THE EFFECTS OF NIACIN AND A SINGLE BOUT OF AEROBIC EXERCISE ON GLUCOSE, INSULIN, AND C-PEPTIDE PROFILES IN POSTMENOPAUSAL WOMEN

A THESIS

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BY

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To the Dean of the Graduate School:

I am submitting herewith a thesis written by Heidi Bidstrup entitled "The Effects of Niacin and a Single Bout of Aerobic Exercise on Glucose, Insulin, and C-peptide Profiles in Postmenopausal Women." I have examined this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science with a major in Kinesiology.

David L. Nichols, Major Professor

We have read this thesis and recommend its acceptance:

Department Chair

Accepted:

Dean of the Graduate School

DEDICATION

A ma famille, pour sa patience et son soutien.

Je vous embrasse très fort.

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ABSTRACT

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THE EFFECT OF NIACIN AND A SINGLE BOUT OF AEROBIC EXERCISE ON GLUCOSE, INSULIN AND C-PEPTIDE PROFILES IN POSTMENOPAUSAL WOMEN

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The purpose of this investigation was to determine the effects of niacin and a single bout of aerobic exercise on glucose, insulin, and C-peptide profiles in postmenopausal women. Seventeen sedentary, women (57 ± 6 years) served as participants. A rest and exercise (treadmill walking at 60% HRR, expending 400 kcal) trial without niacin was performed first followed by a with niacin trial (1000 mg/day for 4 weeks). Fasting blood samples were collected for three consecutive days for all trials. The 24 hour time point results found niacin significantly increased glucose from 95.03 mg/dL to 105.07 mg/dL; insulin from 16.98 μU/mL to 27.48 μU/mL; and C-peptide from 1.65 ng/mL to 2.41 ng/mL. Exercise alone or combined with niacin showed no significant change in values. Given the adverse effects of niacin, the use of niacin in postmenopausal women should be conducted with caution and under medical supervision until further investigations are conducted.

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CHAPTER I

INTRODUCTION

The leading causes of death in the Western World are cardiovascular disease (CVD) and coronary heart disease (CHD). Smoking, leading a sedentary lifestyle, the metabolic syndrome, and Type 2 diabetes mellitus (T2DM) are contributing risk factors for developing the aforementioned diseases. Impaired insulin sensitivity and insulin resistance resulting in impaired glucose tolerance and impaired fasting glucose and hyperinsulinemia are contributing risk factors in the development of T2DM. The frequency of impaired fasting glucose is more common in men and plateaus around middle age whereas impaired glucose tolerance is more common in women and its frequency increases with age (Unwin, Shaw, Zimmet, & Alberti, 2002). Postmenopausal women with impaired fasting glucose of $\geq$ 110 mg/dL have a higher risk of sustaining cardiovascular events (Kanaya et al., 2005). The rise in postchallenge glucose levels has a significant correlation to increases in age (Rhee, Ziemer, Kolm & Phillips, 2006). In as little as 3 years glucose tolerance has been shown to deteriorate from normal levels to impaired glucose tolerance or T2DM (Hiltunen, Läärä, & Keinänen-Kiukaanniemi, 1999).

Aging and menopause are associated with weight gain, subcutaneous abdominal fat and visceral abdominal fat accumulation in the abdominal and truncal areas and loss of fat free mass. Menopause is also associated with changes in insulin secretion,

metabolism, and sensitivity which result in decreased glucose tolerance and T2DM (Gaspard, Gottal, van den Brûle, 1995). The decrease in glucose tolerance in middle-aged men and women is attributed to visceral abdominal fat per se, not age, (Imbeault et al., 2003) while subcutaneous abdominal fat has been found to have no correlation with glucose disposal in older women (Brochu et al., 2001; Yeo et al., 2007). In addition to the changes in body composition, aging also brings about metabolic changes resulting in insulin resistance (Cefalu et al., 1995), hyperinsulinemia (Gumbiner et al., 1989), and impaired glucose tolerance. Investigations into the underlying cause of the metabolic changes have ended with mixed results. Aerobic exercise and weight loss are helpful in reversing insulin resistance and increasing insulin sensitivity in obese elderly men and women (O'Leary et al., 2006). In contrast, aerobic exercise was not found to improve insulin sensitivity in men and women aged 40 and older, but did improve insulin sensitivity in those 39 year old and younger (Short et al., 2003). Increasing physical activity increases insulin sensitivity and glucose tolerance in middle aged men and women (Ekelund, Franks, Sharp, Brage, & Wareham, 2007). Regular aerobic exercise has been reported to decrease fasting insulin levels in obese young men and women (Björntorp et al., 1977; LeBlanc, Nadeau, Richard, & Tremblay, 1981) and in sedentary, postmenopausal women (Frank et al., 2005). Asikainen et al. (2003) found aerobic exercise did not affect fasting insulin levels in postmenopausal women (PMW) but did lower fasting glucose levels whereas Fox et al. (1996) found neither fasting insulin nor fasting glucose levels to be affected by regular aerobic exercise.

Dyslipidemia is a contributing risk factor of the metabolic syndrome and causes atherosclerosis. For reasons not completely understood, low-density lipoprotein cholesterol (LDL-C) concentrations, mostly of the small, dense LDL-C phenotype, increase approximately 15 to 25% in women upon entering menopause resulting in a sharp increase in the rate of CHD in this population (Davidson, Maki, Katz Karp, & Ingram, 2002). The decline in circulating estrogen observed during menopause is believed to be the underlying cause of these adverse changes. The primary prevention plan for dyslipidemia is diet and lifestyle changes (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). When the desired lipid levels are not achieved through primary prevention drug therapy is required. The use of niacin or the combination of niacin and statin drugs can favorably alter lipid levels. The beneficial effects niacin has on lipid profiles and the vascular system may play a significant role in the prevention of cardiovascular events like CVD or CHD. Niacin decreases LDL-C and triglycerides (TG) (Grundy, Mok, Zech & Berman, 1981; Poynten et al., 2003), very low-density cholesterol (VLDL-C) (Garg & Grundy, 1990), free fatty acids (FFA) (Vega et al., 2005) and increases high-density lipoprotein cholesterol (HDL-C), a key anti-atherogenic lipoprotein (Garg & Grundy, 1990; Guyton et al., 1998; Vega, Cater, Meguro, & Grundy, 2005). In patients diagnosed with CHD, niacin has been shown to significantly lower total mortality and CHD (The Coronary Drug Project Research Group, 1975) and had a reduction in the occurrence of nonfatal myocardial infarctions and a decrease in total mortality 9 years post trial (Canner et al., 1986).

A plethora of studies have been conducted involving the affect of niacin on lipid profiles in men and younger women (Altschul, Hoffer, & Stephen, 1955; Elam et al., 2000; Grundy et al., 1981; Vega et al., 2005), but none have looked at glucose, insulin, and C-peptide profiles in PMW. Taking niacin at bedtime in a dosage of 1000 to 3000 mg/day effectively lowers LDL-C and TG (Goldberg et al., 2000; Grundy et al., 1981; Morgan, Capuzzi, & Guyton, 1998, Poynten et al., 2003). Niacin is also an effective method for increasing HDL-C (Garg & Grundy, 1990; Goldberg et al., 2000; Knopp et al., 1998). In spite of niacin's beneficial effect on dyslipidemia, its use can cause hyperglycemia (Molnar et al., 1964; Garg & Grundy. 1990; Gaut et al., 1971). This effect is a cause for concern when prescribing niacin to people with hyperglycemia or T2DM which is unfortunate since this population could greatly benefit from niacin therapy due to the strong association between T2DM and elevated LDL-C and TG and low HDL levels (McKenney, 2004). Treating hypercholesterolemia with 1 g/day for 3 months followed by 4 months of 3 g/day of IR niacin has resulted in glucose levels rising from a normoglycemic level of 5.44 mmol/L (98 mg/dL) to a life threatening hyperglycemia level of 58 mmol/L (1046 mg/dL) in less than 6 months of therapy (Schwartz, 1993). In contrast, patients with T2DM taking 1500 mg of niacin per day were able to maintain glucose control by adjusting dosages of antidiabetic medications (Grundy et al., 2002). Niacin therapy has been shown to increase both fasted and postprandial insulin levels in adult men taking 1500 mg/day of extended release niacin (Plaisance et al., 2008), significantly increase fasting insulin levels in men and women between the ages of 19

and 86 who took 500 mg/day of nicotinic acid for Week 1followed by 1000 mg/day for Week 2 (Chang, Smith, Galecki, Bloem, & Halter, 2006) and double insulin levels in healthy men who took 500 mg/day of nicotinic acid during Week 1 and 2 g/day for Week 2 (Kahn et al., 1989). In contrast, taking 500 mg/day of Nicanagin nicotinic acid during Week 1 and 2 g/day during Week 2 did not affect insulin and C-peptide levels in healthy men and women (Alvarsson & Grill, 1996).

Statement of the Problem

Niacin used in the treatment of dyslipidemia can cause insulin resistance which can exacerbate glucose control and could lead to hyperglycemia. There is a lack of published studies involving extended release niacin therapy in the population of PMW. Therefore, the purpose of this study was to determine if niacin and a single bout of aerobic exercise, expending 400 kcal, would affect glucose, insulin and C-peptide profiles in sedentary PMW. This was tested using an 8 week protocol in 17 participants who met the eligibility criteria. Participants were randomly assigned to the resting (R) or exercise (EX) week without niacin, followed by 4 weeks of niacin supplementation, and ending with 1 week of R with niacin and 1 week of EX with niacin. Blood samples were collected the morning of the first 3 days of each week of R and EX protocols.

Hypotheses

1. There are no significant effects of niacin on fasting glucose, insulin, or C-peptide values.
2. There are no significant effects of exercise on fasting glucose, insulin, or C-peptide values.
3. There is no significant interaction of niacin and exercise on fasting glucose, insulin, or C-peptide values.

Definitions

Acute aerobic exercise: a single session of exercise performed on a treadmill.

Atherosclerosis: the buildup of plaque inside the walls of the arteries which can result in heart attack, stroke, or death

Caloric expenditure: the number of calories expended per unit of time.

Calorie: a unit of heat. The amount of heat needed to raise 1 g of water 1 °C from 14 to 15 °C. Each participant will expend 400 calories via treadmill walking at 60% of her VO_{2max}.

C-peptide: an inactive amino acid, is short for connecting peptide. C-peptide is cleaved from proinsulin during insulin synthesis which happens in the pancreatic beta cells, is stored in the secretory granules, and is then released, along with insulin, in equal amounts by the pancreas. The level of C-peptide in the blood can serve as a gauge as to the amount of insulin the pancreas is producing. Normal fasting levels of C-peptide range between 0.17-0.83 μmol/L (Nissl, 2004) or 0.5-2.0 ng/mL (Rennert, 2007).

Diet record: a written record in which all food and beverages are recorded over a given period of time. Each participant will record all food and beverages consumed for three consecutive days; starting the day prior to the first day of the trial and ending the night before the last day of each trial.

Dyslipidemia: classified as primary (genetic) or secondary (sedentary lifestyle) and is characterized by elevated LDL-C and/or TG or low HDL-C (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001).

Free fatty acids: fatty acids in the blood that have attached themselves to albumin, also known as nonesterified fatty acids.

Glucose: a six-carbon sugar, also a vital source of energy for the body.

Heart rate reserve (HRR): the participant's resting heart rate subtracted from the maximum heart rate (HR_{max}).

Insulin: a hormone produced in the beta cells in the Islet of Langerhans located in the pancreas. When blood glucose becomes elevated insulin is secreted from the beta cells to help move the glucose from the blood into tissue. The liver is the key organ for removing insulin from the blood stream.

Insulin resistance: a state when a normal concentration of insulin produces a less than normal biologic response, due to a decrease in sensitivity to insulin, a decrease in the maximal response to insulin, or a combination of both (Kahn, 1978). Insulin is unable to increase glucose uptake and utilization by the muscles and other tissues (Hawley &

Zierath, 2008). Insulin resistance usually develops with obesity and is a precursor to T2DM.

Insulin sensitivity: the dose-response of insulin that exists between no effect and the maximal response (Kahn, 1978). It is an index of how muscle and other tissue respond to insulin. The higher the concentration needed to produce a half-maximal stimulation equates to a lower level of sensitivity. Methods commonly used to measure insulin sensitivity are the homeostasis model assessment (HOMA), the quantitative insulin sensitivity check index (QUICKI), and euglycemic hyperinsulinemic clamp technique (Monzillo & Hamdy, 2003).

Metabolic syndrome: a constellation of lipid and nonlipid risk factors of metabolic origin (abdominal obesity, atherogenic dyslipidemia, raised blood pressure, insulin resistance: with or without glucose intolerance) and is closely linked to insulin resistance and CHD (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001).

Metabolism: the breakdown of food and changing it into energy for the body within living organisms. It involves biochemical processes consisting of anabolism and catabolism.

Niacin: also known as nicotinic acid (NA) and vitamin B_3, when taken in large dosages (1000 to 3000 mg/day), has shown beneficial effects on cholesterol and triglyceride levels and adverse effects on glucose and insulin levels.

Postmenopausal: the cessation of the menstrual cycle for at least one year, either naturally or surgically. At the time of the phone interview, each potential participant was asked her current age and date of last period.

Sedentary: not participating in physical activity more than 3 times per week, 20 min or more per session.

Submaximal Oxygen Consumption Test: a walking exercise test conducted on a treadmill at a constant rate of speed of 3 MPH and 2 min stages. At the end of each stage the incline raises by 2%. The test ends once 70% of HRR has been reached.

Three site skinfold measurement: a body composition test performed with skinfold calipers measuring the thickness of skinfolds at the triceps, suprailiac and thigh. From the skinfold measurement body density is obtained which is then converted to percent fat using the following formula: $\%BF = (457/D_B) - 414.2$ (Jackson et al., 1980).

Type 2 diabetes (T2DM): a disorder of metabolism where the body does not produce enough insulin or the cells do not respond to insulin causing elevated levels of blood glucose (Diabetes Guide, 2005). A diagnosis of T2DM requires a fasting plasma glucose value of $\geq$ 126 mg/dL.

Waist-to-hip ratio: a ratio of waist and hip circumferences. The waist is measured at the narrowest part of the torso and the hips are measured at the widest part of buttocks (American College of Sports Medicine, 2006).

Assumptions

1. The participants are an accurate representation of the population of interest.
2. All participants followed the protocol for the entire length of the study and followed the dosing schedule for the niacin ingestion as outlined in the protocol.
3. Each participant was required to keep a 3-day dietary record and a 5-day physical activity record and it was assumed that each participant has accurately documented these two records.

Limitations

1. The value of this study is limited to the population composed of sedentary, PMW between the ages of 40 and 80 years.
2. The accuracy of the results is only as valid as the participants' compliance with the protocol and the researcher's ability to measure and record all variables of the study.

Significance of the Study

Although the effects of niacin and exercise on lipid and glucose metabolism are well documented in men and premenopausal women, to date no studies have been conducted that looked at these variables in PMW. Therefore, the purpose of this study was to investigate whether or not niacin and a single bout of aerobic exercise would affect fasting glucose, insulin, or C-peptide profiles in sedentary, PMW. Given the positive effect aerobic exercise has on glucose regulation (Boulé et al., 2005; Ekelund, Franks, Sharp, Brage, & Wareham, 2007; Healy et al., 2007), and the positive effect

niacin has on lipid profiles (Garg & Grundy, 1990; Grundy, Mok, Zech & Berman, 1981; Guyton et al., 1998; Poynten et al., 2003; Vega, Cater, Meguro & Grundy, 2005), niacin and exercise could possibly be prescribed as a treatment plan for PMW who have elevated lipids without adversely affecting their glucose profiles. Improving lipid profiles in this population could lower CVD and metabolic syndrome risk factors thus decreasing the risk of developing insulin resistance and/or T2DM.

CHAPTER II

REVIEW OF THE LITERATURE

The purpose of this study was to investigate the effect niacin and a single bout of aerobic exercise had on glucose, insulin, and C-peptide profiles in PMW. The literature regarding this topic was reviewed in the following section heading: (a) glucose metabolism, (b) types of niacin-their effects and uses, (c) niacin and glucose, (d) niacin and insulin, (e) niacin and C-peptide, (f) niacin and free fatty acids, (g) exercise and glucose, (h) exercise and insulin, (i) exercise and postmenopausal women, and (j) health consequences of Type II diabetes.

