AN ABSTRACT FOR THE THESIS OF

Tanya R. Littrell for the degree of Master of Science in Human Performance presented on June 16, 2000. Title: Behavioral Determinants of Insulin Resistance in Non-Diabetic Patients With Coronary Artery Disease.

Abstract approved: _____

Daniel P. Williams

Greater degrees of insulin resistance are associated with increased rates of coronary artery disease (CAD) progression. However, the specific behavioral determinants of insulin resistance are not well known in patients with CAD. Although abdominal obesity contributes to insulin resistance, the extent to which abdominal obesity may modify the relationship between health behaviors and insulin resistance is unclear in coronary patients. Thus, the aims of this study are to determine whether selected health behaviors (physical activity, dietary patterns, and psychosocial indexes) are associated with insulin resistance and whether the associations differ between those with and those without abdominal obesity in 26 non-diabetic patients (19 men and 7 women, aged 43-82 years) with CAD after physician referral yet prior to participation in a cardiac rehabilitation program.

Greater degrees of insulin resistance were quantified as higher areas under the insulin response curve over a 75g 2-hour oral glucose tolerance test. The Stanford Physical Activity Recall and the Ainsworth Compendium of Physical Activities were

used to estimate physical activity energy expenditures. The Block 95 Food Frequency Questionnaire was used to estimate nutrient and vitamin intakes from foods. The Center for Epidemiologic Studies Depression Scale was used to quantify symptoms of depression, and the Cook-Medley Questionnaire was used to quantify feelings of hostility. Abdominal obesity was defined by gender-specific National Institutes of Health criteria (waist circumference $\geq$ 102 cm for men and $\geq$ 88cm for women).

The patients with abdominal obesity (N=14) had a higher insulin response (Insulin AUC) to the oral glucose load ($p=0.020$), weighed more ($p<0.001$), and reported lower physical activity energy expenditures ($p=0.017$), and lower dietary fat intakes ($p=0.041$) than the patients without abdominal obesity. Taken together, the similar self-reported energy intakes and lower physical activity energy expenditures are suggestive of a more positive energy balance in the patients with abdominal obesity. Higher insulin AUC values were associated with heavier body weights ($r=0.57$, $p=0.002$), lower dietary vegetable intakes ($r=-0.45$, $p=0.023$), lower dietary (i.e., from foods rather than supplements) vitamin C ($r=-0.40$, $p=0.027$) and vitamin E ($r=-0.43$, $p=0.044$) intakes, and higher depression scores ($r=0.47$, $p=0.016$). After adjusting for abdominal obesity, higher insulin AUC remained associated with heavier body weights (partial $r=0.43$, $p=0.034$), lower dietary vegetable intakes (partial $r=-0.51$, $p=0.011$), and lower dietary vitamin C (partial $r=-0.48$, $p=0.019$) and vitamin E (partial $r=-0.54$, $p=0.007$) intakes.

Insulin AUC was independently associated ($p\leq0.039$) with the interactions of body weight, dietary vegetable intake, and dietary vitamin E intake with abdominal obesity, indicating a stronger association between insulin resistance and these health behaviors in patients with versus those without abdominal obesity. We conclude that

higher self-reported depression scores, lower dietary vegetable, fruit and vitamin E intakes, and lower physical activity levels may be important behaviors to identify for better managing insulin resistance and abdominal obesity in non-diabetic patients with CAD who are referred to cardiac rehabilitation.

Behavioral Determinants of Insulin Resistance in Non-Diabetic Patients with Coronary Artery Disease

by

Tanya R. Littrell

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CONTRIBUTION OF AUTHORS

Dr. Dan Williams was involved in the overall study design, analysis of the data, and writing of the manuscript. Jessica N. Jacks served as project coordinator. Kerri R. Eason, R.N., Good Samaritan Hospital, is the director of cardiac rehabilitation and Diane C. Arney, R.N., coordinated patient screening and case management. Dr. Chris C. Draheim assisted with data collection at Good Samaritan Hospital and Oregon State University.

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INTRODUCTION

Individuals with coronary artery disease (CAD) are more insulin resistant than are individuals with no evidence of CAD.[1,2] Greater degrees of insulin resistance are also strongly associated with larger arterial wall intima-media thicknesses[3] and with greater degrees of atherosclerotic coronary artery occlusion[4,5] and restenosis[6] in patients with CAD. Preventing the progression of insulin resistance to diabetes[7] is an important treatment goal because diabetes greatly increases the risk for CAD mortality and rehospitalization, even in those CAD patients enrolled in aggressive risk reduction programs.[8]

In addition to drug therapy[9-11], behavior modification[12-14] may be an effective way to reduce the magnitude of insulin resistance. Patients with CAD tend to have self-reported hostility and/or depression[15], altered dietary patterns, such as increased levels of saturated fat intake[12], and low fitness and/or physical activity levels[8]. While these behavioral patterns are strong determinants of insulin resistance[16-18] in healthy populations, the joint impact of these detrimental behavioral patterns on insulin resistance has not been extensively studied in a select non-diabetic coronary population.

Participation in structured cardiac rehabilitation programs reduces the rate of progression of atherosclerosis and rehospitalizations in CAD patients.[19,20] Specifically, 3 to 4 months of cardiac rehabilitation yield increases in exercise capacity, reductions in depression, increases in plasma high-density lipoprotein cholesterol, and reductions in

plasma triglycerides in CAD patients.[21] Therefore, the American Heart Association (AHA)[22] established secondary prevention program guidelines that, in addition to drug therapies, focus on changing physical activity, dietary, and smoking behaviors associated with dyslipidemia, obesity, and hypertension. By contrast, the current AHA risk reduction strategies[22] may not be optimally designed to manage insulin resistance. The guidelines may need to be more specific with regard to recommendations for physical activity energy expenditures, intakes of food sources high in fiber and antioxidant vitamins, and assessment of psychosocial factors such as depression and hostility.

Obesity is common in CAD patients, with one study reporting a prevalence as high as 40%.[23] Obesity, and more specifically abdominal obesity, is linked with[14,24] and may even contribute to[25-27] insulin resistance. Behaviors associated with increased obesity or abdominal obesity include a low physical activity level[28,29], and an increased saturated fat intake[30]. In addition, obese CAD patients may enter cardiac rehabilitation reporting different behaviors than non-obese CAD patients.[13] Thus, it is possible that the health behaviors associated with insulin resistance may differ between obese and non-obese CAD patients.

What is unknown is which of the behavioral determinants of insulin resistance and/or abdominal obesity may be *most* crucial to address for managing insulin resistance in patients with CAD, specifically non-diabetic patients. Answering this question can have important implications for identifying high-risk behaviors prior to participation in cardiac rehabilitation programs. Thus, the aims of this study are to determine whether the selected health behaviors (physical activity, dietary patterns, and psychosocial indexes)

are associated with insulin resistance and whether the associations differ between those with and without abdominal obesity in non-diabetic patients with CAD.

METHODS

The present study examines the baseline descriptive interrelationships of behavioral determinants of insulin resistance in patients with CAD prior to their entrance into an outpatient phase II & III cardiac rehabilitation program. The longitudinal effects of three months of cardiac rehabilitation on insulin resistance in patients with CAD are reported elsewhere.[31]

Patients Twenty-six patients with valid, physician-diagnosed coronary artery disease were studied. Study participants were recruited through physician referrals to the cardiac rehabilitation program at Good Samaritan Hospital. A nurse case manager screened 105 patient referrals, and out of these, 57 were ineligible to participate due the following study exclusion criteria: presence of diabetes, non-definitive diagnosis of CAD, unable to commit to the entire intervention, transportation constraints, a medical condition limiting physical activity, and moving out of the geographical area. Of the remaining 48 eligible subjects, 31 agreed to participate in the study. Of these 31 patients, five were further excluded. Three patients were excluded because their baseline oral glucose tolerance test (OGTT) uncovered the presence of covert diabetes (2 hour postload serum glucose levels $\geq$ 200mg/dl)[32], one patient failed to report an earlier diagnosis of diabetes at screening, and another subject had incomplete data due to a missed venipuncture during the OGTT. The resulting study participants are 26 adult men and women (19 men, 7 women), ages 43-82 years. The CAD diagnosis composition of the patients is as follows: 68% coronary artery bypass graft patients, 10% percutaneous

transluminal coronary angioplasty and stent procedure patients, and 22% who were not surgically treated. All participants signed an informed consent form, and all procedures were approved by the Institutional Review Boards at the university and the hospital.

Organization of Data Collection Eligible study subjects were scheduled for two data collection visits within a 1-2 week span. Subjects arrived at the hospital between 8-9am after a 12-hour fast for a fasting blood draw and an oral glucose tolerance test (OGTT). Time of awakening, elapsed time between awakening and the fasting blood draw, elapsed time between the last acute bout of physical activity and the fasting blood draw, and the type, duration, and intensity of last acute bout of physical activity were recorded to assess possible inter- and intra-individual variability in blood assessments. On a separate occasion, the subjects visited the OSU Endocrine and Metabolism Lab for the anthropometric measures and a battery of questionnaires to assess the behavioral variables.

Blood Collection and OGTT After the fasting blood draw, participants were given a 75g glucose solution to drink and their insulin and glucose responses were measured through subsequent blood draws at 1 and 2 hours after the oral glucose load. The whole blood was collected in serum vacutainer tubes with gel clot activator, then allowed to clot for 30 minutes at room temperature prior to centrifugation. Serum samples were separated and aliquoted into analyte-specific cryovials. The hospital lab completed the assessment of glucose on the same day, and all other samples were stored at –70°C for subsequent analysis at the OSU lab.

Insulin and Glucose Assessment The serum insulin concentrations were assessed on thawed frozen samples. Fasting, 1 and 2 hour postload serum insulin concentrations for each blood sample were determined by a human-insulin-specific radioimmunoassay (Linco Research, St. Charles, MO). Unlike other more commonly used assays, the antibody in the insulin-specific assay has a low cross-reactivity with other insulin-like molecules and fragments secreted by the pancreas. The interassay coefficients of variation ranged from 1.8% to 3.0%.[31] Insulin levels at fasting, 1 and 2 hour post glucose load were used to determine the total area under the insulin response curve (insulin $AUC_{0\text{-}120}$) by the trapezoid method[33]: (fasting insulin level x 30 minutes) + (1-hour insulin level x 60 minutes) + (2-hour insulin level x 30 minutes). To quantify levels of insulin resistance, increased levels of insulin $AUC_{0\text{-}120}$ are used as a marker of increased insulin resistance in this study. Serum glucose levels for each blood draw were measured using Boehringer Mannheim reagents (Indianapolis, IN) for a colorimetric hexokinase method[34] by the hospital lab. The coefficient of variation for serum glucose assessment was 1.8%.

Assessment of Anthropometric Variables According to standardized procedures[35], body weight was measured in kilograms (kg) using a balance scale and waist circumference was measured in centimeters (cm) using a tape measure. Waist circumference is taken at the level of the natural waist, which is the narrowest part of the torso viewed anteriorly. If no natural waist is apparent, the measurement is taken halfway between the ribs and the iliac crest. The patient population was stratified by

abdominal obesity status, which was defined as a waist circumference ≥ 102 cm for men and ≥ 88cm for women.[36]

Assessment of Behavioral Variables *Physical activity*, reported as total weekly activity energy expenditure, was assessed with The Stanford Physical Activity Recall[37,38]. The questionnaire is an interviewer-administered recall that classifies subject activities by intensity (moderate, hard, and very hard) and then uses a single metabolic equivalent to estimate the energy expenditure in each intensity category. To improve the accuracy of the resulting estimates of energy expenditure, the Ainsworth Compendium for Physical Activities[39] was used to estimate the energy expenditure for each individual activity instead of assuming that one metabolic equivalent is specific enough for all activities within each intensity category.[40] The Block 95 Food Frequency Questionnaire was used to assess *dietary behavior*. This self-administered food questionnaire determines eating patterns, nutrient intake, energy intake and has been validated with multiple diet record methods.[41] To quantify the psychosocial factor of *depression*, subjects were given the self-report, Center for Epidemiologic Studies Depression Scale, shown to be a reliable and valid tool for quantifying clinical symptoms of depression.[42] An index to quantify feelings of *hostility* was obtained for each patient through the self-report, Cook-Medley Questionnaire.[43] An extensive *medical history* questionnaire was used to assess gender, age, income, education, personal medical history, family history of CAD and diabetes, reproductive functions, smoking behavior, alcohol consumption, time since last event (either myocardial infarction or cardiac surgery procedure), and use of

blood pressure medications (beta-blockers and diuretics), which have a detrimental effect on insulin resistance[44,45].

