The Effect of High-Protein Diets on Coronary Blood Flow

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ABSTRACT

Recent research has demonstrated that successful simultaneous treatment of multiple risk factors including cholesterol, triglycerides, homocysteine, lipoprotein (a) [Lp(a)], fibrinogen, antioxidants, endothelial dysfunction, inflammation, infection, and dietary factors can lead to the regression of coronary artery disease and the recovery of viable myocardium. However, preliminary work revealed that a number of individuals enrolled in the original study went on popular high-protein diets in an effort to lose weight. Despite increasing numbers of individuals following high-protein diets, little or no information is currently available regarding the effect of these diets on coronary artery disease and coronary blood flow.

Twenty-six people were studied for 1 year by using myocardial perfusion imaging (MPI), echocardiography (ECHO), and serial blood work to evaluate the extent of changes in regional coronary blood flow, regional wall motion abnormalities, and several independent variables known to be important in the development and progression of coronary artery disease. Treatment was based on homocysteine, Lp (a), C-reactive protein (C-RP), triglycerides, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and fibrinogen levels. Each variable was independently treated as previously reported. MPI and ECHO were performed at the beginning and end of the study for each individual. The 16 people (treatment group/TG) studied modified their dietary intake as instructed. Ten additional individuals elected a different dietary regimen consisting of a "high-protein" (high protein group/HPG) diet, which they believed would "improve" their overall health.

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(Abstract continued)

Patients in the TG demonstrated a reduction in each of the independent variables studied with regression in both the extent and severity of coronary artery disease (CAD) as quantitatively measured by MPI. Recovery of viable myocardium was seen in 43.75% of myocardial segments in these patients, documented with both MPI and ECHO evaluations. Individuals in the HPG showed worsening of their independent variables. Most notably, fibrinogen, Lp (a), and C-RP increased by an average of 14%, 106%, and 61% respectively. Progression of the extent and severity of CAD was documented in each of the vascular territories with an overall cumulative progression of 39.7%. The differences between progression and extension of disease in the HPG and the regression of disease in the TG were statistically (p<0.001) significant.

Patients following recommended treatment for each of the independent variables were able to regress both the extent and severity of their coronary artery disease (CAD), as well as improve their myocardial wall motion (function) while following the prescribed medical and dietary guidelines. However, individuals receiving the same medical treatment but following a high-protein diet showed a worsening of independent risk factors, in addition to progression of CAD. These results would suggest that high-protein diets may precipitate progression of CAI) through increases in lipid deposition and inflammatory and coagulation pathways.

Introduction

The pathogenesis of coronary artery disease (CAD) has been shown to be related to several independent risk factors[1-65] with efforts focused at reversing CAD leading to mixed results over the last 50–60 years despite the efforts of countless researchers. Recent work[65] has demonstrated that CAD may in fact be more of an immunologic problem, precipitated by a number of factors, including dietary indiscretions. With ever-increasing numbers of Americans becoming overweight, diets promising quick weight loss are consumed almost as rapidly as the foods they promote. Of particular concern is the unknown health risks these different dietary regimens may have. Recent work[65] has demonstrated just how hard it is to reverse or even minimize heart disease when people follow popular dietary plans.

In an effort to further investigate this immunologically mediated theory of vascular disease[2-3,65] and the effect of dietary factors on it, 26 subjects were studied for 1 year. Patients were instructed to follow a recommended dietary program previously shown[6,7] to successfully lower serum lipid concentrations and reverse CAD. Throughout the study, each individual was questioned regarding dietary habits. Several independent variables including serum lipid concentrations (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, and triglycerides), fibrinogen, C-reactive protein (C-RP), lipoprotein (a) [Lp(a)], and homocysteine were monitored. Coronary blood flow was quantitated via myocardial perfusion imaging (MPI), and regional wall motion abnormalities were assessed by means of both MPI and echocardiography (ECHO).

At the conclusion of the study, it became apparent that 10 of the 26 individuals, despite receiving dietary instruction as outlined below, had adopted a high-protein diet throughout the study. The results of 16 individuals who followed the prescribed treatment program (TG) and the 10 individuals who received the same medical treatment while following a high-protein diet (HPG) were subsequently compared to determine differences in outcomes based on differences in dietary regimens including (1) differences in the independent blood variables and (2) differences in myocardial blood flow.