Glucose Metabolism

The metabolism of glucose begins in the small intestine where it is taken up into the blood stream. The level of glucose in the blood is not constant, but varies to meet the demands of the body. Glucagon, epinephrine, and insulin regulate the amount of glucose in the blood stream. In persons without diabetes, normal blood glucose concentrations (euglycemia), range between 5 to 6 mM or 90 to 108 mg/dL (Houston, 2006). When glucose levels are elevated, the beta cells of the pancreas release insulin which stimulates glucose to be transferred into the cells. For the transfer process to happen, glucose relies on glucose transporters (GLUT) to move it from the blood into the tissues. The liver uses GLUT-2 while heart and skeletal muscles, peripheral and adipose tissue use GLUT-4. Once inside the cells of the liver and muscle, glucose is converted into glycogen via the

anabolic process known as glycogenesis and stored for later use. At times of low blood glucose the process known as glycogenolysis, a catabolic process, is activated through the release of glucagon and epinephrine to convert glycogen to glucose. Glycolysis, also a catabolic, metabolic process, is activated when the energy from the glucose just entering the cells is needed immediately. Glycolysis results in the creation of pyruvate and adenosine triphosphate (ATP). From this point pyruvate has two options: it can be oxidized (aerobic) or turned into lactate (anaerobic). During aerobic glycolysis, pyruvate enters into the mitochondrion, is converted to Acetyl-CoA via pyruvate dehydrogenase and then enters the Kreb's or Citric Acid Cycle to produce ATP via oxidative phosphorylation. When skeletal muscle is highly active it produces pyruvate at a rate faster than the mitochondrion can oxidize it. This excess pyruvate is converted into lactate via anaerobic glycolysis regardless of the availability of oxygen. When skeletal muscle is at rest, lactate is converted back into pyruvate which is converted into glucose via gluconeogenesis. If this glucose is not needed, then it undergoes glycogenesis to convert it into glycogen. The total number of ATP that can be produced from one metabolized molecule of glucose in muscle is 36, six from the anaerobic pathway and 30 aerobically (McArdle, Katch, & Katch, 2006).

During menopause circulating estrogen drastically decreases while abdominal and intraabdominal fat increases, possibly a result of the decrease in estrogen (Gaspard, Gottal, & van den Brûle, 1995). Changes in insulin secretion, metabolism, and sensitivity also occur resulting in insulin resistance, hyperinsulinemia, and impaired glucose

tolerance. Hyperinsulinemia is possibly linked to the loss of ovarian function, aging, and decreased insulin clearance (Gaspard et al., 1995). Basu et al. (2003) investigated why glucose tolerance deteriorates as the body ages. The 67 elderly (70 ± 0.7 years old) and 21 young (23.7 ± 0.8 years old) men and women ate a standard meal on Day 1, a mixed-meal with blood draws on Day 2, and an intravenous glucose tolerance test (IVGTT) with blood draws on Day 3. The plasma glucose concentrations in the elderly group were higher (0.4 mmol/L before the meal and 1.5 mmol/L after the meal) than the young group for both trials. The plasma insulin concentrations for both groups did not differ for the pre- or postprandial trial. Prior to the glucose injection no difference was seen in plasma insulin concentration between the two groups though the amount secreted by the elderly was lower than the young group. Immediately following the glucose injection (0.3 g/kg total body wt of glucose), insulin levels increased, but it did not result in a significant difference between the two groups. There was a significantly higher concentration of C-peptide in the elderly group for both protocols for the fasted state. This finding indicated that the liver increased its extraction of insulin to coincide with the increased secretion of insulin from the pancreas. They attributed the decline in insulin secretion and insulin action to be responsible for the decline in glucose tolerance seen in elderly men and women. The strongest determinant of insulin action was body fat, therefore the authors also concluded that the amount of visceral abdominal fat (measured by DXA), not age per se, was attributed to the decline in insulin (Basu et al., 2003).

A study of 19 nonelderly (35 ± 2 years old) and 14 elderly (70 ± 2 years old) men and women looked at the metabolic clearance of insulin and how age alters insulin secretion (Fink, Revers, Kolterman, & Olefsky, 1985). They found a significant increase in fasting insulin levels in the elderly group (17 ± 2 μU/ml) compared to 11 ± 1 μU/ml in the nonelderly group. C-peptide levels were also higher in the elderly group (0.95 ± 0.12 pmol/ml) compared to 0.47 ± 0.07 pmol/ml in the nonelderly group. Fasting and postprandial serum glucose levels were also significantly increased in the elderly group. A significant inverse relationship (r = -0.81) was observed between the metabolic clearance rate of insulin and total insulin response during the meal tolerance test suggesting the hyperinsulinemia seen with aging may be due to a decrease in the hepatic uptake and clearance of insulin, not an increase in insulin secretion from the pancreas (Fink et al., 1985). Proudler, Felton, & Stevenson (1992) investigated if aging affected the response of insulin, glucose and C-peptide concentrations to an IVGTT in 86 PMW. This study found menopausal age to have a significant association with plasma insulin concentrations but not with plasma glucose and C-peptide concentrations. The level of circulating insulin is determined by the rate of secretion by the pancreas and the clearance rate by the liver and peripheral tissues. Postmenopausal women typically have more visceral adipose tissue resulting in a decrease in peripheral insulin sensitivity and clearance of insulin by the liver. The authors believed the increase in insulin areas and fasting plasma insulin levels, but not in glucose was indicative of insulin resistance. They

suggested the observed hyperinsulinemia was due to loss of ovarian function in PMW and could increase the risk for developing CVD (Proudler, et al., 1992).

Types of Niacin—Their Effects and Uses

Niacin, also called nicotinic acid, comes in three different formulas; immediate-release (IR), sustained-release (SR), and extended-release (ER), each with a different efficacy, safety, and pharmacokinetic profile. The IR and ER formulas are very effective in treating dyslipidemia, have been approved by the FDA to treat this condition, and require a prescription (Pieper, 2003). The IR has a low compliance rate due to the need to take a pill two to three times per day and the high occurrence of side effects: flushing, redness, and itching of the facial and chest areas. The ER formula's ability to lower lipid levels is comparable to the IR and SR formulas, but has lower side effects in regards to flushing and liver toxicity (Pieper, 2003). The recommended dosing schedule for the ER formula includes taking it shortly before bed with a low-fat snack, titrating the dosage slowly up to 1000 mg/day, avoiding spicy food, hot beverages and showers post-niacin ingestion, and ingesting an aspirin or ibuprofen 30 min prior to taking niacin (Reasner, 2006). This dosing schedule prevents the formation of TG and LDL-C because FFA is not able to mobilize (Knopp, 2000). The SR formula has not been approved to treat dyslipidemia although it does change lipid levels. It has a lower occurrence of flushing, but a higher occurrence of gastrointestinal issues and elevated liver enzymes (Knopp, 2000). No prescription is required for the SR niacin formula and it is available over the counter. Each formula has a different absorbency rate. A 1000 mg IR dose takes 2 hr to

fully absorb; approximately 500 mg are absorbed per hour. A 1000 mg SR dose takes much longer to absorb, approximately 20 hr, since this formula releases only 50 mg/hr. A 1000 mg dose of the ER formula takes approximately 10 hr, absorbing at a rate of approximately 100 mg/hr. Although the beneficial effects niacin has on LDL-C and TG profiles has been well documented (Garg & Grundy, 1990; Grundy, Mok, Zech & Berman, 1981; Guyton et al., 1998; Poynten et al., 2003; Vega, Cater, Meguro, & Grundy, 2005), its use as a lipid lowering medication has been limited due to the associated side effects of flushing, nausea, vomiting, edema, hypertension, elevated liver enzymes, elevated uric acid, and elevated serum glucose. A meta-analysis conducted by Goldberg (2004) found women were more likely to suffer from the common side effects of niacin, but also received the same, if not better, favorable lipid altering effects of ER niacin therapy that were seen in men.

Interest in studying niacin first came about when a deficiency of B_3 vitamin was linked to pellagra, a nutritional deficiency which causes diarrhea, dementia, dermatitis, and eventually death if left untreated. Red meat, liver, legumes, milk, eggs, alfalfa, cereal grains, yeast, fish, and corn are excellent sources of niacin (Cervantes-Laurean, McElvaney, & Moss, 1998). Aside from the use of niacin to cure pellagra this vitamin performs a plethora of atherosclerotic benefits. Niacin decreases vascular inflammation and blood viscosity, decreases the formation of new plaque while stabilizing existing plaque, increases vasodilation, inhibits thrombosis, and favorably alters lipid levels (Rosenson, 2003). In the mid 1950's the ability of niacin to effectively decrease serum

cholesterol was first reported (Altschul, Hoffer, & Stephen, 1955). Later studies have found niacin administered in doses of at least 1000 mg favorably decreased LDL-C and TG levels (Grundy, Mok, Zech & Berman, 1981; Poynten et al., 2003), decreased total cholesterol (TC), TG, VLDL-C, and LDL-C, and increased HDL-C (Garg & Grundy, 1990), decreased LDL-C, TG and lipoprotein(a) and increased HDL-C levels (Guyton et al., 1998; Vega, Cater, Meguro, & Grundy, 2005). A plateau in the beneficial changes in LDL-C and HDL-C levels was observed at the 2500 mg/day dose while significant changes in TG started at the 1000 mg/day, remaining significant until the final dose of 3000 mg/day (Goldberg et al., 2000). Niaspan (Kos Pharmaceuticals, Miami Lakes, FL), an ER formula, changed LDL-C, TG, and HDL-C concentrations to levels which are equivalent to those seen in IR niacin; decreasing LDL-C and TG by 22% and 44%, respectively, and increasing HDL-C by 30%, (Goldberg et al., 2000).

Niacin and Glucose

Niacin favorably changes lipids profiles, but it can also negatively affect glycemic control in some patients. An extensive search for published research involving the effect of niacin on glucose profiles in PMW yielded no articles. However, several articles do exist involving the effect of niacin on glucose profiles in men and/or women with or without T2DM; results are mixed. The first niacin studies were conducted using IR niacin. The data from these studies found glucose levels to be adversely affected, increasing levels as much as 51 mg/100ml (Molnar, Berge, Rosevear, McGuckin, & Achor, 1964), becoming and remaining elevated above baseline levels throughout the 6

week study (Gaut, Pocelinko, Solomon, & Thomas, 1971), and increasing 16% in patients with T2DM (Garg & Grundy, 1990). Glucose levels returned to baseline or near baseline values upon termination of niacin therapy in the former two studies. Garg & Grundy, (1990) did not advise the use of niacin as an option for lipid therapy for patients with T2DM though Molnar et al. (1964) thought if glucose levels were carefully monitored niacin could be used to treat dyslipidemia. The Arterial Disease Multiple Intervention Trial also concluded that niacin would be safe for use in people with diabetes due to its insignificant effect on glucose levels, ranging from baseline values of 95 mg/dL to follow-up values of 102 mg/dL (Elam et al., 2000). The Coronary Drug Project, involving men who had sustained one or more myocardial infarctions (MI), found after 5 years of niacin therapy fasting and 1 hr post challenge glucose levels increased from baseline values, 8.1 mg/100ml and 16.6 mg/100ml, respectively (The Coronary Drug Research Group, 1975). The initial conclusion of the study found niacin provided no health benefit in regards to influencing mortality in MI patients. A follow-up study conducted approximately 15 years after the start of the study, found patients in the niacin group had an 11% lower rate of mortality than those in the placebo group (Canner et al., 1986).

In studies using the ER niacin formula the main point of interest was its effect on dyslipidemia, but some also investigated its affect on glucose levels. Goldberg et al. (2000) studied 131 men and women (21 to 75 years old) who followed a 25 week Niaspan regime. The dosage schedule was as follows: Week 1-375 mg/day; Week 2-500

mg/day; the remaining weeks-increases of 500 mg/day every 4 weeks until 3000 mg/day was reached. Mean fasting blood glucose increased as the dose increased: 3.5% at 500 mg/day, 5.4% at 1000 mg/day, 5% at 1500 mg/day, 1.8% at 2000 mg/day and 5.7% at 2500 mg/day. At the 3000 mg/day dose mean fasting blood glucose decreased by 0.4%. Grundy et al. (2002) conducted a similar study in males and females with T2DM who were divided into 3 groups: placebo, 1000 mg/day, and 1500 mg/day dosages of Niaspan. A modest increase in fasting blood glucose (8.7 mg/dL) was observed between Weeks 4 and 8 which had reverted to baseline values by Week 16. The authors concluded that the use of low doses of niacin was acceptable in persons with T2DM because any fluctuation in glucose levels could be controlled with oral medication. Glycemic control was maintained by altering oral medication or insulin doses in patients with T2DM during the administration of over the counter, rapid acting niacin (Pan et al. 2002a) and Niaspan niacin (Pan et al., 2002b). Vega et al. (2005) also found 4 months of low doses of Niaspan niacin minimally effected glucose levels from baseline values in both males with or without diabetes. Capuzzi et al. (1998) found glucose levels increased by 4% (95.3 mg/dL at baseline to 99.4 mg/dL post therapy) which was statistically significant but values were within reference values for normal glucose values.

Niacin and Insulin

An extensive search for published research involving the effect of niacin on insulin profiles in PMW yielded no articles. Only one study by Chang, Smith, Galecki, Bloem & Halter (2006) was found to have a participant population composed of both

young and older men and women. The researchers were interested in the β-cell, its sensitivity to glucose and how it would respond in the presence of insulin resistance due to niacin administration. Their participants were divided into 15 younger people (19-35 years old) with normal glucose tolerance (NGT) and 16 older people (62-86 years old) with NGT and 14 older people with impaired glucose tolerance (IGT). The three groups were randomly assigned to the placebo protocol or the niacin protocol for the first trial and the opposite protocol for the second trial. Both protocols consisted of a daily dose of 500 mg placebo or niacin capsule that was gradually increased to a 1000 mg capsule taken twice daily for 2 weeks. A frequently sampled IVGTT and ramp clamp was performed on each participant upon completing each protocol. After 2 weeks of niacin the fasting insulin levels significantly increased in all groups; Young NGT: 69 ± 9 pM to 131 ± 26 pM, Old NGT: 54 ± 4 pM to 116 ± 10 pM; and Old IGT: 62 ± 6 pM to 127 ± 14 pM. There was also a significant decrease in insulin sensitivity (10^{-5}·min^{-1}/pM): Young NGT: 2.9 ± 0.4 to 2.0 ± 0.5, Old NGT: 2.7 ± 1.3 to 1.3 ± 0.3; and Old IGT: 2.9 ± 0.3 to 1.2 ± 0.3. There was a significant decrease in insulin secretion in the older IGT group compared to the younger and older NGT group though the cause of this decline could not be determined from this study. Both of the older groups had the most noticeable β-cell dysfunction. The authors concluded that the decline in β-cell sensitivity to glucose is related to human aging as is the impaired β-cell compensation to insulin resistance (Chang et al, 2006).

Three men and four women took nicotinic acid for 2 weeks, 500 mg/day for Week 1 and 1000 mg for Week 2 and decreased insulin sensitivity by 18% without significantly increasing fasting plasma insulin levels (Kelly et al., 2000). After a 12 hr intravenous infusion of nicotinic acid (2 g/500 ml 0.9% NaCl solution) changes in insulin levels paralleled changes in glucose levels in 10 normal, healthy men paralleling the levels seen in the control study (Schlierf & Dorow, 1973). In 14 hypercholesterolemic patients chronic administration (1 g thrice daily for 10-14 days) of niacin (Nicangin ®) was found to induce insulin resistance, decrease glucose tolerance and only slightly increase insulin secretion (Miettinen, Taskinen, Pelkonen & Nikkilä, 1969). Alvarsson & Grill (1996) investigated the effect Nicangin nicotinic acid had on glucose tolerance, insulin secretion and insulin sensitivity in nine healthy men and three healthy women (25 to 61 years old) who took niacin for 2 weeks starting with an initial dose of 500 mg which was slowly increased to 2 g/day by Day 7 and remained at 2 g/day until Day 14. Mean fasting insulin levels were not significantly altered by niacin, neither was insulin secretion during administration of glucose and arginine. Although insulin sensitivity decreased by 18% between Day 0 and Day 14 insulin sensitivity, the decrease was not considered significant, but was correlated ($r = - 0.72$) to incremental increases in levels of fasting nonesterified fatty acids. The authors concluded that niacin induced only a minor amount of insulin resistance.