Statistical Analysis To assess differences in health outcomes, health behaviors, and potential confounding variables in patients with (N=14) versus without (N=12) abdominal obesity, independent t-tests were used for all continuous variables, whereas contingency table-derived chi square tests were used for all categorical variables. A simple intercorrelation matrix was constructed to quantify the shared variance between each of the selected health behaviors. To avoid the interpretative difficulties associated with multiple hypothesis testing using highly intercorrelated independent variables, we reduced the number of behavioral predictors from 15 to 9 by excluding those behavioral variables with intercorrelations at or above r=0.70 (r^2=49%). Simple correlations were also used to quantify the shared variance between insulin $AUC_{0\text{-}120}$ and the following independent variables: body weight, selected health behaviors (physical activity, diet, depression, and hostility), and potential confounding variables (age, number of days since most recent CAD even/surgery/invasive diagnostic procedure, gender, attainment of college education, alcohol intake as a percentage of total daily caloric intake, no present or past history of smoking, use of diuretics, and use of β-blockers).

To determine whether the associations between insulin $AUC_{0\text{-}120}$ and body weight, selected health behaviors, and potential confounding variables differed between patients with versus those without abdominal obesity, multiple regression models were constructed rather than stratify the sample by abdominal obesity. Each multiple regression model predicted insulin $AUC_{0\text{-}120}$ from a specific independent variable of

interest, an abdominal obesity contrast (+1=presence, and –1=absence), and the specific independent variable of interest by abdominal obesity interaction term. The multiple regression models were then used to determine partial correlations between insulin $AUC_{0\text{-}120}$ and a) a specific independent variable of interest, and b) the interaction between a specific independent variable of interest and abdominal obesity after adjusting for the other two variables in the model.

RESULTS

Descriptive characteristics of the 26 patients are shown in Table 1. The patients with abdominal obesity (N=14) had a higher insulin response (Insulin AUC) to the oral glucose load ($p=0.02$), and weighed more ($p<0.001$) than the patients without abdominal obesity (N=12). Patients with abdominal obesity also reported significantly lower physical activity energy expenditures, whether expressed in absolute units of kilocalories (kcal) per day or in relative units of kcal/kg of body weight per day, than the patients without abdominal obesity ($p=0.017$ to 0.030). However, total energy intakes (kcal/d) did not differ between the two groups. By contrast, patients with abdominal obesity reported lower percentages of total fat ($p=0.041$) and saturated fat ($p=0.045$) intakes, and higher percentages of carbohydrate ($p=0.035$) and protein ($p<0.001$) intakes, than the patients without abdominal obesity. Patients with abdominal obesity also displayed nonsignificant trends toward higher depression scores ($p=0.092$) and lower percentages of alcohol intake ($p=0.068$), than the patients without abdominal obesity.

The intercorrelations among the health behaviors are shown in Table 2. With the exception of some of the dietary intake variables, most of the health behaviors were not *highly* intercorrelated ($r<0.70$). To eliminate the statistical redundancy and inflation in Type I error resulting from the highly intercorrelated dietary variables, we removed total energy, total fat, carbohydrate, fiber, grain, and fruit intakes from the subsequent hypothesis testing for dietary associations with insulin AUC. By contrast, we retained the specific dietary intakes of saturated fats and antioxidant vitamins for comparison to other studies.

Table 1. ***Descriptive Characteristics of 26 Non-Diabetic Patients (19 men, 7 women) with CAD Classified by Abdominal Obesity***[a]

Variable	*Non-Abd. Obese (n=12)*	*Abd. Obese (n=14)*	*T-test*
Health Outcomes	***Mean±SD***	***Mean±SD***	***P value***
Insulin AUC[b], $\mu U \cdot ml^{-1} \cdot min$	**8,024 ± 2656**	**14,190 ± 8421**	**0.020**
Waist Circumference, cm	**88.2 ± 9.5**	**109.4 ± 8.1**	**<0.001**
Weight, kg	**72.1 ± 11.2**	**91.0 ± 10.6**	**<0.001**
Health Behaviors			
Physical Activity Energy Expenditure, kcal/d	**495 ± 434**	**163 ± 228**	**0.030**
Energy Intake, kcal/d	2070 ± 708	1790 ± 614	0.296
Fat, % of energy/d	**37.0 ± 6.1**	**31.9 ± 5.6**	**0.041**
Saturated Fat, % of energy/d	**11.9 ± 2.9**	**9.8 ± 1.9**	**0.045**
Protein, % of energy/d	**15.8 ± 2.2**	**19.1 ± 1.9**	**<0.001**
Carbohydrates, % of energy/d	**43.5 ± 4.9**	**48.4 ± 6.3**	**0.035**
Total Dietary Fiber, g/d	15.8 ± 5.8	15.5 ± 5.9	0.878
Fruit Intake, N of servings/d	1.5 ± 0.6	1.6 ± 1.1	0.800
Vegetable Intake, N of servings/d	3.7 ± 1.9	3.1 ± 1.4	0.401
Grain Intake, N of servings/d	5.8 ± 1.7	5.8 ± 2.4	1.000
Dietary Vitamin E, α-TE/d[c]	10.8 ± 4.9	8.5 ± 2.6	0.155
Dietary Vitamin C, mg/d	114.5 ± 45.7	107.0 ± 37.8	0.656
Dietary Vitamin A, IU/d	9,244.1 ± 6688.1	9,937.4 ± 4347.1	0.762
Depression Score[d]	4.8 ± 7.0	10.3 ± 8.9	0.092
Hostility Index[e]	11.1 ± 6.2	14.8 ± 8.0	0.224
Potential Confounders			
Age, years	63.5 ± 9.0	67.5 ± 9.2	0.274
Days since event/diagnosis	49 ± 55	272 ± 599	0.188
Female Gender[f]	4 (57%)	3 (43%)	0.495
College Education[f]	9 (47%)	10 (53%)	0.838
Alcohol, % of energy/d	5.3 ± 6.6	1.3 ± 1.9	0.068
Non-Smoker, past and present[f]	3 (38%)	5 (62%)	0.555
Use of Diuretics[f]	2 (33%)	4 (67%)	0.473
Use of β-Blockers[f]	8 (62%)	5 (38%)	0.116

[a] Abdominally Obese: Waist circumference ≥ 102cm Men, Waist circumference ≥ 88cm Women.[36]

[b] AUC = Area under the oral glucose loading curve.

[c] Alpha tocopherol units (vitamin E activity of 1mg α-tocopherol).

[d] Summary score from the Center for Epidemiologic Studies Questionnaire[42].

[e] Summary score from the Cook-Medley Scale[43].

[f] Reported as within group N (%), p value for contingency table-derived χ^2.

Table 2. ***Intercorrelation Matrix (Pearson r values) between the Health Behavior Variables in 26 Non-Diabetic Patients (19 men, 7 women) with CAD***

	EEx	EIn	Fat	SFat	Prot	Carb	Fib	Frui	Vegt	Grai	VitE	VitC	VitA	DS	HI
Energy Expenditure (EEx), kcal/kg•d	-														
Energy Intake (EIn), kcal/d	0.19	-													
Fat (Fat), % of energy/d	0.00	0.27	-												
Saturated Fat (SFat), % of energy/d	0.13	0.36	**0.81**†	-											
Protein (Prot), % of energy/d	**-0.40***	-0.10	**-0.53**†	**-0.60**†	-										
Carbohydrates (Carb), % of energy/d	-0.07	-0.37	**-0.78**†	**-0.80**†	**0.40***	-									
Total Dietary Fiber (Fib), g/d	0.07	**0.65**†	-0.34	-0.30	0.32	0.35	-								
Fruit Intake (Frui), N of servings/d	0.07	0.23	-0.29	-0.14	0.17	**0.45***	**0.62**†	-							
Vegetable Intake (Vegt), N of servings/d	0.25	0.39	-0.26	-0.14	0.29	0.07	**0.65**†	0.33	-						
Grain Intake (Grai), N of servings/d	-0.05	**0.82**†	0.24	0.17	-0.03	-0.25	**0.52**†	0.07	0.06	-					
Dietary Vitamin E (VitE), α-TE/d	0.15	**0.83**†	**0.50***	0.39	-0.17	-0.37	**0.49***	0.20	0.28	**0.65**†	-				
Dietary Vitamin C (VitC), mg/d	0.21	**0.44***	-0.29	-0.09	0.17	0.26	**0.70**†	**0.81**†	**0.59**†	0.22	0.37	-			
Dietary Vitamin A (VitA), IU/d	0.05	**0.51**†	**-0.43***	-0.33	**0.43***	0.32	**0.73**†	0.34	**0.64**†	0.34	0.28	**0.59**†	-		
Depression Score (DS)	-0.32	-0.21	0.11	0.11	0.05	0.02	-0.34	-0.22	**-0.48***	-0.08	-0.18	-0.33	-0.12	-	
Hostility Index (HI)	-0.17	-0.12	-0.23	-0.30	0.30	0.12	0.02	0.07	0.08	-0.08	-0.19	-0.11	0.08	0.07	-

* $p<0.05$, † $p<0.01$

In the entire population of 26 non-diabetic patients with CAD, greater degrees of insulin resistance (or higher insulin AUC) were associated with heavier body weights ($p=0.002$), lower dietary vegetable intakes ($p=0.023$), lower dietary (i.e., from foods rather than supplements) vitamin C ($p=0.027$) and vitamin E ($p=0.044$) intakes, and higher depression scores ($p=0.016$) (Table 3). After adjusting for abdominal obesity status and the specific independent variable of interest x abdominal obesity interaction term, higher insulin AUC remained associated with heavier body weights ($p=0.034$), lower dietary vegetable intakes ($p=0.011$), and lower dietary vitamin C ($p=0.019$) and vitamin E ($p=0.007$) intakes. Higher insulin AUC was not significantly associated with dietary vitamin A intake ($p=0.122$) before statistical adjustment. However, after adjusting for abdominal obesity and for the vitamin A intake x abdominal obesity interaction, higher insulin AUC was associated with lower dietary vitamin A intakes ($p=0.013$). Insulin AUC was not associated with any of the potential confounders either before or after adjusting for abdominal obesity ($p=0.172$ to 0.937).

Insulin AUC was also independently associated with the interactions of body weight (Figure 1), dietary vegetable intake (Figure 2), and dietary vitamin E intake (Figure 3) with abdominal obesity. The interactive associations suggest that the associations of higher insulin AUC with heavier body weights, lower vegetable intakes, and lower dietary vitamin E intakes are present in patients with abdominal obesity ($p=0.039$) but not in those patients without abdominal obesity.

Table 3. ***Correlation Coefficients (r) Between Insulin AUC, Selected Health Behaviors, and Potential Confounders in 26 Non-Diabetic Patients (19 men, 7 women) with CAD***

	Unadjusted		*Adjusted*[a]	
Independent Variable ***Health Outcome***	***r***	***P value***	***Partial r***	***P value***
Weight, kg	**0.57**	**0.002**	**0.43**	**0.034**
Health Behaviors				
Physical Activity Energy Expenditure, kcal/d	-0.31	0.122	-0.19	0.367
Saturated Fat, % of energy/d	0.01	0.995	0.24	0.268
Protein, % of energy/d	0.07	0.753	-0.34	0.102
Vegetable Intake, N of servings/d	**-0.45**	**0.023**	**-0.51**	**0.011**
Dietary Vitamin E, α-TE/d	**-0.40**	**0.044**	**-0.54**	**0.007**
Dietary Vitamin C, mg/d	**-0.43**	**0.027**	**-0.48**	**0.019**
Dietary Vitamin A, IU/d	-0.31	0.122	**-0.50**	**0.013**
Depression Score	**0.47**	**0.016**	0.31	0.147
Hostility Index	-0.10	0.622	-0.17	0.432
Potential Confounders				
Age, years	0.08	0.685	-0.02	0.937
Days since event/diagnosis	0.11	0.601	0.08	0.708
Gender	0.04	0.838	0.13	0.557
College Education	-0.15	0.467	0.29	0.172
Alcohol, % of energy/d	-0.07	0.722	0.25	0.246
Non-Smoker, past and present	-0.22	0.283	-0.11	0.605
Use of Diuretics	0.15	0.462	0.09	0.672
Use of β-Blockers	-0.23	0.263	-0.09	0.677

[a] Adjusted for abdominal obesity status and the specific independent variable of interest x abdominal obesity interaction term.

