Effect of Diet and Exercise Intervention on Inflammatory and Adhesion Molecules in Postmenopausal Women on Hormone Replacement Therapy and at Risk for Coronary Artery Disease

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Inflammation and the recruitment of monocytes into the artery wall are thought to be important aspects in the initiation and progression of atherosclerosis. The present study was designed to examine the effects of a rigorous diet and exercise intervention on plasma lipids and inflammatory and circulating adhesion molecules. Twenty postmenopausal women at risk for coronary artery disease (CAD) were placed on a high-fiber, low-fat diet, where food was provided ad libitum and daily aerobic exercise, primarily walking, was performed. In each subject, pre- and postintervention fasting blood was drawn for serum lipid, insulin, glucose, C-reactive protein (CRP), serum amyloid A (SAA), interleukin-6 (IL-6) and both soluble (s) intracellular and vascular adhesion molecule (sICAM-1 and sVCAM-1) were measured. After 2 weeks, significant reductions in body mass index (BMI) ($P < .001$), glucose ($P < .05$), insulin ($P < .01$), all serum lipids, and total cholesterol (total-C): high-density lipoprotein-cholesterol (HDL-C) ($P < .01$). Reductions in homeostasis model assessment for insulin resistance (HOMA-IR) ($P < .01$), CRP ($P < .01$), SAA ($P < .01$) and sICAM-1 ($P < .05$) were noted, as well as an increase in the quantitative insulin sensitivity check index ($P < .05$). Reductions were also noted in 5 women not using hormone replacement therapy (HRT). No significant reductions were found in IL-6 or sVCAM-1 in response to the intervention. Overall, this intervention resulted in improved metabolic and lipid profiles, reduced inflammatory, and cell adhesion molecules in postmenopausal women in the absence of caloric restriction. The rapid improvements may reduce the risk of acute myocardial infarction (MI), and if sustained, these changes may mitigate the risk for atherosclerosis progression and its clinical consequences.

ATHEROSCLEROTIC DISEASE is the leading cause of mortality in developed countries with coronary artery disease (CAD) being the number one killer of both men and women. Women are generally protected from atherosclerosis during their early years, which is thought to be due, in part, to hormonal differences. The American Heart Association and American College of Physicians had recommended hormone replacement therapy (HRT) for postmenopausal women to reduce the risk of CAD. However, the Women's Health Initiative was discontinued due to the increase in myocardial infarction (MI), stroke, and breast cancer in women receiving estrogen/progestin.[1,2] As a result of the uncertainty of the risks/benefits with HRT, there is an ever-increasing need for alternative therapies that reduce the risk of CAD in postmenopausal women.

Early clinical and epidemiologic studies established a link between dietary saturated fat, dietary cholesterol, serum cholesterol, and CAD mortality.[3,4] Serum lipid levels alone, however, cannot completely explain the incidence of atherosclerosis. Attention has recently focused on the involvement of inflammation in CAD, with numerous studies suggesting that elevated C-reactive protein (CRP) is a sensitive predictor of CAD and when considered in conjunction with plasma total cholesterol (total-C), serves as a better predictor of CAD risk than cholesterol alone.[5] Serum amyloid A (SAA), cytokines such as interleukin-6 (IL-6), and cell adhesion molecules (CAM) are involved in the complex etiology of CAD.[6] Given evidence that diet and exercise modifications have been documented to lower CAD risk,[7] we hypothesized that an intervention consisting of a high-fiber diet, combined with daily exercise, would reduce inflammation and monocyte-endothelial interactions in postmenopausal women at high risk for clinical outcomes associated with CAD.

MATERIALS AND METHODS

Diet and Exercise Intervention

The study protocol was approved by the Human Subjects Protection Committee, and informed consent of all subjects was obtained prior to enrollment. The subjects for this study were 20 postmenopausal women (age, 51 to 79 years) who voluntarily participated in the Pritikin Longevity Center 14-day residential diet and exercise intervention. According to clinical evaluation questionnaires, 15 of the women were taking estrogen/progesterone HRT and 4 were on statin therapy prior to the study and remained on drug therapy. All had multiple risk factors for CAD. Of the 20 women, 16 were overweight or obese, 1 was previously diagnosed with CAD alone, 5 were hypertensive, 3 had type 2 diabetes, and 5 suffered from diabetes combined with hypertension. Six subjects were on vitamin supplements prior to the intervention and remained on them during the study.