Kahn et al. (1989) had a similar protocol to Alvarsson & Grill (1996), but had very different results. Eleven healthy men (21-37 years old) followed a 14 day protocol

consisting of an initial IR niacin dose of 500 mg/day, gradually increased to 2 g/day by Day 7, and continuing at 2 g/day until Day 14. Bergman's minimal model was used to measure insulin sensitivity. During niacin administration, insulin resistance developed and fasting insulin levels doubled in all subjects, jumping from 75 ± 7 to 157 ± 21 pM ($p < .001$) with no change in fasting glucose levels or FFA levels. Niacin induced prolonged insulin resistance to which the pancreatic islet adapted by increasing insulin secretion and decreasing glucagon secretion.

Niacin and C-peptide

An extensive search via MedLine resulted in two published studies that reported the effect niacin has on C-peptide. Therefore, in addition to reporting the findings of the two published studies, this section will focus on C-peptide and its role in the body. In the first study the decrease in C-peptide paralleled the decrease in insulin levels in the control group and after receiving a single injection of niacin (50 ml with 0.9% sterile saline) in the treatment group but then returned to baseline after FFA levels were restored with Intralipid and heparin (Dobbins, Chester, Daniels, McGarry, & Stein, 1998). In the second study no significant changes in C-peptide levels were seen after 14 days of niacin treatment that consisted of an initial dose of 500 mg with incremental increases up to 2000 mg/day (Alvarsson & Grill, 1996).

The discovery of C-peptide was made in 1967. C-peptide and insulin come from the same precursor called proinsulin. Proinsulin is converted into insulin in the pancreatic β cells and is then secreted in equimolar amounts along with C-peptide by the islets of

Langerhans (Horwitz, Starr, Mako, Blackard, & Rubenstein, 1975). Normal values of C-peptide range between 0.5 and 2.0 ng/mL in normal persons. C-peptide which forms a bridge in the midsection of proinsulin between the insulin A and B chains (Wahren et al., 2004), is composed of a single chain of 31 amino acids, and is excreted by the kidneys. C-peptide levels are a determinant of how much insulin the body is producing. The status of one's health can be determined by abnormal C-peptide levels. Low or nonexistent levels of C-peptide are an indicator of little to no insulin production by the pancreas, as seen in persons with Type 1 diabetes. Normal levels of C-peptide can indict normal insulin production, though normal levels, as well as elevated levels, can also be seen in persons with T2DM. A person exhibiting elevated values for both glucose and C-peptide is an indication for insulin resistance or T2DM. Persons with T2DM who have normal C-peptide levels indicate insulin production is normal, but the response to insulin by the muscles and peripheral tissues is abnormal resulting in elevated blood glucose levels. C-peptide is considered a more accurate method in determining Type 1 or T2DM because the liver extracts almost half the circulating insulin. The metabolic clearance rate of C-peptide is constant whereas insulin levels vary in response to meals. Elevated levels of C-peptide can also be an indicator of a tumor called insulinoma. Certain medications, alcohol, kidney failure, and obesity can all adversely affect C-peptide test results (Nissl, 2004).

The former belief was that C-peptide had no biological activity, but that may no longer be the case. A study involving 29 patients with T2DM, 21 PMW and 8 men with

an average age of 68.1 years old, investigated C-peptide as a possible predictor of CVD risk (Haban, Simoncic, Zidekova, & Ozdin, 2002). The average fasting C-peptide value was 0.627 nmol/l. The participants were divided into two subgroups; A (n = 14, C-peptide < 0.56 nmol/l) & B (n = 15, C-peptide ≥ 0.56 nmol/l). The results showed a positive correlation between C-peptide and BMI, a significant relationship between C-peptide and TG, a negative correlation between C-peptide and HDL-C, and a significant increase in the ratio of TC/HDL-C and TG/HDL-C to C-peptide. A significantly higher rate of hyperlipoproteinemia was seen in Subgroup B than A. It was concluded that C-peptide was an important predictor in CVD risk in those with metabolic syndrome.

Niacin and Free Fatty Acids

FFA have a high energy density therefore are an ideal energy source during exercise. Chronically elevated FFA, often seen in obese individuals, is cause for concern because high levels of FFA are toxic and are believed to be linked to insulin resistance (Houston, 2006). Elevated FFA causes more fatty acid to be taken up and stored in the skeletal muscles as TG resulting in muscles becoming less insulin sensitive (Houston, 2006). Individuals with excessive stores of adipose tissue have less insulin sensitivity or more insulin resistance which increases their chances for developing T2DM. The administration of nicotinic acid for 2 weeks has been found to increase serum levels of FFA as much as 598 μEq/L (Molnar et al., 1964). Vega et al. (2005) gave 17 male participants (9 with T2DM and 8 had impaired fasting glucose) 2 g/day of Niaspan for 4 months. By Hour 4 of the niacin therapy the data showed a decrease of 37% from

baseline FFA values in the group with T2DM and a decrease of 30% in the group without T2DM followed by an increase from baseline values of 56% and 43%, respectively, by Hour 9. This study suggested that 4 months of niacin therapy had a minimal effect on insulin sensitivity as there were no significant differences in FFA, glucose, and insulin levels between baseline and post niacin therapy. The administration of niacin to participants with poorly controlled T2DM resulted in their plasma FFA levels becoming comparable to persons without T2DM and persons with well controlled T2DM (Hawkins et al., 2003). The significant increase in glucose effectiveness in response to hyperglycemia in individuals with poorly controlled T2DM was attributed to niacin altering plasma FFA levels to normal levels. FFA gradually increasing over time may be an underlying cause of normal glucose levels progressing to hyperglycemia and finally to T2DM.

Exercise and Glucose

The decline in glucose tolerance seen with aging, especially after the age of 60 years, is correlated to age itself and to the decline in physical activity and increase in body fat. Various intensities of exercise have been shown to improve metabolic risk factors such as aerobic fitness, glucose, and insulin levels, blood pressure (BP), and body fat. The amount of physical activity in men and women is associated with glucose levels; lifestyles involving light or moderate to vigorous intensity activities have lower glucose levels whereas elevated glucose levels are typically seen in sedentary individuals (Healy et al., 2007).

An acute exercise study found no significant difference in fasting glucose and insulin levels taken 14 hr after a single 30 min bout or three, 10 min bouts of aerobic exercise performed at 65% VO_{2max}, or in the no-exercise control group of PMW with T2DM (Baynard, Franklin, Goulopoulou, Carhart, & Kanaley, 2005). The authors suggested an exercise intensity higher than 65% of VO_{2max} was needed to cause a beneficial effect on glucose and insulin levels. A single bout of cycling (45 min at 50% VO_{2max}) resulted in a gradual decrease of 1% in plasma glucose levels during exercise and remained lower than baseline levels throughout the 150 min recovery period in obese men and women with T2DM and mild hyperglycemia but showed no change in lean or obese participants without T2DM (Giacca, Groenewoud, Tsui, McClean & Zinman, 1998). The decrease was attributed to the increased rate of glucose utilization.

A training study found regular bouts of aerobic exercise performed by men and women at 75% VO_{2max} is required to maintain the glucose homeostasis enhancements incurred after 20 weeks of training when no significant loss in body weight occurs (Boulé et al., 2005). Regardless of weight loss or aerobic fitness levels in middle-aged men and women, insulin sensitivity and glucose tolerance increased when physical activity levels were increased by the participants (Ekelund, Franks, Sharp, Brage, & Wareham, 2007). A study by Weiss et al. (2006) involved nonobese middle-aged men and women (50-60 years old) who lost weight by reducing caloric intake 20% (CR group) or by maintaining caloric intake and increasing energy expenditure 20% through exercise (EEX group). Both treatments showed an increase in the Matsuda and DeFronzo insulin sensitivity

index: 2.0 ± 3.9 in CR group and 3.0 ± 2.7 in EEX group; a decrease in fasting glucose levels: -5.3 ± 6.3 mg/dL in CR group and -1.4 ± 4.6 mg/dL in EEX group; and a decrease in the insulin areas under the curve: -1.3 ± 2.1 (x 10^3 μU min/mL) in CR group and -3.4 ± 3.0 (x 10^3 μU min/mL) in EEX group (Weiss et al., 2006). The authors concluded weight loss due to exercise was not superior to weight loss through caloric restriction. In contrast, fasting and 2 hr postchallenge glucose levels were not affected in 180 PMW and 197 men who performed 16 km/week of brisk walking or jogging for 1 year (Stefanick et al., 1998).

Another study assigned PMW to a protocol involving walking 5 days/week for 15 weeks at 65% VO_{2max}, expending 300 kcal during one or two exercise bouts which effectively lowered fasting glucose levels and diastolic BP thus decreasing their risk for developing CHD (Asikainen et al., 2003). On the other hand, fasting glucose levels were not affected in PMW who walked at 45-55% VO_{2max}, expending 200 kcal or 300 kcal/day, indicating a higher level of exercise was needed to incur beneficial changes in glucose and BP. In contrast, no significant decrease in fasting glucose and insulin concentrations or CVD risk factors were seen in PMW who followed a 24 week diet or diet and exercise program despite significantly decreasing mean body weight (6.52 kg), BMI, and percent body fat (Fox et al., 1996).

One study investigated how the loss of visceral abdominal fat and intramuscular fat due to weight loss alone or combined with aerobic exercise affected glucose utilization (Ryan, Nicklas, & Berman, 2006). The participants were 33 healthy,

overweight or obese, PMW (50-70 years old). The women were divided between two groups: the weight loss (WL) program or weight loss with aerobic exercise (WL + AEX) program. The WL program was composed of classes held weekly regarding instruction of a hypocaloric diet taught by a registered dietician. In addition to attending the weekly WL classes, the WL + AEX performed 45 min bouts of aerobic exercise 3 times/week at > 60% VO_{2max}. The protocols were 6 months in length and resulted in a decrease in body weight, 6% in WL and 8% in WL + AEX. An 18% decrease in visceral abdominal fat was seen in WL, while WL + AEX reported a 17% decrease. Fasting plasma glucose decreased in WL while fasting insulin, glucose utilization or insulin sensitivity showed no changed. The WL + AEX group had a decrease in both fasting plasma glucose and fasting insulin. Contrary to WL, WL + AEX showed a 15% increase in glucose utilization and a 21% increase in insulin sensitivity. When the two groups were compared, no differences in changes of body composition were found though VO_{2max} in WL + AEX was significantly different than WL. The authors concluded significant increases in glucose utilization and insulin sensitivity in PMW required WL coupled with AEX and decreasing visceral abdominal fat was required to improve glucose metabolism.

In summary, performing regular bouts of moderate to vigorous intensity aerobic exercise ($\geq$ 65% VO_{2max}) can lower glucose levels and BP in men and women. Aerobic exercise (> 60% VO_{2max}) coupled with visceral abdominal fat lose is also affective at lowering fasting glucose levels.

Exercise and Insulin

Various methods exist for determining insulin sensitivity. The hyperinsulinemic euglycemic clamp, a direct measurement method, is the "gold standard" but is expensive and time consuming. Indirect methods for measuring insulin sensitivity are quantitative insulin sensitivity (QUICKI), homeostasis model assessment (HOMA) and McAuley index (Monzillo & Hamdy, 2003). The QUICKI and HOMA indexes are calculated using fasted glucose and insulin concentrations or concentrations obtained after a glucose load. Using the hyperinsulinemic euglycemic clamp method in conjunction with measurements of adiposity is more effective at identifying PMW who are at risk of developing T2DM than methods without OGTT or adiposity data (Piché et al., 2007). A single bout of exercise increases insulin sensitivity up to 48 hr (Jamurtas et al., 2006). When high intensity exercise (80% VO_{2peak}) expending ~300 kcal is performed every two days the level of postexercise insulin sensitivity is retained in older women (DiPietro et al., 2006). In lean men and women, a single bout of cycling (50% VO_{2max} for 45 min) did not alter insulin levels during exercise or during the 150 min postexercise (Giacca et al., 1998). Obese participants without T2DM had a significant rebound ($p < .001$) in insulin levels postexercise (Giacca et al., 1998). A study involving a single bout of cycling at 65% VO_{2max} for 45 min decreased insulin levels and increased insulin sensitivity in 24 hr and 48 hr postexercise in young overweight men (Jamurtas et al., 2006).

An early training study regarding the effect of exercise on glucose and insulin homeostasis was published in 1977 (Björntorp et al., 1977). This study was composed of

4 men and 4 women (35 ± 2 years old) who were severely obese and 4 men and 4 women (36 ± 2 years old) control subjects who were nonobese and sedentary. After completing a 6-week physical training protocol consisting of 1 hr training sessions 3 times/week, the fasting plasma insulin concentrations in the obese subjects decreased by 30% while their plasma glycerol and insulin sensitivity in the peripheral tissues increased though glucose tolerance showed no change. LeBlanc, Nadeau, Richard, & Tremblay (1981) found, after a glucose load was administered, fasting plasma insulin levels notably increased from training values in trained young male and female distance runners who ate ad libitum (3291 kcal/day) and refrained from running for 3 days. Following a diet of 2076 kcal/day the insulin levels obtained during training was maintained during the 3 days of inactivity in the trained subjects. Untrained subjects had fasting plasma insulin levels higher than the trained subjects though one bout of treadmill walking at 70% VO_{2max} the day before the glucose load resulted in a lower insulin response. A study involving healthy, physically fit PMW who exercised at 70 to 85% of their maximum heart rate (HR_{max}) on a treadmill for 20 min/day 3 times/week for at least 6 months reported the response to an OGTT was a decrease in the first phase of insulin release and had lower insulin areas under the curve (μU/mL/min) than the control group, 45.5 ± 8.3 versus 81.6 ± 40.6 at min 5 and 125.1 ± 16.1 versus 216.9 ± 88.4 at min 10 (van Dam, Gillespy, Notelovitz & Martin, 1988). Another study involving PMW showed no statistically significant changes in fasting plasma insulin, measured after the training period of 5 days/week at 65% VO_{2max} for 15 weeks or 45-55% VO_{2max} for 24 weeks (Asikainen et al., 2003). In

contrast, Frank et al. (2005) found fasting insulin concentrations in overweight or obese PMW decreased 4% from baseline values after exercising at 60-75% HR_{max} 5 days/week for 12 months, whereas the control group had a 12% increase. The decrease in insulin concentrations in those who exercised between 131 and 190 min/week reached statistical significance. Houmard et al. (2004) also found improvements in insulin sensitivity were more dramatic in middle-aged men and women exercising ~170 min/week rather than ~115 min/week. In the Boulé et al. (2005) study comprised of young men and women (30 – 37 years old) a decrease of 8% in fasting insulin levels was observed 24 hr after the completion of the 20 week protocol of 55% VO_{2max} 30 min/day for 14 weeks and 75% VO_{2max} for 50 min/day for 6 weeks, though these levels had returned to near baseline by 72 hr post-exercise.

The improvements in insulin sensitivity (determined by IVGTT) seen in younger women (29.1 ± 4.6 years old) who followed an aerobic training program at 75-85% of HR_{max} for 6 months remained whereas the improvements in insulin sensitivity had disappeared in PMW (62.3 ± 4.7 years old) when measured 72-120 hr post exercise suggesting beneficial changes in insulin sensitivity requires aerobic exercise on most days of the week in older women (Goulet, Mélançon, Aubertin-Leheudre, & Dionne, 2005). In contrast, sedentary PMW (73 ± 10 years old) who exercised at 80% peak aerobic capacity (VO_{2peak}) for 4 days/week, expending 300 kcal/session for 9 months continued to display the improvements in insulin sensitivity 72 hr post-exercise whereas

those in the 65% and 50% VO_{2peak} groups did not (DiPietro, Dziura, Yeckel, & Neufer, 2006).

In summary, aerobic exercise can decrease fasting insulin levels and insulin sensitivity in all ages of men and women, obese or trained, for up to 72 hr postexercise. In order to maintain these changes in PMW, performing aerobic exercise > 4 days/week is required (Goulet et al., 2005).