Figure 1. ***Association of Insulin Area Under the Curve (AUC) with the Interaction Between Body Weight and Abdominal Obesity in 26 Non-Diabetic Patients with CAD (r=0.45, p=0.027)***

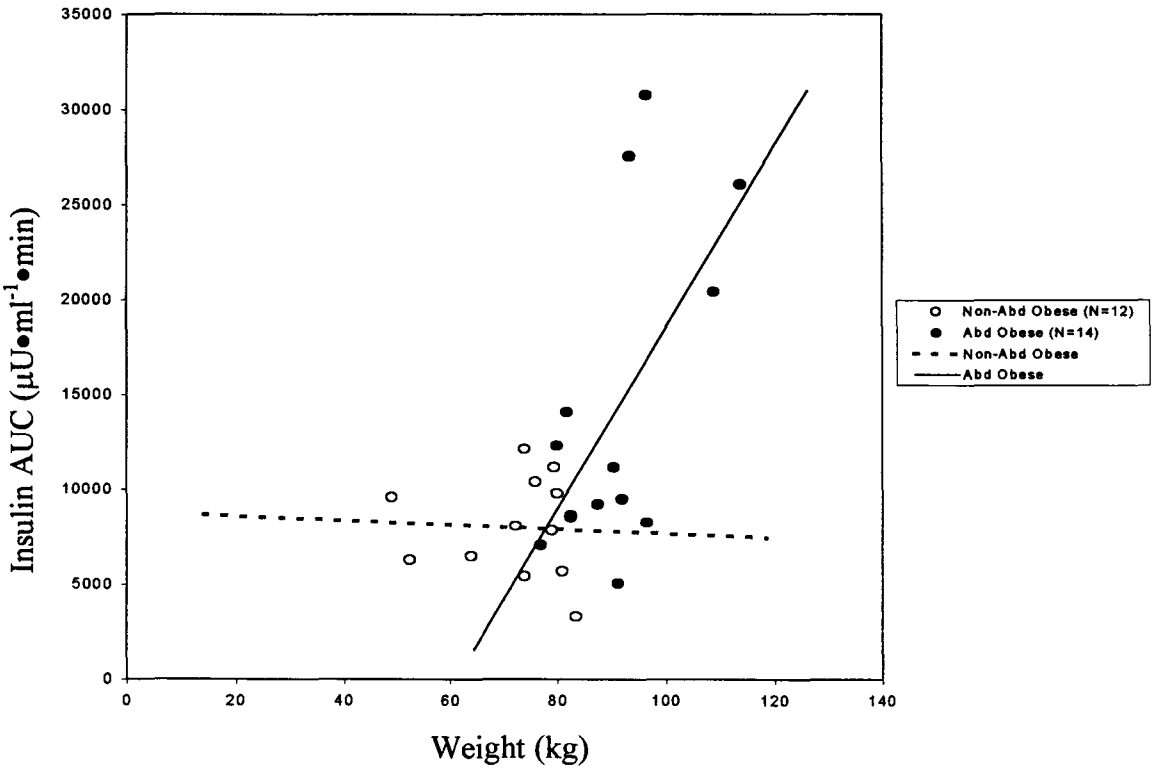


Figure 2. ***Association of Insulin Area Under the Curve (AUC) with the Interaction Between Vegetable Intake and Abdominal Obesity in 26 Non-Diabetic Patients with CAD (r=-0.42, p=0.039)***

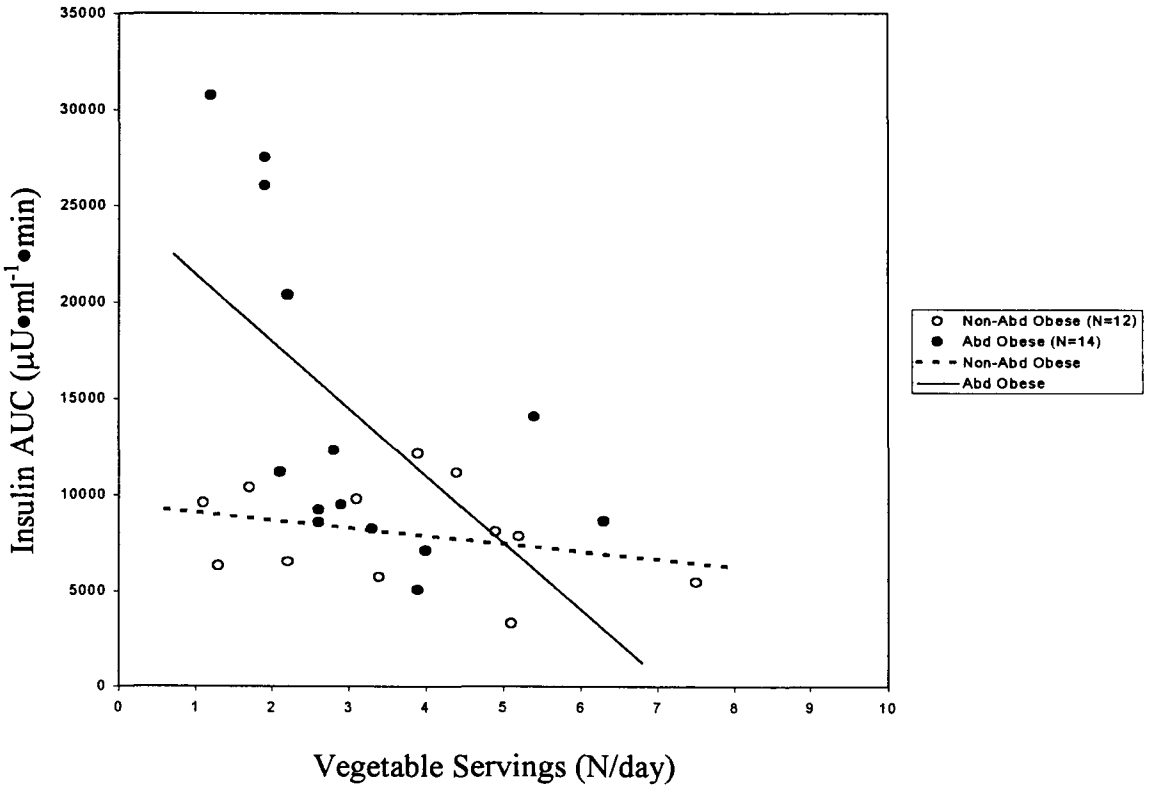
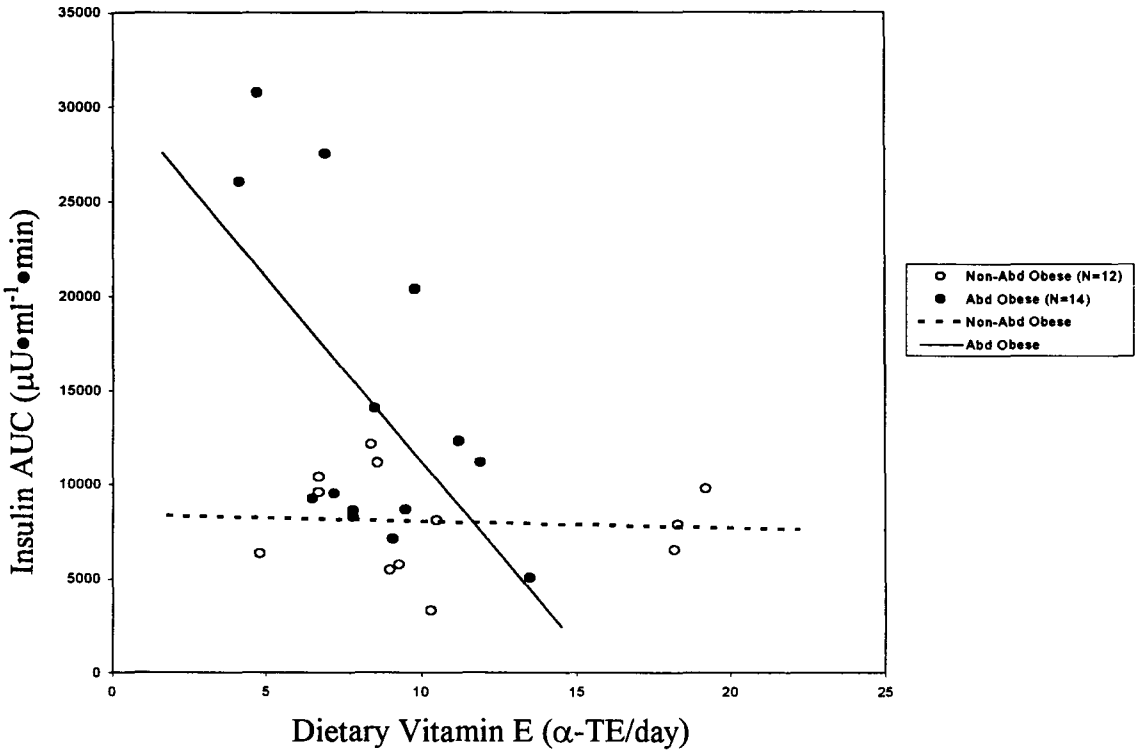


Figure 3. ***Association of Insulin Area Under the Curve (AUC) with the Interaction Between Dietary Vitamin E Intake and Abdominal Obesity in 26 Non-Diabetic Patients with CAD (r=-0.52, p=0.009)***



DISCUSSION

The key finding of this descriptive, cross-sectional study is that in a non-diabetic CAD patient population entering cardiac rehabilitation, altered behaviors such as lower physical activity levels, lower dietary fruit, vegetable, and vitamin E intakes, and higher self-reported depression are all associated with increased abdominal obesity and/or greater insulin resistance. Although the association of abdominal obesity and insulin resistance is documented in CAD patients[12,14], the combined reporting of the relationships between the selected health behaviors, abdominal obesity, and insulin resistance is unique to the present study.

Current risk reduction strategies recommended by the American Heart Association (AHA) for secondary prevention of CAD focus on behavior changes and drug therapy for lipid, platelet, and blood pressure management[22], which are all consequences of metabolic disturbances associated with CAD. The pre-diabetic state of insulin resistance, an underlying cause of metabolic disturbances associated with CAD[7], is generally present in recently diagnosed CAD patients[1], and is associated with severity of coronary disease in CAD patients[2]. The present associations suggest that in addition to the current AHA guidelines[22], assessing abdominal obesity, level of depression, overall daily energy expenditure, and fruit, vegetable, and dietary vitamin E intakes, in addition to, fat, saturated fat and cholesterol intakes may be optimal first steps for managing insulin resistance in patients with CAD.

The cross-sectional associations found in the present study support the use of the recently developed clinical cut-off values for waist circumference (≥102cm for men,

≥88cm for women)[36] for detecting elevated CAD risk. Abdominal obesity is an important link between insulin resistance, diabetes, and CAD.[24,46-49] Increased abdominal obesity is associated with increased lipolysis of fat cells in the abdominal region, thus an increased release of free fatty acids into the portal circulation[13], which is linked to increased plasma glucose and insulin levels particularly in insulin resistant individuals[50,51]. The circulating free fatty acids may promote progression of atherosclerosis[52] and thus worsening of CAD risk.

Although body mass index (BMI) is frequently associated with altered metabolic profiles and CAD risk[16,53-55], the waist-to-hip ratio was the best predictor of elevated fasting insulin levels in female coronary patients[14]. However, Katzel et al[49] found that decreases in waist circumference were correlated with improved glucose metabolism but changes in the waist-to-hip ratio were not. Moreover, our parent study reported cardiac rehabilitation-related reductions in both the hip and the waist circumferences.[31] Thus, monitoring treatment-related changes in the waist-to-hip ratio may be misleading.

