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Cardiometabolic risk reduction in an intensive cardiovascular health program

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Low-fat diet;
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Abstract *Background and aims:* Insulin and leptin are important markers of insulin resistance and vascular inflammation in metabolic and cardiovascular diseases. This study evaluated changes in circulating levels of insulin and leptin during a cardiovascular health program to improve our understanding of cardiometabolic risk reduction.
Methods and results: Participants ($n = 76$) completed a prospective, nonrandomized program designed to stabilize or reverse progression of coronary artery disease through dietary changes, exercise, stress management, and group support. Controls ($n = 76$) were matched to participants based on age, gender, and disease status. Traditional cardiovascular risk factors were assessed at baseline, 12 weeks, and 52 weeks by standard methods. Dietary data were collected by 72-h recall and evaluated by Food Processor® v8.4.0. Ultrasensitive insulin and leptin levels were measured by radioimmunoassay. Participants successfully reduced their total caloric intake from >2000 calories per day to ~1700 calories per day ($p < 0.05$ compared to controls), lowered daily fat intake by >60% ($p < 0.001$ compared to controls), and increased carbohydrate intake by >30% ($p < 0.001$). Repeated-measures ANOVA indicated significant beneficial changes ($p < 0.001$ compared to controls) in plasma insulin (−19%) and leptin (−33%) during the lifestyle program, as well as improvement in traditional cardiovascular risk factors. Response was similar between men and women for most risk factors and was not markedly influenced by medication use.
Conclusion: Lifestyle changes focusing on diet, physical activity, and stress reduction can successfully modify both cardiovascular and metabolic risk factors, with the potential to mediate cardiometabolic risk through beneficial anti-inflammatory and anti-oxidative effects on the vasculature.

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Introduction

Insulin and leptin represent two important and well-characterized markers of insulin resistance and vascular inflammation in metabolic and cardiovascular diseases (CVD). Insulin is a polypeptide hormone that affects the vascular endothelium by modulating glucose homeostasis and glycogen synthesis [1]. Fasting insulin levels have increased dramatically in non-diabetic adults over the past two decades, often developing as a consequence of resistance to the action of insulin in peripheral tissues [2]. Hyperinsulinemia has been linked to dyslipidemia, impaired glucose regulation, and hypertension [3], as well as overall risk for cardiovascular mortality [4].

Leptin is an adipocytokine secreted by white adipose tissue that functions mainly in energy balance and metabolism, but plays an important role in vascular physiology through interactions with the vascular endothelium [5,6]. High circulating levels of leptin may accelerate atherosclerosis and contribute to CVD risk by inducing oxidative stress on endothelial cells [7] and impairing arterial reactivity [8]. Clinical studies have shown that high leptin contributes to CVD risk in the general population and is associated with myocardial infarction and coronary events, independent of traditional cardiovascular risk factors [9,10].

Insulin resistance, vascular inflammation, and oxidative stress play important roles in endothelial dysfunction. Pharmacologic therapies to improve endothelial function show marked variability in their ability to lower circulating markers of inflammation [11], and are often used in combination to be most effective in reducing inflammation and oxidative stress. An alternative approach for treating patients with high cardiovascular risk involves lifestyle modification to reduce traditional CVD risk factors and slow or reverse progression of coronary atherosclerosis [12]. Lifestyle programs focusing on nutrition and exercise can improve endothelial function and enhance insulin sensitivity, in part by reducing markers of systemic vascular inflammation and insulin resistance [13].

Insulin and leptin have important effects on vascular biology, but may function through different molecular pathways — insulin through metabolic pathways and leptin through inflammatory and thrombogenic factors [14]. We investigated the impact of an intensive cardiovascular health program on circulating levels of insulin and leptin to improve our understanding of cardiometabolic risk factor reduction by (1) measuring changes in physiological risk factors for CVD throughout a year-long cardiac health program and (2) assessing response of insulin and leptin and relating changes in these inflammatory markers to improvement in vascular health.

Methods

Study population

The intervention group consisted of 76 white men and women who completed a prospective, nonrandomized program to stabilize or reverse progression of coronary artery disease (CAD) through dietary changes, exercise, stress management, and group support. Eligibility criteria were (1) a diagnosis of CAD, including acute myocardial infarction, bypass surgery, stent placement, stable angina, angioplasty, or evidence of $\geq$50% luminal narrowing on coronary angiogram; or (2) two or more CAD risk factors such as high blood pressure (BP) defined as systolic pressure $>$140 mm Hg or diastolic pressure $>$90 mm Hg, high total cholesterol ($>$200 mg/dL), physician diagnosed diabetes, obesity — body mass index (BMI) $\geq$30 kg/m^2, or family history of heart disease in parents or siblings. Physician approval, motivation to commit to following the guidelines of the program, and successful abstinence from smoking for at least three months prior to enrollment also were part of the acceptance criteria.

Controls ($n = 76$ white men and women) were matched to participants based on gender, age at baseline within five years, and CAD status (overt CAD or risk factors) using a prospective individual matching strategy to achieve a balanced distribution of risk factors between intervention participants and controls in nonrandomized clinical trials [15]. Controls receiving only standard care from their primary physicians underwent identical examinations at baseline, 12 weeks, and 52 weeks, but did not participate in the program or receive healthy lifestyle information.

This study was approved by the Institutional Review Board at Windber Medical Center. All participants voluntarily enrolled in the program and provided written informed consent.

Intervention

The lifestyle program included four components: (1) low-fat vegetarian diet ($<$10% of calories from fat); (2) 180 min/week of moderate aerobic exercise; (3) 1 h of stress management each day; and (4) two 1-h group support sessions per week for the first 12 weeks and one group session per week during the remainder of the year [16]. Adherence was self-reported by summarizing diet (fat, carbohydrate, protein intake), exercise (frequency and duration), stress management (frequency and duration), and group support (frequency of meeting attendance) for each day. Program staff reviewed compliance forms weekly and provided immediate feedback to participants on progress and guidance for improving adherence.

From January 2004 to February 2009, approximately 35 participants or controls were enrolled each year in separate cohorts of $\sim$12 individuals per cohort. The dropout rate was $\sim$32% ($n = 53$) among participants in the program, likely attributable to the magnitude of lifestyle changes required.

Physiological measures

Data collection and reporting followed recommendations of the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) group [17]. Clinical examinations conducted by physicians or trained personnel at baseline, 12 weeks, and 52 weeks collected information on age, gender, ethnicity, smoking status, cardiovascular history, and medication use. Height and weight measurements were used to calculate BMI. Blood pressure was recorded using a mercury sphygmomanometer on the arm of