THE EFFECT OF EXERCISE AND EXTENDED-RELEASE NIACIN ON C-REACTIVE PROTEIN AND LIPOPROTEIN (A) LEVELS IN INDIVIDUALS WITH TYPE II DIABETES

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Chapter I

Introduction

In the United States, the American Diabetes Association reports, 24 million Americans have diabetes. Of this number, 18 million have been diagnosed, but a staggering 6 million cases of type II diabetes have gone undiagnosed. Approximately 90-95% of these cases are Type II diabetics [1]. Type II diabetes, also known as non-insulin dependent diabetes mellitus (NIDDM) is a metabolic disease associated with varying levels of insulin resistance and impaired insulin secretion [2-4]. NIDDM is associated with obesity, hypertension, hyperglycemia and dyslipidemia[2-5].

Over the past three decades, obesity rates have been rapidly increasing, and are estimated at 44.3 million as of 2002 [5]. The prevalence of obesity has reached epidemic proportions, mainly related to sedentary lifestyles and poor nutrition. Eighty percent of NIDDM cases are obese. Obesity is closely linked with hypertension, dyslipidemia, glucose intolerance, and insulin resistance, which increases the risk of arteriosclerosis. In individuals with diabetes, this corresponds to an associated threefold increased risk of coronary artery disease (CAD)[10,15,16]. NIDDM is associated with increased risk of macrovascular and microvascular disease, and diabetic neuropathy. Due to this risk, the American Heart Association (AHA) and the National Cholesterol Educational Program (NCEP) now recognize diabetes to be a coronary heart disease (CHD) risk equivalent[17,20]. People with diabetes have a greater risk of mortality from coronary
heart disease and stroke. Despite advances in medicine and technology, coronary heart disease is the leading cause of death in the United States [17-20].

Epidemiological studies have recognized major independent contributing risk factors in NIDDM patients such as cigarette smoking, high serum cholesterol, hypertension and other predisposing risk factors including sedentary lifestyle, obesity and advancing age[8,15]. Recently the development of C-reactive protein (CRP) and lipoprotein (a) [Lp (a)] are drawing great attention as coronary disease markers [26,31].

Lipoprotein (a) is a sub-fraction of lipoproteins (LDL) and structurally similar to plasminogen. Hence Lp(a) interferes with the process of fibrinolysis and causes impairments in plasminogen activation and fibrinolysis [26]. Lp(a) has been shown to have marked elevation after acute ischemic coronary syndromes, and oxidized Lp(a) promotes atherosclerosis. The Framingham Study and Lipid Research Clinic have both shown a 2.3x higher risk for coronary heart disease with Lp(a) levels >10mg/dl [31,34].

According to NCEP, 37% of individuals who possess high risk profiles for CAD, also have elevated levels of Lp(a) compared to those with low risk profiles. Research has shown increased concentrations of Lp(a) to be an established risk factor for coronary heart disease [26,35,39,41], hence a better understanding of Lp(a) and importance to assess Lp(a) levels in this high risk population. Lp(a) is primarily genetically determined and varies between racial groups, an observation which has added to the controversy for screening and therapy.

Since the 1990s, CRP has been strongly associated with prediction of future coronary events. CRP is an acute-phase protein, which is a systemic marker of inflammation and tissue damage. In the recent past, CRP has become an
emerging/independent risk factor for prediction of myocardial infarction, stroke and arteriosclerosis [44-49]. CRP levels are measured in assays (hs-CRP) and can be used to assess cardiovascular risk in conjunction with other factors such as cholesterol levels. Recently, AHA/CDC released a position statement stating that hs-CRP assays are the best marker of inflammation at this time [53-54]. This study used these assays to quantify CRP.

Ridker et al. has shown the relationship between elevated CRP levels and future cardiovascular events are independent of age, smoking, cholesterol and diabetes. In one study, 27,000 women followed over eight years showed CRP to be a better indicator of risk CAD events and atherosclerosis, than LDL cholesterol levels [53].

There is a direct correlation between Body Mass Index (BMI) and CRP. The Third National Health and Nutritional Examination Survey found higher levels of CRP in overweight (25-29.9 kg/m²) and obese (30 kg/m²) individuals than in normal weight individuals. Hence, this investigation looked at the effect of exercise and weight loss on CRP levels. In addition, CRP levels are thought to be affected by smoking, age, sex, adiposity and inactivity [45,47,49].

Niacin is well recognized for treating dyslipidemia in adults because of its wide variety of effectiveness. Niacin has been shown to increase high-density lipoproteins (HDL) cholesterol as well as decrease triglycerides (TG) and Lp(a) [21-24]. In the past the prescription of niacin has been discouraged in diabetic populations due to potential glucose elevation [21-23]. Extended release (ER) niacin (Niaspan®; Abbott Laboratories, Chicago, IL), specially formulated to reduce side-effects compared to immediate release or over the counter formulas now available.
The ADVENT study showed the best therapy for Lp(a) reduction is niacin. In the study, a majority of Type II diabetics taking 1500 mg of niacin can successful reduce Lp(a) and increase HDL cholesterol without much change in glucose levels. Presently, statin medications are the preferred therapy for treating dyslipidemia, due to their powerful lowering of LDLs, but there is only a modest effect on HDL cholesterol and TG [24]. The extended release niacin at doses of 1500mg seems to be the ideal dosage for less flushing and effective lipid control [22].