Patients with and without abdominal obesity had elevated insulin levels, but the association between body weight and insulin resistance was stronger in those with abdominal obesity. Lavie and Milani[23] found that in obese (BMI defined) CAD patients, weight loss through cardiac rehabilitation was associated with greater improvements in blood lipid profiles than obese CAD patients who did not lose weight. If Lavie and Milani had measured regional adiposity they may have found that the importance of weight loss on improving the metabolic profile of CAD patients is due to a concomitant reduction in abdominal obesity or that reductions in waist circumferences can occur independently of reductions in body weight[31]. For instance, greater improvements in

insulin sensitivity after weight loss were associated with reductions in computed tomography (CT)-derived estimates of visceral adiposity but not with reductions in dual energy X-ray absorptiometry (DEXA)-derived estimates of fat mass.[56]

In the present study, the association of physical activity and insulin AUC did not reach statistical significance (r=-0.31, p=0.122). However, lower physical activity energy expenditures were associated with larger waist circumferences (r=-0.49, p=0.011), and coronary patients with abdominal obesity were more insulin resistant (p=0.020) than those without abdominal obesity. Thus, our data do not support the recent suggestion that the assessment of self-reported health behaviors may be of limited value in coronary patients.[13] By contrast, our data suggest that phase I cardiac rehabilitation and/or "usual care" following surgical treatment or diagnosis may not succeed in convincing patients with abdominal obesity to increase physical activity levels sufficiently for creating a more negative energy balance, despite the possible reduction in dietary fat and saturated fat intakes. Moreover, patients with larger waist-to-hip ratios may expend fewer calories during supervised exercise classes.[13] Thus, cardiac rehabilitation programs should strongly emphasize, monitor, and reinforce the importance of increasing the frequency and duration of daily and weekly bouts of physical activity outside of the supervised exercise classes to improve the management of abdominal obesity and insulin resistance in coronary patients.

In accordance with AHA Step II Diet recommendations[57], coronary patients in the present study with abdominal obesity entered cardiac rehabilitation reporting lower fat and saturated fat intakes, accompanied by higher carbohydrate and protein intakes, than patients without abdominal obesity. However, the lack of associations between fat,

saturated fat, carbohydrate, and protein intakes and insulin AUC values indicates that, in patients with abdominal obesity, lowered fat and saturated fat intakes may not be associated with improved insulin resistance in the absence of increased intakes of fruits, vegetables, and dietary sources of vitamin E.

Consistent with the apparent CAD risk-reducing effects of a diet high in vegetable fiber intake[58], we found that patients reporting higher intakes of vegetable servings per day had lower insulin resistance and that the inverse association between vegetable intake and insulin resistance was strongest in patients with abdominal obesity. These results indicate that the AHA Diet recommendations, which currently provide a nonspecific guideline of 5 or more vegetables, fruits or fruit juice per day[57], should consider including more specific guidelines regarding vegetable intakes, apart from fruit and fruit juice intakes.

Although we found that lower dietary vitamin E intakes (mean=9.6 mg/d) were associated with greater degrees of insulin resistance, particularly in patients with abdominal obesity, we caution against the interpretation of a beneficial antioxidant effect of vitamin E per se. By contrast to our assessment of *food* sources of vitamin E, *supplemental* vitamin E intake was associated with higher insulin AUC values ($r=0.55$, $p=0.004$) in our coronary patients. The paradoxical association between supplemental vitamin E intake and insulin AUC values can be explained by the finding that higher supplemental vitamin E intakes were also associated with larger waist circumferences ($r=0.55$, $p=0.003$). Thus, the present sample of coronary patients with abdominal obesity are reporting higher supplemental vitamin E intakes and are more insulin resistant than the patients without abdominal obesity. In addition, higher levels of dietary vitamin E

were associated with total dietary fiber ($r=0.49$, $p=0.012$) and grain intakes ($r=0.65$, $p<0.001$). This suggests that dietary vitamin E may be a marker of healthy dietary patterns in coronary patients.[59] However, the strong associations between dietary vitamin E intakes and energy intake ($r=0.83$, $p<0.001$), and dietary vitamin E intakes and total fat intakes ($r=0.50$, $p=0.010$), indicate that a more specific dietary assessment of the food sources of vitamin E may be needed.

The present finding that higher dietary intakes of vitamins A and C were correlated with lower insulin AUC values should also be interpreted with caution. Higher vitamin A intakes were correlated with higher vegetable intakes, and higher vitamin C intakes were correlated with higher fruit and vegetable intakes (Table 2). Moreover, supplemental vitamin A and vitamin C intakes were not associated with insulin AUC either before or after adjustment for abdominal obesity ($r=-0.01$ to $r=0.16$, $p\geq0.448$). Our data provide preliminary evidence that diets rich in antioxidant vitamins, rather than supplements, may help to manage insulin resistance in patients with CAD. Thus, future experimental studies should consider whether the use of more specific dietary goals for fruit, vegetable, and food sources of vitamin E is better than a standard AHA Step II Diet[57] for managing insulin resistance in coronary patients without diabetes.

Severe depression is associated with greater degrees of insulin resistance.[18] In the present study, more moderate self-reported symptoms of depression were associated with greater degrees of insulin resistance. It has been shown that depression is fairly common (18-23%) after major CAD events but is frequently unrecognized by the primary cardiologist.[15,60] This has important implications for cardiac rehabilitation because psychological depression assessed during the hospital stay is a strong predictor of

rehospitalizations in CAD patients.[61] However, the extent to which higher levels of depression result from a prior CAD event, surgery, or diagnosis and the extent to which depression may contribute to the development and progression of abdominal obesity and insulin resistance is not yet known. In the present study, depression and hostility were not related with each other ($r=0.07$, $p=0.742$). We were also unable to detect an association between self-reported hostility and insulin resistance. Thus, our data suggest that self-reported symptoms of depression may be a stronger psychosocial determinant of insulin resistance than hostility in coronary patients. However, future studies should examine whether social isolation and anxiety may be additional psychosocial determinants of insulin resistance in non-diabetic coronary patients.

Several study limitations are noteworthy. The small sample size may limit the ability of the study to detect associations in a similar population and the select population may indicate that the results are not generalizable to coronary patients with diabetes or to healthier individuals with no known CAD. Interviewer and self-report questionnaires that may be subject to interviewer and reporting bias were used to assess the health behaviors. Thus, the magnitude of the reported associations between insulin resistance and the health behaviors may be underestimated. In addition, the physical activity, dietary, and psychosocial patterns reported herein may represent relatively recent changes in behavior resulting from a prior CAD event, surgery, or diagnosis rather than lifelong habits that may have contributed to the development of insulin resistance and/or abdominal obesity.

In summary, patients with abdominal obesity may be more insulin resistant than patients without abdominal obesity due to their heavier body weights, lower physical

activity levels, and inadequate dietary reductions in fat intake that do not compensate for their lower physical activity levels and that are not replaced by higher intakes of fruits, vegetables and food sources of vitamin E. Assessment and identification of individuals who are at a higher risk for insulin resistance, diabetes, and worsening CAD is essential for developing effective cardiac rehabilitation programs with low incidence rates of recurrent CAD.[20] Lower physical activity levels, lower dietary fruit, vegetable, and vitamin E intakes, and greater symptoms of depression may be important behaviors to identify for better managing insulin resistance and abdominal obesity in non-diabetic coronary patients.

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APPENDICES

Appendix A

BACKGROUND LITERATURE REVIEW

The Need for Effective Cardiac Rehabilitation Programs

Coronary artery disease (CAD) is the leading killer of Americans, and current estimates indicate that an American will suffer a coronary event every 29 seconds.[62] Due to advances in medical technology, the death rate from CAD has been declining since its peak in 1963.[63] The prevalence of the disease is gradually increasing, in part, due to increased survival of people suffering coronary events. Individuals who have survived an acute heart attack have a chance of illness or death that is 2-9 times higher than the general population, and in 1999, there will be an estimated 450,000 recurrent attacks.[62] The increased survival of first heart attacks has elevated CAD to the leading cause of premature, and permanent disability in the U.S. labor force.[62] The cost of acute and recurrent coronary events combined with costs of ongoing care for survivors is staggering with the estimate for 1999 at $100 billion.[62]

The need for effective cardiac rehabilitation (secondary prevention) programs is greater than ever, and indications are that the need will continue to rise. CAD patients need effective secondary prevention programs to save and increase the quality of their life, as well as, to reduce the costs associated with the disease progression. A recurrent event will most likely involve costly medical treatments that are highly invasive and thus, potentially high risk. Common invasive cardiology procedures include cardiac catheterization, percutaneous transluminal coronary angioplasty (PTCA), stents, and coronary artery bypass surgery/graft (CABG). Currently, the average costs are $10,000

per catheterization, $20,000 per PTCA, and $45,000 per CABG.[62] To limit acute events, disease progression, and to contain the considerable costs associated with disease management, secondary prevention programs designed for maximal effectiveness are needed.

The target population for secondary prevention programs used to include only people who had suffered an acute coronary event, such as a myocardial infarction; however, with the advent of advanced medical equipment, an individual can be diagnosed with coronary arteriosclerosis and thus CAD without an acute event.[64] Evidence of the effectiveness of secondary prevention programs to extend survival, increase the quality of life, and decrease subsequent myocardial infarctions and medical interventions is documented in various studies.[11,19,20,65,66] Specifically, Ornish et al found that changes in lifestyle were correlated with a slowed, halted, or reversed progression of atherosclerosis.[65] In support, Haskell et al found that a multi-factor risk reduction program reduced not only atherosclerosis, but also hospitalizations for cardiac events in their CAD population.[20] Secondary prevention programs are varied and usually include behavior modification interventions in the areas of diet, exercise, and psychosocial support and/or medication interventions (i.e. drug therapy). The secondary preventive treatments recommended by the American Heart Association (AHA) are outlined in a scientific statement released in 1995 which advocates intensive efforts toward risk reduction strategies.[22] These strategies include smoking cessation, dietary modification, physical activity, weight management, and drug therapy to reduce LDL-C, control blood pressure, manage arrhythmias, reduce platelet aggregation, and reduce blood coagulation.

While the AHA strategies are comprehensive with regard to coronary patient management, revision of recommendations may need to occur, given more current research. For example, HDL-C and TG should be considered as treatment outcomes, rather than exclusively focusing on total LDL-C, for lipid and lipoprotein management.[16,67-71] Treatments should also consider targeting reduction of abdominal obesity[24,47,48,72,73], rather than general weight management guidelines. Lowered HDL-C, increased TG, and abdominal obesity can be the metabolic consequences of insulin resistance that is not being effectively managed. In addition, more careful recommendations about blood pressure medications that are not detrimental to insulin action are needed, as certain beta-blockers and diuretics have been shown to contribute to insulin resistance.[44,45] The current AHA recommendations for physical activity and diet may not be designed to address insulin resistance, and there are currently no psychosocial recommendations.[22]

The proposed study will provide insight into an alternate method of approaching CAD patient management. Instead of trying to assess and treat each risk factor consequence separately, the focus is shifted to reducing the underlying neuroendocrine disorder, insulin resistance, that is creating the metabolic risk factor consequences. By learning how to treat insulin resistance, we hope to improve the efficiency and effectiveness of secondary prevention programs. The proposed study will assess which behaviors underlie the insulin resistant metabolic syndrome (IRMS), by their association with insulin resistance, in CAD patients.

Rationale for a New Treatment Focus on Insulin Resistance

The IRMS, also referred to as Syndrome X, is an important and common metabolic disorder which is linked to an increased risk of CAD through vascular inflammation or damage, atherogenesis, atherosclerotic progression, impaired fibrin clot breakdown, and an increased chance of developing diabetes mellitus.[7] The metabolic abnormality that has been shown to tie all the above processes together with CAD risk is insulin resistance.[2,3,7,51,74,75] Each process along with the underlying biological mechanisms for each will be considered in turn, in relation to their connection with insulin resistance and CAD.

Inflammation and/or vascular damage are precursors to atherogeneis, which is the formation and accumulation of lipid-containing plaques on the innermost layer of the artery wall. Atherogenesis is the initial process that ultimately results in arterial lesions, plaque formation, and plaque progression[64], and it involves an increase in the arterial wall intima-media thickness. Greater degrees of insulin resistance are strongly associated with larger arterial wall intima-media thicknesses[3], which suggests that the prevention or reversal of insulin resistance may be important for preventing new arterial lesions and plaques.

