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The Effect of High Intensity Exercise Training Verses Low Intensity Exercise Training on Fractionated Plasma High-Density Lipoprotein Cholesterol

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THE EFFECT OF HIGH INTENSITY EXERCISE TRAINING VERSUS LOW INTENSITY EXERCISE TRAINING ON FRACTIONATED PLASMA HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

By

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"ABSTRACT"

THE EFFECT OF HIGH INTENSITY EXERCISE TRAINING VERSUS LOW INTENSITY EXERCISE TRAINING ON FRACTIONATED PLASMA HIGH-DENSITY LIPOPROTEIN CHOLESTEROL

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Exercise training is thought to result in an elevation of high-density lipoprotein (HDL) and the cardioprotective subfraction HDL_2. Twenty-five healthy women (39 $^+$ 7.8 yrs; 70 $^+$ 14 kg) walked two miles three times per week for 12 weeks to examine the effect of exercise intensity on the HDL profile. The L.I. group (N=12) walked at 60% of the heart rate reserve (HRR) and the H.I. group (N=13) walked at 80% HRR both maintaining the prescribed distance and frequency. A 22% increase in total HDL (from 32 $^+$ 6 to 39 $^+$ 8 mg/dl) and a 35% increase in HDL_2 (from 14 $^+$ 3 to 19 $^+$ 9 mg/dl) was elicited as a result of the walking program ($p<.005$). Slight increases in HDL_3 were also observed. However, no significant differences in total HDL or HDL_2 were observed between the L.I. and H.I. groups. These findings demonstrate an exercise induced enhancement of the cardioprotective mechanism thought to be associated with the HDL_2 subfraction. Moreover, it appears that walking at 80% of the HRR offers no advantage over walking at 60% of the HRR in enhancing the HDL profile.

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Dedication

This work is dedicated to my parents, William C. and Barbara J. Spate. Their never-ending support of my endeavors has given me the inspiration and courage to take on new challenges. They taught me the importance of dedication and commitment which has been invaluable in my personal, academic and professional life.

Table of Contents

Page

List of Tables iv

List of Appendices v

CHAPTER

1 INTRODUCTION 1

Purpose 3

2 REVIEW OF LITERATURE 4

Hypothesis 9

3 METHODOLOGY 10

Research Design 10

Subjects 10

Apparatus and Instrumentation 11

Procedure 13

Statistics 16

4 RESULTS 17

5 DISCUSSION 22

Recommendations 26

Conclusion 27

List of Tables

Table		Page
1	Demographic Description of Subjects	18
2	Exercise Response Before Training	19
3	Exercise Response to Training	20
4	HDL Profile Changes with Exercise Training	21
5	Gain Score Difference of the HDL Profile Between Groups	21

List of Appendices

Appendix		Page
I	Health History	29
II	Contraindications to Exercise Testing	31
III	Consent Form	32
IV	Indications for Stopping an Exercise Test	34
V	Bruce Protocol	35
VI	Exercise Log	36

CHAPTER ONE

INTRODUCTION

Over 6 million Americans have a history of myocardial infarction, angina pectoris, or both. Coronary heart disease (CHD) claimed the lives of 478,530 Americans in 1991 and is the leading cause of death in the United States. This year as many as 1,500,000 Americans will have a heart attack, and about one third of them will die. Coronary heart disease will cost the American economy an estimated 56.3 billion dollars in 1994. (1) Although these numbers have been decreasing due to improved diagnostic and interventional technology, these data underscore the need for continued research in the areas of cardiovascular risk factors and prevention.

Risk factors for coronary heart disease can be divided into modifiable and non-modifiable categories. The modifiable risk factors include hypertension, cigarette smoking, physical inactivity and elevated total cholesterol. The non-modifiable risk factors include age, gender and family history of coronary heart disease.

Elevated total cholesterol level, as a risk factor, has received much attention in the current literature. However, it has been well documented that one's total cholesterol level does

not adequately define an individual's risk for coronary heart disease (12,25). Total cholesterol is comprised of 3 major components: very low-density lipoproteins (VLDL), low-density lipoproteins (LDL) and high density lipoproteins (HDL). Each component must be studied separately to understand its independent contribution to the risk profile for coronary heart disease.

It has been documented that serum HDL cholesterol levels have a strong inverse relationship to the risk of coronary heart disease (2,12). The higher the HDL level, the lower the coronary risk. High levels of serum LDL cholesterol have been shown to have a direct relationship to the risk of coronary heart disease.

Plasma HDL concentration has been suggested to be a better predictor of coronary heart disease than total cholesterol levels. Each 10 milligram per deciliter (mg/dl) change in HDL cholesterol concentration is associated with a 50 percent alteration in cardiovascular risk (29). Other studies (10,12) have found a 1 mg/dl increment in HDL was associated with a 3.2 - 3.9% decrement in CHD incidence. Thus, even small increases in HDL may result in a large reduction in the risk for coronary heart disease.

The HDL profile is comprised of subfractions HDL_2 and HDL_3. The antiatherogenic properties of HDL appear to be specific to the subfraction HDL_2 (3,25,26,30). Although total HDL levels may be increased by factors other than physical activity, increases in HDL_2 have been found to occur primarily with exercise training

(25,30). The intensity of training required to elicit significant increases in HDL_2 has not been established.

Purpose

The purpose of this study was to determine the effect of exercise intensity on the HDL profile.

CHAPTER TWO

REVIEW OF LITERATURE

For several decades, evidence has been accumulating to indicate a causal relationship between elevated plasma cholesterol levels and coronary atherosclerosis (2). Recent studies have indicated that total plasma cholesterol levels may be more predictive of coronary heart disease when the components are analyzed separately (4,16,25).

