

Brief Rapid Communications

Effect of Diet and Exercise Intervention on Blood Pressure, Insulin, Oxidative Stress, and Nitric Oxide Availability

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Background—Diet and exercise can affect blood pressure and atherosclerotic risk.

Methods and Results—The present study was designed to examine the effects of a short-term, rigorous diet and exercise intervention on blood pressure, hyperinsulinemia, and nitric oxide (NO) availability. Men (n=11) were placed on a low-fat, high-fiber diet combined with daily exercise for 45 to 60 minutes for 3 weeks. Pre- and post fasting blood was drawn for serum lipid, insulin, 8-isoprostaglandin $F_{2\alpha}$ (8-iso-PGF $_{2\alpha}$), and glucose measurements. Anthropometric parameters, blood pressure (BP), and 24-hour urinary NO metabolite excretion (NO $_x$), a marker of NO bioavailability, were measured. Systolic ($P<0.01$) and diastolic BP ($P<0.01$) and 8-iso-PGF $_{2\alpha}$ decreased ($P<0.05$), whereas urinary NO $_x$ increased ($P<0.05$). There was a significant reduction in fasting insulin ($P<0.01$) and a significant correlation between the decrease in serum insulin and the increase in urinary NO $_x$ ($r^2=0.68$, $P<0.05$). All fasting lipids decreased significantly, and the total cholesterol to high-density lipoprotein cholesterol ratio improved. Although body weight and body mass index ($P<0.01$) decreased, obesity was still present and there were no correlations between the change in body mass index and the change in insulin, BP, or urinary NO $_x$.

Conclusions—This intervention resulted in dramatic improvements in BP, oxidative stress, NO availability, and the metabolic profile within 3 weeks, mitigating the risk for atherosclerosis progression and its clinical sequelae. (*Circulation*. 2002;106:2530-2532.)

Key Words: hypertension ■ free radicals ■ oxygen ■ insulin

Hypertension affects more than 50 million people in the United States and is a hallmark risk factor for stroke, congestive heart failure, renal insufficiency, and coronary artery disease.¹ It has been estimated that one quarter of all adults have hypertension and only 47% have optimal blood pressure (BP, <120/80) in the United States.² Hypertension is a major component of the metabolic syndrome which affects ≈23% of the population in Westernized societies.³

Recently, attention has focused on oxidative stress as a causative factor in hypertension.⁴ We have shown that a high-fat, refined carbohydrate diet results in oxidative stress, decreased NO availability, and endothelial dysfunction in animals.⁵ One study in humans has demonstrated that a low-fat diet with fruits, vegetables, and low-fat dairy can reduce BP in both hypertensive and normotensive individuals.⁶ Furthermore, exercise has been shown to lower BP in hypertensive individuals.⁷ Accordingly, this study was designed to investigate the effects of a combined, short-term diet and exercise intervention on hypertension, oxidative stress, and NO availability in men.

Methods

Diet and Exercise Intervention

The study protocol was approved by the Human Subjects Protection Committee and informed consent of all subjects was obtained before

enrollment. Serum was obtained from 11 men (age range=38 to 72 years) who voluntarily participated in the Pritikin Longevity Center 21-day residential diet and exercise intervention. Diseases under drug therapy included hypercholesterolemia and hypertension in 3 individuals each. Hypertension was present in 7 patients and type 2 diabetes in 2 patients.

Once enrolled, a complete history was taken and participants received a physical examination and underwent a 21-day diet and exercise intervention. Meals were served buffet style, and all participants were allowed to eat ad libitum. This was intended to explore the effect of altered food composition as opposed to its quantity. Prepared meals contained ≈10% of calories from fat (polyunsaturated/saturated fatty acid ratio=1.24), 15% to 20% from protein, and 70% to 75% from primarily unrefined carbohydrate. Carbohydrates were from high-fiber whole grains (≥5 servings/d), vegetables (≥4 servings/d), and fruits (≥3 servings/d). Protein was primarily derived from plant sources, with nonfat dairy (up to 2 servings/d) and fish or fowl served (in 3 1/2 oz. portions) 1 d/wk and soups or casseroles (2 d/wk). Alcohol, tobacco, and caffeinated beverages were not allowed.

BP at rest was measured using standard auscultation techniques after several minutes of quiet rest in the supine position. The exercise regimen consisted of daily walking at the training heart rate for 45 to 60 minutes, determined by a graded treadmill stress test. The training heart rate was defined as 70% to 85% of the maximal heart rate obtained during the treadmill exercise tolerance test.

Fasting blood samples were drawn on days 1 and 21, and serum was separated by centrifugation and stored at -80°C until analyzed.