After the initial atherogenesis, atherosclerotic progression generally ensues, with plaques becoming larger and more fibrous through endothelial cell, monocyte/macrophage, smooth muscle cell, platelet, and chemical messenger interactions.[64] The atherosclerotic process is complex and multi-dimensional involving many of the documented markers of the IRMS, including elevated fasting insulin, impaired fasting glucose, impaired glucose tolerance, low high-density lipoprotein

cholesterol (HDL-C), high triglycerides (TG), and an increased abdominal obesity.[5,7,74,76] Each of the metabolic markers of the IRMS, and thus insulin resistance as the underlying metabolic disorder, has been associated with an increased risk of CAD, and in one study, the subjects with CAD who possessed a greater number of the markers had more atherosclerotic progression than those with fewer.[5]

Elevated fasting insulin or hyperinsulinemia is a compensatory mechanism to maintain normal plasma glucose levels in the presence of peripheral tissue insulin resistance.[7] This increased level of circulating insulin is associated with an adverse lipoprotein profile called dyslipidemia, which includes low HDL-C and high TG levels[7], and an increased risk of CAD[77-79]. However, Korpilahti et al[5] and Suzuki et al[3] found that a measure of insulin resistance, a reduced insulin sensitivity index, was more highly correlated with atherosclerotic progression than fasting insulin levels. In addition, Bressler et al[2] reported that the magnitude of insulin resistance as assessed by insulin responses to an oral glucose load, not hyperinsulinemia, was positively correlated with severity of CAD. Thus, the proposed study will quantify insulin resistance as lower levels of an insulin sensitivity index. The insulin sensitivity index, in turn, estimates peripheral tissue sensitivity to insulin over 2-hour oral glucose tolerance test from the amount of the oral glucose load and from the endogenous glucose and insulin responses to the oral glucose load.[80]

Impaired fasting glucose and impaired glucose tolerance are altered in response to peripheral tissue insulin resistance. Blood glucose level is the physiological stimulus of insulin secretion by the pancreas and thus the levels of insulin and glucose are metabolically linked. Eschwège et al.[81] performed a meta-analysis that demonstrated the

connection between insulin and glucose, concluding that hyperglycemia (elevated fasting glucose) alone is not an independent risk factor for CAD. Although the American Diabetes Association (ADA) diagnostic criteria for diabetes mellitus is fasting plasma glucose level, the ADA Committee Report acknowledges that impaired fasting glucose and glucose tolerance may not be directly involved in the pathology of CAD but are CAD risk factors by their association to the IRMS[32]. Due to this, and the fact that the study excludes those individuals with diabetes, the proposed study will use a lowered insulin sensitivity index, which takes into account blood glucose levels, to determine insulin resistance magnitude.

The atherogenic potential of the dyslipidemic state is due to the ability of elevated levels of TG to induce lipid accumulation in macrophages, creating foam cells, the cell type associated with increased atherosclerotic lesions, and to reduced reverse cholesterol transport from low HDL-C levels.[64,66] This dyslipidemic state is an integral part of the IRMS, shown to correlate with CAD risk[67,68], and with atherosclerotic progression[5]. In addition, high circulating TG may have a detrimental effect on insulin induced glucose disposal.[82] While improvements in insulin resistance are predicted to improve the dyslipidemic profile in persons with CAD, evaluation of this hypothesis is addressed in the parent study, which assessed cardiac rehabilitation intervention-related changes in markers of the IRMS.

The atherosclerotic progression results in an increasing plaque formation on the arterial wall that is subject to injury induced by a stressor. High blood pressure resulting in shear stress on the arterial wall is common. This stress on atherosclerotic plaque triggers the thrombotic enzyme cascade, in which activated fibrinogen molecules attach

to one another to form a fibrin clot. Impaired fibrin clot breakdown is another consequence of the IRMS that links the syndrome to an increased CAD risk. Elevated levels of plasma fibrinogen have been related to coronary atherosclerosis and an elevated risk for CAD.[71] The breakdown of fibrin clots or fibrinolysis is essential to reduce the risk of an acute cardiac event, most frequently precipitated by a thrombus or clot that occludes arterial blood supply to a segment of the heart. Tissue plasminogen activator (tPA) activates plasminogen to plasmin which dissolves fibrin clots. Inhibiting tPA is plasminogen activator inhibitor-1 (PAI-1), which can then lead to an accumulation of extracellular matrix, accelerating coronary atherosclerosis.[71] Accordingly, elevated levels of PAI-1, are associated with an increased risk of CAD.[64] PAI-1 is secreted from adipose tissue, and upregulated in obesity due to mediating factors (e.g., TNF-α, insulin, and proinsulin) that enhance its secretion.[25,26,71,83-85] Evidence exists for a relationship between insulin resistance and PAI-1 levels[7], particularly due to the close connection with PAI-1 and consequences of insulin resistance (increased fasting insulin, TG, and abdominal obesity)[26,86]. An excess of adipose tissue, which in turn secretes PAI-1 in excess, appears to be an important mechanistic contributor to the impaired insulin resistance that increases the risk for CAD events.

Lastly, insulin resistance and the subsequent development of hyperinsulinemia are precursors to NIDDM, which is a risk factor for CAD and other metabolic disorders.[27,32,54,68] If the insulin resistant state can be detected and improved before full-blown diabetes develops, a number of negative consequences associated with NIDDM can be avoided. First of all, diabetes, either NIDDM or insulin-dependent diabetes (IDDM), is much less manageable than insulin resistance, and treatment options

frequently include expensive drug therapy.[32] Subsequently, a decrease in quality of life may occur with diabetes management, not only due to medication and financial concerns but also because the consequences of diabetes include blindness, kidney disease, nerve disease and amputations.[87] The fact that persons with diabetes are 2-4 times more likely to have heart disease or suffer a stroke, contributes, along with the above complications, to the $92 billion annual cost (IDDM and NIDDM) of health care, treatment, and lost productivity associated with the disease.[87]

Management, control, and possibly reversal of the IRMS, as indicated, may reduce vascular damage and atherogenesis, slow atherosclerotic progression, and improve fibrin clot breakdown. This can be an effective way to reduce morbidity and mortality from coronary causes in patients with coronary artery disease. In order to efficiently address the IRMS, there is a need to assess common links within the above mechanisms, insulin resistance and abdominal obesity. Insulin resistance appears to be the underlying metabolic disorder that if improved can have a positive effect on all the other mechanisms involved.[7] Abdominal obesity has been associated with increased risk of CAD through an association to insulin resistance and the related metabolic disturbances associated with the IRMS.[24,47,48,72,88] The connection of abdominal obesity to the IRMS may also involve the associated secretions and metabolic consequences of TNFα and PAI-1.

Tissue injury or vascular damage due to infection, myocardial infarction, or hypertension will result in the release of proinflammatory cytokines, such as, TNFα.[89,90] TNFα is secreted from adipose tissue and is important in modulating lipid metabolism.[91] Specifically, obesity related increases in TNFα has been shown to stimulate PAI-1

biosynthesis from adipose tissue[83,84,91,92], promote reactive oxygen intermediates, such as, superoxide and hydrogen peroxide[92], increase plasma free fatty acid (FFA) levels by inhibition of lipoprotein lipase (LPL) activity[91], and impair the insulin receptor signaling pathway, subsequently inducing insulin resistance[91-93]. Thus, studies have shown that plasma levels of TNFα are elevated in persons with CAD[89], diabetes[94], and obesity[95]. Reduction of plasma TNFα levels and an increase in glucose response to insulin was reported in obese noninsulin-dependent (NIDDM) diabetics after a 4-week program of diet and exercise that resulted in an overall reduction in abdominal obesity.[94] This study is an indication that insulin resistance is improved by behavioral modifications such as diet and exercise that result in a reduction of abdominal obesity; and that these improvements may be mediated through reductions in plasma TNFα levels.

Determining whether behavior related reductions in insulin resistance and abdominal obesity are mechanistically co-dependent or coincidental is important for designing CAD prevention programs. In one study abdominal obesity, in obese subjects, was not correlated with the exercise training-induced improvements in responsiveness of adipose tissue LPL to insulin[96], indicating that the exercise training improvements in IRMS were independent of any change in body composition or abdominal obesity. However, cardiorespiratory fitness level has also been shown to be inversely related to waist circumference.[54] Interestingly, Katzel et al[49] found that a decrease in fat mass, but not an increase in maximal oxygen consumption (VO_2 max), was an independent predictor of changes in HDL-C and TG. Thus, the proposed study will assess abdominal obesity (as measured by the waist circumference[97]) to determine whether the association

between the behavioral risk factors (physical inactivity, dietary considerations, and psychosocial indexes) and insulin resistance is independent of abdominal obesity.

Potential Impact of Lifestyle Modification

Secondary prevention programs are designed to help individuals modify their lifestyle such that their risk of a coronary event or progression of disease is reduced. Addressing the behavioral lifestyle components that are most highly associated with insulin resistance will help to refine the management of insulin resistance, thereby reducing the risk for future events and surgical treatments in patients with CAD.

Physical Activity

Increased physical activity and improved cardiorespiratory fitness have been shown to reduce risk of CAD.[76,98-100] It is a controversial issue as to whether fitness gains are necessary for reducing insulin resistance and CAD risk. Low cardiorespiratory fitness levels are associated with increased insulin resistance as compared to moderate and high cardiorespiratory fitness levels[54], while, improved levels of cardiorespiratory fitness are associated with enhanced insulin action[27,96,101]. A low physical activity level has been shown to be associated with insulin resistance markers, such as, hyperinsulinemia after a glucose load[16] and reduced insulin sensitivity[102]. Després and Lamarche have suggested that improving health-related fitness (physical activity level), as opposed to performance-related fitness(cardiorespiratory fitness level), will have clinical implications in the prevention of CAD and diabetes.[99] During an acute bout of exercise, repeated skeletal muscle contractions have an insulin-like effect on muscle glucose transport, decreasing insulin resistance.[27] Regular physical activity is thought to

improve hepatic insulin sensitivity, decrease abdominal and whole body adiposity, increase skeletal muscle mass and blood flow, and change the quality of muscle fibers (fiber type, increased capillary density, and biochemical changes), resulting in improved control of blood glucose and diminished peripheral tissue resistance to insulin.[27] Thus, the proposed study aims to provide information about the physical activity level of patients with CAD prior to cardiac rehabilitation, and how this level is associated with insulin resistance. This approach may provide preliminary information about the dose of physical activity required to induce reductions in insulin resistance and thus CAD risk. The measure of insulin resistance (insulin sensitivity) will be associated with physical activity energy expenditure so that an estimate of the magnitude of improvement in insulin resistance per unit of energy expenditure can be calculated. Thus, the amount of increase in physical activity needed to achieve a clinically meaningful reduction in insulin resistance can be determined and ultimately used to set realistic physical activity goals for treating patients with CAD.

Dietary Considerations

Dietary components such as higher % total fat and saturated fat intakes are considered risk factors of CAD. By contrast, higher levels of CHO and fiber intakes may have a protective effect for CAD. The mechanism by which dietary changes induce changes in CAD risk factors or insulin resistance is not entirely clear. The primary undetermined factor is whether the endocrine and metabolic changes that accompany specific dietary behaviors are the result of a direct mechanism, or whether they occur indirectly through alterations in adipose tissue.[103,104] In support of a direct mechanism, increased levels of total and saturated fat in the diet are associated with adverse plasma

lipoprotein levels[105], such as increased LDL-C, and increased insulin resistance.[16,103,104] In studies where fatty acids were assessed via in vivo levels, increased saturated fatty acids in the plasma phospholipids was associated with an increased carotid intima-media thickness[106], and increased saturation in the muscle membrane phospholipids was associated with increased insulin resistance[103]. In the Zutphen Elderly Study, Feskens et al[16] found that the relationship between saturated fat intake and insulin sensitivity remained strong even after statistically adjusting for body mass index (weight / height^2). However, high amounts of dietary fat intake may induce insulin resistance through the indirect mechanism of contributing to obesity, as higher levels of total fat and saturated fat intakes are also associated with greater weight gain.[103] A number of metabolic alterations (increased TNFα, plasma free fatty acid, and intramuscular TG levels) can occur with increased adiposity, especially abdominal adiposity, that directly increase insulin resistance and CAD risk.[27]

A diet high in CHO and fiber is shown to have protective effects for CAD and insulin resistance.[107,108] Soluble fiber[109], and insoluble fibers, especially cereal grains[110-112], are associated with improvements in insulin sensitivity.[16,113] The mechanisms by which fiber may exert its protective effects are not entirely known. One possibility is that high fiber foods are digested slowly and have a low glycemic index. An increased intake of low glycemic foods is associated with lower LDL-C levels[114] and C-peptide excretion rates (suggestive of lower β cell insulin secretion from the pancreas).[107] Thus, a diet high in fiber may help to reduce insulin secretory demand. Another possibility is the connection of dietary fiber to some of the nutrients contained with in such as vitamin E (associated with enhanced insulin action[115], and decreased risk

of CAD[116]) and folate (associated with decreased risk of CAD[117,118]). Since most of the studies on fiber intake and insulin resistance or CAD risk are in healthy subjects without CAD, the proposed study will examine the association between dietary fiber intake and insulin resistance in a population of CAD patients before a secondary prevention program intervention.