Methods

Patient Recruitment

Twenty-six people were enrolled in a prospective study to determine the effect of treatment and dietary management on MPI, wall motion, weight, and several independent variables (described below under blood work) over a 12-month period. Patients were excluded from the study if they had undergone any prior coronary revascularization or interventional procedure (coronary artery bypass grafting [CABG], percutaneous transluminal coronary angioplasty [PTCA], atherectomy, or stent). They were excluded if they had a history of documented heart disease, had "severe" aortic stenosis, were pregnant, or planned to become pregnant. All patients signed institutional consent forms before participation.

These 26 individuals ranged from 29 to 71 years of age and included 14 men and 12 women. Of these there were 22 whites, two African-Americans, one Hispanic, and one Italian immigrant.

Echocardiographic Evaluation

Conventional two-dimensional (2D), M-mode and Doppler (including color flow) echocardiographic evaluation was performed by using standard views consisting of parasternal long- and short-axis views, apical two-, four-, and five-chamber views, as well as subxiphoid views. These evaluations were performed at the beginning and end of the study to look for evidence of regional wall motion abnormalities including diastolic dysfunction.

Myocardial Perfusion Imaging

Single-photon emission computed tomography (SPECT) imaging with high-dose dipyridamole (HDD) and sestamibi was used to look for CAD and regional wall motion abnormalities as previously described.[1,66-71] Patients underwent imaging at the beginning and end of the study. The extent and severity of perfusion through each of the coronary beds was determined quantitatively as previously described.[65,72]

Blood Work Analysis

All blood work was obtained following a 12-hour fast. Venous samples included homocysteine, Lp (a), fibrinogen, C-RP, triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, and VLDL cholesterol. Samples were obtained every 6 weeks.

Table I

Treatment Protocol Based on Independent Variables

Independent Variables	Dietary (Calories and Saturated Fats)	Folate, Vitamins B_6 and B_{12}	Statins	Fenofibrate
LDL (< 100 mg/dL)	X		X	+/−
TG (< 150 mg/dL)	X		+/−	X
Fibrinogen (200–400 mg/dL)				X
Lp(a) (< 30 mg/dL)				Lovastatin
Homocysteine (< 9.0 μmole/L)	X	X		
Pos CRP (< 0.9 mg/dL)			Pravastatin	

LDL = low-density lipoprotein cholesterol, TG = triglycerides, Lp(a) = lipoprotein (a),
Pos CRP = elevated C-reactive protein.

Treatment of Blood Work Results

Medical management was individualized based on the blood work obtained every 6 weeks. Independent adjustment of medications was made as a result of each patient's blood work and was not based on the patients dietary habits. Table I shows the treatment guidelines employed. For example, a patient with elevated triglycerides and lipoprotein (a) would be treated with fenofibrate while a patient with only elevated lipoprotein (a) would receive Lovastatin. The range of acceptable levels for each of these independent factors is also shown in Table I.

Dietary Recommendations

Each patient was advised to consume a diet consisting of 10 kCal/pound/day. On the basis of caloric calculations, patients were instructed to consume 15% of their daily calories in protein, 70% in carbohydrate (principally complex carbohydrates), and 15% in fat with a 2:1 ratio of nonsaturated (polyunsaturated, monosaturated) to saturated fat intake. For example, a 170-pound person would be instructed to eat 1,700 calories per day, including 255 calories from protein (64 grams), 1,190 calories from carbohydrates (297 grams) from a variety of (mostly complex) carbohydrates, and 255 calories fat (28 grams), of which no more than 9 grams could be "saturated."