This investigation is the first to test the role of exercise and niacin with NIDDM individuals. Exercise is a vital component in the treatment of Type II diabetes. Therefore, the emphasis must be placed on regular physical activity in order to control blood glucose levels and prolong the onset of microvascular, macrovascular and neural complications [4]. Regular exercise has also been shown to have favorable effects on HDL and TG levels. Other benefits of regular aerobic exercise include weight loss, improved aerobic capacity and improved psychological status.

**Purpose of the Investigation:**

The purpose of this study was to determine the effect of regular aerobic exercise and extended release niacin on C-reactive protein levels and lipoprotein (a) levels in individuals with type II diabetes in the management of dyslipedemia.

**Hypothesis:**

This investigation hypothesis was: 1) CRP levels to decrease after a 16-week aerobic exercise program in Type II diabetics taking extended release niacin; 2) Lp (a) levels decrease in Type II diabetics, exercising and taking extended release niacin.
Significance of Problem:

The epidemic prevalence of 97 million Americans who are overweight or obese continues to rise [5]; these individuals are pre-disposed to NIDDM due to sedentary lifestyles and excess body fat. According to the CDC, the total cost of diabetes mellitus in the United States in 2002 was $132 billion. Dyslipidemia is directly correlated with diabetes. There is a need to examine the potential benefits of extended release niacin and aerobic exercise as treatment in this specific population.

Definitions:

1. Type II Diabetes: A chronic metabolic disease characterized by diminished insulin secretion or tissue resistance to insulin.

2. C-Reactive Protein (CRP): Is a plasma protein and acute phase reactant released into the bloodstream as a result of inflammation. CRP is exclusively made in the liver and released by the body in response to acute injury, infection, or other inflammatory stimuli.

3. Lipoprotein (a):Lp (a) is a low-density lipoprotein produced in the liver with structural similarity to plasminogen. Increased concentrations are a risk factor for myocardial infarction and coronary disease.
CHAPTER II
REVIEW OF LITERATURE

Cardiovascular disease is the leading cause of mortality in diabetes patients in the United States. Already, an estimated 24 million Americans have diabetes and a furthermore 6 million have been undiagnosed [1]. An estimated 80% of these patients develop or die of macrovascular disease (CVD) [7]. The combination of an increasing aging population, obesity epidemic and sedentary lifestyle, the enormity of the disease is epidemic. This epidemic is associated with an annual medical expense of approximately $174 billion annually, both direct and indirectly [3]. Once physicians identify greater risk for CVD, aggressive measures encompassing both long term lifestyle modification and drug therapy must be the primary goal. The development of type II diabetes has numerous risk factors ranging from age, race, hypertension, dyslipidemia, obesity, family history and even socio-economic background [5-6,8]. Majority of these risks are modifiable through lifestyle changes and pharmacological intervention. Research has shown a decrease in mortality with the aggressive treatment of these risk factors.

Diabetes Mellitus

Of the 24 million Americans with diabetes, only 5-10% are categorized as having Type I diabetes. This is caused by B-cell destruction resulting in an absolute deficiency of insulin production. In these individuals, insulin must be administered by regular injections or pumps. The other major category is Type II diabetes, which covers 90-95%
of all diabetic cases. Although the diagnosis of this metabolic disease usually comes after the age of 40 due to the increase in obesity levels, inactivity, and diet, there is epidemic within children and adolescences. According to present figures from the Centers for Disease Control and Prevention (CDC), among children and teens aged 9-16, 9% of the population which equates to 9 million are overweight [1].

Type II diabetes is characterized by insulin resistance and reduction of insulin secretion, which simply means a state of reduced sensitivity of the body tissues to the action of insulin [8-10]. Insulin resistance has been attributed to hereditary disposition of the disease, causing mutations of insulin receptors, glucose transporter, and signaling proteins, coupled with environmental factors such as physical inactivity, diet, hyperglycemia (glucose toxicity) and the aging process [8-12].

Decades of epidemiological and observational studies, have firmly established that Type II diabetes is independently correlated to CVD. Besides mortality and morbidity associated with nephropathy, retinopathy and neuropathy, cardiovascular disease remains the leading cause of death in type II diabetes [2,15]. In conjunction to these disease states, other predisposing factors such as obesity, hypertension, hyperlipidemia, physical inactivity and aging compound the disease. In the Framingham Study and Heart Study, individuals with diabetes with CVD are at three-fold increased risk of CVD, compared with non-diabetics without CVD [2-3,6,5-7,10]. According to Geiss et al CVDs is listed as the cause of death in 65% of persons with diabetes and CVD mortality was equal between men and women [15].

The pathogenesis of hyperglycemia is not fully understood, but can contribute to endothelial cell dysfunction which could hasten the development of atherosclerosis.
The endothelial cells produce nitric oxide which acts as a vasodilator and prevents smooth muscle proliferation [3,9,18,13]. Compelling data on endothelial dysfunction has been noted in patients with diabetics, hypertension and dyslipidemia, but also in non-diabetics with insulin resistance. This dysfunction inhibits vasodilation and increases vascular smooth muscle proliferation and thrombogenesis [3,10-13].

The pathophysiology of diabetes is characterized by peripheral insulin resistance, impaired regulation of hepatic glucose production, and declining Beta-cell function, eventually leading to Beta-cell failure [3,13,18-19]. Skeletal muscle is the main state of insulin-dependent glucose deposit. Resistance to insulin-dependent glucose uptake and phosphorylation in muscle is primary in type 2 diabetes. This causes disruption of the insulin-sensitive glucose transporter Glut 4 in muscle, causing reduction of glucose transport resulting in increased glucose levels [4,18,20]. Insulin resistance is also found in hypertension, hyperlipidemia and CVD. This raises the issue if, insulin resistance occurs from different processes or is unique to type 2 diabetes [2-3,6].