Persons with CAD are usually recommended to follow either the American Heart Association (AHA) and the National Cholesterol Education Program (NCEP) Step II Diet or the Ornish Lifestyle Heart Trial Diet. These two diets differ considerably and controversy surrounds which is the best recommendation for the CAD patient. In the Step II Diet the recommendations are for total fat intake to equal 30% or less of total calories, with less than 7% coming from saturated fat sources, cholesterol intake at less than 200mg/day, and intake of CHO at 55% or more of total calories.[22,57,66] While the Step II Diet does not have a specific fiber recommendation, the AHA separately recommends that CAD patients should consume 25-30 grams per day from food, not supplements.[57] Ornish et al have advocated a more radical dietary approach, recommending that CAD patients consume a diet of 10% fat total and from vegetarian sources (unsaturated) only.[19] The specific intakes of CHO and fiber are not outlined extensively in the Ornish diet, but both would be relatively high by the vegetarian design of the diet. In the Lifestyle Heart Trial conducted by Ornish et al, investigators found that a highly controlled intervention program of diet, exercise, and stress reduction reduced LDL-C and reversed atherosclerosis in patients in only 1 year[65] and continued to improve after 5 years[19]. However, while the very low fat Lifestyle Heart Trial diet reduced atherosclerosis in CAD patients, it actually worsened dyslipidemia by lowering

HDL-C and increasing TG after 5 years[19]. In addition, critics of the Ornish diet express concerns over how realistic an expectation it is that CAD patients will adhere to such extreme lifestyle changes. The more moderate AHA/NCEP Step II Diet has been shown to lower cholesterol levels but only when combined with an aerobic exercise intervention.[100]

Both the dietary approaches are aimed at reducing CAD risk by lowering total LDL-C levels in patients with CAD. The current dietary treatment focus may have limitations for optimally managing insulin resistance, because insulin resistance is more strongly associated with low HDL-C and high TG, than with high LDL-C.[16,69-71] The AHA/NCEP Step II diet may not result in significant improvements in insulin resistance, whereas the Ornish diet may even have detrimental effects.[19] A redirection of diet approaches toward a focus on reducing insulin resistance would likely result in a reduction of TG and in an increase in HDL-C, thereby reducing CAD risk. Thus, the proposed study will assess those dietary variables that are hypothesized to have an association with insulin resistance and that can be effectively modified by educated lifestyle changes (total fat, saturated fat, CHO, and fiber).

Psychosocial Indexes

The psychosocial states of depression and hostility have been connected to an increased risk of IRMS and CAD-related problems. *Hostility* is associated with adverse health outcomes such as hypertension, CAD, premature mortality[119], and an elevated level of TG[17], but this finding remains inconsistent in the literature due to differing methods, populations and surveys used within the research designs. While it has been found that hostility scores may not be predictive of CAD[120], low levels of hostility or

high trust in others may be protective against CAD[121]. *Depression* scores are associated with an increased CAD risk[122] and completing a group cardiac rehabilitation program is associated with reductions in depression and hostility.[60] In addition, a 4-month program of stress management in CAD patients produced lower self-reported depression and hostility scores, while improving risk of cardiovascular morbidity through reduced mental stress and myocardial ischemia.[123] Because insulin resistance has been reported in patients with depression[18], self-reported feelings of depression may be associated with insulin resistance in CAD patients, but the mechanisms are not completely understood. One possibility is effect that psychosocial stress can have on insulin resistance through psychoneuroendocrine pathways, such as the activity of the hypothalamic-pituitary-adrenal (HPA) axis. Traits of depression and anxiety are associated with an increased activation of the HPA axis, which results in abnormalities in stress-related cortisol secretion.[124] Cortisol is an antagonist to insulin, and in a recent study from our laboratory, elevated cortisol excretions were associated with insulin resistance in postmenopausal women.[125] Thus, the proposed study will examine whether hostility and depression are associated with insulin resistance in CAD patients. The result could potentially provide focus for secondary prevention programs to more effectively assess patients and design interventions to reduce the potential psychosocial mediators of insulin resistance.

Appendix B

IRB APPROVAL LETTER

INSTITUTIONAL REVIEW BOARD FOR THE PROTECTION OF HUMAN SUBJECTS

OREGON STATE UNIVERSITY

Report of Review

TO: Daniel P. Williams, ExSS

RE: Cardiac rehabilitative effects on insulin resistance in coronary artery diseased patients.

The referenced project was reviewed under the guidelines of Oregon State University's Committee for the Protection of Human Subjects and the U.S. Department of Health and Human Services. The committee has **approved** your application. The approval of this application expires upon the completion of the project or one year from the approval date, whichever is sooner. The informed consent form obtained from each subject should be retained in program/project's files for three years beyond the end date of the project.

Any proposed change to the protocol or informed consent form that is not included in the approved application must be submitted to the IRB for review and must be approved by the committee before it can be implemented. Immediate action may be taken where necessary to eliminate apparent hazards to subjects, but this modification to the approved project must be reported immediately to the IRB.

Date: 03/11/98

Warren N. Suzuki, Chair
Committee for the Protection of Human Subjects
(Education, 7-6393, suzukiw@ccmail.orst.edu)

Appendix C

INFORMED CONSENT DOCUMENT

OREGON STATE UNIVERSITY ENDOCRINE AND METABOLISM LABORATORY

Informed Consent Document

A. Title of Research Project

Cardiac rehabilitative effects on insulin resistance in patients with coronary artery disease.

B. Investigator

Daniel P. Williams, Ph.D.

C. Purpose of the Research Project

Prior studies have demonstrated that regular participation in a cardiac rehabilitation program that includes increases in physical activity, reductions in dietary fat intake, reductions in smoking behavior, and improvements in stress management favorably reduce the risk for heart attacks in patients with coronary artery disease (CAD). Most cardiac rehabilitation programs encourage reductions in blood cholesterol, blood pressure, and body weight to reduce the risk for heart attacks in patients with CAD. However, more recent studies suggest that reductions in body fat around the abdomen as well as reductions in blood insulin levels after eating may be "newer" risk factors, which if properly controlled, may result in improved prevention of heart attacks in patients with CAD. Therefore, the present study will determine the effectiveness of the first three months of the cardiac rehabilitation program at Good Samaritan for 1.) reducing body fat around the abdomen, and 2.) reducing blood insulin levels after eating. Because it would be difficult to get everyone to eat the same amount of food within the same amount of time, the present study will draw blood samples (for measuring insulin levels) once before and twice after drinking a sugar solution. Finally, because the present cardiac rehabilitation program will encourage increases in physical activity, reductions in dietary fat intake, a stop to smoking (for all smokers), and improvements in stress management, the present study will also be measuring physical activity levels, dietary intake, smoking behavior, and two possible components of stress (symptoms of depression and feelings of hostility), so that the extent to which positive changes in behavior may help to reduce body fat around the abdomen as well as reduce blood insulin levels after drinking a sugar solution may be better understood in patients with CAD.

D. Procedures

I have received an oral and written explanation of this study, and I understand that I was selected to participate in this study because I have been diagnosed with coronary artery disease. In addition, I was selected because I have no previous history of diabetes, and I am not taking insulin or oral medications aimed at controlling my blood sugar. Furthermore, I understand that as a participant in this study the following things will happen as a result of my participation in the study:

SUGAR SOLUTION TEST AT GOOD SAMARITAN. On the day of the sugar solution test before and after the three-month cardiac rehabilitation program, I will arrive at the Good Samaritan clinical laboratory in the morning, without having consumed anything but water for the previous 12 hours. *No more than 18 mL (3-4 teaspoons*) of blood will be drawn from a forearm vein in a single blood draw, and no more than three complete blood draws totaling *no more than 54 mL (10-11 teaspoons)* of blood will be collected within a single laboratory visit. Of the total amount of blood drawn, no more than 5 mL (approximately 1 teaspoon) will be stored frozen for future research studies in the event that the analysis of additional CAD risk factors can be completed with support from future research grants. After the initial blood draw, I will be given a lime-flavored sugar solution to drink. My blood will be drawn again at 1 and 2 hour intervals after I finish drinking the sugar solution. The sugar solution will stimulate insulin secretion from the pancreas (a digestive organ) and into the blood. Greater amounts of blood insulin after drinking the sugar solution are associated with a greater risk for heart attacks. Thus, the study will determine whether participation in the three-month cardiac rehabilitation program effectively reduces blood insulin levels after drinking a sugar solution. Although all of my blood for the present study will be drawn at Good Samaritan Hospital, some of the blood will be analyzed in the Clinical Laboratory at Good Samaritan Hospital, and some of the blood will be stored frozen for later analysis in the Endocrine and Metabolism Laboratory at Oregon State University.

CLINICAL EXAM AT OSU ENDOCRINE AND METABOLISM LABORATORY. On the day of the clinical exam before and after the three-month cardiac rehabilitation program, I will arrive at the OSU Endocrine and Metabolism Laboratory, and the following will happen:

BODY MEASUREMENTS. I will wear light shorts and a short-sleeve shirt that can be easily moved for the accurate measurement of body weight, height, girth, and diameter measurements. My body weight will be measured on a beam scale. My height and the length of my trunk from the neck to the hip will be measured with a wall-mounted measuring stick. My abdominal fat will be measured by body girths and an abdominal thickness measurement. My body girths will be measured with a measuring tape at the waist, abdomen, hip and thigh. A special caliper will be used to measure the thickness of my abdomen while I lie on an examination table. **If I have a heart pacemaker, I will not undergo the bioelectrical impedance testing**. However, if I do not have a heart pacemaker, then the fat and non-fat composition of my whole body and my trunk will be determined by a bioelectrical impedance analyzer. The bioelectrical impedance analyzer

will introduce a painless, low-voltage (less voltage than that delivered by a small transistor radio battery) electrical current into my body, so that the research staff can assess my body composition. Because muscle is primarily composed of water and typically contains very little fat, muscle is an excellent conductor of electricity, and it provides little impedance (or resistance) to an electrical current. Fat tissue, by contrast, typically contains very little water. As a result, body fat is a poor conductor of electricity, and it provides a lot of impedance (or resistance) to an electrical current. Thus, by measuring the extent to which my body and my trunk conduct or resist the electrical current, the research staff can estimate the amount of fat and non-fat tissues contained in my body and in my trunk.

During the bioelectrical impedance measurement, I will lie on my back on a padded examination table while a technician attaches small electrodes to the wrist, the ankle, the neck, and the thigh on the right side of my body. The technician will then attach electrical wires to: a.) my right wrist and ankle to assess my whole body impedance, and b.) my neck and the upper part of my right thigh to assess my trunk impedance. Once the electrical wires are attached to the electrodes, the technician will push a button on the impedance analyzer which will introduce the low voltage current into my body, and within only a few seconds of time, the impedance analyzer will assess the extent to which my body conducts or resists the electrical current.

QUESTIONNAIRES. I will complete a medical history questionnaire, and I will respond to questions posed during an interview with a member of the laboratory staff about my physical activity over the past 7 days. I will also complete a questionnaire related to my dietary habits, my use of vitamin and mineral supplements, and my cigarette smoking behavior. Finally, I will complete two additional questionnaires designed to assess different components of stress that I may or may not have. One questionnaire focuses on assessing symptoms of depression, and the other questionnaire focuses on assessing feelings of hostility. Although the stress questionnaires focus on depression and hostility, I understand that neither questionnaire may be used to diagnose depression or a hostile personality trait. Furthermore, I understand that neither Dr. Williams nor any member of his research staff is trained in psychology and therefore cannot or will not make any psychological evaluations based on my responses. Instead, my responses to the stress questionnaires will solely be interpreted relative to their known association with heart attacks or with their possible association with the **physical** CAD risk factors assessed in the present study. I understand that the questionnaires are detailed and that they include many questions about my own and my family's health that may even seem burdensome or intrusive. I understand that if I find any part or parts of the questionnaires to be overly burdensome or intrusive, I am under no obligation to complete it, and that my decision will in no way affect my participation in the other parts of the study.

3-MONTH CARDIAC REHABILITATIVE INTERVENTION. I will be participating in a supervised cardiac rehabilitation program that is managed by a nurse. The program will be individualized and specific to my risk factors for heart disease. I will be involved in an exercise program that will consist of both aerobic and low-level weight training. Activities in which I can expect to participate include walking on a treadmill, using a

rowing machine, riding a stationary bicycle, and some moderate weightlifting. In addition to the exercise program, there will be educational opportunities designed to increase my personal knowledge about my risks for heart disease. These opportunities will include information related to my diet, blood pressure, and stress levels.