Once enrolled in the program, participants underwent a complete medical history and physical examination and underwent a 14-day diet and exercise intervention. All subjects were free of any viral infections during the study (CRP < 10 mg/L). Meals were served buffet style, and all participants were allowed unrestricted eating except for the meals when 3½ oz of fish or fowl were provided. Prepared meals contained

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Table 1. Anthropometric and Metabolic Parameters in Postmenopausal Women Undergoing a 14-Day Diet and Exercise Intervention

	Preintervention	Postintervention	% Decrease
Body weight (kg)	84.4 ± 14.6	81.5 ± 13.9*	4
BMI (kg/m^2)	32.2 ± 1.5	30.7 ± 1.2*	4
Blood glucose (mg/dL)	122.9 ± 38.5	109.3 ± 18.5*	11
Insulin (μU/mL)	13.5 ± 10.1	10.0 ± 7.3*	26
HOMA-IR	4.6 ± 4.3	2.9 ± 1.8*	34
QUICKI	0.32 ± 0.03	0.34 ± 0.04*	−6
Total-cholesterol (mg/dL)	214.9 ± 35.5	178.5 ± 33.2*	17
LDL-cholesterol (mg/dL)	119.0 ± 29.0	96.9 ± 25.8*	19
HDL-cholesterol (mg/dL)	62.9 ± 18.5	54.5 ± 14.9*	13
Total-cholesterol/HDL-cholesterol	3.63 ± 1.01	3.48 ± 1.13*	11
LDL-cholesterol/HDL-cholesterol	2.1 ± 0.8	1.9 ± 0.8	7
Triglycerides (mg/dL)	159.7 ± 70.1	135.5 ± 57.3*	15

NOTE. All data are expressed as mean ± SD, N = 20.

Abbreviations: HOMA-IR, homeostasis-model assessment for insulin resistance; QUICKI, quantitative insulin-sensitivity check index.

*$P \leq .01$ post *v* pre.

10% to 15% of calories from fat (polyunsaturated/saturated fatty acid ratio = 1.24), 15% to 20% of calories from protein, and 65% to 75% of calories from carbohydrates, primarily unrefined. Carbohydrates were in the form of high-fiber whole grains (≥5 servings/d), vegetables (≥4 servings/d), fruits (≥3 servings/d). Protein was primarily derived from plant sources with nonfat dairy allowed for up to 2 servings/day. Fish or fowl was served in 3½ oz portions 1 day per week and in soups or casseroles 2 days per week. The diet contained <100 mg/d cholesterol, and alcohol, tobacco, and caffeinated beverages were not allowed during the program.

Prior to starting the exercise training, subjects underwent a graded treadmill stress test according to a modified Bruce protocol to determine the appropriate individual level of exercise intensity. Based on the results, the subjects were provided with a training heart rate value and given an individualized walking program. The exercise regimen consisted of daily walking at the training heart rate for 45 to 60 minutes. The training heart rate was defined as 70% to 85% of the maximal heart rate attained during the treadmill test.

Twelve-hour fasting blood samples were drawn from the subjects in Vacutainers (Becton-Dickinson Vacutainer Systems) containing serum separation tube (SST) clot activating gel between 6:30 AM and 8 AM on days 1 and 14 of the regimen. The blood was transported on ice to the laboratory, and the serum was separated by centrifugation and stored at −80°C until analyzed.

Determination of Serum Lipids, Insulin, and Glucose

Total-C, high-density lipoprotein-cholesterol (HDL-C), and triglyceride (TG) levels were measured using standard enzymatic procedures on an Olympus Autoanalyzer (Quest Laboratories, Teterboro, NJ). The low-density lipoprotein-cholesterol (LDL-C) was calculated as follows: LDL-C = total-C − [HDL-C + (TG/5)], as described by Friedewald et al,[8] except when TG values were >400 mg/dL. Glucose concentration was determined using standard enzymatic procedures on the Olympus Autoanalyzer. Fasting insulin concentration was measured by radioimmunoassay (Diagnostic Systems Laboratories, Webster, TX). Insulin resistance was evaluated using homeostasis model assessment (HOMA-IR), which has been utilized and correlated with insulin sensitivity by the hyperinsulinemic-euglycemic clamp.[9,10] HOMA-IR was calculated as [fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5. Quantitative insulin-sensitivity check index (QUICKI)[11] is determined from a mathematical transformation of fasting blood glucose and plasma insulin levels and has been shown be to a surrogate for insulin sensitivity that correlates well with the minimal model and the hyperinsulinemic-euglycemic clamp. QUICKI = 1/[log(fasting insulin (μU/mL)) + log(fasting glucose (mg/dL))]. Because QUICKI is the reciprocal of the log-transformed product of fasting glucose and insulin, it is a dimensionless index without units.