Exercise and Postmenopausal Women

A woman experiences menopause around the age of 50 years, resulting in numerous physical and metabolic changes, such as loss of muscle strength, aerobic fitness, and bone mineral density (BMD), increasing the risk of developing CHD, T2DM, and bone fractures (Asikainen, Kukkonen-Harjula & Miilunpalo, 2004). The aforementioned physical and metabolic changes are especially seen in sedentary, PMW. Menopause also can cause weight gain predominantly in the abdominal area, thus altering body composition which increases the risk of CVD (Hernandez-Ono et al., 2002; You, Ryan & Nicklas, 2004). The intensity and type of exercise are important factors when considering an exercise program. Favorable changes in morphological, functional, or physiological measurements in PMW were not achieved by performing habitual physical activity, such as household chores or walking as one's form of transportation (da Silva, Costa-Paiva, Pinto-Neto, Braga & Morais, 2005). Tsang, Orr, Lam, Comino, & Singh (2008) reported Tai Chi, a low-impact, low-intensity exercise, does not significantly affect glucose homeostasis and insulin sensitivity, waist circumference or fat free mass in

sedentary adults with T2DM (> 50 years old) indicating a decrease in fat or increase in muscle mass is necessary to improve glucose and insulin levels in older adults with T2DM. Asikainen et al. (2002) found expending 300 kcal in one bout or divided between two bouts of brisk walking at 65% VO_{2max} was equally effective in increasing aerobic fitness by 8% and decreasing body mass by 2% in PMW signifying training effects can be produced by brisk walking if the total amount of exercise if sufficient.

Performing regular bouts of moderate-intensity aerobic exercise and two bouts of resistance exercise/week a PMW reduces her chances of developing one or more of the CVD risk factors. A study involving 118 PMW looked at the association between the intensity of physical activity, visceral abdominal fat, and metabolic risk factors (Major et al., 2005). They concluded that PMW had a lower Body Mass Index (BMI), visceral abdominal fat and a healthier metabolic profile when they participated in moderate to intense physical activity. Their results also suggested that physical activity plays positive role in reducing the risk of developing T2DM and impaired glucose tolerance; increasing physical activity can decrease visceral adipose tissue which in turn decreases impaired glucose tolerance and T2DM. When PMW with T2DM added resistance training to aerobic training Cuff et al. (2003) discovered glucose disposal increased and loss of subcutaneous abdominal fat and visceral abdominal fat resulted in improved insulin sensitivity. A study involving 173 sedentary overweight or obese PMW was conducted using two groups: exercising and control. The exercising group performed moderate intensity exercise at least 45 min/day, 5 days/week for 12 months while the control group

performed one bout of stretching for 45 min/week for 12 months (Frank et al., 2005). The data showed that the exercising group had statistically significant decreases in their mean fasting insulin and leptin concentration as well as greater improvements in their insulin sensitivity (Frank et al., 2005). The Women's Health Initiative Observational Study investigated the prevention of cardiovascular events in 73,743 PMW who walked or participated in vigorous exercise for an average of 3.2 years and up to 5.9 years (Manson et al., 2002). The data of this study indicated women who engaged in walking or vigorous exercise for at least 2.5 hr/week reduced their risk of total cardiovascular events by approximately 30% and if she did both types of exercise her risk reduction was even greater. Whereas the type and amount of exercise was negatively correlated to CVD risk, time spent sitting was positively correlated to CVD risk factors in PMW.

A 12 month weight loss intervention study of 22 premenopausal and 50 PMW consisting of meal replacements, dietary counseling, and increased physical activity found large and significant reductions in anthropometric and metabolic risk factors in both groups though the PMW group had a higher reduction (Deibert et al., 2007). The study also found a significant reduction in fasting insulin levels in the PMW, thus lowering their risk of CHD. Giannopoulou et al. (2005) found a diet high in monounsaturated fats reduced total body fat by 14.6% and fasting glucose levels by 2.3 mmol/L in obese PMW with T2DM. Diet combined with aerobic exercise reduced total body fat by 14.7% and fasting glucose by 1.3%. To favorably alter fasting insulin levels (16%) in this same population, a reduction in visceral abdominal fat via diet and aerobic

exercise was required. Aubertin-Leheudre, Lord, Khalil & Dionne (2007) found aerobic exercise coupled with an isoflavone supplementation reduced body weight by 5%, significantly reduced BMI, and reduced total fat and visceral abdominal fat which resulted in lower CVD risk factors in obese PMW.

The visceral abdominal fat lost following an aerobic exercise program consisting of 1 hr/day, 5 days/week for 12 weeks has been shown to improve glucose metabolism and reverse insulin resistance in obese elderly men and women (O'Leary et al., 2006). In another study 3234 men and women without diabetes, but at high risk of developing T2DM were randomly assigned to one of three groups: intensive lifestyle intervention, lifestyle intervention plus placebo, or lifestyle intervention plus metformin (Knowler, 2002). After almost 3 years those participants assigned to the lifestyle intervention group and the metformin group were found to have prevented or delayed the onset of T2DM by 58 and 31%, respectively.

A summary of exercise studies in PMW is presented in Table 1.

Table 1

The Effects of Exercise in Postmenopausal Women

Author	Subjects	Mode	Intensity	Duration	Kcal	Results
Asikainen et al., 2002	130 PMW Control = 45 1 bout = 46 2 bouts = 43	Brisk walking	65% VO_{2max}	5 days/wk for 15 wk	1500/wk or 300/bout	↑ in VO_{2max} and ↓BMI was equal in both exercise groups
Aubertin et al., 2007	50 PMW Control = 25 Supp = 25	Aerobic exercise	65% - 75% HR_{max}	1 year: month 7-12 EX, Three-1 hr sessions/week	nr	EX & Supp together significantly lowers body weight thus lowering CVD risk factors
Cuff et al., 2003	28 T2DM PMW Control = 9 Ae = 9 Ae + Rt = 10	Aerobic exercise, Aerobic + resistance exercise	60 - 75% HRR	75 min/day, 3 times/wk for 16 wks	nr	Ae + Rt resulted in significant improvements in S_I
Deibert et al., 2007	72 Women 22 PRMW 50 PMW	Aerobic or endurance type activities	nr	12 month: 6 months supervised-60 min, 2 times/wk, 6 months unsupervised	nr	Significant ↓in anthropometric and metabolic risk factors in both groups, though PMW group had higher ↓
Frank et al., 2005	173 PMW Control = 86 EX = 87	Treadmill, outdoor walking, stationary bike	60% - 75% HR_{max}	12 months: 5 times/wk, at least 45 min/session	nr	Significant ↓ in mean [insulin] values from baseline to 12 months, regular moderate intensity EX improves MD risk profiles

Table 1 (Continued)

The Effects of Exercise in Postmenopausal Women

Author	Subjects	Mode	Intensity	Duration	Kcal	Results
Giannopoulou et al., 2005	33 T2DM PMW D = 11 EX = 11 D+E = 11	Walking, bicycling, stepping	65-70% VO_2 Peak	3 times/wk, 50 min/session	250-300	D and D+E reduces total and SAT, EX ↑ S_I and ↓abdominal fat loss, Loss in VAT requires diet and exercise
Major et al., 2005	118 PMW	PA record	Ranked PA on 1-9 scale, 1 = very low energy expenditure	3 days: 2 weekdays, 1 weekend	nr	Moderate to intense PA yielded lower BMI, lower VAT, improved metabolic profile
Manson et al., 2002	73,743 PMW	Detailed recreational PA questionnaire, 1 wk of walking and PA, subject estimated total hr spent sedentary/day	Walking = > 10 min, Moderate EX = "not exhausting," Vigorous = "you work up a sweat and your heart beats fast"	Up to 5.9 years follow up, mean of 3.2 years	nr	At least 2.5 hr/wk of walking and vigorous EX ↓rate of CV events almost 30%, ↑hours of sedentary behavior ↑ CV risks

Note: PMW = postmenopausal women; VO_{2max} = maximal oxygen uptake; BMI = body mass index; Supp = supplementation; HR_{max} = maximal heart rate; nr = not reported; EX = exercise; T2DM = Type 2 diabetes mellitus; Ae = aerobic exercise; Ae + Rt = aerobic exercise + resistance exercise; S_I = insulin sensitivity; HRR = heart rate reserve; PRMW = premenopausal women; MD = metabolic disease; D = Diet; D+E = Diet + Exercise; SAT = subcutaneous abdominal fat; VAT = visceral abdominal fat; PA = physical activity; CV = cardiovascular

Health Consequences of Type II Diabetes

In 2005, a reported 20.8 million people in the United States had diabetes (Caspersen & Fulton, 2008). The latest data from the Centers for Disease Control and Prevention published in 2008 states the number has increased to nearly 24 million Americans with diabetes; 17.9 million diagnosed cases and 5.7 million who are undiagnosed (CDC, 2008b). In addition to those with diabetes there is another 57 million Americans who are prediabetic and at risk for developing T2DM. By the year 2050, the number of cases of diabetes is expected to increase by 165% (Boyle et al., 2001). The majority of all cases of diabetes, 90-95% of them, are T2DM. A person is considered diabetic if he or she has two separate fasted plasma glucose tests $\geq$ 126 mg/dL. Obesity, physical inactivity, hypertension, race, family history and age are contributing risk factors for developing T2DM. Diabetes afflicts both men and women of all ages, usually developing at age 40 and older. Persons aged 60 and older have the higher incidence of T2DM, almost 25% (CDC, 2008b). This disease is present in all races though Native Americans and Alaskan Natives, African Americans, and Hispanics have the highest occurrence rate, 16.5%, 11.8%, and 10.4%, respectively (CDC, 2008b). There is no cure for T2DM, though it can be managed by diet and exercise, and if necessary, medication.

Both short and long-term complications are associated with T2DM. Short-term complications include hyper- and hypoglycemia and diabetic ketoacidosis. In people without diabetes, hyperglycemia is associated with increasing CVD risk profiles in all quintiles of NGT levels in men and women 26 to 82 years old (Meigs, Nathan, Wilson,

Cupples, & Singer, 1998). Postchallenge hyperglycemia (2 hr glucose levels > 11.1 mmol/l) in adults without diabetes (30-89 years old) alone increases the risk of all-cause and CVD mortality (Barrett-Connor & Ferrara, 1998; de Vegt et al., 1999; & Saydah et al., 2001). The 2 hr glucose test is considered the superior method in determining mortality due to all-cause and CVD than fasting glucose (DECODE Study Group, 2001). Long-term complications include: heart disease and stroke, atherosclerosis, high BP, nerve and kidney damage, amputations, and blindness. Persons with T2DM have higher rates of CVD, congestive heart failure, and dying after a heart attack than persons without T2DM. Newly diagnosed women with T2DM are at greater risk of dying from CVD than men with T2DM (DECODE Study Group, 2003; Zandbergen, Sijbrands, Lamberts, & Bootsma, 2006). Each year diabetes accounts for 12,000 to 24,000 new cases of blindness, is the leading cause of kidney failure, and is responsible for more than 60% of nontraumatic lower leg amputations (CDC, 2008b). T2DM also increases the risk of hip fractures in women (Nicodemus & Folsom, 2001) and results in lower cognitive tests scores than women without T2DM (Grodstein, Chen, Wilson & Manson, 2001).

In addition to the impact diabetes has on the human body it also has a major impact on the healthcare system and society as a whole. The estimated healthcare cost for diabetes, both direct and indirect, is steadily rising: $98 billion in 1997 (Killilea, 2002), $132 billion in 2002 (Diabetes guide, 2005), and $174 billion in 2007, $116 billion in direct medical costs and $58 billion in indirect costs (CDC, 2008a). Missing work, permanent disability, and premature death are major contributors to the economic strain

imposed by diabetes (Blonde, 2007). Compared to a patient without diabetes, hospital admissions for a patient with T2DM is more frequent and longer, 3 days and 7 days, respectively (Killilea, 2002). Although diabetes was listed as the sixth leading cause of death in 2002, this ranking could be higher given that a number of deaths due to diabetes are credited to other causes (Blonde, 2007). Controlled glucose levels improves quality of life and cognitive function, reduces lost work days and doctor and hospital visits (Testa & Simonson, 1998).

Summary

As the body ages, it can develop glucose intolerance, insulin resistance, and impaired insulin sensitivity, conditions which contribute to the development of T2DM, a disease with both societal and healthcare implications. Performing aerobic exercise has a positive influence on glucose and insulin levels, especially when coupled with visceral abdominal fat loss. Aerobic exercise is especially beneficial to PMW given the physiological changes associated with menopause which can increase the risk for developing CVD and T2DM. Taking the IR and ER formula of niacin effectively modifies lipid profiles which in turn reduces CVD risk factors. Compliance in the IR formula is low given its adverse side effects and instability in glucose homeostasis which can result in the termination of niacin therapy and/or changes in diabetic medication dosages. The ER formula is usually well tolerated when taken in conjunction with aspirin without negatively altering glucose or insulin homeostasis, though its use has not been studied in the population of PMW. Following a regime consisting of eating a proper diet,

stretching, aerobic and resistance exercise a woman can help prevent weight gain, preserve BMD and improve flexibility and muscle strength. Exercise is also thought to possibly play a role in deceasing BP, lipid and glucose profiles and maintaining balance and coordination though there is not enough existing data to draw an accurate conclusion.

CHAPTER III

METHODOLOGY

Participants

Eighteen postmenopausal women (N = 18) between the ages of 40 and 80 years were solicited via an advertisement in the Denton newspaper and flyers posted around the Texas Woman's University campus. Prior to acceptance into the study each participant underwent a phone interview (Appendix A) to determine study eligibility. The criteria were as follows: (a) Postmenopausal at least one year, naturally or surgically; (b) Not on hormone replacement therapy; (c) Had no known heart or organ ailments or disease; (d) Did not have diabetes mellitus; (e) Did not take any medications that effects the levels of glucose, insulin, C-peptide, lipids, or lipoprotein metabolism; (f) Did not take omega-3 supplements; (g) Did not smoke or had not within the past 6 months; and (h) Did not participate in regular physical activity (three or more times per week, at least 20 min per session). In addition to meeting these requirements each participant abstained from partaking in any form of physical activity throughout the duration of her participation in this study. Upon acceptance into the study each participant signed a consent form (Appendix B), filled out a medical history questionnaire (Appendix C) and received permission from her personal physician to participate (Appendix D). The methods and procedures for this study were submitted to and accepted by the Institutional Review Board of Texas Woman's University (Appendix E).

Submaximal Oxygen Consumption Test

Participants performed a submaximal exercise test to predict their maximal oxygen uptake ($VO_{2\ max}$). The test was conducted on a Quinton Q65 motor driven treadmill (Quinton Instruments, Bothell, WA) using a preprogrammed exercise protocol. The exercise protocol consisted of a warm-up stage of 2 min at 0% grade at a rate of 3 mph. After the initial 2 min the grade increased by 2% while the rate remained unchanged. The grade continued to increase by 2% every 2 min until the participant reached 60% of her heart rate reserve (HRR). The HRR was calculated by subtracting the resting heart rate from the age-estimated HR_{max} (220-age). This value was then multiplied by 60% (the percent intensity of this study), followed by adding the resting heart rate (HR) resulting in the value of the target HRR (ACSM, 2006). In equation form it is as follows: 60% HRR = [(220-age) – resting HR] x 60% + resting HR.

Each participant was prepped for a 12 lead electrocardiograph (ECG). Once the placement of the electrodes was complete, the participant sat in a chair and remained so for at least 5 min. At the conclusion of this rest period, resting HR, and BP were taken. During the submaximal exercise test HR, BP, and the ratings of perceived exertion (RPE) were recorded. Expired respiratory gases were also collected. Heart rate was continuously monitored during the exercise test via a Quinton Q4500 12 lead ECG (Quinton Instruments, Bothell, WA). During the final minute of each stage BP was taken. At the end of each stage RPE was determined by the participant using the 6-20 Borg's scale (Borg, 1982). Respiratory gases were collected and analyzed via Parvo Medics Truemax

2400 metabolic measurement system (Consentius Technologies, Sandy, UT). Once the participant reached her 70% HRR the test was terminated, the grade of the treadmill was reduced to 0% and the speed slowed to a slow gait to allow for a cool down period of approximately 5 min. Immediately following the termination of the submaximal exercise test, HR and BP was measured until the participant's values had returned to resting values.