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Metabolic Characteristics

	Preintervention	Postintervention	% Decrease
Body weight, kg	107.1±5.8	103.1±5.7†	3.7
BMI	37.6±2.8	36.1±2.6†	3.9
Total-C, mg/dL	191.5±9.2	154.5±6.9†	19.3
LDL-C, mg/dL	113.2±6.1	87.5±6.0†	22.7
HDL-C, mg/dL	41.6±3.1	35.5±1.8†	14.8
TG, mg/dL	223±52	131±20*	41.3
Total-C/HDL-C	4.95±0.42	4.39±0.35*	11.3
Systolic BP, mm Hg	137.8±4.3	119.0±2.9†	13.6
Diastolic BP, mm Hg	81.4±2.2	73.4±2.4†	9.8
Insulin, μ U/mL	22.9±3.9	12.3±1.8†	46.2
Blood glucose	105.8±5.6	98.5±3.9	7.0

All data are expressed as mean±SEM.

* $P<0.05$, † $P<0.01$ postintervention vs preintervention.

Determination of Metabolic Parameters, 8-Iso Prostaglandin $F_{2\alpha}$, and Urinary NO Metabolite Excretion

Triglycerides (TG), total cholesterol (Total-C), HDL-cholesterol (HDL-C), glucose, and insulin were measured as previously described.⁸ Serum 8-isoprostaglandin $F_{2\alpha}$ (8-iso-PGF_{2 α}) was measured using an enzyme immunoassay kit (Cayman Chemical). Twenty-four-hour urine was collected on days 1 and 21, and urinary NO metabolite excretion (NO_x) was measured as previously described.⁵

Statistical Analysis

Statistical analyses were performed with Graph Pad Prism (Graph Pad Software, Inc). Pre- and post values were compared using matched pair *t* tests. Data are expressed as mean±SEM, with $P<0.05$ considered significant.

Results
Anthropometry, BP and Metabolic Parameters

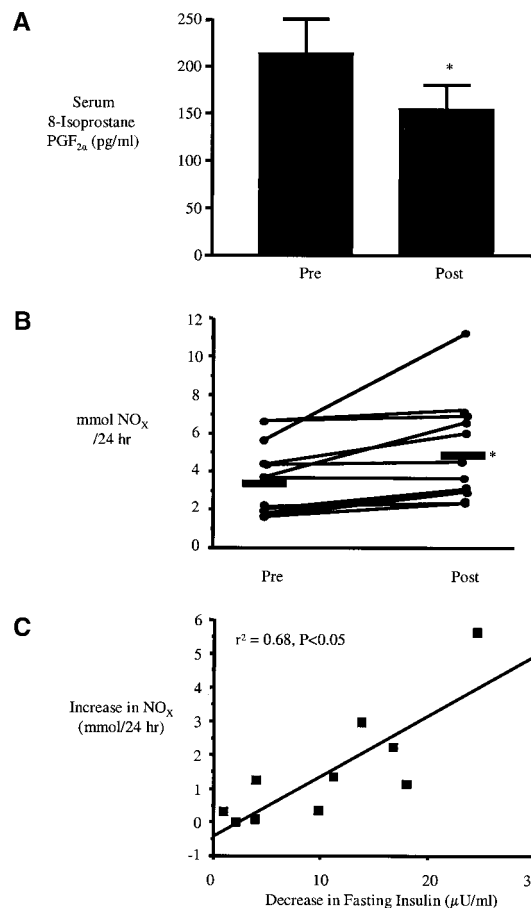
The 21-day diet and exercise intervention significantly reduced body weight ($P<0.01$) and body mass index (BMI; $P<0.01$) without eliminating obesity (BMI>30 kg/m²) (Table). Both systolic ($P<0.01$) and diastolic ($P<0.01$) BP and fasting insulin decreased substantially. The decrease in plasma glucose was not significant; however, the fasting insulin to glucose ratio, a marker of insulin sensitivity, improved significantly ($P<0.01$). Serum lipids fell significantly, and the Total-C:HDL-C ratio improved ($P=0.05$).

Oxidative Stress and Urinary NO_x

Serum 8-iso-PGF_{2 α} decreased ($P<0.05$) and urinary NO_x increased ($P<0.05$) (Figure). There was a significant correlation between the decrease in serum insulin and the increase in urinary NO_x ($r^2=0.68$, $P<0.05$).

Discussion

Presently, most recommendations for lifestyle modification to reduce BP emphasize weight loss and reducing salt and alcohol consumption. Interventions such as daily exercise and other dietary modifications (ie, carbohydrate type, fiber intake, dietary fat type, and intake), however, have received less attention. The present study is the first to show that unrestricted consumption of a low-fat, high-fiber diet and daily exercise can mitigate oxidative stress, improve NO availability, and normalize BP in obese men within 3 weeks. The men exhibited significant reductions in systolic and diastolic BP, BMI, serum lipids, insulin, and 8-iso-PGF_{2 α} ,



Effect of diet and exercise intervention on 8-iso-PGF_{2 α} (A). Effect of diet and exercise intervention on urinary NO_x (B). Relationship between urinary NO_x and insulin (C). Values are means±SE. * $P<0.05$ versus Post versus Pre.

with significant improvement in insulin sensitivity and increase urinary NO_x.