Determination of Serum CRP, SAA, IL-6, Soluble Intracellular Adhesion Molecule-1, and Soluble Vascular Adhesion Molecule-1

Serum CRP, IL-6, soluble intracellular dhesion molecule-1 (sICAM-1), and soluble vascular adhesion molecule-1 (sVCAM-1) were measured in duplicate using enzyme-linked immunosorbent assay (ELISA) kits purchased from Diagnostic Systems Laboratories and R&D Systems (Minneapolis, MN). SAA was also measured in duplicate with an ELISA kit purchased from Antigenix America (Huntington Station, NY). According to the manufacture's inserts, these assays have coefficients of variation ± 3%.

Statistical Analysis

Statistical analyses were performed with Graph Pad Prism (GraphPad, San Diego, CA). Preintervention and postintervention values were compared using matched paired Wilcoxon signed-ranks tests for nonparametric data and Student's *t* test for normally distributed data. All data are expressed as mean ± SD unless otherwise noted. Figures are graphed using box plots with median and interquartile ranges. A *P* value of <.05 was considered statistically significant.

RESULTS

Fasting Lipids, Glucose, Insulin, and Anthropometry

Anthropometric and metabolic data are presented in Table 1. Following the diet and exercise intervention, mean weight loss was 2.91 ± 1.08 kg ($P < .01$), resulting in a decrease in body mass index (BMI) ($P < .01$), but subjects who were obese (BMI >30 kg/m^2) at the beginning of the program remained obese. Total-C, LDL-C, HDL-C, TG, and total-C/HDL-C ratio were all significantly decreased ($P < .01$). The 7% decrease in LDL-C/HDL-C ratio did not reach significance ($P = .1$). There were significant reductions in glucose (11%), insulin (26%), and HOMA-IR (34%) ($P < .01$), whereas QUICKI increased (6%).

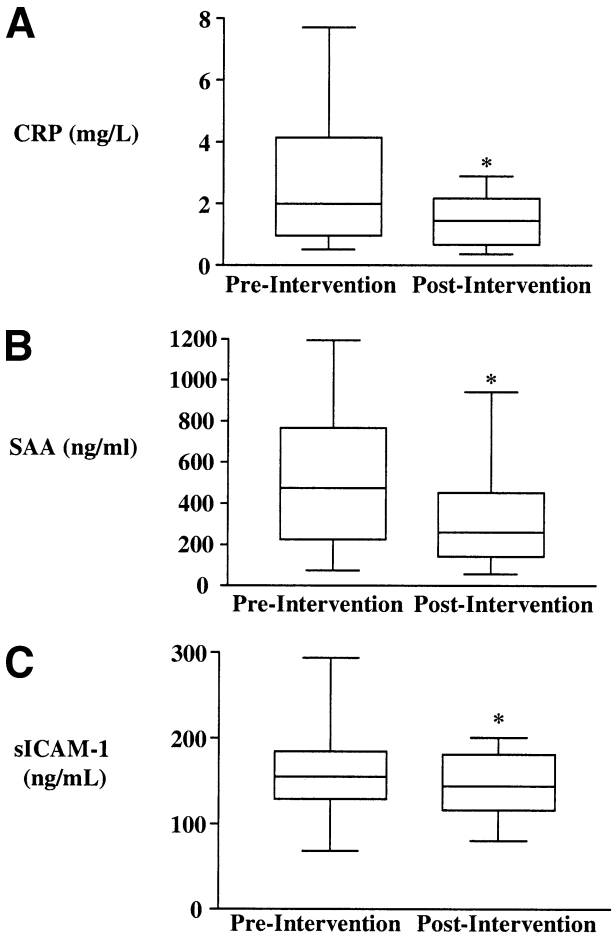

Fig 1. (A) Effect of diet and exercise intervention on serum concentration of serum CRP in postmenopausal women (N = 17), *$P <$ .01 post *v* pre. (B) Effect of diet and exercise intervention on serum concentration of SAA in postmenopausal women (N = 18), *$P <$ .01. (C) Effect of diet and exercise intervention on serum sICAM-1 in postmenopausal women (N = 20), *$P <$ .05. Box plots demonstrate median, 25th, and 75th percentile values.