PRE- AND POST-INTERVENTION TESTING. I understand that I will be asked to complete the sugar solution test at Good Samaritan Hospital and all of the clinical tests to be conducted at the OSU Endocrine and Metabolism Lab twice - once before and once again after participating in the three-month cardiac rehabilitation program at Good Samaritan Hospital.

FORESEEABLE RISKS OR DISCOMFORTS. I understand that I may experience some discomfort while my blood is being drawn, and that this procedure could result in a small amount of bleeding, bruising, and slight soreness at the site of the needle insertion. I have been informed that my blood will be drawn by trained hospital personnel who will apply a bandage to my arm to prevent bleeding or bruising as a result of my blood being drawn.

I understand that I may experience some muscle and joint pain, soreness, and possible injuries related to my participation in the exercise part of this study. I have been told that my exercise program will be individualized to my abilities, and all attempts will be made to gradually increase my exercise to reduce the potential for exercise-related pain, soreness, and injury.

I understand that after drinking the sugar solution, there is a remote chance that my blood sugar levels may drop to low levels, which could produce dizziness, headache, and loss of consciousness. In the rare event of a low blood sugar reaction, appropriate medical personnel at Good Samaritan will be available to monitor my condition and, if necessary, correct my blood sugar deficiency. Furthermore, the possibility of experiencing a low blood sugar reaction will be minimized by using a dose of sugar that is similar to the amount of sugar consumed in a typical meal.

I understand there exists the possibilities of some unfavorable changes during exercise in the cardiac rehabilitation program. They include abnormal blood pressure, fainting, disorders of the heart beat, and in rare instances, heart attack, stroke, and death. Appropriate heart monitoring during exercise, supervision by an experienced cardiac rehabilitation staff, and the close proximity of the emergency room during the exercise classes at Good Samaritan Hospital will minimize the risks associated with regular exercise in the cardiac rehabilitation program.

I understand that there may be some psychological risks associated with completing the stress questionnaires. For instance, I may observe that my responses are consistent with possible symptoms of depression or with trends toward a hostile personality that I have never before considered. Such new considerations may be painful or upsetting.

POTENTIAL BENEFITS. I understand that my regular participation in the cardiac rehabilitation may reduce some of my risk factors for future heart attacks. I also understand that the measurements of body fat around the abdomen, blood insulin levels, blood cholesterol levels, physical activity, dietary intake, smoking behavior, and stress levels, which will be sent to me at the end of the study, may be important to me or my physician for assessing potential changes in my own personal risk for future heart attacks. Furthermore, I understand that the information obtained in the present study may help Dr. Williams and his associates learn how to better prevent excess amounts of body fat around the abdomen and high levels of blood insulin after drinking a sugar solution, which in turn, may lead to better prevention of heart attacks in patients with CAD.

E. Confidentiality

I understand that any information obtained from me, including test results, will be kept confidential. A code number will be used to identify any samples, test results, or other information I might provide. The only persons who will have access to this information will be the investigators.

F. Compensation for injury

I understand that Oregon State University does not provide research subjects with compensation or medical treatment in the event that I become injured as a result of participation in this research project. However, if I sustain any injury during the data collection, trained personnel will provide first aid.

G. Voluntary Participation

I understand that my participation in the project is completely voluntary, and that I may withdraw from or refuse to participate in the study at any time with no effects on my participation in the cardiac rehabilitation program.

H. Questions regarding the study

I understand that any questions I have about the study or any specific procedures should be directed to Daniel P. Williams, Ph.D. (principal investigator at Oregon State University) at 737-5922 or to Kerri Eason, R.N. (cardiac rehabilitation program supervisor at Good Samaritan Hospital) at 757-5323. Any other questions that I have should be directed to Mary Nunn, Sponsored Programs Officer, OSU Research Office at 737-0670.

I. Understanding and consent

My signature below indicates that I have read and that I understand the procedures described above. I give my informed consent to participate in this study. I understand that I will receive a signed copy of this consent form.

Signature of Subject Name of Subject

Date Signed

Subject's Present Address

Subject's Phone Number

Signature of Investigator Date Signed

Appendix D

PATIENT SCREENING FORM

1. **Name** _____ **Screen ID** _____
   Last First Middle
   Best time/place to contact?

2. **Telephone**
   Home ( ) _____ - _____ _____
   Work ( ) _____ - _____ _____

3. **Interviewer** _____ **Date** ___/___/___ **Time** ___:___ AM/PM
   mo day yr

4. Whether eligible or not, would you be willing to be contacted in future for other studies? (If yes, get address) Circle: **1=yes** **2=no**

Mailing Address: _____
Street Apt. #

_____
City State Zip Code

5. **Definitive diagnosis of coronary artery disease** **1=yes** **2=no**

Subjects responding affirmatively to any of 5a-5e are eligible with a definitive diagnosis of CAD, whereas subjects answering negatively to all of 5a-5e are ineligible for the present study.

Why were you referred to cardiac rehabilitation?

a.	recent coronary artery bypass surgery?	**yes**	**no**
b.	recent heart attack?	**yes**	**no**
c.	recent positive angiographic, ECG, or thallium test?	**yes**	**no**
d.	recent angioplasty procedure?	**yes**	**no**
e.	recent stent procedure?	**yes**	**no**

For all subjects with and without a definitive diagnosis CAD, please determine whether items 5f-5k apply to their current medical condition or whether items 5f-5k may explain why they were referred to cardiac rehabilitation.

f.	recent heart valve replacement?	**yes**	**no**
g.	recent diagnosis of cardiomyopathy?	**yes**	**no**
h.	recent diagnosis of cardiac arrhythmia?	**yes**	**no**

i. recent cardiac transplant? **yes no**
j. recent diagnosis of non-CAD heart disease? **yes no**
k. recent multiple risk factor diagnosis? **yes no**

6. **Exclusion Criteria (continued)**

Subjects responding affirmatively to 6a-6e are ineligible for the present study.

Medical History **1=yes 2=no**

Has a physician ever told you that you have or had the following?

a. diabetes (both NIDDM and IDDM are exclusionary) **yes no**
b. any medical conditions that severely limit physical activity **yes no**

- severe orthopedic conditions **yes no**
- severe COPD **yes no**
- severe CHF **yes no**
- severe claudication pain **yes no**

Medication **1=yes 2=no**

c. Are you currently taking insulin (humulin, humalog, novolin, velosulin, etc)? **yes no**

Personal Factors **1=yes 2=no**

d. Will you be moving away from the Corvallis area in the next 3-6 months? **yes no**

e. Do you reside more than 50 miles away from Corvallis and/or anticipate time or transportation constraints that may limit your participation in activities promoted by the rehab program and the four separate rounds of clinical tests in the research study? **yes no**

f. Besides time and transportation constraints, do you have any other personal considerations that may limit your participation in activities promoted by the rehab program and the four separate rounds of clinical tests in the research study? **yes no**

7. **Intervention Information (non-exclusionary information)**

a. Is the subject at "high risk" for events or complications resulting from participation in the cardiac rehab program that will require that the participant undergoes a modified rehab program? **yes no**

b. Comments regarding basis for and nature of modifications required:

Appendix E

MEDICAL HISTORY QUESTIONNAIRE

Subject Number _____
Test Date (mm/dd/yy) _____
Birth Date (mm/dd/yy) _____
Visit _____
(A=pre-cardiac rehab intervention; B=post-cardiac rehab intervention)

Instructions: Please mark an "x" in the space to the left of the most appropriate response. Please choose only the most appropriate single response for each question.

1. What is your gender?
   _____ 1. Female
   _____ 2. Male

2. What is your current marital status?
   _____ 1. Now married
   _____ 2. Widowed
   _____ 3. Divorced
   _____ 4. Separated
   _____ 5. Never married

3. What is your current employment status (please mark only the best response)?
   _____ 1. Employed and working
   _____ 2. Employed and on a leave of absence
   _____ 3. Performing volunteer work
   _____ 4. Homemaker
   _____ 5. Unemployed
   _____ 6. Retired

4. What is the highest level of formal education that you have completed?
   _____ 1. Attended school but did not complete high school
   _____ 2. Completed high school
   _____ 3. Attended but did not complete college bachelor's degree
   _____ 4. Completed college bachelor's degree
   _____ 5. Attended graduate school but did not complete graduate degree
   _____ 6. Completed master's degree
   _____ 7. Completed doctoral degree

5. In which group do you consider yourself?
   _____ 1. Caucasian
   _____ 2. Asian, Asian-American, Pacific Islander
   _____ 3. African-American
   _____ 4. Hispanic
   _____ 5. Native American, American-Indian
   _____ 6. Other, please describe:
   _____

6. How much was your household's total income for the past year?
   _____ 01. under $5,000
   _____ 02. $5,000 to $9,999
   _____ 03. $10,000 to $14,999
   _____ 04. $15,000 to $19,999
   _____ 05. $20,000 to $24,999
   _____ 06. $25,000 to $29,999
   _____ 07. $30,000 to $34,999
   _____ 08. $35,000 to $39,999
   _____ 09. $40,000 to $44,999
   _____ 10. $45,000 to $49,999
   _____ 11. $50,000 to $99,999
   _____ 12. $100,000 and over
   _____ 00. don't know

7. Which is the best description of your cigarette smoking habits?
   _____ 1. never smoked regularly (skip to question 9)
   _____ 2. former smoker (skip to question 9)
   _____ 3. current smoker

8. How many cigarettes do you smoke on average per day?
   _____ 1. 1 to 9 cigarettes
   _____ 2. 10 to 19 cigarettes
   _____ 3. 20 or more cigarettes

9. What is the best description of your alcohol consumption habits?
   _____ 1. never drank alcohol (skip to question 11)
   _____ 2. quit drinking alcohol (skip to question 11)
   _____ 3. currently drink alcohol

10. How many alcoholic drinks do you consume on average per day (1drink=12 oz of beer, 4 oz of wine, or 1 shot of hard liquor)?
   _____ 1. less than or equal to 1 drink
   _____ 2. 2 drinks
   _____ 3. 3 drinks
   _____ 4. 4 drinks
   _____ 5. 5 or more drinks

11. What is the best description of your caffeinated beverage consumption habits?
    _____ 1. never drank caffeinated beverages (skip to question 13)
    _____ 2. quit drinking caffeinated beverages (skip to question 13)
    _____ 3. currently drink caffeinated beverages

12. How many cups of caffeinated beverage do you consume on average per day?
    _____ 1. less than or equal to 1 cup
    _____ 2. 2 cups
    _____ 3. 3 cups
    _____ 4. 4 cups
    _____ 5. 5 or more cups

13. Has your mother ever had a heart attack?
    _____ 1. yes
    _____ 2. no
    _____ 3. don't know

14. Has your father ever had a heart attack?
    _____ 1. yes
    _____ 2. no
    _____ 3. don't know

15. Have any of your siblings ever had a heart attack?
    _____ 1. yes
    _____ 2. no
    _____ 3. don't know

16. Have either of your maternal grandparents ever had a heart attack?
    _____ 1. yes
    _____ 2. no
    _____ 3. don't know

17. Have either of your paternal grandparents ever had a heart attack?
    _____ 1. yes
    _____ 2. no
    _____ 3. don't know

18. Has your mother ever had diabetes?
    _____ 1. yes
    _____ 2. no
    _____ 3. don't know

19. Has your father ever had diabetes?
_____ 1. yes
_____ 2. no
_____ 3. don't know

20. Have any of your siblings ever had diabetes?
_____ 1. yes
_____ 2. no
_____ 3. don't know

21. Have either of your maternal grandparents ever had diabetes?
_____ 1. yes
_____ 2. no
_____ 3. don't know

22. Have either of your paternal grandparents ever had diabetes?
_____ 1. yes
_____ 2. no
_____ 3. don't know

23. Thinking back over the past year, about how many times did you see a physician for medical attention (count office and hospital visits only)?

Number of visits : _____ (please write in approximate number)

24. Has a physician ever told you that you have had a heart attack or a myocardial infarction?
_____ 1. yes
_____ 2. no
_____ 3. don't know

25. How many heart attacks or myocardial infarctions have you had?
_____ 1. 0
_____ 2. 1
_____ 3. 2
_____ 4. 3
_____ 5. more than 3
_____ 6. don't know

If your answer to question 25 is "0", please skip to question 29.