Other Treatment

Patients with anginal symptoms were treated with standard drug regimens including the use of long-acting nitroglycerine (Imdur®, Ismo®), slow calcium channel antagonists (Procardia XL®, Diltiazem®), β-blockers (Tenormin®, Atenolol®), L-arginine (endothelial dysfunction), and macrolide antibiotics (Biaxin®) for elevated C-RP with acute-phase antibodies[65,73] to *H. pylori*, *C. pneumoniae,* or *S. pneumoniae.*

Statistical Analysis

Descriptive statistics including mean ± standard deviation and standard error was determined for each of the independent blood variables, in addition to weight and age of patients. Following determination of the extent and severity of coronary artery disease, the percent of involvement was determined for each individual along with changes from beginning to the end of the study. The results between the two groups, treatment group vs high-protein group (TG vs HPG) were then compared by using a two-tailed Student's t test.

Table II

Changes in Extent and Severity of Disease

	Percent Extent LAD	Percent Severity LAD	Percent Extent RCA	Percent Severity RCA	Percent Extent LCx	Percent Severity LCx	Percent Extent L-C	Percent Severity L-C	Percent Extent Total	Percent Severity Total
TG	−4.7	−5.0	−6.1	−10.3	−6.9	−8.2	−5.2	−3.2	−22.9	−21.8
HPG	+1.5	+8.0	+5.2	+18.1	+15.3	+12.7	+17.7	+13.2	+39.7	+52.0
p Value	<0.20	<0.005	<0.005	<0.001	<0.001	<0.001	<0.001	<0.005	<0.001	<0.001

TG = treatment group, HPG = high-protein group, LAD = left anterior descending, RCA = right coronary artery, LCx = left circumflex, L-C = left anterior descending-left circumflex, p value = level of statistical significance between groups.

Results

There were eight women and eight men in the TG with an average age of 48 ±11 years compared with an average age of 55 ±14 years in the HPG. The TG consisted of 12 whites, two African-Americans, one Hispanic, and one Italian immigrant. The HPG consisted of six men and four woman—all whites.

Patients who went on high-protein diets reported varying degrees of satisfaction. Family reports typically reflected initial patient satisfaction, the patients getting to eat foods they "enjoyed" along with initial weight loss, but difficulty sustaining the dietary pattern for the entire year. Instead patients tended to adhere to the diet for several months at a time, return to prior eating habits, and then return again in an effort to lose weight. By the end of the study, patients had lost only an average of 1.0% body weight, dropping from an average of 182.3 pounds to 181 pounds. This reduction of 1.3 pounds was accompanied by a 3% increase in homocysteine (7.0 to 9.0 μmole/L), a 106% increase in Lp (a) from 5.2 to 10.7 mg/dL, a 14% increase in fibrinogen from 292 to 332 mg/dL, and a 61% increase in C-RP from 3.0 to 4.9 mg/dL. The results of changes seen in the TG have been reported elsewhere[65] and showed reductions in homocysteine, Lp (a), fibrinogen, and C-RP. Despite differences in the TG and HPG, the differences in the independent variables were not statistically significant.

The effect on changes in the extent and severity of coronary artery disease was statistically different between patients in the TG and HPG as shown in Table II. Specific case examples of differences in coronary blood flow following treatment in the TG and HPG are shown in Figure 1. The extent and severity of disease in the left anterior descending (LAD) artery showed an average regression of –4.7 ±6.4% and –5.0 ±6.1, respectively, in individuals in the TG, compared with progression of disease in the HPG. The progression of LAD disease for patients in the HPG was 1.5% (extent) and 8.0% (severity), respectively.

As shown in Table II, there was regression of both the extent and severity of disease in the right coronary artery (RCA), left circumflex (LCx) and left anterior descending-left circumflex (L-C) distributions, which were statistically significantly different from the results seen in the

HPG. The overall effect seen in the TG was a 23% regression in the extent of CAD and a 22% reduction in the severity of CAD, which was statistically significantly (p < 0.001) different from the effects seen with advancement in CAD following a high-protein diet (HPG). The overall effect seen in patients treated who followed high-protein diets was a progression in the overall extent of CAD of 39.7%.