Serum CRP, SAA, IL-6, sICAM-1, and sVCAM-1

After the diet and exercise intervention, there was a decrease in both markers of systemic inflammation (CRP: 2.62 ± 2.3 to 1.43 ± 0.9 mg/L, $P < .01$, Fig 1A; SAA: 517.4 ± 346.2 to 327.8 ± 246.4 ng/mL, $P < .05$, Fig 1B). IL-6 did not change (4.94 ± 2.48 to 4.93 ± 1.90 pg/mL). Additionally, there was a significant reduction in sICAM-1 (158.8 ± 48.3 to 145.6 ± 38.2 ng/mL, $P < .05$, Fig 1C). No change was found in sVCAM-1 (670.2 ± 245.7 to 678.8 ± 205.6 ng/mL).

In the 5 women not on HRT, the responses were similar. The only differences were a lower CRP prior to the intervention and no change in TG as a result of the intervention, most likely attributable to low TG preintervention (107 mg/dL).

DISCUSSION

The present study investigated whether a high-fiber, low-fat diet combined with daily aerobic exercise affects multiple CAD risk factors, such as lipids, inflammation, and cell adhesion in postmenopausal women at risk for CAD, most of who were on HRT. Postintervention, the women showed significant reductions in body weight, BMI, metabolic parameters (serum lipids, glucose, insulin, HOMA-IR), inflammatory proteins CRP and SAA, and the CAM sICAM-1, yet all remained overweight or obese.

Inflammatory Markers

In the present study, diet and exercise reduced CRP by 45%. CRP is an acute phase inflammatory protein, which is frequently used as a marker of inflammation and has been shown to be as stable as serum cholesterol[12] and has a long half-life, with no observable circadian variation.[13] Elevation of CRP is associated with increased risk of cardiovascular disease[14] and CAD risk in healthy postmenopausal women.[5,6] In addition, elevated plasma CRP compounds the effect of dyslipidemia on the risk of MI[15] and may be a stronger predictor of cardiovascular events than LDL-C.[16] Elevated CRP is associated with decreased nitric oxide bioavailability in human endothelial cells[17,18] and induces plasminogen activator inhibitor.[19] Along these lines, this diet and exercise intervention decreases plasminogen activator inhibitor[20] and improves nitric oxide bioavailability.[21]

Heilbronn et al[22] reported a reduction in CRP after obese women underwent a 3-month weight loss program using a low-fat, caloric-restriction diet (1,360 kcal/d, 15% fat). Bastard et al[23] reported that IL-6, but not CRP, was reduced in obese women associated with weight loss using a short-term, very–low-calorie diet for 3 weeks. Differences between these studies and the present study may be explained by the more intensive lifestyle changes, including an exercise component, as well as the type of foods consumed, which may have contributed to CRP reduction. Using a 1,200 kcal, National Cholesterol Education Program (NCEP) Step II diet for 12 weeks, Tehernof et al[24] noted that CRP reduction was associated with weight loss; a 16% weight loss was associated with a 32% decrease in CRP. In the present study, a 4% weight loss occurred with a 45% decrease in CRP. Additionally, these investigators[22,24] suggested that adipose–tissue-secreted IL-6 may mediate the increased CRP noted in obesity. If this pathway is involved in regulating CRP production, one would expect a reduction in IL-6 to parallel reductions in CRP levels in obese patients with weight loss. However, neither of the above studies measured IL-6. No change in IL-6 was noted in the present study, suggesting other regulators were involved in CRP reduction. There are several potential explanations for this finding. First, the diet and exercise treatment lasted only 2 weeks, which may not be a long enough time period to see a substantial decrease in IL-6. Along these lines, Ziccardi et al[25] showed that both IL-6 and CRP decreased after 1 year of diet, exercise, and behavioral counseling. Second, additional proinflammatory cytokines or other factors may be involved in the transcriptional control of CRP production at different stages of atherosclerotic lesion development. Third, it is possible that soluble serum IL-6 does not reflect the amount of membrane-bound IL-6.

Elevated SAA, another acute phase reactant, has been observed in subjects at risk for future CAD.[6] There was a signif-

icant reduction in SAA after the intervention. To our knowledge, our study is the first to assess the effects of diet and/or exercise on SAA. Ridker et al[6] noted that baseline levels of SAA were higher among postmenopausal women who subsequently had cardiovascular events, and SAA was significantly associated with risk of cardiovascular events even in the subgroup of women with a mean LDL-C of 104 mg/dL, underscoring the importance of inflammation in women with low cholesterol.