26. On what date did you experience your *first* heart attack or myocardial infarction?
Month _____ _____ (i.e., "January" is "01")
Day _____ _____
Year _____ _____

27. On what date did you experience your *most recent* heart attack or myocardial infarction?

Month _____ _____ (i.e., "January" is "01")
Day _____ _____
Year _____ _____

28. Was your original heart attack the first time that a physician had informed you that you had coronary artery disease?

_____ 1. yes
_____ 2. no
_____ 3. don't know

29. On what date did a physician *first* inform you that you had coronary artery disease?

Month _____ _____ (i.e., "January" is "01")
Day _____ _____
Year _____ _____

30. How many surgical treatments have you received for your coronary artery disease? (A surgical treatment includes a coronary artery bypass operation, a balloon angioplasty procedure, a stent procedure, or an atherectomy procedure)

_____ 1. 0
_____ 2. 1
_____ 3. 2
_____ 4. 3
_____ 5. more than 3
_____ 6. don't know

31. Which of the below best describes your most recent treatment for coronary artery disease?

_____ 1. single vessel bypass
_____ 2. multiple vessel bypass
_____ 3. balloon angioplasty procedure
_____ 4. stent
_____ 5. combination of surgical procedures
_____ 6. no surgical treatments

32. On what date were you *originally* surgically treated for coronary artery disease? (A surgical treatment includes a coronary artery bypass operation, a balloon angioplasty procedure, a stent procedure, or an atherectomy procedure)

Month _____ _____ (i.e., "January" is "01")
Day _____ _____
Year _____ _____

33. On what date were you *most recently* surgically treated for coronary artery disease?

Month _____ _____ (i.e., "January" is "01")
Day _____ _____
Year _____ _____

34. Has a physician ever told you that you have had a stroke or a transient ischemic attack (a "TIA")?

_____ 1. yes
_____ 2. no
_____ 3. don't know

35. Has a physician ever told you that you have peripheral vascular disease?

_____ 1. yes
_____ 2. no
_____ 3. don't know

36. Has a physician ever told you that you have congestive heart failure?

_____ 1. yes
_____ 2. no
_____ 3. don't know

37. Has a physician ever told you that have diabetes?

_____ 1. yes
_____ 2. no
_____ 3. don't know

38. Has a health professional (physician, nurse, etc.) ever told you that have high blood pressure?

_____ 1. yes
_____ 2. no
_____ 3. don't know

39. Has a health professional (physician, nurse, etc.) ever told you that have high blood cholesterol levels?

_____ 1. yes
_____ 2. no
_____ 3. don't know

40. Has a physician ever told you that you have cancer?

_____ 1. yes
_____ 2. no
_____ 3. don't know

41. Are you currently undergoing treatment for cancer?
_____ 1. yes
_____ 2. no

42. Has a physician ever told you that you have pneumonia?
_____ 1. yes
_____ 2. no
_____ 3. don't know

43. Has a physician ever told you that you have gout?
_____ 1. yes
_____ 2. no
_____ 3. don't know

44. Has a physician ever told you that you have liver trouble or hepatitis?
_____ 1. yes
_____ 2. no
_____ 3. don't know

45. Has a physician ever told you that you have inflammatory bowel disease or diverticulitis?
_____ 1. yes
_____ 2. no
_____ 3. don't know

46. Has a physician ever told you that you have gall bladder trouble or stones?
_____ 1. yes
_____ 2. no
_____ 3. don't know

47. Has a physician ever treated you for a duodenal or gastric ulcer?
_____ 1. yes
_____ 2. no
_____ 3. don't know

48. Has a physician ever told you that you have had a parasitic infection?
_____ 1. yes
_____ 2. no
_____ 3. don't know

49. Do you frequently get upper respiratory infections?
_____ 1. yes
_____ 2. no

50. Has a physician ever told you that you have had a urinary tract infection?
_____ 1. yes
_____ 2. no
_____ 3. don't know

51. Has a physician ever told you that you have rheumatoid arthritis or lupus?
_____ 1. yes
_____ 2. no
_____ 3. don't know

52. Has a physician ever told you that you have asthma?
_____ 1. yes
_____ 2. no
_____ 3. don't know

53. Has a physician ever told you that you have emphysema?
_____ 1. yes
_____ 2. no
_____ 3. don't know

Questions 54-57 are for females only (for males, please skip to question 58).

54. Have you stopped having menstrual periods?
_____ 1. yes
_____ 2. no (skip to question 57)

55. At what age did you stop having menstrual periods?
Age: _____ (please write in the exact or approximate age in years)

56. Why did you stop having menstrual periods?
_____ 1. reached menopause
_____ 2. had uterus surgically removed
_____ 3. had ovaries or ovaries and uterus surgically removed
_____ 4. uncertain
_____ 5. other reason, please describe: _____

57. Which of the below best describes your hormone replacement therapy history?
_____ 1. have never taken hormone replacement therapy
_____ 2. took hormone replacement therapy during menopause only
_____ 3. took hormone replacement for less than one year after menstrual periods stopped
_____ 4. have taken hormone replacement therapy ever since menstrual periods stopped
_____ 5. other, please describe: _____

58. Do you currently take any medication for chest pain (called "nitrate" or "nitroglycerin" medications)?

_____ 1. currently take nitroglycerin
-common names include: *Deponit NTG, Nitro-Bid, Nitro-Dur, Nitrilingual, Nitrostat, Transderm-Nitro.*

_____ 2. currently take other nitrates
-common names include: *Dilatrate SR, Imdur, Ismo, Isordil, Monoket, Sorbitrate.*

_____3. currently take another type or a combination of medications for chest pain, if so please list name of medication(s):_____

_____ 4. do not currently take any medication for chest pain.

59. Do you currently take any medication to improve the pumping effectiveness of your heart (called "inotropic" medications)?

_____ 1. currently take digitalis
-common names include: *Cristodigin, Lanoxicaps, Lanoxin.*

_____ 2. currently take other inotropic medications
-common names include: *Dobutrex, Inocor, Primacor.*

_____ 3. currently take another type or a combination of medications for improving the pumping effectiveness of my heart, if so please list name of medication(s):_____

_____ 4. do not currently take any digitalis or other inotropic medications.

60. Do you currently take any medication to improve the stability of your heart rhythm (called "antiarrhythmia" medications)?

_____ 1. currently take a group I antiarrhythmia medication
-common names include: *Cardioquin, Ethmozine, Mexitil, Norpace, Procanbid, Quinaglute, Quinidex, Rhythmol, Tambocor, Tonocard.*

_____ 2. currently take a group II antiarrhythmia medication
-common names include: *Brevibloc, Inderal, Sectral.*

_____ 3. currently take a group III antiarrhythmia medication
-common names include: *Betapace, Cordarone, Corvert.*

_____ 4. currently take a group IV antiarrhythmia medication
-common names include: *Calan, Cardizem, Isoptin.*

_____ 5. currently take a miscellaneous group of antiarrhythmia medication
-common names include: *Adenocard, Lanoxicaps, Lanoxin.*

_____ 6. currently take another type or a combination of medications for improving the stability of my heart rhythm, if so please list name of medication(s):_____

_____ 7. do not currently take any antiarrhythmia medications.

61. Do you currently take any medication to reduce the risk for blood platelet aggregation (called "antiplatelet" medications)?

_____ 1. currently take aspirin or "ASA"
-common names include: *Bayer, Bufferin, Ecotrin, Halfprin.*

_____ 2. currently take other antiplatelet medications
-common names include: *Flolan, Persantine, Reopro, Ticlid.*

_____ 3. currently take another type or a combination of medications for reducing the risk for blood platelet aggregation, if so please list name of medication(s):_____

_____ 4. do not currently take aspirin or other antiplatelet medications.

62. Do you currently take any medication to reduce the risk for blood coagulation (called "anticoagulent" medications)?

_____ 1. currently take coumadin (also called warfarin sodium)

_____ 2. currently take heparin
-common names include: *Fragmin, Heparin Sodium, Lovenox.*

_____ 3. currently take another type or a combination of medications for reducing the risk for blood coagulation, if so please list name of medication(s):_____

_____ 4. do not currently take coumadin or other anticoagulent medications.

Questions 63 and 64 are for females only (for males, please skip to question 65)

63. Do you currently take hormone replacement therapy (called "estrogen, progestin" medications)?

_____ 1. currently take conjugated estrogens only
-common name: *Premarin.*

_____ 2. currently take estrogen sulfates only
-common names include: *Estropipate, Estrogen Sulfate, Ogen, Ortho-Est.*

_____ 3. currently take a plant estrogen only
-common name: *Phyto-estrogen.*

_____ 4. currently take premarin + a progestin
-common progestin names include: *Cycrin, Medroxyprogesterone Acetate, Progestin, Provera.*
-common premarin + progestin combination names include: *Premphase, Prempro.*

_____ 5. currently take any non-premarin estrogen + any progestin

_____ 6. currently take another type or a combination of hormone replacement therapies, if so please list name of medication(s):_____

_____ 7. do not currently take any hormone replacement therapy.

64. Do you currently take a selective estrogen receptor modulator (called "SERM" medications)?

_____ 1. currently take a SERM
-common name: *Raloxifene*.

_____ 2. do not currently take any SERMs.

65. Do you currently take any medication to lower your blood pressure (called "antihypertensive" medications)?

_____ 1. currently take a diuretic (a water pill)
-common names include: *Diazide, Enduron, Hydrochlorothiazide, Triamterene*.

_____ 2. currently take an ACE inhibitor
-common names include: *Accupril, Altace, Capotil, Lotensin, Mavik, Monopril, Prinivil, Univasc, Vasotec, Zestril*.

_____ 3. currently take a calcium channel blocker
-common names include: *Adalat, Calat, Cardene, Cardizem, Covera, Dilacor, Dynacirc, Isoptin, Nimotop, Norvasc, Plendil, Procardia, Sular, Tiazac, Vascor, Verelan*.

_____ 4. currently take a beta blocker
-common names include: *Atenolol, Betapace, Blocadren, Brevibloc, Cartrol, Inderal, Kerlone, Levatol, Lopressor, Sectral, Tenormin, Toprol, Visken, Zebeta*.

_____ 5. currently take another type or a combination of medications for lowering blood pressure, if so please list name of medication(s):_____

_____ 6. do not currently take any blood pressure-lowering medications.

66. Do you currently take any medication to alter your blood cholesterol levels (called "hypolipidemic" medications)?

_____ 1. currently take a cholesterol synthesis inhibitor
-common names include: *Lescol, Lipitor, Mevacor, Pravachol, Zocor*.

_____ 2. currently take niacin

_____ 3. currently take a fibrate
-common names include: *Atromid, Lopid*.

_____ 4. currently take a bile acid-binding resin
-common names include: *Colestid, Questran*.

_____ 5. currently take another type or a combination of medications for altering blood cholesterol levels, if so please list name of medication(s):_____

_____ 6. do not currently take any blood cholesterol-altering medications.

67. Do you currently take any medication to lower your blood sugar levels (called "hypoglycemic" medications)?

_____ 1. currently take a class I hypoglycemic
-common name: *Glucophage*.

_____ 2. currently take a class II hypoglycemic
-common name: *Precose*.

_____ 3. currently take a class III hypoglycemic
-common name: *Amaryl, Diabeta, Diabinese, Glucotrol, Glynase, Micronase*.

_____ 5. currently take another type or a combination of medications for lowering blood sugar, if so please list name of medication(s):_____

_____ 6. do not currently take any blood sugar-lowering medications.

68. Do you currently take any medication to improve your mood (called "antidepressant" medications)?

_____ 1. currently take an SSRI antidepressant
-common names include: *Paxil, Prozac, Zoloft*.

_____ 2. currently take a tricyclic or other antidepressant
-common names include: *Adapin, Asendin, Elavil, Etrafon, Limbitrol, Norpramin, Pamelor, Sinequan, Tofranil, Triavil, Vivactil*.

_____ 3. currently take another type or a combination of medications for reducing depression, if so please list name of medication(s):_____

_____ 4. do not currently take any antidepressant medications.

69. Do you currently take any antioxidant medications or supplements?

_____ 1. currently take probucol

_____ 2. currently take Vitamin E supplements

_____ 3. currently take Vitamin C supplements

_____ 4. currently take another type or a combination of antioxidants, if so please list name of medication(s) or supplement(s):_____

_____ 5. do not currently take any antioxidants.