Hyperglycemia can impair both insulin can also cause glycosylation. The process of glycation occurs due to oxidation of lipoproteins to form complex and irreversible function to the arterial wall, producing arterial changes leading to susceptibility to atherosclerosis and possibly ischemia [10,17-20].

Niacin:

Niacin or vitamin B³ is a water soluble vitamin. According to National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines, niacin has been shown to have a clinically important effect on lipids and lipoproteins [22,31]. Niacin (Nicotinic Acid), in the management of dyslipidemia, has proven to have
significant and beneficial effects on most lipoprotein profiles for decades. Clinical trials have shown niacin to effectively reduce triglycerides, lipoprotein (a), low-density lipoprotein (LDL), and most importantly increasing high-density lipoprotein cholesterol (HDL) (17,22,25). To add to the favorable lipid management, niacin has shown to consistently reducing levels of Lp a by 20-25%, better than any other lipid managing therapy [23-24].

The advantageous ability to increase HDL is a major contributing factor in reducing morbidity and mortality for coronary heart disease. This unique ability to increase HDL offers an important advantage not available with other dyslipidemia therapies [22-27].

Niacin works by inhibiting the release of free fatty acids from adipose tissue leading to reductions in triglycerides and very- low density-lipoproteins (VLDL) cholesterol synthesis. It is thought that, niacin inhibits synthesis and secretion of apolipoprotein B directly reducing triglyceride levels and enhancing VLDL catabolism [31-32]. During reverse cholesterol transport, the liver absorbs the cholesterol carried by HDL particles which reduces catabolism of HDL. This increases HDL cholesterol and makes the main therapeutic benefit of niacin, enhanced HDL levels [29-32].

The attractiveness of niacin has been overshadowed by poor tolerance and low compliance amongst patients. At present there are three variations of niacin available, immediate-release (IR), sustained-release (SR) and extended release (ER) formulations, each with their own distinct safety and efficacy profiles. Over the counter, formulations have shown to have a lower tolerance level, and adverse reactions such as cutaneous flushing, rashes, nausea and gastrointestinal effects [27] The American Heart Association does not recommend these because their efficacy, safety, and tolerability are not
established [26]. Niacin has shown other adverse effects including cardiac arrhythmias, hypotension, dizziness, chills, migraine, and activation of peptic ulcer disease, but only 5% of users have been forced to discontinue treatment due to severe symptoms [12,24,27].

According to Capuzzi et al [23] niacin is metabolized by two pathways: the conjugate pathway in which there is lower affinity and saturation producing nicotinic acid which in turn causes cutaneous flushing, while the nonconjugate pathway shows higher affinity and saturation, but results in hepatotoxicity. In comparison the extended release version (Niaspan; Abbott Laboratories, Chicago, IL) demonstrates a balance between the two pathways, resulting in fewer incidence of adverse effects and safety.

In the type II diabetic population, hyperglycemia and dyslipidemia are two main CVD risk factors. The common characteristic in the lipid profile is excessively high triglycerides and low HDLs. Although niacin has been shown to be the most potent drug to increase HDLs, it has also been shown to have modest increase blood glucose in diabetic patients versus non-diabetics. It is estimated that 10-30% of patients with diabetes have some increase in glucose levels, but only 10% would require to discontinue niacin [11,23]. According to Grundy et al, HbA1c levels increased 0.07% and 0.29%, but of no significance [23]. Therefore, there has been reluctance from health providers of prescribing niacin despite the advantages for reduced CVD risk in treatment of dyslipidemia in this population. According to Arterial Disease Multiple Intervention Trial (ADMIT), levels of HbA1c were unchanged from baseline to follow-up [62-63] while the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT), showed that 10-30% of patients encountered increased blood glucose, but 70% had no change in glucose levels [23]. These short-term alterations in glycemic
control can occur with niacin, less is known on the effect of Niaspan’s glycemic control with extended absorption times [61-63].

Hence, it is possible for similar diabetic patients to take niacin and it not contradictory to managing or preventing adverse effects associated with its use. More research is required to determine whether the rise in blood sugar levels caused by niacin can be offset by exercise. Health care providers must weigh the risk versus benefits of using niacin in this population. Majority of diabetic patients can successfully take niacin without increases in glucose levels. It is possible for clinicians to increase hypoglycemic therapy, as long as patients are adhering with the tolerance of flushing [14,23].

The greatest challenge facing clinicians is poor adherence with dyslipidemia therapy, in particular niacin. Niacin has its own unique adverse effects, but mainly flushing. It is important to mention, that patient education is important to fully achieve compliance. In order to aid with reduced flushing, aspirin has been introduced to reduce potential flushing. The flushing caused by niacin is due to prostaglandins, and as acetyl salicylic acid (aspirin) is a highly effective inhibitor of prostaglandin synthesis [28-29]. Besides, the strategy to reduce potential side effects, which could affect patient compliance, aspirin has been recommended by the American Diabetes Association as a primary and secondary prevention measure. As previously documented people with diabetes are two to fourfold risk of CVD and risk of cardiac events. The Early Treatment Diabetic Retinopathy Study (ETDRS) and the Hypertension Optimal Treatment (HOT) Trial have shown that aspirin reduced cardiovascular events as a secondary strategy is beneficial, in addition to the favorable outcomes it provides to patients on niacin [28,29].
Lipoprotein (a)

Lipoprotein(a) also known as Lp(a) is a highly complex macromolecular structure from the lipoprotein(LDL) class found in human plasma [35-36]. Lp(a) is made up of two components, a low-density lipoprotein B-100 and glycoprotein apolipoprotein (a) [apo(a)] attached by a disulphide linkage. Due to the structural complexity of Lp(a), the physiological and mechanism of action are not completely understood. This is part has lead to the difficult treatment in the clinical setting. This lipoprotein in only found in several mammals, including some primates and hedgehogs [40].