Cholesterol is an essential structural component of biologic membranes. Humans derive cholesterol endogenously, from synthesis in the liver and other tissues, and exogenously, from the consumption of animal products (7). A complex system delivers cholesterol and fatty acids to peripheral tissues, including the intimal lining of arterial walls, causing the formation of fatty streaks and eventually the atherosclerotic lesions characteristic of coronary heart disease. A separate system, known as reverse cholesterol transport, is thought to be responsible for returning cholesterol to the liver where it is converted to bile acids and excreted.

Total cholesterol comprises several major lipoprotein

classes, including very low-density (VLDL), low-density (LDL) and high-density (HDL) lipoproteins. The classes of lipoprotein differ not only in structure, but also in metabolism and, most importantly, in function (6). Evidence suggests that HDL, LDL, and VLDL lipoproteins, and their subfractions have different relationships to coronary heart disease risk (8). Epidemiologic studies demonstrate that a reduction in total plasma cholesterol or in LDL, and/or an elevation in HDL, results in decreases in the development of angina, positive exercise test results, and referral for coronary artery bypass surgery. Reductions in more severe cardiovascular end points such as heart attack, death, and atherosclerotic plaque progression also accompany these alterations in lipid profile. (2)

Low-density lipoprotein is the major carrier of cholesterol in the blood stream, transporting 60-80 percent of the total plasma cholesterol (2). LDL levels have been shown to be directly related to the risk of coronary heart disease. The American Heart Association recommends a plasma LDL level of less than 130 mg/dl (32).

High-density lipoprotein is thought to be the carrier of cholesterol in the reverse cholesterol transport system. Among the various lipid subfractions, plasma HDL concentrations have been shown to be the strongest predictor of both the presence and extent of coronary heart disease (4,16). High-density lipoprotein has been shown to have a strong, inverse relationship with risk of coronary heart disease in numerous studies including

the Honolulu Heart Study (11), Framingham Study (12), Coronary Primary Prevention Trial (14) and the Helsinki Heart Study (15). The National Cholesterol Education Program (NCEP) states that an HDL level of 60 mg/dl or greater is a negative risk factor for CHD (27). Data from the Helsinki Heart Study suggest that HDL-increasing therapies are associated with a decrease in incidence of coronary heart disease.

There are a few studies, however, that have failed to make the same associations. Results of angiographic studies range from HDL having a significant inverse relationship to the risk of coronary heart disease to HDL having no association at all (4). These findings may be, in part, the result of failing to analyze total high-density lipoprotein by its subfractions.

Total HDL is comprised of two groups with different biochemical properties, the more lipid-rich HDL_2 and the smaller, denser HDL_3. Data from Drexel et al demonstrate that, among all lipoprotein parameters, HDL_2 cholesterol is the strongest predictor of both the presence and extent of coronary heart disease (4). Patients with angiographically documented coronary heart disease had HDL_2 levels nearly half that of individuals without coronary heart disease. Salonen et al (5) reported that an HDL level of less than 42 mg/dl is associated with a 3.32-fold increase in risk of acute myocardial infarction. Serum HDL_2 cholesterol levels of less than 25 mg/dl is associated with a 4.00-fold increase in risk of acute myocardial infarction and serum HDL_3 cholesterol levels of less than 15 mg/dl is associated

with a 2.04-fold increase in risk. In the same study the investigators confirmed that the HDL_2 subfraction had an inverse association with the risk of acute myocardial infarction whereas the role of HDL_3 remained equivocal. The association of HDL_3 with acute myocardial infarction lost its statistical significance when adjustment was made for HDL_2.

Environmental factors affecting the HDL profile are many. Factors including age, gender, physical activity, certain medications, cigarette smoking, consumption of alcohol, and obesity appear to influence HDL concentrations (19). Dietary intake has not been found to have a significant relationship to plasma HDL levels (17,19). A negative association has been found between HDL, the use of progestin preparations (18), beta-adrenergic antagonists (20,21), and cigarette smoking (13,17,18). A positive association has been found between HDL levels and age (25), regular physical activity (17), the use of estrogen preparations (18), alcohol consumption (17,19,25) and lean body mass (22). HDL levels have also been shown to be higher in women than in men (23).

The difficulty in identifying the independent impact these factors may have on the development of coronary heart disease may be due to the fact that many of these lifestyle-related risk factors are often observed in conjunction with each other. This can easily be demonstrated by looking at individuals who smoke cigarettes. Cigarette smokers have been reported to be less obese and more likely to drink alcohol, both of which are

associated with higher levels of HDL cholesterol. Smokers may also exercise less, which has been associated with lower levels of HDL cholesterol (18).

Although many studies have associated environmental risk factors with either increased or decreased levels of HDL, few studies have examined the impact these factors have on the subfractions of HDL.

Robinson et al studied the effect a variety of risk factors had on total HDL, HDL_2, and HDL_3. Results of this study indicated that there is a positive association between age and HDL_2 whereas there is no correlation to HDL_3 (25). The same study confirmed earlier findings of Haffner et al. that although the HDL profile is negatively associated with cigarette smoking and positively associated with alcohol consumption, the effects are a result of alterations in HDL_3 levels (13). HDL_2 cholesterol was twice as high in active women than it was in inactive women in a study performed by Hartung et al. In the same study, HDL_3 cholesterol values were similar for the two groups. This data suggests that exercise has no effect on HDL_3 levels and therefore increases only HDL_2 levels (23).

Numerous epidemiologic studies have supported the fact that regular vigorous exercise decreases the morbidity and mortality from CHD (26). There are few studies finding no benefit from long-term exercise and none that report that exercise aggravates CHD or hastens the development of clinical disease (26). It has also been suggested that the antiatherogenic effect that is

elicited by exercise is due to the alterations in the lipid profile, specifically increases in HDL_2. Unfortunately, the amount of exercise necessary to elicit these increases in HDL_2 is unclear.