Regional wall motion abnormalities[69,70] which can represent myocardial infarction (MI), stunned or hibernating myocardium, were noted in seven (43.75%) of the patients in the TG, including four instances of anterior/anteroseptal wall motion abnormality, four of inferior wall motion abnormality, and two of anterolateral wall motion abnormality. Of these, five of the individuals had wall motion abnormalities in only one region, one had wall motion abnormalities in two regions, and the last person had wall motion abnormalities in three myocardial regions. In each case, there was normalization of wall motion following treatment, which matched improvement in MPI. None of the patients in the HPG demonstrated improvement in wall motion.

Discussion

Twenty-six people were studied for 12 months to determine the effect of treatment on risk factors based on an immunologically mediated theory of vascular disease. This approach to treatment has previously been shown to successfully regress or stabilize CAD in 100% of those individuals studied, assuming they followed the recommended dietary program described[6-7,65] previously. However, prior studies have shown that individuals following high-protein diets may experience adverse effects on serum lipids[65,74] and that progression[65] of CAD may be a consequence of high-protein diets, in addition to other postulated side effects including ketosis, osteoporosis, renal damage, and others.

Despite fluctuations in weight, minimal weight loss was noted during the 12 months. The differences between dietary approaches did not lead to statistically significant differences; however, those in the HPG showed worsening of serum lipids and inflammatory factors while pa-
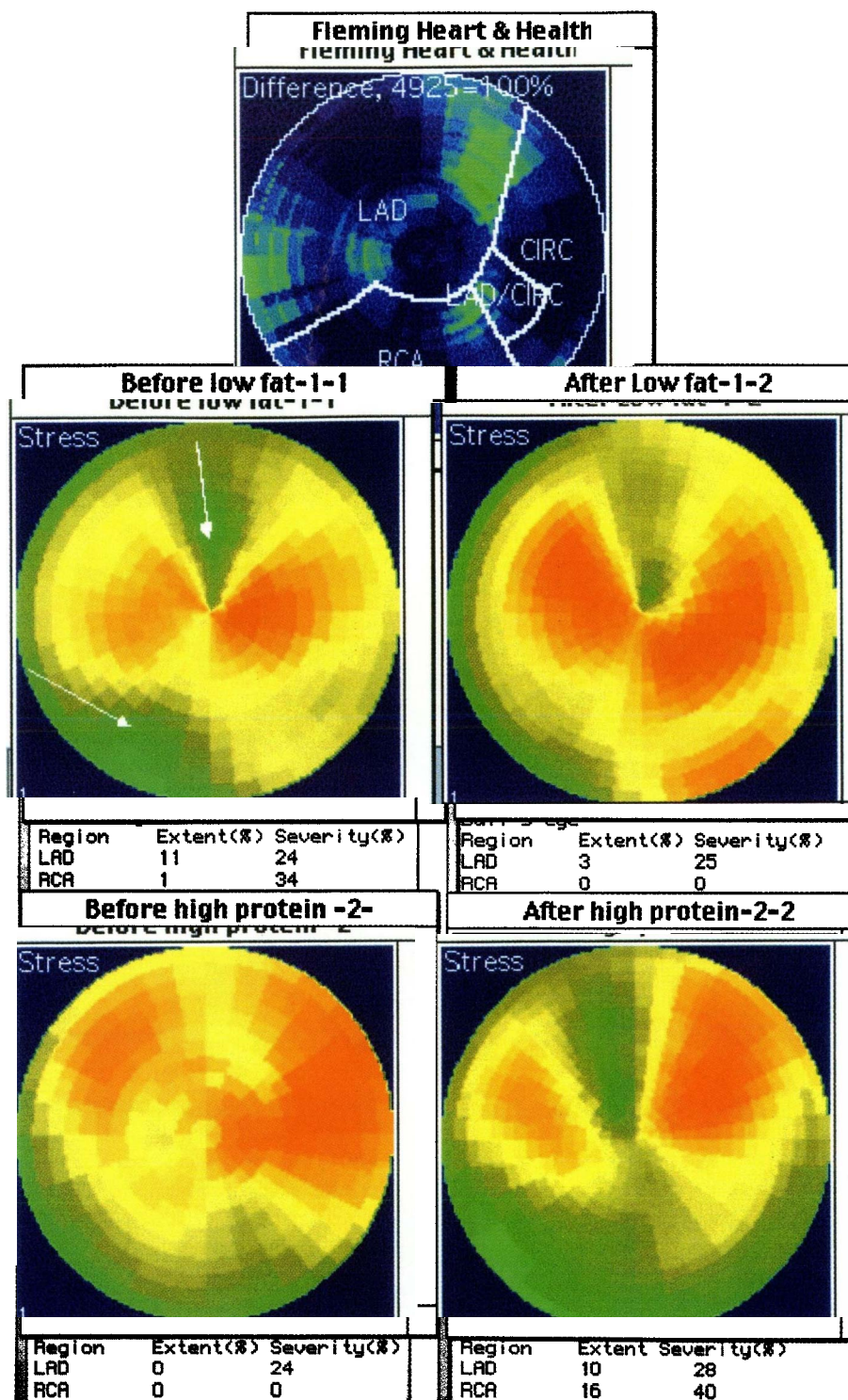
Figure 1.
Example of patients following medical management and recommended dietary changes versus a patient receiving medical management and a high-protein diet.