Since the early 60’s when Kare Berg first discovered the new lipid class, Lp(a) has been researched and linked to being a risk factor in CAD, in particular peripheral vascular disease and cerebrovascular disease[41]. Despite numerous supportive studies, it is still considered an “emerging” factor compared to conventional risk factors including smoking and hypertension [39]. The glycoprotein subfraction apo (a) is highly structurally similar to plasminogen and competes for binding sites to fibrin and endothelial cells; it may reduce fibrinolysis and encourages thrombosis and atherosclerosis (39-40). It is also well documented that Lp(a) accumulates on sites of vascular injury and in vessels with gradient mechanism resulting in the formation of atherosclerotic plaque [35-39].

Lp(a) levels seems to be genetically linked, and have shown great variability between individuals and gender, hormones and glycemic control have been shown to effect levels depending on the apo (a) genotype [42]. Most research on Lp(a) have been done on Caucasians, but African-Americans and Asians have shown higher levels [38]. Howard et al found African-Americans has 72-118% higher concentrations of Lp(a) than
Caucasians. Numerous studies have shown that individuals with high levels of Lp(a) (>300 mg/dl), to be independent predictor of death [40-43]. Hence, due to poor outcomes, these patients can be identified and treated aggressively with medication [26].

In other studies, especially the Copenhagen City Heart Study high levels in conjunction with other risk factors like hypertension, smoking and hypercholestremia, the risk of myocardial infarction was doubled and ten year myocardial infarction risk was >20%.

There is some controversy in regards to the role of Lp(a) in development of CVD in the diabetic population. Danesh and Rees et al have shown a correlation, but some studies have shown no significance. However, there is a balk of evidence linking Lp(a) with vascular diseases, in particular peripheral artery disease in type II diabetics [31].

Many studies have shown that regular exercise can have beneficial effects in lipid profiles, hence decreasing CVD mortality and atherosclerosis risk [33]. Investigation into existing literature regarding exercise training on Lp(a), suggest no affect. Present studies show single bouts of exercise [55], long-duration exercise and resistance training have little impact [56]. However, there are a few studies, that have shown elevated Lp a with high volume weight lifting and prolonged distance running [56,64]. It is theorized that this elevation on Lp(a) levels in high volume weight lifting, could possibly attributed to Lp(a) association with tissue damage and repair[55]. Dufaux et al also found that these elevated levels returned to normal after several days of post-exercise [64]. A possible explanation for this could be Lp(a) acts as an acute reactant in muscle damage and repair.

**C - reactive protein:**

The importance of predicting cardiovascular risk and events has lead to the importance of C-reactive protein (CRP) in the past two decades. Multiple
epidemiological studies, have demonstrated a predictive relationship between CRP and myocardial infarction, stroke, peripheral artery disease and sudden cardiac death [44-49,70-71]. So much so, the Center for Disease Control and Prevention (CDC) in conjunction with the American Heart Association (AHA) published a scientific paper regarding inflammation markers in the clinical and public practice. The AHA has acknowledged that CRP is independent of age, smoking, cholesterol and diabetes. Ranges for CRP are <1.0 mg/l, 1.0-3.0 mg/l and >3.0 mg/l are associated with low, intermediate and high risk respectively [70]. The average CRP levels in a healthy young adult are 0.8 mg/l[70].

CRP is an acute-phase protein and sensitive marker of inflammation. CRP is produced in response to infection, tissue injury and inflammation by hepatocytes in the liver. This acute protein is non-specific marker of inflammation and circulates in the plasma at low concentrations in healthy individuals [42-43]. Prospective epidemiologic data signals that CRP is a more powerful predictor of risk than traditional blood lipid panels especially LDLs [44-49,51]. Patients with near normal or mildly increased total cholesterol are at 50% probability to experience myocardial infarctions [70-71]. Hence, the need to screen for CRP in relatively healthy populations who do not have hypercholesterolemia is necessary. Although the AHA guidelines specify testing for intermediate and high risk, numerous studies state there is predictive value for future cardiovascular events in healthy individuals with low to moderate levels [48]. According to Ridker et al. CRP seems to be the most stable inflammation marker and its long plasma half-life of 18-20 hours, with an established global standardization in testing, make it the best predictor [51].
Atherosclerosis is defined as a chronic inflammatory disease of the arteries. The mechanism of CRP in atherosclerosis is not fully understood. It is possible that CRP is merely a marker for inflammation. Most theories suggest that CRP does play a role in the evolution of atherosclerotic lesions because it is found in the lesions [51].