Improvement in cardiovascular fitness is directly related to the intensity, duration, and frequency of exercise. An exercise intensity of 50 - 85% maximal VO_2, a duration of 15 - 60 minutes of continuous activity, and a frequency of 3 - 5 days per week have been recommended for developing and maintaining fitness in adults (31).

Although the literature defines a threshold necessary to produce cardiovascular fitness, the literature does not provide consensus with regard to the amount or intensity of aerobic exercise that is necessary to cause favorable changes in HDL_2. It is unclear whether the increases in HDL_2 require only a minimal training stimulus or whether greater amounts of exercise will elicit greater benefits.

Hypothesis

High intensity exercise training will improve the HDL profile significantly more than will low intensity exercise training.

CHAPTER THREE

METHODOLOGY

RESEARCH DESIGN

This was a longitudinal, prospective, and randomized, experimental study of the effect of training intensity on changes in plasma HDL_2. The independent variable of this study was exercise intensity. The dependent variable was gain score of HDL_2. Peak oxygen uptake was measured before and after training to determine if a general training adaptation had been elicited.

SUBJECTS

Female employees of a 529 bed, teaching hospital and their acquaintances were recruited for this study. Subjects were included after meeting the following criteria:

1) No contraindications to exercise testing (Appendix I).
2) Taking no medications known to alter lipid metabolism.
3) Taking no antihypertensive medications or medications known to blunt the heart rate response to exercise.
4) Non-exerciser for previous six months.
5) Normal resting and exercise 12 lead electrocardiogram.
6) Normal resting and exercise blood pressure.

7) Agreement to exercise within the guidelines of the study.

8) Between 20 and 50 years old, premenopausal.

Subjects were excluded from the study according to the absolute and relative contraindications for exercise testing adapted from the American College of Sports Medicine, Guidelines for Exercise Testing and Prescription, Fourth Edition (Appendix II).

APPARATUS AND INSTRUMENTATION

Health history form. An instrument to obtain a health history was developed (Appendix I). Items of interest were age, gender, physician, current medications, past history or family history of cardiovascular disease, pulmonary disease and risk factors for coronary heart disease.

Consent form. A form was developed to provide the subject with an informed consent regarding the protocol and the risks of exercise testing. (Appendix III). Subjects were informed of Michigan law requiring blood to be tested for Hepatitis B and HIV in the instance where a health care worker has an accidental exposure to a blood sample. Confidentiality was assured. The consent form was read aloud to each subject to ensure dissemination of information. The form was signed and witnessed.

Indications for stopping an exercise test. Indications for

stopping an exercise test were in accordance with those set forth by The American College of Sports Medicine, Guidelines for Exercise Testing and Prescription, Fourth Edition (Appendix IV). These guidelines were used in the event a subject needed to terminate the test prior to fatigue.

Personal exercise log. A form was developed for subjects to document their heart rate response to exercise, their distance walked, and the time it took to cover that distance. Subjects were instructed to complete the form following each exercise session. Logs were collected biweekly and reviewed for compliance measures.

Blood sampling equipment. A 21-gauge needle was inserted into the median cubital vein for the purpose of drawing a blood sample. Ten milliliters of blood were collected into ten milliliter glass vacutainers. The samples were centrifuged and stored at -70 degrees Celsius.

Exercise testing equipment. A Marquette Case 12 treadmill and ECG system was utilized for each of the exercise evaluations. A MedGraphics Systems 2001 metabolic cart was used to analyze oxygen consumption during each exercise evaluation.

PROCEDURE

General information regarding a walking health promotion program was distributed throughout the hospital. Women who were interested in participating were informed that the walking program was a part of an experimental study. At this point they had the choice of participating in the study or participating in the walking program only. The women who chose to be a subject in the study scheduled an initial interview, blood draw, and maximal graded exercise test (GXT) that was to occur no longer than 24 hours following the blood draw.

The initial interview consisted of the investigator reading the informed consent form (Appendix III) to the subject, answering questions related to the consent, and obtaining a signature from the subject indicating informed consent was given by the subject to participate in all the outlined aspects of the study. The investigator then read the health history form (Appendix I) to the subject and obtained the information recorded on the form. Participants were randomly assigned to one of two exercise intensity groups. The control group was the low intensity (L.I.) exercise group and the experimental group was the high intensity (H.I.) exercise group.

Subjects were instructed to abstain from food, beverages with the exception of water, and exercise for 12-14 hours prior to their scheduled blood draw. Subjects reported to the hospital laboratory where their blood was drawn by a certified phlebotomist according to the previously outlined procedure and

stored for future analysis.

Within 24 hours of the initial blood draw, subjects reported to the exercise testing laboratory where they engaged in a maximal exercise test (T1). A 12-lead ECG monitoring system was applied and the subjects were instructed to lie flat for 5 minutes. Resting heart rates, systolic and diastolic blood pressures and ECG tracings were obtained in the supine, sitting and standing positions. The metabolic cart was calibrated and resting values of metabolic data were recorded.

Subjects performed the exercise test according to the Bruce Protocol (Appendix V). Heart rates, 3 lead ECG's and metabolic data were continuously monitored. Blood pressures and 12 lead ECG tracings were recorded every 3 minutes and at peak exercise. The exercise test was terminated according to the indications for stopping an exercise test (Appendix IV). Subjects remained on the monitoring equipment until their heart rate and blood pressure had returned to baseline.