Lipids

The present study showed significant reductions in serum lipids and insulin, which agrees with previous larger studies using the same intervention for 3 weeks.[26,27] Evidence from several studies are consistent with the concept that high-fiber, low-fat diets reduce total-C and LDL-C, suggestive of decreased CAD risk, as reviewed by Kromhout et al.[7] The decrease in HDL-C is similar to earlier reports using the same intervention,[26,27] as well as studies by Brinton et al[28] using a low-saturated fat, low-cholesterol diet. However, the decrease in HDL-C was coupled with larger reductions in both LDL-C and total-C, thus reducing the total-C:HDL-C and LDL-C:HDL-C ratios. Additionally, it is now apparent that during an acute phase response HDL is proinflammatory, independent of the level of HDL-C.[29-31] In a study of 27 patients with normal levels of plasma HDL with angiographically documented coronary atherosclerosis, Navab et al[32] observed that the HDL from the patients was not protective against LDL oxidation. Although at a population level, higher plasma HDL levels are associated with lower risk for coronary atherosclerosis, at an individual level, the HDL function may be more important than plasma HDL levels and may be related to inflammation.

Adhesion Molecules

Adhesion and transendothelial migration of circulating leukocytes into the vessel wall involves various CAMs and is thought to be a critical step in early atherogenesis. Proinflammatory cytokines and oxidized LDL activate the endothelium and induce the expression of adhesion molecules that are crucial to the recruitment of inflammatory cells to the vessel wall. These adhesion molecules are released in soluble form into the bloodstream from proteolytic cleavage of membrane bound molecules and thus are considered to be markers of endothelial cell activation and inflammation.[33] Oxidized LDL may upregulate the expression of CAMs by endothelial cells, elevating serum sICAM-1 and E-selectin, but not sVCAM-1.[34] We hypothesized that levels of both sICAM-1 and sVCAM-1 would decrease in response to the diet and exercise intervention. This supposition was based on earlier observations by Beard et al,[35] who found reductions in the rate of formation of conjugated dienes and the peak value for them during in vitro LDL oxidation in response to this diet and exercise intervention. The present study found a significant reduction in serum levels of sICAM-1. Ziccardi et al[25] noted decreased sICAM-1 and sVCAM-1 after 1 year of diet, exercise, and behavioral counseling in obese women. The lack of response of sVCAM-1 in the present study may be due to the short duration of the intervention or membrane bound VCAM-1 levels may change in response to diet and exercise, but cannot be detected by the serum ELISA assay used.

Potential Mechanisms

The mechanisms responsible for the observed reductions noted in the present study may be due to direct effects of the intervention. This intervention has previously been documented to improve coronary flow reserve,[36] insulin sensitivity, blood pressure, oxidative stress, and nitric oxide availability.[21] The reduction in serum total-C and LDL-C is primarily due to the increase in fiber and decrease in fat intake,[7] respectively, and the reduction in TG is due to both the exercise[37] and the substitution of unrefined carbohydrates for saturated fat.[38] The reduction in inflammation may be related to attenuation of oxidative stress, as fruits and vegetables have been demonstrated to possess anti-inflammatory activities.[39] The addition of vegetables to the diet has been shown to reverse the increase in sICAM-1 and sVCAM-1 induced by high-fat meal consumption.[40] The exercise component may have contributed to the reduced CRP, as higher levels of physical activity are associated with reduced inflammation.[41] One limitation of the present study is that we cannot determine which component(s) of the intervention were responsible for the individual changes noted. However, currently both diet and exercise are recommended for optimal health.

Conclusions

This study is the first to document that even a short-term regimen of a high-fiber, low-fat diet combined with daily aerobic exercise, results in significant reductions in serum lipids, soluble CAM, and inflammatory proteins in postmenopausal women at risk for CAD, most of who were on HRT. Based on the changes noted, this intervention may provide an important immediate reduction in risk for an acute event. The changes observed appear to be largely independent of weight loss, as the magnitude of weight loss was minimal, no correlations were found between change in the parameters measured and change in BMI or body weight, and the obese subjects remained obese at the conclusion of the study. An intervention of this type may be of clinical benefit for those desiring a reduction in cardiovascular risk. The impressive response observed in a relatively short period highlights the value of intensive lifestyle modification in women at risk for acute MI, and if sustained, has the potential to mitigate the progression of atherosclerosis and its clinical consequences. Larger trials using an intervention of this type are warranted.

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