The lower four images represent a bullseye image of myocardial perfusion with the anterior wall of the heart displayed at the 12 o'clock position, the lateral wall at 3 o'clock, the inferior/posterior region at 6 o'clock, and the septum at the 9 o'clock position. Red represents normal perfusion, and less perfusion is sequentially shown by orange, yellow, and green. Quantitation of each of the vascular beds affected is shown below each image describing the extent and severity of blood flow reduction for each image. The top two panels show the effect of 1 year's treatment with improvement in the extent and severity in coronary artery disease in both the LAD and RCA following recommended dietary changes and medical management. The bottom two images show progression of coronary artery disease in each of the vascular beds shown for a representative patient who was treated medically and followed a high-protein diet. The distribution of each coronary artery is shown in the upper image as described previously.[65]

tients in the TG showed improvement. Individuals following a high-protein diet were treated with the same medications as those individuals in the treatment group. Despite the use of the same medications, increased serum lipids were noted and were consistent with changes reported previously[74] when 24 subjects were studied in the late 1970s. This would suggest that while the

number of individuals in this study who followed the high-protein diet were relatively small, they are representative of larger numbers of individuals studied previously, without MPI or echocardiography. Since the results of blood work are representative of prior studies, the outcomes of regional coronary blood flow as documented by MPI and wall motion abnormalities as assessed by MPI and ECHO should likewise be representative of the population as a whole.

Individuals following our balanced dietary regimen (treatment group) showed improvement in homocysteine levels, while those eating a high-protein diet showed an increase in homocysteine levels. This increase no doubt reflects an increased dietary loading of protein (methionine) and possibly increased physiologic stress. This increased physiologic stress could subsequently adversely affect the body's handling of any increased oxidative load, which in and of itself could lead to a worsening of heart disease.

Of additional interest is the effect that high-protein diets had on C-RP levels. C-RP is indicative of either an inflammatory or infectious process. If people following a high-protein diet have elevations in lipids, fibrinogen, Lp (a), and C-RP, as they did in this study, then one would expect an increase in inflammatory response, which could accelerate the atherosclerotic process as previously described.[2,65]

Finally, in this study seven individuals in the TG had regional wall motion recovery of viable myocardium (43.75%) while none of those in the HPG demonstrated recovery of wall motion. The worsening of atherosclerosis from following a high-protein diet was associated with a progression of both extent and severity of CAD on the order of a 5-10% increase over a 12-month period. This is particularly alarming if this is representative of patients as a whole.

the body's immunologic system appears to attempt to control or minimize. Efforts to control or reduce CAD must therefore address as many of these factors as possible in an effort to reduce not only the extent and severity of CAD but also the end result, which is myocardial damage. The differences seen between these two groups of patients would support the idea that high-protein diets not only produce ketosis, osteoporosis, and renal problems but also appear to increase lipids and inflammatory factors, which lead to the progression of CAD.

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Conclusion

Atherosclerotic coronary artery disease appears to be an immunologically mediated disease precipitated by poor dietary habits and lifestyle choices. These dietary habits and lifestyle choices can result in damage to coronary endothelium with subsequent development of plaques, which

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