The Dietary Approaches to Stop Hypertension (DASH) clinical trial,⁶ which tested a diet high in fruits and vegetables and low-fat dairy and reduced red meat, sugar, and refined carbohydrates, demonstrated significant BP reduction after 8 weeks. In the present intervention, more pronounced reductions in systolic (19 mm Hg) and diastolic (8 mm Hg) BP occurred within 3 weeks. At the beginning of the study, 7 of the 11 subjects were hypertensive, but at the end none had hypertension (>140 mm Hg systolic or >90 diastolic). The more robust reductions in BP and other changes noted in the present study compared with previous studies were most likely due to the more rigorous dietary changes, the added exercise, or a combination of the two. Weight loss per se was probably not a significant contributor in the present study, as there was no association between changes in BP and BMI. The average BMI decreased from 37.5 to 36.1, indicating the presence of obesity post-intervention despite blood pressure normalization. In a recent study,⁹ intentional weight loss achieved by gastric surgery, yielding a sustained weight loss of ≈ 20 kg, had no effect on the incidence of hypertension during an 8-year observation period.

Increased intake of fiber, antioxidants, and other phytochemicals, as well as the reduced fat and refined sugar

consumption, most likely contributed to the reductions in insulin and oxidative stress and the improvements in urinary NO_x and BP in the present study. Vogel et al¹⁰ demonstrated that a single high-fat meal could impair endothelial function in healthy individuals, and this response was blocked by pretreatment with antioxidant vitamins C and E, suggesting an oxidative mechanism.¹¹ Title et al¹² reported an impairment in endothelium-dependent flow-mediated vasodilation in healthy subjects after an oral glucose load, which was also prevented with antioxidant pretreatment. More recent data suggests that fruits and vegetables may reduce BP,¹³ protect against lipid peroxidation, and augment antioxidant capacity as evidenced by increased plasma carotenoids (ie, cryptoxanthin, lutein, β-carotene)^{14,15} and serum oxygen radical-absorbing capacity.¹⁴

Isoprostanes are a family of eicosanoids produced mainly by non-enzymatic oxidation of arachidonic acid by reactive oxygen species. Consequently, their production is increased in the presence of oxidative stress. The reduction of 8-iso-PGF_{2α} in the present study suggests amelioration of oxidative stress by the diet and exercise intervention. Thompson et al¹⁵ documented a 35% reduction in urinary 8-iso-PGF_{2α} after 14 days of consuming an array of fruits and vegetables and suggested that this was important for maximizing exposure to a variety of beneficial phytochemicals, many of which remain undefined. This may contribute to an increase in NO availability, as observed in this study, as well as a decrease in other oxidative processes that contribute to hypertension and other chronic diseases.

There was a significant improvement in NO availability after the diet and exercise intervention. This could be due to either an increase in NO production or a decrease in NO sequestration by reactive oxygen species. The reduction in 8-iso-PGF_{2α} suggests a reduction in reactive oxygen species and hence reduced scavenging of NO. The latter conclusion is based on our previous animal studies, which documented that consumption of a Western-type diet can limit NO availability via enhanced reactive oxygen species-mediated inactivation and sequestration of NO.⁵

The exercise component may have contributed to the improved NO availability and reduction in BP. Exercise training has been shown to increase NO production and NOS expression, enhance antioxidant enzyme levels, and ameliorate endothelial dysfunction.¹⁶ Thus, the added exercise may have contributed to the increased urinary NO_x and decreased 8-iso-PGF_{2α}, as well as the more significant drop in BP noted in the present study compared with previous studies.⁶ In addition, both the diet and exercise could contribute to the improvement in insulin sensitivity in the present study. Petrie et al¹⁷ have shown that insulin sensitivity is related to endothelial function, a process that may account for the significant correlation between the reduction in insulin and the increase in urinary NO_x found in the present study.

One limitation is that the assay used to detect lipid peroxidation is dependent on both the extent of oxidative stress and on lipid substrate abundance. Additionally, 8-iso-PGF_{2α} may be produced by cyclooxygenase-dependent mechanisms, although this is thought to be negligible under physiological conditions.¹⁸

The present study demonstrates that an unrestricted low-fat, high-fiber diet combined with daily exercise can significantly lower BP and ameliorate hypertension, as well as improve risk factors for

other chronic diseases in a very short time. It is of note that merely a change in the food composition without restriction in food consumption resulted in improvements in all parameters. The greater changes observed in the present study compared with previous studies suggests that more intensive changes in lifestyle lead to greater improvements. Additionally, the improvements achieved in the lipids, insulin/glucose, oxidative stress, NO availability, and blood pressure may mitigate the progression of chronic diseases such as coronary artery disease and diabetes.

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