Atherosclerosis is an inflammatory process with known endothelial dysfunction. Injury to the endothelium causes it to have procoagulant properties forming growth cells and cytokine. This process can continue to progress causing macrophages and lymphocytes to multiply releasing further cytokines and chemokines eventually causing rupture to the lesion or death through ischemia [46,48-49]. In addition, smooth muscle proliferation can occur and eventually obstruction of the lumen [46]. It should be noted, that CRP is probably not responsible for this entire process, but a combination of several metabolic pathways from diabetes, smoking, hypertension and genetics [49-51].

C-reactive protein is strongly linked to Body Mass Index (BMI) and weight loss lowers CRP [44-46]. In relation to BMI, several studies have linked the prediction of type II diabetes [45-46,75]. This specific population is normally overweight and obese. A theory is linked to adipose tissue which is the producer of 25% of the pro-inflammatory cytokine interleukin (IL-6), which causes low grade inflammation. This would explain the importance of exercise in this high risk population to help lower risk of cardiac events. CRP has also been shown to be consistent among ethnic groups and sex, although it should be noted in the Women’s Health Study, hormone replacement therapy and oral contraceptives have significantly raised CRP levels, highly correlated to waist circumference, BMI and fasting triglycerides [66-68,73].
**Exercise Training:**

Current evidence supports the view that exercise training (ET) has beneficial effects on risk factors associated with diabetes and cardiovascular risk factor [77]. Through the combination of both aerobic and strength training, benefits can include lowering of body weight, resting blood pressure, improvements in blood lipids and fasting glucose levels [4,77]. Research has shown individuals with type II diabetes have a lower functional capacity than non-diabetics due to insulin resistant tissues, low capillary density and other vascular complications especially among an older age group [58-60,69].

Throughout this paper the repeated macrovascular complications related to diabetes has been shown. There is also the association of hyperglycemia and microvascular complications including retinopathy, nephropathy and neuropathy. ET has been shown to effectively improve insulin sensitivity which leads to better glycemic control in patients with type 2 diabetes [65-67]. The ADA suggests that both cardiovascular and resistance training are both beneficial in the improvement of insulin sensitivity and lowering HbA1c [4,67,69]. According to the American Diabetes Association, the goal in the management of diabetes is maintaining glucose homeostasis. HBA1c is an easily measured indicator of hyperglycemia and guidelines goals are <7% or <6.5%.

Numerous physical activity studies have chosen one mode of exercise over the other, with a lack of research combining the two. There is conflicting data, as to the duration and intensity best suited for the diabetic population. Some studies have found high intensity exercise has raised blood glucose levels, compared to the better controlled
levels with moderate intensity. Numerous studies have shown engaging in ET at mild to moderate intensities decreases the cardiovascular risk and mortality. Helmrich et al showed in a large prospective study, an increase of 500 kcal in energy expenditure decreased incidence in type 2 diabetes by 6% [65,72]. In one study from Segal et al, the combination of both ET reduced HbA1c compared to separate modes of exercise compared to control groups [73]. The intensity of exercise has been widely investigated, most studies showing mild to moderate intensity to be most beneficial.

Obesity is an independent risk factor of CVD, and directly linked to type II diabetes. The common abdominal fat and subsequent loss of muscle mass are highly associated with insulin resistance. Through both resistance and cardiovascular training a decrease in abdominal adiposity, increase in lean mass and better glucose control should significantly help reduce insulin resistance and increase sensitivity [65-66]. The initial weight loss largely results in change of caloric intake compared to energy expenditure from ET, but greatly aids in the maintenance of body weight.

Regular ET can improve glycemic control due to exercise on glucose metabolism. Acute bouts of exercise increase skeletal muscle glucose uptake even if inhibited by insulin resistance. Insulin stimulates increased glucose uptake by skeletal muscle and activates glycogen synthase, the enzyme used for production of glycogen from glucose [74]. Research has been established that ET regulates fat and glucose metabolism, both resulting in increased insulin action [74]. There is a need for further investigation on the mechanisms both aerobic and resistant training in individuals with diabetes. It is the duty of clinician to educate patients on the importance of physical activity and dietary restrictions to control blood glucose levels.
CHAPTER III
METHODOLOGY

The purpose of this study was to observe the effect of a 16-week aerobic exercise program on C-reactive protein levels and lipoprotein (a) concentrations in individuals with type II diabetes taking extended release niacin.

Subjects

Originally twenty seven subjects clinically diagnosed with type II diabetes were recruited from Ball State University and the community of Muncie, IN. Nineteen subjects fully completed the study requirements. Eight subjects were discontinued from the study due to personal reasons, schedule conflicts, inadequate glucose control or flushing from the medication. Subjects were recruited via flyers, brochures, and media releases. Physicians in the Muncie area were contacted and informed of the study and the potential recruitment of their patients. Subjects required written consent from their personal physician and a prescription for Niaspan®. All subjects had the risks associated with the study and the health benefits thoroughly explained to them. Subjects signed an institutional approved informed consent form (Appendix C) prior to participating in the study.

Quiet Testing

All subjects completed a health history questionnaire to provide medical history information. The height and weight of each subject were measured and body mass index
calculated. Body composition was determined using the seven site method (Lange skinfold caliper) and waist and hip girths were measured for calculation of waist-hip ratio. Advanced body compositions were measured using the BOD POD (Life Measurement Instruments, Concord, CA). Subjects were prepped with a standard 12 lead electrocardiogram (ECG) (Mac® 5000 Resting ECG Analysis System, GE, Milwaukee, WI) to record a supine and standing electrocardiogram (ECG) for presence of any abnormalities contraindicated to exercise testing based on American College of Sports Medicine (ACSM) guidelines.