Individual training heart rates (THR) were calculated based on the heart rate reserve (HRR) formula:

$$THR = (PHR - RHR) \times 60\% + RHR$$

or

$$THR = (PHR - RHR) \times 80\% + RHR$$

PHR = Peak Heart Rate
RHR = Resting Heart Rate

Subjects assigned to the L.I. group exercised at their training heart rates calculated at 60% HRR. Subjects assigned to the H.I. group exercised at their training heart rates calculated at 80% HRR.

Subjects were instructed to walk 2 miles 3 times per week at their prescribed target heart rate. A warm up period of 5 minutes, in which the subject gradually raised her heart rate to the prescribed level, was not to be included in the 2 miles. Exercise logs (Appendix VI) were distributed with instructions for their use. Compliance was measured using the logs. Accepted minimal compliance was 80%. The subjects were required to walk at least two times per week but no more than four times per week to be considered compliant. This corresponds to 29-43 total exercise sessions.

Subjects were taught to take their radial pulse. Training intensity was monitored by the subject palpating the radial pulse before exercise and frequently during each exercise session to ensure maintenance of the target heart rate. The walking pace was adjusted accordingly.

Subjects followed the prescribed regimen for 11 weeks. A post-training blood draw and GXT (T2) was scheduled for the 12th week. Procedures and protocols for these tests were identical to the initial test prior to training.

Blood samples were kept frozen until all samples had been collected and could be analyzed with the same equipment on the same day. Total HDL was fractionated into HDL_2 and HDL_3 using a

procedure modified from Warnick and Abers published procedure for measuring total HDL cholesterol (24). This method required two precipitations with dextran sulfate solution containing different amounts of magnesium chloride. Total HDL cholesterol was measured after serum LDL and VLDL were selectively precipitated by magnesium-dextran sulfate and removed by centrifugation. The supernatant contained the cholesterol associated with the soluble HDL fraction which was precipitated again with a high concentration of magnesium chloride-dextran solution to precipitate HDL_2. The final supernatant was analyzed for HDL_3 and the difference in the total HDL cholesterol and the HDL_3 was recorded as it was a close approximation of the HDL_2 concentration.

STATISTICS.

All statistics were analyzed using the ICS software package on IBM compatible computers. The data was statistically compared using Student's dependent and independent t-tests. Dependent t-t-tests were used when comparing pre and post training values within a group and when comparing initial differences between groups. Independent t-tests were used when comparing the differences in pre to post training values among groups. Necessary and sufficient sample size was computed to be 19 subjects per group at a power of .80. In all cases, an alpha level of less than .05 indicated a statistically significant difference ($p<.05$).

CHAPTER FOUR

RESULTS

Characteristics of Subjects

Forty-four subjects were included in this study. One woman did not report for her initial evaluation. Three women did not meet the criteria for selection. Of the three who did not meet the criteria, two had abnormal exercise ECG's and one was taking an antihypertensive medication.

Forty remaining candidates participated in the study. Twenty subjects were randomly assigned to the control group, L.I., and twenty subjects were randomly assigned to the experimental group, H.I. Thirteen subjects did not adhere to the regimen. Data from these subjects were not included in the analysis. Two of the subjects' post test results were not accurate due to equipment failure.

Twenty-five subjects met the criteria and completed participation in the study. Twelve individuals exercised at 60% of their heart rate reserve (L.I.), and thirteen individuals exercised at 80% of their heart rate reserve (H.I).

Descriptive characteristics between groups were

statistically similar at the beginning of the study. Table 1 summarizes physical and physiologic characteristics for L.I. and H.I. groups.

Table 1

Demographic Description of Subjects

	L.I.		H.I.		
Characteristic	$\bar{X}$	SD	$\bar{X}$	SD	Significance
Age (yrs)	40.5	8.1	37.8	7.8	NS
Height (cm)	162.1	8.1	165.5	3.7	NS
Weight (kg)	76.1	19.4	63.7	6.8	NS
RHR (b/min)	79.5	9.1	78.4	9.7	NS
RSBP (mmHg)	122.7	7.9	120.2	16.8	NS
RDBP (mmHg)	78.7	6.1	76.7	7.6	NS

RHR = Resting Heart Rate
RSBP = Resting Systolic Blood Pressure
RDBP = Resting Diastolic Blood Pressure

The exercise response before training is summarized in table 2. Both heart rate and systolic blood pressure increased significantly from rest to peak exercise ($p<.05$). No significant difference in heart rate, systolic blood pressure or diastolic blood pressure response was observed between groups.

Table 2

Exercise Response Before Training

	L.I.				H.I.			
	Rest		Peak		Rest		Peak	
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
HR (b/min)	79.5	9.1	180.4	14.4	78.4	9.7	177.8	10.7
SBP (mmHg)	122.7	7.9	153.6	13.3	120.2	16.8	146.0	15.1
DBP (mmHg)	78.7	6.1	80.7	12.3	76.7	7.6	79.2	7.2

HR = Heart Rate
SBP = Systolic Blood Pressure
DBP = Diastolic Blood Pressure

Both L.I. and H.I. groups increased their exercise test duration and peak VO_2 on the post training GXT ($p<.005$). Table 3 summarizes these results.

Table 3

Exercise Response to Training

	L.I.				H.I.			
	T1		T2		T1		T2	
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
PHR (b/min)	180.4	14.4	178.6	14.3	177.8	10.6	181.8	11.8
Time (min)	7:59	1:41	9:13*	1:57	8:32	2:00	9:45*	2:19
PVO_2 (ml/kg/min)	29.0	5.0	31.9*	5.4	30.7	5.2	33.5*	6.3

PHR = Peak Heart Rate
PVO_2 = Peak Oxygen Consumption
* indicates significantly increased when compared to T1.