Prediction of Maximal Oxygen Consumption

The prediction of VO_{2max} for each participant was estimated by using a line of best fit and an extrapolation graph created in Microsoft Excel. The x-axis represents the values of VO_2 ($ml \cdot kg^{-1} \cdot min^{-1}$) while the y-axis represents the HR (bpm) values collected during the submaximal exercise testing. The line of best fit was extrapolated to the age estimated HR_{max}. A straight line was drawn from where the extrapolated line and age estimated HR_{max} intersects on the y-axis. The point where the lines intersect represents the predicted VO_{2max}.

Study Design

This study was comprised of two conditions: without niacin (WON) and with-niacin (WN). All participants commenced with the WON condition due to the potential side effects from taking niacin. Upon completion of the WON trial they performed the WN trial. During WON trial participants were randomly assigned to perform the R or the E trial; the following week the opposite trial was performed. During the WN the R and E trials were randomly assigned. The E trial consisted of performing a single bout of

aerobic exercise at 60% of estimated $VO_{2\,max}$ on a treadmill until 400 kcal had been expended. At least one week between the R trial and E trial was required to avoid any effects the bout of exercise might have on the blood profiles.

On testing days all participants reported to the laboratory between the hours of 0530 and 0800. For the R trial the participant rested in a chair for at least 5 min prior to the blood draw. For the E trial the participants rested in a chair at least 5 min prior to the blood draw followed by the bout of aerobic exercise. Expired gases, BP, and HR were continuously monitored throughout the exercise. Heart rate was also monitored via a polar heart rate monitor (Polar Electro, Woodbury, NY). To determine the expenditure of 400 kcal, expired gases were collected and analyzed via methods previously described, at commencement, midway, and the last 15 min of exercise. These gases during the last 10 min of each stage were then averaged to determine energy expenditure. A thermal equivalents table of O_2 for RER (McArdle, Katch & Katch, 1999) was used to determine energy expenditure.

Body Composition Measurements

To determine waist to hip ratio (WHR) each participant had her waist and hips measured with an inelastic tape to determine the amount of body fat distributed around her torso. The areas measured were the narrowest point of the waist and the widest point of the hips. Multiple measurements of the each area were made to determine the narrowest waist and widest hip measurement. To insure accuracy, each area was measured twice. If the measurement differed by more than 2 mm a third measurement

was taken, then averaged. Each participant also underwent a 3-site skinfold test in duplicate. The sites used were the triceps, suprailiac, and thigh (Jackson, 1980) of the right side of the body. A Lange skinfold caliper (VacuMed, Ventura, CA) was the apparatus used to take these measurements. In accordance with ACSM guidelines (ACSM, 2006) all duplicate skinfold measurements differing by > 2 mm were measured again. These measurements were used to determine body density using Jackson's 3-site equation (Jackson, 1980). The Brozek equation (Brozek, 1963) was used to determine percent body fat.

Body composition was also determined via the FDA-approved Dual Energy X-ray absorptiometry (DXA). The purpose of this test was to determine both total body as well as regional body composition. It was conducted at the Institute for Women's Health at Texas Woman's University by a registered technician. Each participant was fully dressed while lying on her back on the padded table for the duration of the scan.

Niacin Supplements

The specific number of niacin tablets to be taken per week were placed in a plastic bag, labeled, and given to each participant by the investigator after she completed Week 2 of the trial along with a bag of ibuprofen tablets if she so chose. Week 3 marked the commencement of the with-niacin (WN) trials where participants began the ingestion of one 250 mg dose of niacin/day. Week 4 through 8 the extended-release niacin supplement, known as Niaspan (Kos Pharmaceuticals, Miami, FL) was taken. Week 4 the dosage was increased to 500 mg niacin/day. Week 5 through Week 8 the dosage was

1000 mg niacin/day. The extended-release supplement was taken with a low fat snack 1 to 2 hr prior to bedtime the night before the WN trial. To minimize the possibility of the participant sustaining the possible side affect of flushing, if she so chose, she ingested a 325 mg aspirin or a 200 mg ibuprofen 30 min prior to administering the niacin. Following this dosing schedule, the flushing side effect should have been minimized. During Week 7 participants reported to the laboratory for either an R or E trial. During Week 8 the trial was opposite that of Week 7. Niacin was the only supplement allowed to be taken throughout the course of this study.

Diet and Physical Activity

Each participant was required to keep a 3-day dietary record (Appendix F) and a 5-day physical activity record (Appendix G). The dietary record started the day prior to the first blood draw and ended the day prior to the last blood draw. The original 3-day dietary record was to be replicated for the remaining three trials to insure consistency in the participant's diet. Evaluation of the dietary records was accomplished using the Nutritionist Pro™ program (First Data Bank, Indianapolis, IN). The physical activity record consisted of 5 days. The first day of recording was 3 days prior to the first blood draw and the 2 days following the first blood draw.

Blood Analysis

The participants arrived at the laboratory between the hours of 0530 and 0800 the mornings of each blood draw having fasted for a minimum of 10 hr. After resting in the seated position for 5 min a venous blood sample of approximately 20 ml was collected

into one 5.0 ml BD Vacutainer tube (Becton, Dickinson, and Company, Franklin Lakes, NJ) and two 7.5 ml Corvac serum separator tubes (Sherwood Medical Company, St. Louis, MO). Blood samples were taken immediately before exercise (0 hr), and 24 and 48 hr post exercise. There were a total of 12 blood draws, three per each treatment. For this study only the 24 hr time point was analyzed and reported in the results.

Immediately following each blood draw a sample of approximately 500 µl of whole blood was placed into a 1.5 ml graduated micro-centrifuge tube from which 2 Drummond Hemato-Clad Heparinized Mylar Wrapped 75 mm Hematocrit tubes (Drummond Scientific Co, Broomall, PA) were filled. These tubes were immediately centrifuged for 2 min then analyzed for hematocrit levels using the standard microhematocrit method. The remaining sample of whole blood was immediately placed in to a -70 °C freezer for later analysis of hemoglobin concentration. The concentrations of glucose, insulin, and C-peptide were corrected for any post exercise plasma volume changes. These changes were determined by taking the values of post exercise hematocrit and hemoglobin and calculating the percent volume change via the Dill & Costill equation (Dill & Costill, 1974). Existing data (Koh, 2008) for hemoglobin and hematocrit were used to determine plasma volume changes.

All blood samples remained at room temperature at least 15 min followed by centrifuging for 15 min at 3000 rpm to separate serum from the red blood cells in the Corvac serum separator tubes and to separate plasma from the red blood cells in the BD Vacutainer tubes. Both the serum and plasma were then pipetted into separately labeled,

1.5 ml graduated micro-centrifuge tubes and placed in to a -70° C freezer for later analysis. Plasma samples were used in the analysis of glucose (Raichem, San Diego, CA). Enzymatic measurement of glucose was conducted in duplicate on the PowerWave^{TM} XS microplate spectrophotometer (Bio Tek Instruments, Winooski, VT). Serum samples were used in the analysis of insulin (Insulin Elisa DSL-10-1600, Diagnostic Systems Laboratories, Inc Webster, TX) and C-peptide (C-peptide of insulin Elisa DSL-10-7000, Diagnostic Systems Laboratories, Inc., Webster, TX). Enzymatic measurements for insulin and C-peptide were conducted in duplicate on the Infinite M200 microplate reader (Tecan, Grödig, Austria) which included washing each plate with a Columbus Pro microplate washer (Tecan, Grödig, Austria). All procedures regarding the analysis of glucose, insulin, and C-peptide are described in Appendix (H).

Statistical Analysis

Changes in glucose, insulin, and C-peptide were determined via a 2 x 2 repeated measures analysis of variance (ANOVA) for each dependent variable and the Bonferroni adjustment served as the post hoc test. Primary assumption associated with repeated measures ANOVA is the assumption of sphericity. For this study because of only two trials for each factor, the assumption of sphericity is not relevant. All serum and plasma data was analyzed using the Statistical Package for Social Sciences 12.0 (SPSS Inc., Chicago, IL). The data are reported as mean ± SD. The level of statistical significance was set at $p < .05$.

CHAPTER IV

RESULTS

Of the 45 sedentary, postmenopausal women who responded to the advertisement of this study, 20 initially qualified as participants. The disqualification of the other 25 applicants was due to not meeting the study criteria, a scheduling conflict, and were unable or unwilling to participate. Upon acceptance into the study, each participant read and signed an informed consent form, completed a medical history questionnaire, and submitted a signed consent to participate form from the primary care doctor of the participant. Two participants were taking Levothyroxine for thyroid issues; one was taking Sertraline for depression; and one was taking Estradiol; and another was taking Prometrium for hormone therapy. Of the initial 20 participants, the data of three have been excluded: two dropped out of the study prior to completion due to the adverse reactions of itching, flushing, and/or swelling incurred during the 1000 mg dosage of niacin; and one completed the study, but was later found to have abnormally high glucose values (> 126 mg/dL). The remaining 17 participants (N = 17) were included in all data analysis. The baseline measurements of the participants are presented in Table 2. Only the 24 hr time point was used in this data analysis. Fasting plasma volumes for rest and exercise trials were not different; therefore no correction was made for plasma volume.

Table 2

Baseline Measurements of Participants

	Mean ± SD	Minimum	Maximum
Age (years)	57.6 ± 7.5	46.0	71.0
Height (cm)	160.1 ± 7.0	147.0	171.4
Weight (kg)	77.2 ± 14.8	57.5	115.4
BMI	30.1 ± 4.8	21.1	39.3
% Body Fat	47.0 ± 6.2	34.1	55.6
WHR	0.8 ± 0.03	0.8	0.9
HRrest (bpm)	71.2 ± 9.7	60.0	96.0
HR_{max} (bpm)	163.5 ± 6.5	149.0	174.0
60% HRR (bpm)	134.1 ± 6.2	118.0	141.0
VO_2 (L/min) at 60% HRR	1.4 ± 0.25	1.0	2.0
VO_2 (ml/kg/min) at 60% HRR	19.1 ± 2.3	12.9	22.2
VCO_2 (L/min) at 60% HRR	1.2 ± 0.24	0.7	1.7
V_E (L/min) at 60% HRR	29.6 ± 5.7	19.8	40.0
RER at 60% HRR	0.9 ± 0.06	0.7	0.9
Total exercise time (min) to expend 400 kcal	61.6 ± 9.0	45.0	80.0

Note. All values expressed as mean ± standard deviation (SD). BMI = body mass index; WHR = waist to hip ratio; HR_{rest} = resting heart rate; HR_{max} = age-estimated maximum heart rate (220-age); HRR = heart rate reserve [(HR_{max} - HR_{rest}) x intensity + HR_{rest}]; VO_2 = volume of oxygen; VCO_2 = volume of carbon dioxide; V_E = expired ventilation; RER = respiratory exchange ratio (VCO_2/VO_2)

Effects of Niacin on Glucose, Insulin, or C-peptide Values

Four weeks of niacin therapy consisting of 1000 mg/day resulted in a statistically significant increase in fasting glucose, insulin, and C-peptide values. A significant main effect for niacin on fasting glucose values was found ($F(1, 16) = 16.58$, $p = .001$). The results are displayed in Table 3.

Table 3

Glucose: Tests of Within-Subjects Effects

Source	Type III Sum of Squares	Df	Mean Square	F	Significance
Supplement	1713.23	1	1713.23	16.58	0.001
Exercise	179.56	1	179.56	2.78	0.115
Suppl*Exer	0.39	1	0.39	0.006	0.941
Error (Suppl*Exer)	1111.34	16	69.46		

Note. Suppl = Supplement; Exer = Exercise; df = degrees of freedom

A significant main effect for niacin on fasting insulin values was found ($F(1, 16) = 16.84$, $p = .001$). The results are displayed in Table 4.

Table 4

Insulin: Tests of Within-Subjects Effects

Source	Type III Sum of Squares	Df	Mean Square	F	Significance
Supplement	1876.14	1	1876.14	16.84	0.001
Exercise	224.01	1	224.0	3.53	0.079
Suppl*Exer	0.30	1	0.30	0.01	0.945
Error (Suppl*Exer)	972.74	16	60.80		

Note. Suppl = Supplement; Exer = Exercise; df = degrees of freedom

A significant main effect for niacin on fasting C-peptide values was found ($F(1, 16) = 39.13$, $p = .001$). The results are displayed in Table 5.

Table 5

C-peptide : Tests of Within-Subjects Effects

Source	Type III Sum of Squares	Df	Mean Square	F	Significance
Supplement	9.73	1	9.73	39.13	< 0.001
Exercise	0.34	1	0.34	3.32	0.087
Suppl*Exer	0.16	1	0.16	0.46	0.506
Error (Suppl*Exer)	5.39	16	0.34		

Note. Suppl = Supplement; Exer = Exercise; df = degrees of freedom

The mean value of fasting glucose without niacin was 95.03 ± 10.67 mg/dL which significantly increased to 105.07 ± 13.56 mg/dL with niacin (Figure 1), an increase of 10.6%.

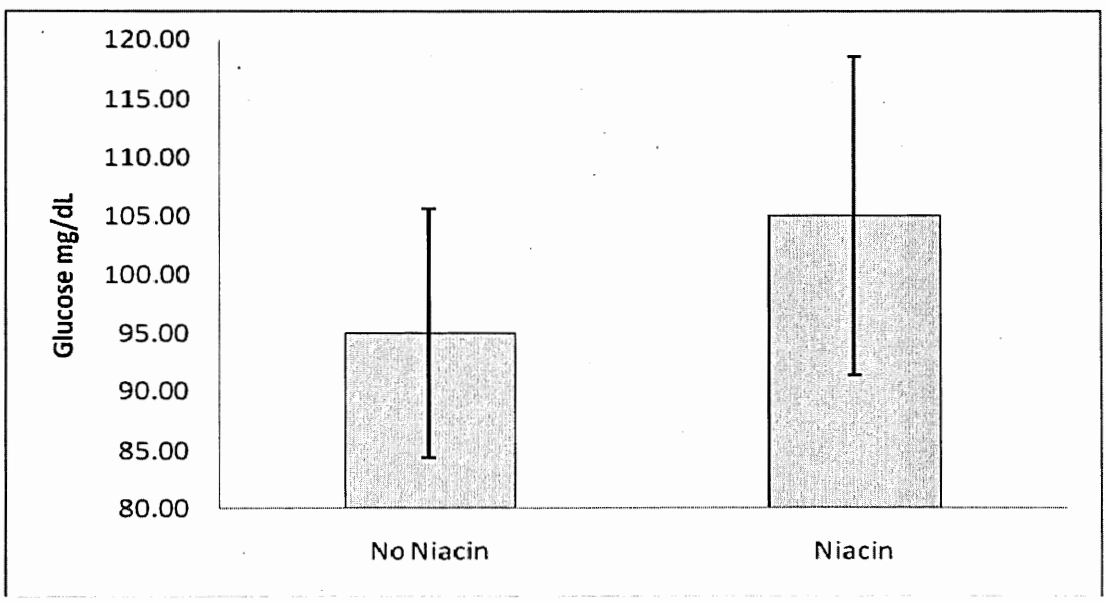

Figure 1. Glucose means. With niacin values are significantly different from the no niacin values, $p < 0.001$.

The mean value of fasting insulin without niacin was 16.98 ± 12.49 μU/mL and significantly increased to 27.48 ± 14.84 μU/mL with niacin (Figure 2), an increase of 61.8%.

