treated. Also provide their age and the date of occurrence or diagnosis if known.

Medical Condition	List Relative & Age at Diagnosis	Date Diagnosed (M / Yr)
High Blood Pressure before age 40		
High Cholesterol		
Obesity		
Diabetes		
Stroke under age 50		
Heart Attack under age 50		
Heart Operation		
Cancer under age 60		

Physical Activity Information

Please check the box that best describes you.

1. In general, compared to other persons your age, rate how physically fit you are:

Not at all fit	Slightly below average fitness	Average fitness	Slightly above average fitness	Extremely fit
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Outside of your normal work, or daily responsibilities, how often do you engage in physical exercise?

☐ 5 or more times per week ☐ 3 - 4 times per week ☐ 1 - 2 times per week

☐ Less than 1 time per week ☐ Seldom or never

3. On average, how long do you exercise on each occasion?

☐ 10 - 20 min ☐ 20 - 30 min ☐ 30 - 40 min ☐ 40 - 50 min ☐ > 50 min

4. On a scale of 1 to 10 (1 being the lowest, 10 being the highest), how would you rate your exercise intensity ?

☐ Very Low (1 - 2) ☐ Low (3 - 4) ☐ Moderate (5 - 6) ☐ Mod. - High (7 - 8) ☐ High (9 - 10)

5. How much strenuous physical work is required on your job?

☐ A great amount (> 60%) ☐ A moderate amount (30 - 50%)

☐ A little (< 30%) ☐ None

6. **How often does your work entail repetitive pushing and pulling or lifting while bending or twisting, leading to back pain?**

☐ All of the time ☐ Most of the time

☐ Some of the time ☐ Rarely or never

Body Weight Information

1. **What is the most you have ever weighed?** _____ **When?** _____

2. **Are you currently trying to:**

☐ Lose weight ☐ Gain weight

☐ Stay the same ☐ Not trying to do anything

Substance Use

1. **How would you describe your tobacco use habits?**

☐ Never smoked ☐ Used to smoke (How long ago did you quit?):

☐ Still smoke (How many cigarettes / day?): ____

2. **How many alcoholic drinks do you consume? (A "drink" is one glass of wine, a wine cooler, a bottle / can of beer, a shot glass of liquor, or a mixed drink).**

☐ Never use alcohol ☐ Less than 1 per week ☐ 1 - 6 per week

☐ 1 per day ☐ 2 - 3 per day ☐ More than 3 per day

5. MEDICATIONS

Please indicate any medications, prescription or "over the counter" by providing the name and dosage:

Medication Type	Name of Medication	Dosage
Heart Medicine		
Blood Pressure Medicine		
Blood Cholesterol Medicine		
Insulin		
Other Medicine for Diabetes		
Thyroid Medicine		
Medicine for Breathing / Lungs		
Medicine for Weight Loss / Weight Control		
Hormones		

Birth Control Pills		
Painkiller Medicine		
Arthritis Medicine		
Medicine for Depression		
Medicine for Anxiety		
Medicine for Ulcers		
Allergy Medicine		
Other (please specify)		

In addition to the above information that you have listed, are you aware of any other conditions, symptoms, or special circumstances that might be related to your overall health and well being or that may influence your ability to participate in this study? _____ If so, please give an explanation below. _____

Appendix E

E X E R C I S E Q U E S T I O N N A I R E

Name: _____ Date: _____

1. Are you currently engaged in aerobic exercise on a regular basis?_____

(Regular exercise is defined as "at least 30 minutes per session, 3 sessions per week for the last 6 months). If not, when was the last time you exercised on a regular basis? _____

2. How many times per week do you exercise?_____

3. In general, how long does each exercise session last?_____

4. What type of activity do you engage in for your workouts? (Circle all that apply)

Walking	Cycling	Aerobics Class or Video	Swimming
Stairclimber	Jogging	Elliptical Rider	Other:_____

5. Which of these activities do you engage in most?_____

6. Do you take your pulse during your workout?_____

If so, What is your typical heartrate range?_____ to _____

7. Please rate the exercise intensity that you ordinarily maintain throughout a typical workout.

6
7 very, very light
8
9 very light
10
11 fairly light
12
13 somewhat hard
14
15 hard
16
17 very hard
18
19 very, very hard
20

Appendix F

Daily Food Record

- RECORD EVERYTHING YOU EAT AND DRINK INCLUDING SNACKS AND BEVERAGES.