These improvements in exercise capacity were similar for the L.I. and H.I. groups.

Oxygen consumption at THR was lower in the L.I. group as compared to the H.I. group at T1 and T2. These values were approximately 17.6 ml/kg/min and 24.7 ml/kg/min at T1, and 18.1 ml/kg/min and 23.1 ml/kg/min at T2 respectively.

Lipoprotein data are presented in table 4. Both the L.I. and the H.I. groups showed increases in all components of the HDL profile ($p<.05$). There were no significant differences in HDL profile gain scores between groups (table 5).

Table 4

HDL Profile Changes with Exercise Training

	L.I.				H.I.			
	Pre		Post		Pre		Post	
	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD	$\bar{X}$	SD
HDL (mg/dl)	32.3	8.5	40.3	10.6	31.6	6.2	38.2	12.0
HDL_2 (mg/dl)	14.2	5.7	18.5	6.9	13.0	6.2	19.6	8.9
HDL_3 (mg/dl)	18.2	5.4	21.7	6.7	17.8	4.9	18.6	5.6

Table 5

Gain Score Difference of HDL Profile Between Groups

	L.I.		H.I.		
	$\bar{X}$	SD	$\bar{X}$	SD	Significance
HDL (mg/dl)	7.9	9.9	6.6	10.3	NS
HDL_2 (mg/dl)	4.4	6.3	6.5	8.3	NS
HDL_3 (mg/dl)	3.6	7.7	.81	4.5	NS

CHAPTER FIVE

DISCUSSION

Numerous epidemiologic studies have suggested that HDL has an inverse relationship with the risk of coronary heart disease (2,12). Furthermore, plasma HDL concentrations have been shown to be the strongest predictor of the development and progression of CHD (4,16). Recently, investigators have suggested that the ability of plasma HDL concentrations to predict CHD may be strengthened by analyzing the individual components of total HDL (4,16,25).

Initiation of an exercise training program is generally a part of first step intervention for treatment of hyperlipidemia. Exercise training is known to increase plasma concentrations of HDL, favorably altering the lipid profile. Recently, it has been suggested that exercise may be responsible for altering only the HDL_2 component of total HDL (23). This finding may further clarify the benefit of exercise training because the antiatherogenic properties of HDL may be specific to the subfraction HDL_2.

The initial HDL profile values in the sample group were less

than what might have been expected. The HDL level of the L.I. group was 32.3 mg/dl with a standard deviation of 8.5 mg/dl. The HDL level of the H.I. group was 31.6 mg/dl with a standard deviation of 6.2 mg/dl. The American Heart Association (AHA) and the NCEP defines an HDL level of < 35 mg/dl indicative of increased risk for CHD (27,32), whereas an HDL level of 60 mg/dl or greater is considered a negative risk factor (27). It was stated that the women in this study had been non-exercisers for the previous six months. This may have contributed to low initial HDL levels.

Total HDL levels increased 24% and 21% in the L.I. and the H.I. groups respectively. HDL_2 levels increased 31% and 50% respectively, and HDL_3 levels increased 20% and 4% respectively. These numbers may suggest clinical importance related to a decreased risk for CHD.

Exercise thresholds necessary to produce cardiovascular fitness have been well documented in the literature. The American College of Sports Medicine (ACSM) makes recommendations for the quantity and quality of exercise necessary to enhance health and fitness. An exercise frequency of three to five days per week at an intensity of 40-85% maximal VO_2 for 15 to 60 minutes are the guidelines established (31). Intensity of exercise may be calculated according to a variety of calculations. It has been determined that the HRR method for calculating training heart rates corresponds to approximately the same percentage as methods calculated using maximal VO_2 (31).

Not so clearly documented however, is the exercise threshold necessary to produce favorable alterations in the HDL profile, and even more specifically, favorable alterations in HDL_2. Results of the present study indicted that training at an intensity of between 60% and 80% HRR provided a sufficient stimulus for eliciting increases in HDL and HDL_2. However, training at 80% HRR elicited no greater benefit than did training at 60% HRR.

The H.I. training group gained no greater training adaptation than did the L.I. training group. A reason for this similarity may have been that training intensities of 60 and 80% HRR were too similar to elicit a varied response. Surprising was the fact that the H.I. group's RHR increased from pre training to post training. This may have been the result of not allowing an adequate rest period for the heart rate to truly reach resting values prior to collecting data.

Metabolic intensity of exercise, as measured by oxygen consumption, did not appear to change in either group as a result of exercise training. This observation may be explained by walking not being an adequate stimulus to elicit significant changes in cardiovascular function. This is does not assume however, that walking will not elicit significant health benefits. This observation also indicates that there was a clear differentiation in exercise intensities between L.I. and H.I. throughout the 11-week training period.

Evidence cited by Hartung et al stated that exercise has no

effect on HDL_3 levels (23). HDL_3 increased in both the L.I. and the H.I. groups in this study. These increases may have been due to variables not controlled in this study. One such variable may have been increased alcohol consumption (13). Robinson et al hypothesizes that HDL_3 may be a precursor to HDL_2 formation. If this is found to be true, the noted increases may be clinically important. Based on the cited results of this study, the hypothesis that high intensity training improves the HDL profile more than low intensity training was rejected.

Although subjects were encouraged not to alter their dietary habits or alcohol and cigarette use during the course of the study, lifestyle-related risk factors were not controlled since HDL_2 concentrations are not affected by factors other than exercise. The observed increases in total HDL were primarily the result of increases in HDL_2.