**Exercise testing**

All subjects were prepped for 12-lead ECG using the modified Mason-Likar landmarks with disposable Quinton electrodes. Resting heart rates were measured in the supine and standing position using the Marquette Case 16 (Marquette Electronics, Inc., Milwaukee, WI). Blood pressures obtained before and during exercise were measured from the left arm using a sphygmanometer and the appropriate adult blood pressure cuff.

A graded exercise test was completed on the treadmill using the Bruce Ramp protocol or Balke protocol in the presence of a physician, depending on individuals estimated VO$_{2\text{max}}$ calculated from regression equations [44]. During the test, ECG was continuously monitored and recorded by the Marquette cardiograph. Heart rate and rating of perceived exertion (RPE) were recorded each minute, and blood pressure was recorded every three minutes.

Metabolic data was obtained during maximal exercise testing via standard open circuit spirometry. Expired respiratory gases were collected through a mouthpiece connected to a one-way valve. Nose clips remained in place throughout the test. Oxygen
consumption and carbon dioxide produced were determined using SensorMedics Vmax229 Metabolic Cart (Yorba Linda, California). Standard reference gas tanks containing oxygen and carbon dioxide were used for the calibration of the metabolic cart.

The metabolic cart calculated maximal oxygen uptake (VO2max). If the maximal test was deemed positive due to ST-Segment depression greater than 1mm, subjects were referred back to their physicians for further evaluation. Written physician approval was required for such individuals to participate in the study. Once the graded exercise tests were complete, maximal data was analyzed and interpreted.

**Blood Work**

Venous blood samples were taken prior to the exercise program, after four, eight, twelve weeks and post exercise training. Participants were required to fast for 10-12 hours overnight prior to test. Blood was drawn from the arm using basic phlebotomy procedures into one 5ml (13 x 100mm) Tiger Top serum tube. Sample was mixed thoroughly by inverting tube 5-6 times. The specimen was allowed to clot for 20-30 minutes. Samples were then spun in a centrifuge for twenty minutes (at standard 2,500 rpm) and refrigerated. The serum from each sample was then pipetted into 1.5mL microcentrifuge tubes until shipment time. A second sample of whole blood was taken in non-clotting 3 mL vacutainer® and refrigerated until shipment. The serum and whole blood was sent on a monthly basis to University of Alabama at Birmingham for analysis of glycosylated haemoglobin (HbA1c), glucose, serum glutamic oxaloacetic transaminase (SGOT), lactate dehydrogenase (LDH), alanine transaminae (ALT), creatine phosphokinase (CPK), Uric acid and bilirubin. Monthly, blood analysis was monitored to avoid any hepatotoxicity, possibly related to the medication.
All pre and post specimens with appropriate paperwork were placed into an Atherotech® Styrofoam container with absorbent material and pre-frozen cold pack. All packages were labeled biohazard and express shipped to Atherotech Research Department, Birmingham Alabama. Atherotech® carried out a Vertical Auto Profiles (VAP) procedure for determining a cholesterol profile i.e. cholesterol content of all lipoprotein particles in the blood. The VAP consists of three independent steps. 1) Lipoprotein classes are separated using single vertical spin density gradient ultracentrifugation. This is an accurate way of separating lipoproteins because lipoproteins are based upon their densities. 2) The centrifugate containing bands of separated lipoproteins is continuously drained from the bottom of the tube and mixed with enzymatic cholesterol reagent in the VAP instrument generating a cholesterol profile. The analog output of the spectrophotometer representing the cholesterol profile is recorded on the chart recorder and the digital output is recorded in the computer. 3) Cholesterol concentrations of lipoprotein classes and subclasses are quantified from the absorbance peaks of the spectrophotometer using proprietary software. The blood was analyzed for C-reactive protein (CRP), Lipoproteoin(a) (Lp(a), glycosylated haemoglobin (HbA1c) and blood fasting glucose (BFG). Results of the blood work were faxed to the Adult Physical Fitness Program. Exercise testing and venous blood sampling was carried out in the Human Performance Laboratory (HPL) in the Adult Physical Fitness Program (APFP) Testing Laboratory at Ball State University. Exercise sessions and fingertip blood sampling was carried out in the APFP Fitness Laboratory in Irving Gymnasium.
**Exercise Program**

Subjects were given an individual interpretation in the Adult Physical Fitness Programs fitness center of quiet and exercise tests results. During this consult, through explanations covered body mass index (BMI), VO$_{2\text{MAX}}$, description of blood lipids and normal values, body composition, and importance of lifestyle changes. The individualized exercise prescriptions were explained and education material regarding Niaspan® as provided. Subjects were explained the program involved a warm up period followed by aerobic activities such as treadmill walking, stationary cycling, stair climbing, recumbent biking, NuSteps or rowing and concluded with a cool down. Each participant was assigned a personalized exercise prescription for the first four weeks and then progressed for the following four weeks based on exercise test results. Depending on muscular or orthopedic limitations, subjects were prescribed the recumbent bike or nuStep as preferred modes of exercise. During this time, subjects were given an orientation to each mode of exercise and suitable speeds and grades to optimize slow and safe progression during the first four weeks. The intensity and duration was prescribed from the maximal exercise test data and approximate speeds and grades were calculated using specific equations from ACSM guidelines. The exercise prescription was devised using the heart rate reserve method and subjects were provided with polar® heart monitors to follow specific heart rates during the course of the 16 weeks. Each exercise session was supervised by qualified personnel with intensity, duration and frequency set to achieve caloric expenditure goals of 1000 calories per week by week four and 1500 calories per week by week eight. Initially, prior to exercise each subject’s blood pressure was measured and blood glucose. Fitness facility was equipped with an emergency plan
and carbohydrates in cases of hypoglycemia. The exercise training program required an attendance of three to five times weekly for 16 weeks in order to attain caloric goals. Each participant could exercise during three specified periods during the day, convenient with their schedule.