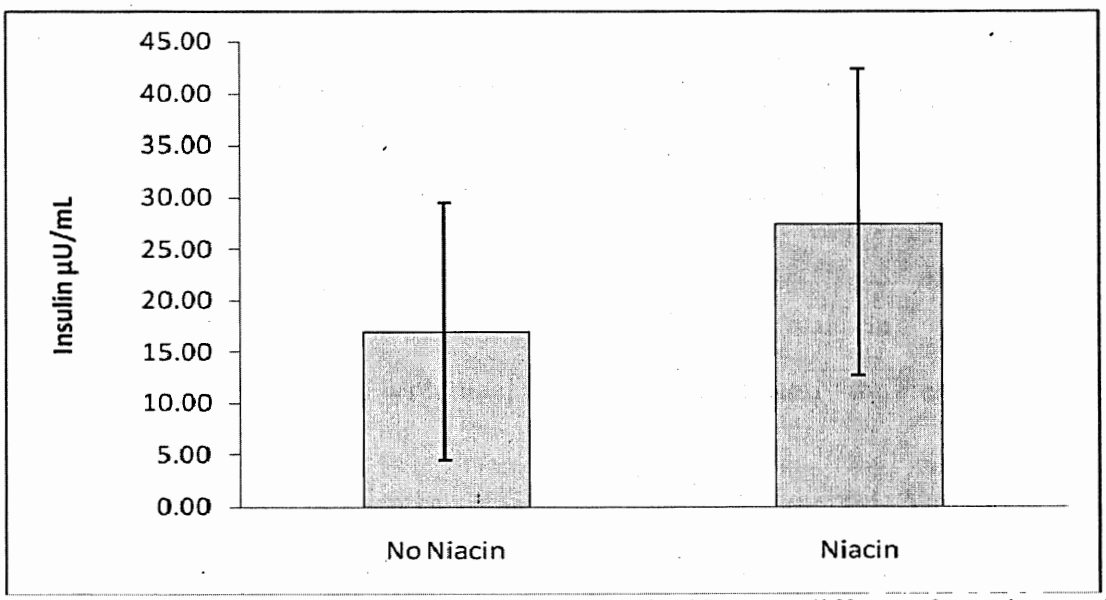

Figure 2. Insulin means. With niacin values are significantly different from the no niacin values, $p < 0.001$.

The mean value of fasting C-peptide without niacin was 1.65 ± 0.75 ng/mL and significantly increased to 2.41 ± 0.97 ng/mL with niacin (Figure 3), an increase of 46.1%.

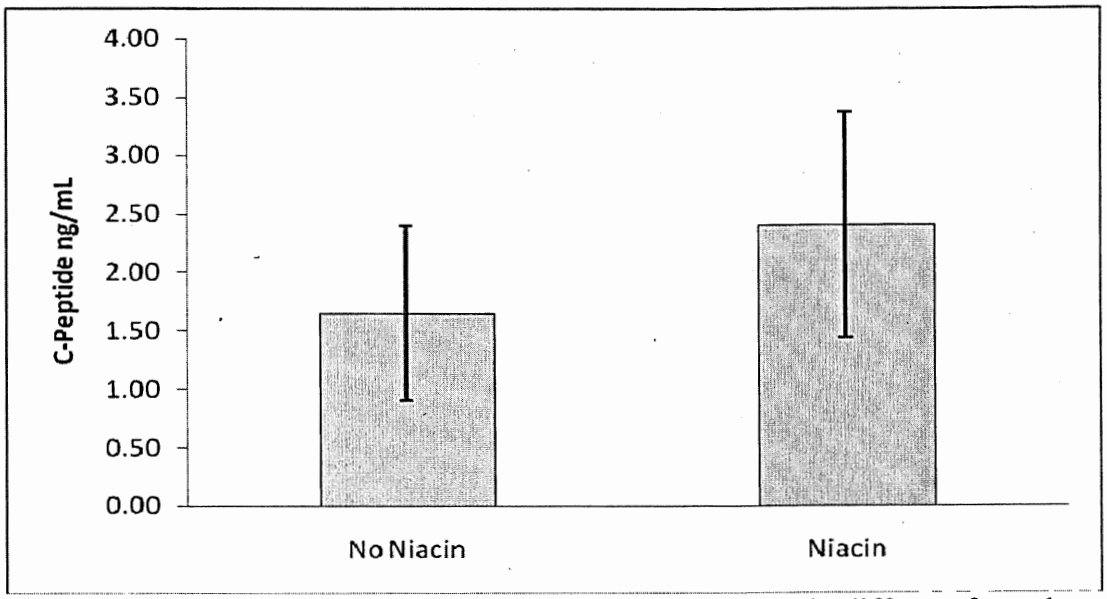

Figure 3. C-peptide means. With niacin values are significantly different from the no niacin values, $p < .001$.

Effects of Exercise on Glucose, Insulin, or C-peptide Values

The main effect for exercise was not significant for any dependent variable. The mean value of fasting glucose during rest was 101.68 ± 11.55 mg/dL and during exercise was 98.43 ± 12.03 mg/dL, a decrease of 3.2%. The change was not statistically significant, $p = .115$ (Figure 4).

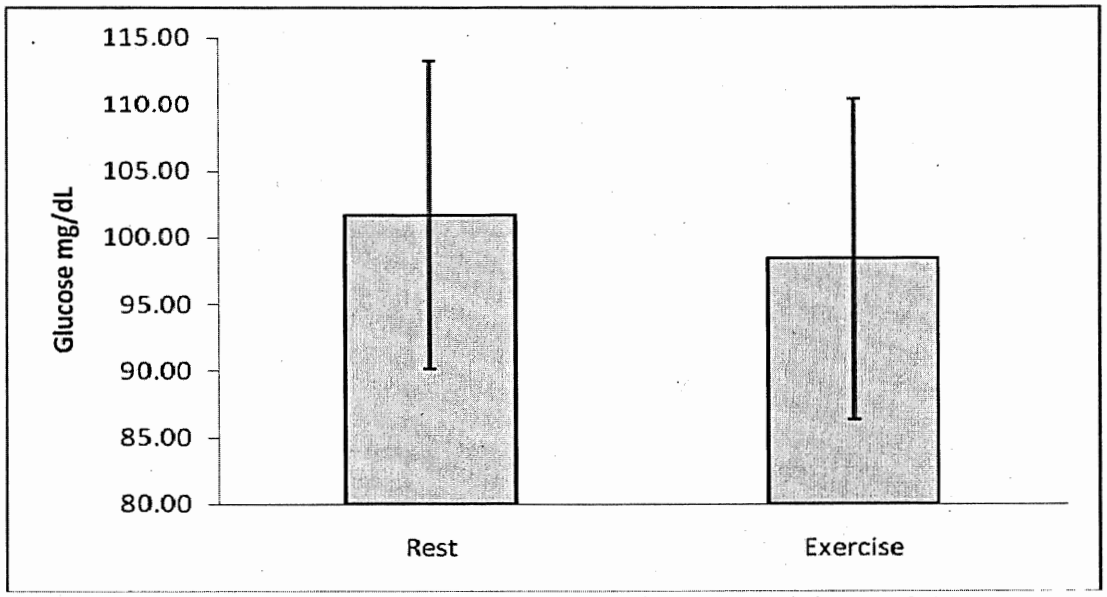

Figure 4. Mean values of glucose during rest and exercise trials, p = 0.115

The mean value of fasting insulin during rest was 24.04 ± 15.25 μU/mL and during exercise was 20.41 ± 10.93 μU/mL, a decrease of 15.1%. This change was not statistically significant, $p = 0.08$ (Figure 5).

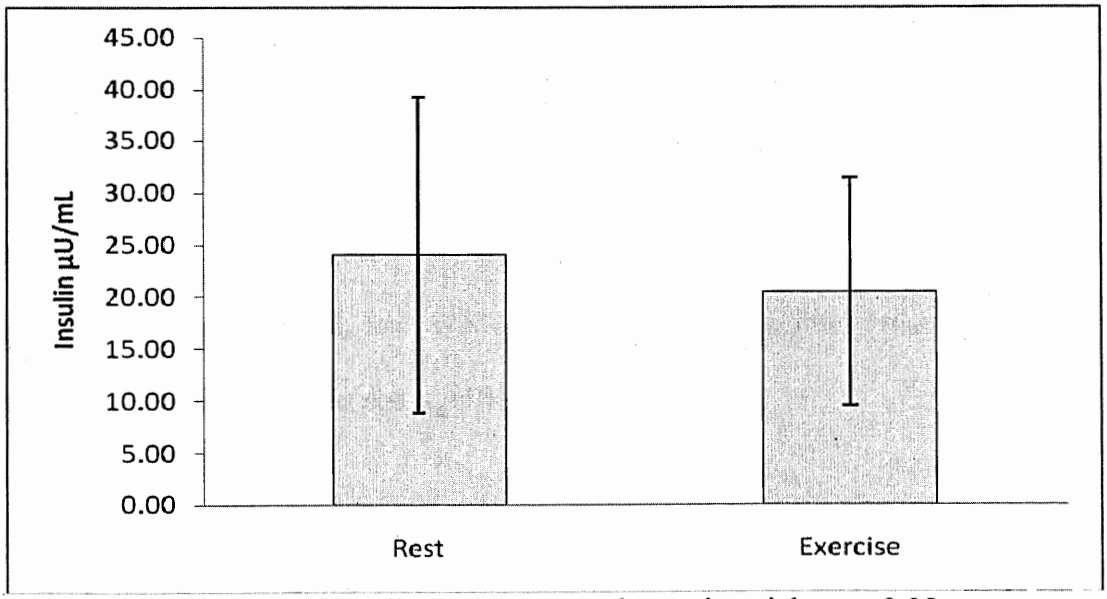

Figure 5. Mean value of insulin during rest and exercise trials, p = 0.08.

The mean value of fasting C-peptide during rest was 2.10 ± 0.94 ng/mL and during exercise was 1.96 ± 0.83 ng/mL, a decrease of 6.7%. The change was not statistically significant, $p = 0.09$ (Figure 6).

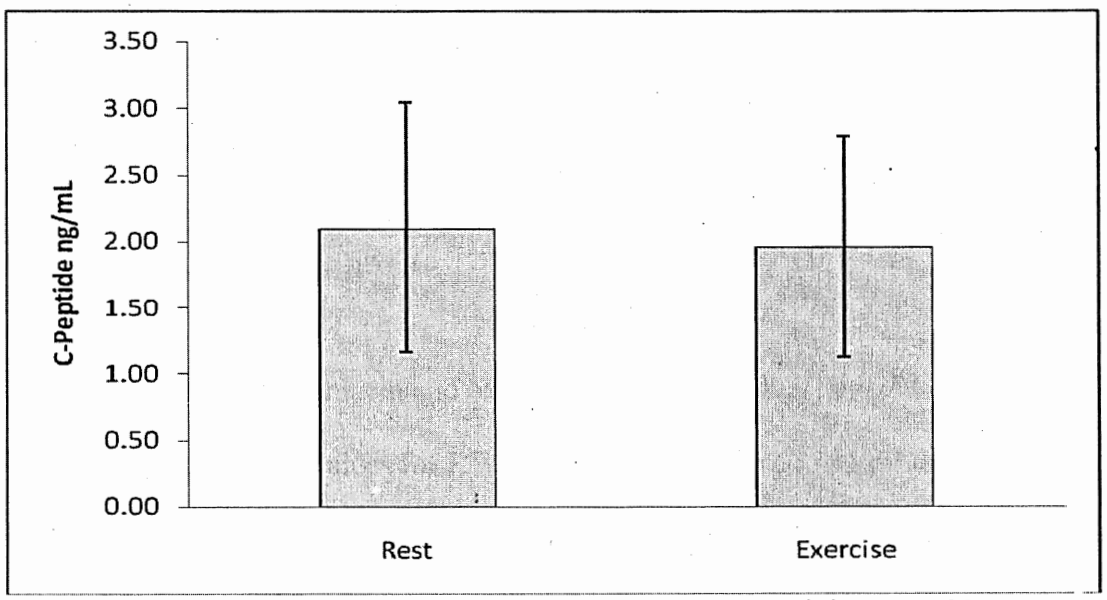

Figure 6. Mean value of C-peptide during rest and exercise trials, p = 0.09

Interaction of Niacin and Exercise on Glucose, Insulin, or C-peptide Values

Fasting glucose values for RWON were 96.58 ± 11.39 mg/dL and 106.77 ± 14.89 mg/dL during RWN (Figure 7). Fasting glucose values for the exercise trials were slightly lower, but not significantly than the rest trials; 93.48 ± 12.98 mg/dL for EWON and 103.37 ± 14.47 mg/dL for EWN (Figure 7). The interaction of niacin and exercise on fasting glucose values was not significant as $p = .94$.

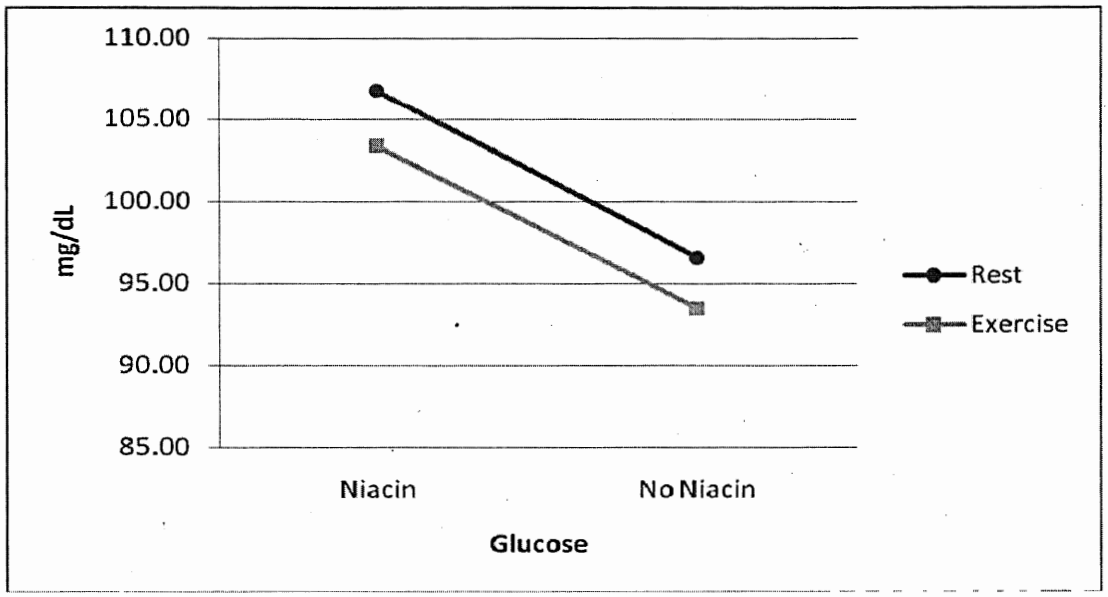

Figure 7. Interaction of niacin and exercise on glucose values, p = .94.

Fasting insulin values for RWON were 18.72 ± 15.63 μU/mL and increased to 29.36 ± 18.21 μU/mL during RWN (Figure 8). For both exercise trials fasting insulin values were lower, but not significantly than resting trials; 15.23 ± 10.21 μU/mL for EWON and 25.60 ± 14.02 μU/mL for EWN (Figure 8). The interaction of niacin and exercise on fasting insulin values was not significant as $p = .95$.

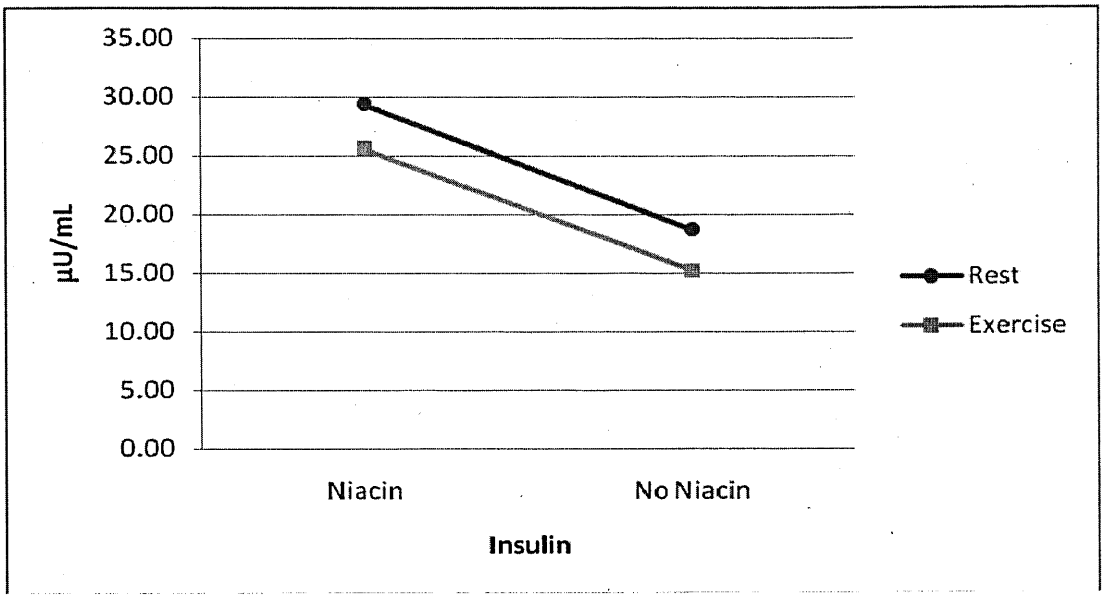

Figure 8. Interaction of niacin and exercise on insulin values, p = 0.95.