Other studies that have attempted to define a training stimulus necessary to produce alterations in the HDL profile have not controlled the volume of exercise (3). Investigators have prescribed the duration of exercise to be a period of time rather than a distance. Consequently, H.I. groups would have accumulated a larger volume of exercise as compared to the L.I. groups. In this study, all subjects, regardless of training group, walked for 2 miles thereby keeping the volume of exercise relatively constant. The results may have suggested that the alteration of the HDL profile is training volume dependent.

Although the volume of exercise was relatively constant

between groups, the initial difference (not statistically significant) in weight between groups resulted in the L.I. group expending approximately 2,000 more calories throughout the total 12 week period. It appeared that the H.I. group expended less calories but had greater improvements in HDL_2 than did the L.I. group. This may be explained by baseline differences in HDL_2 and HDL_3.

It was also important in this study to analyze all blood samples the same day. Samples were kept frozen at -70 degrees Celsius which has been shown not to alter the composition or results of the analysis (33). Mechanical variability was decreased due to this procedure.

Although attrition was high in this study, a significant improvement in the HDL profile was observed. Therefore, these results can be generalized to similar populations. Moreover, the observation of a significant change in the HDL profile suggests that the probability of a type II error was low.

Limitations of this study include an estimation rather than direct measurement of HDL_2, limited assessment of compliance, lack of control of leisure activity, and a small sample size. Based on these limitations, the results of this study can only be generalized to this group of subjects.

RECOMMENDATIONS

Outcomes of this study indicate a need for future research to be done on the effect of high intensity exercise training versus low intensity exercise training on fractionated plasma

high-density lipoprotein cholesterol. Studies should be done to include the following recommendations:

1. a controlled exercise setting in which attendance, distance walked, and heart rate could be monitored
2. develop THR based on VO_2 rather than HRR
3. frequently reasses VO_2 at THR and adjust to assure training intensity is being maintained
4. minimize leisure activity that is beyond the recommendations of the study
5. lengthen duration of exercise training period
6. recruit larger sample size to allow for attrition due to lengthened exercise training period

CONCLUSION

The results of the present study and those reported in the literature suggest that the favorable alterations in HDL profile may occur at the lower range of intensities required to produce improvements in fitness. These data indicated that training at 60% HRR will produce alterations in the HDL profile that are similar to training at 80% HRR. In view of these findings, exercise prescriptions focused on improving the HDL profile may be calculated at the lower end of the range of intensities previously identified to produce cardiovascular fitness. This may be important because lower intensity exercise does not carry the orthopaedic risk that higher intensity exercise does and it may be more enjoyable for the exerciser, thereby improving long term adherence.

APPENDICES

Appendix I

Health History

Name:_____ Date_____

Age:_____ Birthdate:_____ Gender:_____

Physician:_____

Medications:

Past History

I. CV System

MI:_____ CABG:_____

PTCA:_____ Palpitations:_____

Rapid heart rate:_____ Murmur:_____

HTN:_____ CVA:_____

Ankle swelling:_____ PVD:_____

SOB with exercise:_____

Congenital heart disease:_____

Angina at rest or with exercise:_____

II. Pulmonary System

Pulmonary disease:_____

III. Risk Factors

Abnormal blood lipids:_____

Diabetes:_____

Family history:_____

Smoking:_____

Exercise:_____

IV. Other

Recent illness/hospitalization:_____

_____

Orthopaedic problems:_____

Appendix II

Contraindications to Exercise Testing

Absolute Contraindications

1. A recent significant change in the resting ECG suggesting infarction or other acute cardiac event
2. Recent complicated myocardial infarction
3. Unstable angina
4. Uncontrolled ventricular dysrhythmia
5. Uncontrolled atrial dysrhythmia that compromises cardiac function
6. Third degree AV block
7. Acute congestive heart failure
8. Severe aortic stenosis
9. Suspected or known dissecting aneurysm
10. Active or suspected myocarditis or pericarditis
11. Thrombophlebitis or intracardiac thrombi
12. Recent systemic or pulmonary embolus
13. Acute infection
14. Significant emotional distress (psychosis)

Relative Contraindications

1. Resting diastolic blood pressure > 120 mmHg or resting systolic blood pressure > 200mmHg
2. Moderate valvular heart disease
3. Known electrolyte abnormalities (hypokalemia, hypomagnesemia)
4. Fixed rate pacemaker
5. Frequent or complex ventricular ectopy
6. Ventricular aneurysm
7. Cardiomyopathy, including hypertrophic cardiomyopathy
8. Uncontrolled metabolic disease (diabetes, thyrotoxicosis, or myxedema)
9. Chronic infectious disease (mononucleosis, hepatitis, AIDS)
10. Neuromuscular, musculoskeletal, or rheumatoid disorders that are exacerbated by exercise
11. Advanced or complicated pregnancy

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Appendix III

Consent Form

The effect of high intensity exercise training versus low intensity exercise training on high density lipoprotein subfraction 2 (HDL_2) cholesterol.

It is known that exercise training favorably modifies some risk factors for coronary artery disease (CAD). Among these risk factors is an elevated serum cholesterol, primarily a low HDL component and a high low density lipoprotein (LDL) component. Exercise training has been shown to increase HDL cholesterol believed to be the protector against CAD. It is also not known how hard one must exercise before these increases begin to occur. Therefore, your participation in the study may help to determine how hard one must exercise to improve the protective effects.

As a participant you will be asked to complete two exercise evaluations. Both evaluations will require ten electrodes be placed on your chest to permit recording of your heart rate and rhythm. Oxygen consumption will be measured by breathing into a mouthpiece. During the evaluation the treadmill will increase in speed and elevation every 3 minutes. Results of this test will be used in determining an exercise prescription. Three fasting blood samples will be drawn during this study. Each sample will require 10 milliliters of blood be drawn.