**Medication**

Niaspan® of Abbott Laboratories, (Chicago) provided the drug free of charge during the course of the study. Subjects were provided with educational material on taking the drug to minimize potential side effects and given toll free numbers of drug representatives in case of any further questions. Dosages for Niaspan® gradually increased monthly. The dosages for week: 1-4 = 500mg; week: 5-8= 1000mg; week: 9-12 = 1500mg; week: 13-16 = 2000mg. Subjects were responsible for taking their own medication as directed every night. Any side effects were self-reported at the beginning of the following exercise week on participant’s weekly side-effect log. Three subjects who experienced extreme flushing due to increase in dosage were maintained on the lower dosages until side effects subsided. Flushing is common and it usually becomes less frequent within the first several weeks of continued therapy. Subjects were then provided with increase in dosage and closely monitored. After commencement of the study, participants were excluded if they fail to adhere to the protocol or developed signs or symptoms that placed them at greater risk as outlined in Box 2-1 of ACSM guidelines (Franklin et al., 2000) including chest pain, dizziness or heart palpitations. One subject, after consultation with his physician was discontinued due to adverse rise in fasting glucose levels greater than 200mg/dl fasting blood glucose.
**Statistical Analyses:**

A t-test was used to identify significant differences between pre training for all dependent and independent variables. A t-test comparison was conducted to determine if any differences existed pre to post training for each group for all dependent variables.
Chapter IV
Results

The purpose of this study was to assess the effect of niacin on Lp a, CRP and HbA1C levels in individuals with type 2 diabetes who engaged in a 16 week exercise training program. A total of 27 subjects originally enrolled of which 8 subjects were discontinued from the study due to personal reasons, schedule conflicts, inadequate glucose control or flushing from the medication. Of the 19 subjects, age 60 ± 10, 8 women and 11 men fully completed the full requirements of the 16-week program. All 19 participants were Caucasian and were assigned to an exercise training program and prescribed niacin. There was no control group due to small sample size and unwillingness to be assigned to control group.

Research has shown CRP and Lp a are both linked to increased risk of CVD, in particular individuals with type 2 diabetes. The interventions did not significantly reduce the cardiovascular risks factors or profiles. Table 4.1 shows CRP had no significant changes across the whole group (p=0.48), but a sub-group (Table 4.2) was populated with 10 subjects with high risk levels at baseline (>3mg/L) according to the American Heart Association. This sub-group showed significant decrease (p<0.014) after 16 weeks of exercise training and niacin intervention.
Table 4.1

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pre Intervention</th>
<th>Post Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lpa (mg/dl)</td>
<td>5.74 ± 4.86</td>
<td>6.73 ± 3.54</td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>6.54 ± .88</td>
<td>6.63 ± 0.87</td>
</tr>
<tr>
<td>Glucose</td>
<td>122.11±30.59</td>
<td>117.86±31.91</td>
</tr>
<tr>
<td>CRP (mg/L -1)</td>
<td>5.37 ± 5.38</td>
<td>4.29 ± 3.90</td>
</tr>
</tbody>
</table>

Table 4.2 Sub group of 10 subject with baseline CRP measurements > 3mg/L

<table>
<thead>
<tr>
<th>CRP(mg/L)</th>
<th>Pre Intervention</th>
<th>Post Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.67 ± 5.63</td>
<td>5.84 ± 4.10*</td>
</tr>
</tbody>
</table>

*p<.05 Significant difference from pre and post interventions

No differences were noted from baseline (Table 4.3) noted in Lp(a) (p=0.47), even though earlier research has shown that niacin is a unique therapeutic agent with the ability to decrease Lp(a) levels(26,38). According to Framingham heart study, Lp (a) levels greater than 10 mg/dl could be used as a predictor of greater risk of CAD. Only 3 subjects had these values at baseline and no significant changes noted with the interventions.

Table 4.3 Subject with baseline Lp(a) measurements >3mg/L

<table>
<thead>
<tr>
<th>Lp a (mg/dL)</th>
<th>Pre Intervention</th>
<th>Post Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.74± 4.86</td>
<td>6.74 ± 3.54</td>
</tr>
</tbody>
</table>

Table 4.4 shows monthly measurements for HbA1c. Seventeen subjects showed no significant changes over the duration of exercise protocol and administration of increased dosages of niacin (500- 2000mg) on monthly basis. Even though there was no
significant changes noted with blood glucomes, Figure 4.1 shows mean monthly blood sugars declined over the course of the 4 months.

Table 4.4 Sub group of subjects with baseline HbA1c measurements %

<table>
<thead>
<tr>
<th>Pre Intervention</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Post Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 17</td>
<td>7</td>
<td>11</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>% = 6.67 ± 0.9</td>
<td>6.4 ± 0.8</td>
<td>7.0 ± 1.1</td>
<td>6.7 ± 1.0</td>
<td></td>
</tr>
<tr>
<td>5.84 ± 0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 4.1

All subjects during the exercise protocol increased their energy expenditure to 1000 Kcal on a weekly basis. As seen in Table 4.5, there was no decrease in mean body weight over the course of the 16 weeks, and no significant difference was noted in overall BMI (p=0.96). There was a training effect noted (Figure 4.2). This shows heart rates pre and
post from 3 stages of exercise treadmill tests (Bruce Ramp or Balke). At post testing there were no peak heart rates obtained, but submaximal testing was performed. A correlation can be seen with training effect.