- RECORD IMMEDIATELY AFTER FOOD IS CONSUMED

- INDICATE PORTION SIZES. MEASURE AMOUNTS OF EACH FOOD USING MEASURING CUPS OR SPOONS WHEN IT IS PRACTICAL. RECORD PORTION SIZES IN GRAMS, OUNCES, CUPS, TABLESPOONS, TEASPOONS, OR PIECES. (example: 8 oz. orange juice, 1 piece wheat bread, 1 tbsp. butter)

- INDICATE THE BRAND NAME. (3 oz. Ruffles BBQ Potato Chips, 1 cup Uncle Ben's Long Grain Rice, McDonald's Large French Fries)

- INDICATE FORM OF PURCHASE. (fresh, frozen, canned, etc.)

- RECORD TIME OF DAY MEAL WAS EATEN

- RECORD AND CHECK THE NUMBER OF SERVINGS FOR EACH ITEM LISTED

  ST= Starch (bread, pasta, cereal, rice, etc.)
  MT= Meat (poultry, beef, fish, eggs, nuts)
  V=Vegetable
  FR= Fruit
  D= Dairy (milk, yogurt, cheese, etc.)
  FT= Fat (butter, oil)
  B= Beverage (regular soft drinks, sweet tea, sports drinks, etc.)

Please be as specific and thorough as possible with the dietary information you provide. Thank You!

If you have any questions, please contact:

Eric Plaisance

plaisep@auburn.edu

Exercise Technology Lab: 334-844-1482

Time	Food	Quantity	Exchange

Appendix G

Daily Physical Activity Record

Name: _____ **Date:** _____

Please complete the following Physical Activity Record as accurately as possible. Estimate the total number of hours you spend per day performing activities from the categories listed below. Report time spent in the activity to the nearest minute. Similar activities are grouped together. If you perform an activity that is not already included in **Categories 1-9**, choose a category which lists similar activities. If no category applies to your activity, use **Category 10** and specify the activity performed.

Category	Physical Activity Description	Time Spent in Physical Activity
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		

Category 1 = sleeping, resting in bed, sitting quietly
Category 2 = eating, writing
Category 3 = washing dishes, combing hair, cooking, driving
Category 4 = slow walking, dressing, showering
Category 5 = floor sweeping, mopping, slow cycling (5.5 mph), recreational volleyball
Category 6 = recreational golf, baseball, rowing, bowling, walking at moderate speed (3mph)
Category 7 = yard work, loading and unloading goods
Category 8 = jumping, canoeing, bicycling (9mph), dancing, skiing, tennis
Category 9 = weight training, jogging / running (less than 12 minutes per mile), racquetball, swimming, hiking, bicycling (>15 mph)
Category 10 = any activity that does not seem to fit in any of the categories listed above

Appendix H

Pre-Blood Draw Questionnaire

NAME _____ DATE _____

VISIT _____

Please Answer 'YES' or 'NO' to the following questions

_____ 1. Have you fasted overnight (8-12 hours)?

If not, when was your last meal? _____

_____ 2. Have you had anything to drink in the last 12 hours?

If so, please list any the type of drink (e.g. water, coke, juice)

_____

_____ 3. Are you taking any medications to thin your blood?

If so, please list _____

_____ 4. Do you currently have any medications "on board"

_____ 5. Have you engaged in any strenuous physical activity