Fasting C-peptide values for RWON were 1.67 ± .95 ng/mL and increased to 2.52 ± 1.11 ng/mL during the RWN (Figure 9). Fasting C-peptide values for the exercise trials were slightly lower, but not significantly than resting trials; 1.63 ± .84 ng/mL for EWON and 2.29 ± .95 ng/mL for EWN (Figure 9). The interaction of niacin and exercise on fasting insulin values was not significant as $p = .51$.

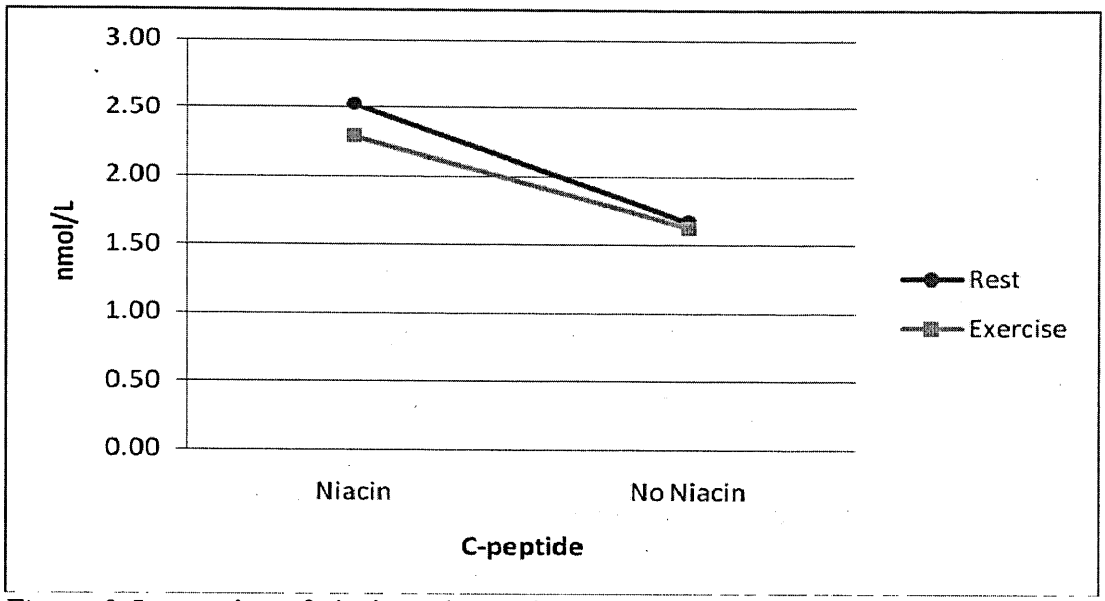

Figure 9. Interaction of niacin and exercise on C-peptide values, p = .51.

After reviewing the physical activity logs it was determined all participants remained sedentary throughout the duration of the study, therefore there is no physical activity data to report. The average of the 3-day dietary log of caloric intake is presented in Table 6. The table displays the average of total kcal, carbohydrate, fat, and protein for each of the four trials. The average of each macronutrient was similar for each trial.

Table 6

Average of 3-day Dietary Consumption for Each Trial

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

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

CHAPTER V

DISCUSSION

Since the mid 1950's niacin therapy has proven to effectively lower lipids, which in turn has lowered the number of myocardial infarctions (The Coronary Drug Project Research Group, 1975) and all-cause mortality (Canner et al., 1986) in men. The first extended release formula to be approved by the Food and Drug Administration for the treatment of dyslipidemia and for reducing cardiovascular risk was Niaspan (Kos Pharmaceuticals, Miami Lakes, FL). By a process not fully understood, niacin can increase fasting glucose levels. The current study is the first to investigate the independent and combined effects of niacin (1000 mg/day for 4 weeks) and a single bout of aerobic exercise (60% HRR) on glucose, insulin, and C-peptide profiles in sedentary, postmenopausal women. The primary finding of the present study was that niacin supplementation significantly affected the glucose, insulin, and C-peptide profiles in PMW. Thus, the first null hypothesis that there are no significant effects of niacin on glucose, insulin, and C-peptide values is rejected.

Effects of Niacin on Glucose, Insulin, and C-peptide Profiles

The findings of the current study that niacin increased glucose levels 10.6% are consistent with Molnar et al. (1964), Capuzzi et al. (1998), Chang et al. (2006), Guyton et al. (1998), and Knopp et al. (1998). Molnar et al. (1964) found nicotinic acid increased glucose values up to 51 mg/100 ml in men and women with diabetes. Capuzzi et al.

(1998) found fasting glucose levels increased a statistically significant amount of 4% from baseline values after participants, both men and women (21-75 years old), took 1000 mg/day of niacin for 96 weeks. Chang et al. (2006) reported 2 weeks of nicotinic acid therapy increased fasting glucose levels, with the largest increase seen in the older impaired glucose tolerance group. Guyton et al (1998) reported a 7% increase in fasting glucose levels in hypercholesterolemic male and female participants who took Niaspan for 96 weeks. Knopp et al. (1998) reported a significant increase of 5.3% in fasting plasma glucose after 16 weeks of 1.5 g/day of Niaspan in male and female participants.

In contrast to the current study, Vega et al. (2005) found fasted glucose levels were not significantly changed after 4 months of niacin therapy. Their study design involved participants who were men (43-69 years old) with T2DM or impaired fasting glucose taking a niacin dosage of 2000 mg/day. The lack of change in glucose concentrations is possibly due to the rebound of FFA concentrations after niacin therapy. This rebound affect could cause insulin resistance to increase resulting in FFA to suppress glucose uptake in the muscle causing glucose levels to rise. Elam et al. (2000) found IR niacin therapy of up to 60 weeks initially increased glucose, but stated glucose returned to baseline with continued therapy in patients (men and women, 65 ± 9 years old) with stable and controlled T2DM. Goldberg et al. (2000) and Grundy et al. (2002) both found initial increases in fasting blood glucose, but by the conclusion of these studies, all increases had returned to baseline. Goldberg et al. (2000) was similar to the current study in that the 1000 mg/day dose caused a significant increase (5.4%) in fasting

glucose concentrations from baseline in men and women (21 -75 years old). The similarity ends at an increased dosage (3000 mg/day) where fasting glucose levels decreased by 0.4% from baseline (significance not reported; Goldberg et al., 2000). The turnaround in glucose levels could be attributed to the 25 week protocol because disturbances in glucose values due to niacin therapy have been found to resolve after a several weeks of niacin therapy (Elam et al., 2000). Grundy et al (2002) also found minimal changes in fasting glucose levels during the 16 week trial involving male and female patients with T2DM (aged 21 years and older) who took 1000 mg or 1500 mg/day of Niaspan. These changes were usually seen during the 1500 mg/day dose, but were negligible and not statistically significant. The overall lack of change in glucose values is credited to adjustments made in diabetic medications for the patients taking the higher dose. Landau et al. (1992) reported both plasma glucose levels and plasma FFA levels decreased from baseline in nonobese, healthy, physically active men and women with normal glucose tolerance during 4 hr of continuous intravenous infusion of nicotinic acid. The combined infusion of nicotinic acid and somatostatin resulted in a greater decrease in fasting glucose levels, 20 to 30% from baseline values and was attributed to the concomitant fall in plasma glucagon concentrations. The changes in FFA metabolism are believed to play a role in carbohydrate metabolism.

Effects of Niacin on Insulin Profiles

In the current study, niacin was found to elevate insulin levels from baseline 61.8%, which is consistent with Chang et al. (2006) and Kahn et al. (1989). Chang et al.

(2006) found a significant increase in fasting insulin levels as well as a significant decrease in insulin sensitivity during niacin therapy in 45 healthy men and women (19 – 86 years old) who were divided into three groups and took 2000 mg of niacin per day for 2 weeks: a younger group (≤ 35 years old with normal glucose tolerance) and two older groups (> 60 years old with normal glucose tolerance) or (> 60 years old with impaired glucose tolerance). Insulin secretion in the older normal glucose tolerance group was also lower than the younger normal glucose tolerance and was significantly lower in the older impaired glucose tolerance group compared to the younger and older normal glucose tolerance group. These changes in insulin were attributed to aging and the impairment of β-cells compensation to insulin resistance (Chang et al., 2006). According to Kahn et al., 2 weeks of niacin administration caused fasting insulin levels to double, insulin sensitivity to decrease, and insulin resistance to develop in 11 healthy men (21 – 37 years old).

In contrast to the present study, the study by Alvarsson & Grill (1996) found 14 days of nicotinic acid therapy did not significantly change mean fasting insulin levels in healthy, nonobese men and women without diabetes (25-61 years old) who were low insulin responders (LIR) or high insulin responders (HIR) to glucose. This could be due to the age and BMI of the participants; the average age for their participants was 42.5 years old and 21.3-25.4 (kg/m^2) for BMI for the HIR group and 47 years old for the LIR and 20.9-28.1 (kg/m^2) for BMI where as the average age of participants in the present study was 57.6 years old and 21.1-39.3 (kg/m^2) for BMI. Aging is associated with β-cell

dysfunction and insulin resistance and an increase in visceral fat resulting in an increase in BMI. Differences may also be attributed to the level of physical activity, inactivity could contribute to the insulin resistance incurred during niacin therapy. Kelly et al. (2000) also found 14 days of niacin did not significantly change mean fasting insulin concentrations in healthy nonobese men and women possibly because the dosage amount of 500 mg/day for 7 days and 1000 mg/day for 7 days was too low to result in hyperinsulinemia. Although Morgan, Capuzzi, & Guyton (1998) found glucose increased slightly, 102.6 mg/dL at 1000 mg/day in dyslipidemic men and women (53 ± 1.9 years old) and 103.6 mg/dL at 2000 mg/day (48 ± 1.9 years old) compared to 94.4 mg/dL in the placebo group (50 ± 1.9 years old), these increases were not statistically significant.

Effect of Niacin on C-peptide Values

In the current study, niacin statistically increased C-peptide by 46.1%. In contrast to the present study, of the two articles reviewed involving niacin and C-peptide, neither study found C-peptide to increase with niacin therapy. Alvarsson & Grill (1996) found 14 days of niacin therapy did not significantly change fasting C-peptide and insulin levels in healthy, nonobese men and women without diabetes (25-61 years old). Possible reasons for the opposite results seen as compared with the present study are the age of the participants was younger and the lack of physical activity. Dobbins et al. (1998) also found no significant change in C-peptide values during the administration of niacin in healthy nonobese men and women. C-peptide nearly paralleled insulin levels which can be expected since C-peptide is released in equimolar amounts to insulin. Though the

exact mechanisms are not fully understood, FFA are believed to play a role in the secretion of insulin and C-peptide. Since C-peptide levels were not affected in the Dobbins et al. (1998) study and insulin levels were, this suggests a change in insulin clearance occurred rather than a change in the rate of insulin secretion.

Effects of Exercise on Glucose, Insulin, and C-peptide Profiles

Exercise can improve metabolic risk factors such as glucose and insulin levels, BP, body fat, and aerobic fitness. One or two bouts of exercise ($\geq$ 65% VO_{2max}) and a caloric expenditure ($\geq$ 1500 kcal/week) have been suggested as minimal requirements to improve CHD risk factors, such as blood glucose and diastolic blood pressure, declining 0.21 $mmol/L^{-1}$ and 3.0 mmHg, respectively (Asikainen et al., 2003). In the current study, a single bout of aerobic exercise did not affect glucose values, insulin, or C-peptide levels. Given these results, the second hypothesis stating there are no significant effects of exercise on glucose, insulin, and C-peptide values is accepted as the changes observed did not reach statistical significance. This finding is consistent with Baynard et al. (2005) who reported single or multiple bouts of aerobic exercise (60% VO_{2peak}) did not alter glucose or insulin levels in sedentary, obese women with T2DM (42-60 years old). The lack of change in glucose or insulin levels could indicate a higher intensity level may be required to modify glucose and insulin in women with T2DM.

Previously published studies involving repeated bouts of aerobic exercise were also consistent with this study (Fox et al., 1996; Giannopoulou et al., 2005; Stefanick et al., 1998). Fox et al. (1996) reported 24 weeks of walking 1 hour, 3 days/week at 60-70%

VO_{2max} did not to alter glucose or insulin levels in healthy, moderately obese, PMW (aged 65.6 ± 3.3 years old), even though there were significant decreases in mean body weight, BMI, and percent body fat from baseline to Week 24 measurements. Multiple bouts of aerobic exercise by obese (BMI: 34.6 ± 1.9 kg/m^2), PMW with T2DM (50 - 70 years old) also resulted in no significant changes in fasting glucose levels (Giannopoulou et al., 2005). One possible reason for the lack of change is the timing of the blood draws. Blood samples were not taken until 48 hr postexercise, so any benefit in glucose levels may have already disappeared.

In contrast to the current study, previous investigations involving repeated bouts of aerobic exercise did alter glucose (Asikainen et al., 2003), insulin levels (Björntorp et al., 1977) or both glucose and insulin (Magkos et al., 2008). Mean blood glucose had a statistically significant decline when exercise was performed by healthy, sedentary, PMW at 65% VO_{2max} and expended 1500 kcal/week even though there was no change in mean fasting insulin levels (Asikainen et al., 2003). A possible explanation for the decrease in mean glucose was the number of expended calories is almost four times as much as the current study and lasted for 15 weeks. Insulin levels were decreased about 30% with aerobic exercise in obese, young men and women (26 – 42 years old) who followed a training program of 1 hr, 3 days/week for 6 weeks (Björntorp et al., 1977). Due to the lack of change in glucose levels, the decrease in insulin levels could be attributed to an increase in insulin sensitivity in the peripheral tissues and liver. During another training study, the 24-hr postexercise time point in healthy men and women (30-37 years old)

yielded an 8% decrease in fasting insulin levels and a 10% increase in insulin sensitivity (Boulé et al., 2005). However, this improvement was short lived, reverting to baseline values by the 72-hr postexercise time point. Regular bouts of exercise are required to maintain improvements in glucose tolerance and insulin secretion. In addition to exercise, insulin secretion may be affected by changes in BMI and waist circumference (Boulé et al., 2005). Blood samples taken the morning after a single bout of aerobic exercise performed the previous evening by nonobese, physically, active but untrained men (27 ± 5 years old) revealed a significant decrease from baseline values in fasting plasma glucose and insulin levels (Magkos et al., 2008).

Effects of Niacin and Exercise on Glucose, Insulin, and C-peptide Profiles

The third hypothesis stating there is no significant interaction of niacin and exercise on glucose, insulin, and C-peptide values is also accepted due to the changes observed did not reach statistical significance. There is a lack of published studies involving the combined effect of niacin and exercise on glucose, insulin, and C-peptide profiles. The main point of interest of one study involving niacin and aerobic exercise was TG, but glucose and insulin were also investigated (Plaisance et al., 2008). The study involved 15 sedentary obese men (30 – 65 years old) performing four trials: high fat meal only, one bout of aerobic exercise at 60-70% VO_{2max} expending 500 kcal, 1 hr before high fat meal, then repeating the first two trials after taking 500 mg/day of Niaspan for Week 1, 1000 mg/day for Week 2 and 1500 mg/day for Weeks 3-6. The results found fasting and postprandial glucose levels did not change from baseline to the end of the

study. Niacin increased fasting insulin concentrations (20 uU/mL at baseline to 45 uU/ml with niacin) possibly due to a decrease in insulin sensitivity which is attributed to a rebound elevation in FFA. Blood samples taken 2 hr postprandial found niacin also increased postprandial insulin levels by 54%, though niacin and exercise attenuated this rise which provides evidence that when taking niacin, aerobic exercise may provide a metabolic benefit in men.