**Figure 4.2**

![Heart Rate (bpm)](chart)

**Table 4.6 Participant Clinical Characteristics:**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Pre Intervention</th>
<th>Post Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>96.71 ± 15.56</td>
<td>96.04 ± 16.45</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>33.5 ± 6.1</td>
<td>33.4 ± 6.3</td>
</tr>
</tbody>
</table>

*p<.05 Significant difference from pre and post interventions*
Chapter V
Discussion

This study investigated the effect of niacin and exercise training on CRP and Lp(a) levels in previously sedentary individuals with type 2 diabetes mellitus. Exercise training has been shown to decrease risk factors such as hypertension, body composition, weight loss, improve plasma lipids and most important in individuals with diabetes, improvement in glucose homeostasis [15,67-69,73-74].

Overweight and obesity are significantly associated with diabetes and CRP. Recent investigations suggest exercise reduces CRP. The finding of this study showed 16-weeks of exercise training and niacin therapy did not improve CRP levels. Higher levels of physical fitness and cardiorespiratory fitness are associated with 6-35% lower CRP levels (7-48, 67-68). These findings are in contrast with those of several cross-sectional reports that reported an inverse association between CRP levels and regular physical activity [68]. There are conflicting results in respect to exercise reducing CRP. This is consistent with the hypothesis that physical exercise acts predominantly by reducing body composition and weight loss. There was no significant change in CRP levels, but a subgroup of 10 subjects with high risk baseline values (>3mg/dl criteria from American Heart Association), exhibited significant changes from baseline values (p<0.014). This reflects several studies that have shown significant CRP improvements in
conjunction with significant weight loss through lifestyle interventions (75-76). This could explain that even though caloric expenditure and compliance was met, minimal changes in weight loss and no changes in CRP. This study showed there was a reduction in higher levels than in individuals with normal values. It could be suggested that exercise has an important role to play in reducing inflammation beyond weight loss. This suggests that the anti-inflammatory effect of physical activity may counteract the CVD associated with high CRP levels.

No significant difference in Lp a concentrations between pre and post intervention was noted. In majority of studies, it has been shown there is no association between physical activity or exercise training, but instead highly influenced by racial or ethnic makeup and genetic factors such as age and sex [22-23,41]. However, conflicting reports on high intensity exercise in elite athletes have shown to increase Lp a by 10-15% (57, 64). In contract, NCEP ATP III has identified niacin as a therapeutic drug in lowering lipoproteins in particular Lp a (22), but after the 16- week duration no changes were noted. There is no particular explanation except for possible lack of adherence from subjects or the monthly increase in dosages was not long enough to see significant changes.

The exercise training protocol did not significantly improve weight loss, body composition, HbA1c or glucose control. The exercise program was designed to increase energy expenditure (>1000Kcal) by week 3 and resistance training was introduced later in the program. Adherence to the protocol was good, but possibly a longer intervention with higher training intensities and volume might have produced greater changes with
these variables. Several studies have failed to show any improvements after 8-16 weeks of training, but others have been more favorably for 6 months-1 year duration [78]. Although there were no significant changes in glucose, there was a trend in glucose levels marginally decreasing over the 16 weeks. It is widely accepted that exercise training is beneficial in improving glucose control as a result of enhanced insulin sensitivity [3-10].

Niacin has been associated with hyperglycemia. According to Grundy et al [21] 10-30% of patients with diabetes see a rise in glucose levels with niacin therapy and possibly a small increase in HbA1C levels. This study proved the importance of exercise training in the diabetic population, but possibly countered any negative effects the niacin therapy might have cause, but a slight decline in glucose levels was noted.

It must be noted this study had limitations such as the absence of a control group, a relatively small number of subjects and a lack of heterogeneity. Some post intervention testing such as VO2 testing was missing due to time constraints that could possibly have shown significant cardiorespiratory improvements. There was also an improvement in training effect; post submaximal exercise testing exhibited a trend in lower heart rates.

Despite these limitations, the study was one of few that incorporated exercise training, in conjunction to a niacin intervention in a diabetic population. Sedentary subjects were also introduced to a various modes of exercise and strength training. Since there is a high correlation of diabetes and CRP, studies need to investigate a better understanding of CRP in its value of predicting diabetes. Also, future designed studies need to investigate larger diabetic populations and the role of niacin on HbA1c levels. Moreover studies should emphasis longer interventions, incorporating interventions to
change in body composition and include dietary intervention, especially in this high risk population.

In conclusion, even though this research project did not show any significant changes across the variables, there was significant change in CRP levels in individuals with high baseline levels. The benefit of exercise training in this high risk population showed slight improvements in glucose control and a definite training effect. Therefore, future studies should use larger populations and a control group.
References:


40. Rader DJ, Cain W, Zech LA, Usher D, Brewer HB. "Variation in lipoprotein(a) concentrations among individuals with the same apolipoprotein (a) isoform is determined by the rate of lipoprotein(a) production". *J. Clin. Invest.* 91 (2): 443–447, 1993.