The associated risks of the exercise evaluations re those that apply to exercise participation in general. These risks are muscle soreness, muscular straining, sprains, chest pain, nausea, dizziness, heart attacks and sudden death. The potential risks of drawing blood include a bruise at the site of the vein puncture, inflammation of the vein and infection. Costs associated with any injury will not be covered by the investigator or by Butterworth Hospital. You have the right to refuse or stop participating at any time during the procedure without penalty or jeopardy of the quality or quantity of treatment you are now receiving or may receive in the future at Butterworth Hospital.

Information obtained from this study will be held in strict confidence and be reported only in research forums. Data will not be identified by name in any presentation.

You will be one of 58 people participating in this study. The benefits of your participation may include a contribution to the overall understanding of the role exercise plays in the reduction of risk for coronary artery disease and may further define optimal training intensities.

Questions regarding your rights as a subject can be answered

by calling Linda Pool at the Butterworth Institutional Review Board at (616) 774-1291/1299. Questions related to other aspects of your participation can be answered by calling Terri Spate at (616) 774-1320.

In accordance with Michigan law your blood will be tested for Hepatitis B and HIV (AIDS virus) in those instances where a health care worker has an accidental exposure to your blood. These results will be noted on your chart due to an employee occupational exposure. You will be notified of any positive results.

I have read the above statements and am aware of the risks involved with participation and my rights as a subject. I agree to participation in this research study.

Subject	Date
Investigator	Date
Witness	Date

Appendix IV

Indications for Stopping an Exercise Test

1. Progressive angina (stop at 3+ level or earlier on a scale of 1+ to 4+)
2. Ventricular tachycardia
3. Any significant drop (20mmHg) of systolic blood pressure or a failure of the systolic blood pressure to rise with an increase in exercise load
4. Lightheadedness, confusion, ataxia, pallor, cyanosis, nausea, or signs of severe peripheral circulatory insufficiency
5. Early onset of deep (>4mm) horizontal or downsloping ST depression or elevation
6. Onset of second or third degree AV block
7. Increasing ventricular ectopy, multiform PVCs, or R on T PVCs
8. Excessive rise in blood pressure; systolic pressure > 250mmHg; diastolic pressure > 120 mmhg
9. Chronotropic impairment; increase in heart rate that is < 25 beats/min below age predicted normal value (in the absence of beta blockade)
10. Sustained supraventricular tachycardia
11. Exercise induced left bundle branch block
12. Subject requests to stop
13. Failure of the monitoring system

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Appendix V

Bruce Protocol

Stage	MPH	Grade	Min.	MET Requirement Men	Women	Cardiac
I	1.7	10%	1	3.2	3.1	3.6
			2	4.0	3.9	4.3
			3	4.9	4.7	4.9
II	2.5	12%	4	5.7	5.4	5.6
			5	6.6	6.2	6.2
			6	7.4	7.0	7.0
III	3.4	14%	7	8.3	8.0	7.6
			8	9.1	8.6	8.3
			9	10.0	9.4	9.0
IV	4.2	16%	10	10.7	10.1	9.7
			11	11.6	10.9	10.4
			12	12.5	11.7	11.0
V	5.0	18%	13	13.3	12.5	11.7
			14	14.1	13.2	12.3
			15	15.0	14.1	13.0

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Appendix VI

Personal Exercise Log

Date	Pre	Pulse Dur	Post	Distance	Time	Comments
M						
T						
W						
T						
F						
S						
S						
M						
T						
W						
T						
F						
S						
S						

REFERENCES

LIST OF REFERNCES

1. American Heart Association (1993). Heart and Stroke Facts: 1994 Statistical Supplement Dallas, TX: National Center.

2. Levy, R.I. (1986). Cholesterol and Coronary Artery Disease. What do clinicians do now? American Journal of Medicine, 80 (suppl. 2A), 18-22.

3. Gaesser, G.A., Rich, R.G. (1984). Effects of High and Low Intensity Exercise Training on Aerobic Capacity and Blood Lipids. Medicine Science in Sport and Exercise, 16(3), 269-274.

4. Drexel, H., Amann, F.W., Rentsch, K., Neuenschwander, C., Leuthy, A., Khan, S., and Follath, F. (1992). Relation of the Level of High Density Lipoprotein Subfractions to the Presense and Extent of Coronary Artery Disease. American Journal of Cardiology, 70, 436-440.

5. Salonen, J.T., Salonen, R., Seppanen, K., Rauramaa, R., and Tuomilehto, J. (1991). HDL, HDL_2, and HDL_3 Subfractions and the Risk of Acute Myocardial Infarction. Circulation, 4(1), 129-139.

6. Gwynne, J.T. (1989). High-density Lipoprotein Cholesterol Levels as a Marker of Reverse Cholesterol Transport. American Journal of Cardiology, 64, 10G-17G.

7. Gordon, D.J., Rifkind, B.M. (1989). High-density Lipoprotein-The Clinical Implications of Recent Studies. New England Journal of Medicine, 321, 1311-1316.

8. Williams, P.T., Haskell, W.L., Vranizan, K.M., Blair, S.N., Krauss, R.M., Superko, R., Albers, J.J., Frey-Hewitt, B. and Wood, P.D. (1985). Associations of Resting Heart Rate with Concentrations of Lipoprotein Subfractions in Sedentary Men. Circulation, 71(3), 441-449.

9. Levy, R.I. (1986). Primary Prevention of Coronary Heart Disease by Lowering Lipids: Results and Implications. American Heart Journal, 110(5), 1116-1122.

10. Jacobs, D.R. (1985). High-density Lipoprotein Cholesterol and Coronary Heart Disease, Cardiovascular Disease and All Cause Mortality. Circulation, 72(suppl.III), III-85.