Limitations of the Current Study

A few limitations exist in this study. The first is the results are applicable only to the sedentary, PMW population between the ages of 40 and 80 years old who have performed a single bout of aerobic exercise. Another limitation is this population in this study consisted of only healthy women without diabetes therefore the results are not applicable to women with diabetes or insulin resistance. The sample size is a limitation. A larger size could possibly determine if the increases in glucose, insulin, and C-peptide induced by niacin therapy were true changes and not the result of differences of the characteristics of the participants (age, race, weight, glucose tolerance). The length of supplementation (1000 mg/day for 4 weeks) is another limitation because increases in glucose levels may dissipate after a few months of therapy. Finally, the possibility exists of type II error as regards to exercise effect and interaction of exercise and niacin. Power for the test of the null hypotheses on each dependent variable ranged from .348 to .423 and .051 to .098, respectively.

Summary and Conclusion

The current study investigated the effects of 4 weeks of niacin therapy consisting of 1000 mg/day and a single bout of aerobic exercise expending 400 kcal on glucose, insulin, and C-peptide profiles in sedentary PMW. The results of this study found niacin significantly affected the glucose, insulin, and C-peptide profiles, while exercise alone or when combined with niacin therapy did not. The use of Niaspan was generally well tolerated by the participants; only two participants dropped from the study due to adverse side effects of the drug. Given the adverse effects of niacin, the use of niacin in postmenopausal women should proceed with caution under medical supervision until further investigations are conducted.

Recommendations for Further Study

Although the use of niacin has been well documented for use in the treatment of dyslipidemia, further study is necessary to determine the safety and efficacy of its use in postmenopausal women, especially those with T2DM given the increased frequency seen in said disease in persons 60 years of age and older. Future clinical studies of niacin, alone or with aerobic exercise, should entail a protocol of several months possibly resulting in an improved metabolic response given that the increases in glucose caused by niacin therapy may return to baseline levels after a few months and participants could increase their tolerance to niacin resulting in an increase in retention of participants.

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APPENDIX A

PHONE INTERVIEW

Niacin Exercise Women (NEW) Phone Screen

Today's Date: _____

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

NAME

First Name:_____ Last Name:_____

PERSONAL INFORMATION

What is your gender? ○ male ○ female

What is your date of birth? _____

How old are you? _____

When was your last period? _____

What is your ethnic identity?

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

MEDICAL HISTORY

Has your physician ever told you that you have high blood pressure? ○ yes ○ no

Has your physician ever told you that your cholesterol level was high? ○ yes ○ no

Have you lost more than 20 lbs in the past 6 months? ○ yes ○ no
If yes, was this weight loss deliberate? ○ yes ○ no

Have you ever had a heart attack? ○ yes ○ no
If yes, was this within the past 6 months? ○ yes ○ no

Have you ever had a stroke? ○ yes ○ no
If yes, was this within the past 6 months? ○ yes ○ no

Do you have diabetes? ○ yes ○ no

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

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

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

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

If yes, what medications? _____

_____

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

If yes, what supplements and how long? _____

_____

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

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

_____

PERSONAL HABITS

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

If yes, how long and what activity? _____

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

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

CONTACT INFORMATION

Number and Street Address: _____

_____

City: _____ State: _____ Zip Code: _____

What is your daytime telephone number? _____

What is your evening telephone number? _____

What is your cellular number? _____

What is your email address? _____

ADDITIONAL INFORMATION

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

If accepted into this study, are you willing to maintain your current diet, exercise, and supplement routine approximately for 3 months without changing any of these factors? ○ yes ○ no

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

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

Thank you for your time. We will contact you to let you know if you are eligible for the Niacin Exercise Women (NEW) Study.

APPENDIX B

PARTICIPANT CONSENT FORM

TEXAS WOMAN'S UNIVERSITY
CONSENT TO PARTICIPATE IN RESEARCH

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

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

Explanation and Purpose of the Research

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

Research Procedures

Submaximal Oxygen Consumption (VO_2) Test
You will perform a submaximal exercise test on a motor-driven treadmill. Your data obtained from submaximal exercise testing will be used to predict your maximal oxygen consumption (VO_2max), the maximal volume of oxygen that you can consume during exercise. After three minutes of warm-up at a speed of 2.0 mph with 0 % grade, the treadmill walking exercise protocol will start at 3.0 mph with 0 % grade. The treadmill speed will be held constant at 3.0 mph throughout the test. However, the treadmill grade will be elevated by 2.0 % every three minutes until you reach 70% heart rate reserve. To calculate heart rate reserve your resting heart rate is first subtracted from the age-estimated heart rate max (220 – age (yrs)). This value will be multiplied by percent intensity (e. g., 70% in this study), and resting heart rate will be added to this value to obtain a target heart rate reserve. Resting heart rate and blood pressure will be measured after you quietly sit in a chair at least five minutes. During submaximal exercise testing heart rate will be continuously monitored using a 12-lead electrocardiograph (ECG), and blood pressure will also be measured in the last minute of each stage. In addition, ratings of perceived exertion will be monitored at the end of each stage. The submaximal exercise test will be terminated when you reach 70% heart rate reserve or wish to stop exercise testing. During submaximal exercise testing expired respiratory gases will be continuously collected and analyzed using an oxygen uptake system. After exercise testing is terminated, you will cool down for approximately five minutes. During recovery, blood pressure and heart rate will be immediately measured post exercise, and every minute thereafter until your heart rate and blood pressure return to resting values.

Participant
Initials _____

Study Design

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

Niacin Supplementation

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

Dietary and Physical Activity Considerations

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

Body Composition Assessment

The waist-to-hip ratio will be determined from your minimum waist and maximum hip circumference while you are in a standing position, and at the end of a normal breath. An additional waist circumference measure will be taken to approximate central (intra-abdominal) fat mass. Body composition: skin-fold measures will be taken at 3 sites including back of your upper arm, top of your hip, and thigh. All skin-fold measures will be made on the right side of the body, and each site will be measured twice. Female lab assistants will be taking all the body composition measurements.

Participant
Initials _____

Blood Analyses

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

Exercise Considerations

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

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

Maximum total time commitment

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

Potential Risks

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

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

A risk of hematoma (bruise) may result from the blood collection procedure. To reduce the potential risks of discomfort, trained medical personnel will draw all the blood samples. In addition there is a

Participant
Initials _____

risk of contamination from blood products. To reduce this risk all personnel handling tubes associated with any blood products will be wearing latex or vinyl gloves. In addition, all needles and syringes will be disposed of in sharps container. All table tops will be covered with a non-porous, absorbent disposable pad.

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

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

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

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

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

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

The risks of side effects caused by aspirin or ibuprofen include heart burn, diarrhea, stomach upset, vomiting, faint ringing in the ear, black, bloody, tarry stools, or blurred vision. If you experience any

Participant
Initials _____

side effects, you will immediately stop taking aspirin or ibuprofen. The side effects will be reversible once aspirin or ibuprofen is stopped.

There is a possible risk that you may be allergic to aspirin or ibuprofen. If you are, you are not required to take aspirin or ibuprofen prior to niacin ingestion.

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

Participation and Benefits

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

Questions Regarding the Study

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

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

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

☐ _____

_____

_____

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

Participant's Signature **Date**

APPENDIX C

MEDICAL HISTORY QUESTIONNAIRE

MEDICAL HISTORY FORM

Name _____

Street _____

City _____ State_____ Zip_____

Age _____ Sex _____ Current Weight _____lbs Email _____

Telephone (Day) (_____) _____ - _____ Night (_____) _____ - _____

Personal Physician Name and Address _____

_____

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

I. Heart and Circulatory:

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

II. Respiratory:

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

III. Other Disease or Ailments:

___ Back injuries
___ Epilepsy
___ Allergies
___ Liver disease
___ Kidney disease
___ Arthritis
___ Orthopedic (joint or bone) leg or arm problems
___ Other, Specify: _____

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

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

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

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

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

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

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

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

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

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

Signature _____ Date_____

APPENDIX D

PERMISSION LETTER FROM PRIMARY CARE PHYSICIAN

TWU
TEXAS WOMAN'S UNIVERSITY
DENTON DALLAS HOUSTON

Department of Kinesiology
College of Health Sciences
P.O. Box 425647, Denton, TX 76204-5647
940-898-2575 Fax 940-898-2581

Permission to Participate in a Research Study
SPRING-SUMMER 2007

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

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

Dear Physician:

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

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

Sincerely

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

APPENDIX E

APPROVAL LETTER FROM IRB OFFICE

TWU
TEXAS WOMAN'S UNIVERSITY
DENTON DALLAS HOUSTON

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

May 3, 2007

Ms. Heidi Bidstrup
P.O. Box 424752
Denton, TX 76204

Dear Ms. Bidstrup:

Re: The Effects of Niacin and a Single Bout of Exercise on Glucose, Insulin, and C-peptide Profiles in Postmenopausal Women

The above referenced study has been reviewed by the TWU Institutional Review Board (IRB) and was determined to be exempt from further review.

If applicable, agency approval letters must be submitted to the IRB upon receipt PRIOR to any data collection at that agency. Because you do not use a signed consent form in your study, the filing of signatures of participants with the TWU IRB is not required.

Another review by the IRB is required if your project changes in any way, and the IRB must be notified immediately regarding any adverse events. If you have any questions, feel free to call the TWU Institutional Review Board.

Sincerely,

Dr. Kim Grover-Haskin, Co-Chair
Institutional Review Board - Denton

cc. Dr. Charlotte Sanborn, Department of Kinesiology
Dr. David Nichols, Department of Kinesiology
Graduate School

APPENDIX F

DIETARY LOG

INSTRUCTIONS FOR RECORDING DIET RECORD

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

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

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

4. Describe your food thoroughly:

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

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

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

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

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

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

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

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

3-DAY DIET RECORD

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

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

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

Food	Amount	Location

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

APPENDIX G

PHYSICAL ACTIVITY LOG

5-DAY PHYSICAL ACTIVITY RECORD FORM

ID: NEW_____

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

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

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

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

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

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

APPENDIX H

ANALYSIS OF BLOOD

Analysis of glucose

All standards and samples were run in duplicate in a 48 well microplate and analyzed by a PowerWave™ XS microplate spectrophotometer (BioTek Instruments, Winooski, VT). The analysis of glucose consisted of:

1. One 100 mL vial of glucose color reagent (Raichem, San Diego, CA) dissolved into 100 mL of distilled water (dH_2O).
2. 1.5 mL of prepared glucose color reagent added to each well.
3. The curve: Blank, 10 µL dH_2O, 2.5 µL, 5.0 µL, 7.5 µL, and 10 µL of Standard, and 10 µL of Control I and II.
4. Immediately following curve, 10 µL per sample added into corresponding well.
5. Lid was placed on microplate, placed on a Lab-Line Instruments Inc shaker (Melrose Park, IL) and shaken for 5 min at 225 rpm.
6. After shaking the lid was removed, plate was placed into the microplate spectrophotometer, and incubated 10 min at 37° C.
7. After incubation the plate was immediately analyzed by the microplate spectrophotometer using a 500 nm wavelength.

Analysis of insulin

The insulin ELISA kit (Webster, TX), the Columbus Pro™ Microplate washer (Tecan, Grödig, Austria) and the Infinite M200 microplate reader (Tecan, Grödig, Austria) were used in the analysis of insulin. All standards and samples were in duplicate using the following method:

1. Washing Solution preparation: 60 ml of Wash Concentrate diluted in reservoir jug with1500 mL of dH_2O, then attached jug to washer.
2. 25 µL of Standard A, B, C, D, and E, Control I and II, and samples consecutively added to 96 well anti-insulin-coated microtitration strip microplate.
3. Insulin Antibody-Enzyme Conjugate Solution preparation: 200 µL of Insulin Antibody-Enzyme Conjugate Concentrate added to 10 mL of Assay Buffer.
4. Added 100 µL Insulin Antibody-Enzyme Conjugate Solution to each well.
5. Microplate was placed into microplate reader and shook for 60 min at 700 rpm at room temperature.
6. After shaking, the microplate was placed on the microplate washer where each well was automatically washed 5 times with the Washing Solution.
7. 100 µL of TMB Chromogen Solution added to each well, the plate was placed into the microplate reader, and incubated for 10 min at 700 rpm at room temperature.
8. After incubation, 100 µL of Stopping Solution added to each well, the plate was placed into microplate reader and immediately read using a 450 nm wavelength.

Analysis of C-Peptide of Insulin

The C-peptide of insulin ELISA kit (Webster, TX), the Columbus Pro™ Microplate washer (Tecan, Grödig, Austria) and the Infinite M200 microplate reader (Tecan, Grödig, Austria) were used in the analysis of C-peptide. All standards and samples were in duplicate using the following method:

1. Washing Solution preparation: 60 ml of Wash Concentrate diluted in reservoir jug with1500 mL of dH_2O, then attached jug to washer.
2. 20 µL of Standards A, B, C, D, E, and F, Control I and II, and samples added to 96 well Anti- C-Peptide -Coated Microtitration microplate.
3. Insulin Antibody-Enzyme Conjugate Solution preparation: 420 µL of Antibody-Enzyme Conjugate Concentrate diluted in 21 mL of Assay Buffer.
4. 200 µL of Antibody-Enzyme Conjugate Solution added to each well.
5. Microplate placed in microplate reader and shook for 60 min at 700 rpm at room temperature.
6. After shaking, microplate was placed in microplate washer where each well was washed 5 times with the Washing Solution.
7. 100 µL of TMB Chromogen Solution was added to each well and incubated for 15 min at 500 rpm at room temperature.
8. After incubation was completed, 100 µL of Stopping Solution was added to each well, the plate was placed in microplate reader and immediately read using 450 nm wavelength.

APPENDIX I

RAW DATA

Participants' Glucose Data

N	RWON	EWON	RWN	EWN
1	79.47	66.30	84.61	80.70
2	101.89	92.43	133.99	118.35
3	86.26	66.71	86.87	66.91
4	112.18	88.31	126.17	115.27
5	105.39	96.96	100.04	103.95
7	90.58	103.33	102.92	102.92
8	94.49	110.54	120.62	101.69
9	98.60	95.10	101.28	104.57
11	99.42	90.58	101.69	102.92
12	96.75	103.54	108.27	106.42
13	99.22	98.19	113.42	98.19
15	118.97	101.48	96.13	111.56
16	103.75	108.27	113.83	111.15
17	86.26	96.54	96.34	98.19
18	100.66	91.61	126.17	133.79
19	95.72	102.92	116.91	99.84
20	72.26	76.38	85.84	100.86

Key

N = participant's id number

RWON = rest without niacin at 24 hr

EWON = exercise without niacin at 24 hr

RWN = rest with niacin at 24 hr

EWN = exercise with niacin at 24 hr

Participants' Insulin Data

N	RWON	EWON	RWN	EWN
1	32.83	21.60	33.86	34.22
2	9.78	18.04	62.91	23.65
3	12.67	18.00	17.16	31.28
4	22.65	14.11	39.71	32.06
5	9.43	13.12	46.75	37.60
7	38.71	14.79	27.79	16.83
8	11.98	4.87	14.59	12.55
9	68.41	50.14	75.78	58.50
11	18.19	17.69	33.20	26.00
12	13.43	13.43	18.89	10.67
13	6.65	14.49	10.60	6.92
15	6.69	5.50	12.87	12.66
16	19.30	16.63	27.05	26.39
17	18.86	14.38	21.28	25.17
18	8.50	5.92	26.03	48.84
19	11.38	8.53	14.40	20.94
20	8.86	9.93	16.30	10.92

Key

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

Participants' C-peptide Data

N	RWON	EWON	RWN	EWN
1	3.08	1.99	3.03	3.08
2	1.46	3.08	4.99	2.95
3	1.25	1.93	2.01	2.33
4	3.23	2.61	3.97	4.47
5	1.50	1.27	2.54	1.72
7	2.06	2.27	3.34	2.35
8	1.11	0.82	2.39	1.81
9	4.01	3.23	3.77	3.32
11	2.22	2.22	3.14	3.71
12	1.47	1.84	2.93	1.70
13	0.87	0.88	1.35	1.12
15	0.94	0.94	1.03	1.21
16	1.39	1.22	2.10	1.83
17	1.04	0.82	1.26	1.94
18	0.82	0.58	2.27	2.55
19	0.82	0.77	1.09	1.23
20	1.16	1.20	1.71	1.58

Key

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