11. Rhoads, G.G., Gullbrandsen,C.L., Kagan, A. (1976). Serum Lipoproteins and Coronary Heart Disease in a Population Study of Hawaiian-Japanese Men. New England Journal of Medicine, 294, 293-298.

12. Gordon, T., Castelli, W.P., Hjortland, M.C., Kannel, W.B., and Dawber, T.R. (1977). High Density Lipoprotein as a Protective Factor Against Coronary Heart Disease: The Framingham Heart Study. American Journal of Medicine, 62, 707-714.

13. Haffner, S.M., Applebaum-Bowden, D., Wahl, P.W. (1985). Epidemiological Correlates of High-density Lipoprotein Subfractions, Apolipoproteins A-I, A-II and D, and Lecithin Cholesterol Acyitransferase: Effects of Smoking, Alcohol and Adiposity. Arteriosclerosis, 5, 169-177.

14. Gordon, D.J., Knoke, J., Probstfield, J.L., Superko, R., and Tyroler, H.A. (1986). High-density Lipoprotein Cholesterol and Coronary Heart Disease in Hypercholesterolemic Men: The Lipid Research Clinics Coronary Primary Prevention Trial. Circulation, 74, 1217-1225.

15. Manninen, V., Huttunen, J.K., Heinonen, O.P., Tenkanen, L., Frick, H. (1989). Relation Between Baseline Lipid and Lipoprotein Values and the Incidence of Coronary Heart Disease in the Helsinki Heart Study. American Journal of Cardiology. 63, H42-H47.

16. Romm, P.A., Green, C.E., Reagan, K., Rackley, C.E. (1991). Relation of Serum Lipoprotein Cholesterol Levels to Presense and Severity of Angiographic Coronary Artery Disease. American Journal of Cardiology, 67, 479-483.

17. Salonen, J.T., Hamynen, H., Leino, U., Kostiainen, E., and Sahi, T. (1985). Relation of Alcohol, Physical Activity, Dietary Fat and Smoking to Serum HDL and Total Cholesterol in Young Finnish Men. Scandanavian Journal Soc. Medicine, 13, 99-102.

18. Griqui, M.H., Wallace, R.B., Heiss, G., Mishkel, M., Schonfeld, G., and Jones, G.T.L. (1980). Cigarette Smoking and Plasma High-density Lipoprotein Cholesterol. The Lipid Research Clinics Program Prevalence Study. Circulation, 62(Suppl IV), IV70-IV76.

19. Ernst, N., Fisher, M., Smith, W., Gordon, T., Rifkind, B., Little, J., Mishkel, M.A., and Williams, O.D. (1980). The Association of Plasma High-density Lipoprotein Cholesterol with Dietary Intake and Alcohol Comsumption. Circulation, 62(Suppl IV), IV41-IV51.

20. Lehtonen, A. (1986). Effect of Beta Blockers on Blood Lipid Profile. American Heart Journal, 109(5), 1192-1196.

21. Wallace, R.B., Hunninghake, D.B., Reiland, S., Barrett-Conner, E., Mackenthun, A., Hoover, J., and Wahl, P. (1980). Alterations of plasma high-density lipoprotein cholesterol levels associated with consumption of selected medications. Circulation, 62(suppl IV), IV77-IV82.

22. Glueck, C.J., Taylor, H.L., Jacobs, D., Morrison, J.A., Beaglehole, R., and Williams, O.D. (1980). Plasma high-density lipoprotein cholesterol: Association with measurements of body mass. Circulation, 62(suppl IV), IV62-IV69.

23. Hartung, G.H., Reeves, R.S., Foreyt, J.P., Patsch, W., and Gotto, A.M. (1986). Effect of alcohol intake and exercise on plasma high-density lipoprotein cholesterol subfractions and apolipoprotein A-1 in women. The American Journal of Cardiology, 58, 148-151.

24. Warnick, G.R., Benderson, J.M., and Abers, J.J. (1982). Quantitation of high-density lipoprotein subclass separation by dextran sulfate and MG^{++} Precipitation. Clinical Chemistry, 28(7),1574.

25. Robinson, D., Ferns, G.A., Bevan, E.A., Stocks, J., Williams, P.T., and Galton, D.J. (1987). High density lipoprotein subfractions and coronary risk factors in normal men. Arteriosclerosis, 7(4), 341-346.

26. Hooper, P.L, Crouse, S.F. Exercise and high-density lipoprotein: A mechanism for coronary artery disease risk reduction. In O. Appenzeller (Ed.). Sports Medicine: Fitness, Training, Injuries. Third Edition, Baltimore, MD: Urban & Schwarzenberg, 221-238.

27. National Cholesterol Education Program. (1993). Summary of the NCEP Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel). Journal of American Medical Association, 269(23), 3015-3023.

28. Stein, R.A., Michielli, D.W., Glantz, M.D., Sardy, H., Cohen, A., Goldberg, N., and Brown, C.D. (1990). Effects of different exercise training intensities on lipoprotein cholesterol fractions in healthy middle-aged men. American Heart Journal, 119(2), 277-283.

29. American Heart Association and National Heart, Lung, and Blood Institute. (1990) A summary of the evidence relating dietary fats, serum cholesterol, and coronary heart disease. Circulation, 81(5), 1721-1733.

30. Wood, P., and Haskell, W. (1979). The Effect of Exercise on Plasma High Density Lipoprotein. Lipids, 14, 417-427.

31. American College of Sports Medicine. Guidelines for Exercise Testing and Prescription. Fourth Edition. Philadelphia: Lea & Fegiger, 1991.

32. American Heart Association. (1990). Nurses' Cholesterol Education Handbook. Guidelines for Education and Counseling of the Individual with Hypercholesterolemia.