Dietary fiber and progression of atherosclerosis: the Los Angeles Atherosclerosis Study

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ABSTRACT

INTRODUCTION

Cardiovascular disease (CVD) due to advanced atherosclerosis is the leading cause of death and disability in the United States (1). Numerous risk factors, including dietary pattern, physical inactivity, serum lipids, diabetes, smoking, obesity, and psychological stress, have been proposed as contributing to the initiation and development of atherosclerosis and its clinical manifestations (2). The possible health benefits of dietary fiber in reducing the risk of CVD were hypothesized in the 1970s (3). Evidence of associations between dietary fiber and atherosclerosis has accumulated from epidemiologic observa-

Background: Several epidemiologic studies found weak protective relations between dietary fiber intake and the risk of cardiovascular disease events. However, few of the studies addressed possible mechanisms of the effect.

Objective: In the present study, we estimated relations between the progression of atherosclerosis and the intake of selective dietary fiber fractions. Mediation of the relations by serum lipids was also investigated.

Design: Participants who were free of heart disease and aged 40–60 y were recruited into the cohort (n = 573; 47% women). The intima-media thickness (IMT) of the common carotid arteries was measured ultrasonographically at the baseline examination and at 2 follow-up examinations (n = 500), dietary intakes were assessed with six 24-h recalls (3 at baseline and 3 at the first follow-up examination), and blood samples were analyzed at baseline and at both follow-up examinations.

Results: A significant inverse association was observed between IMT progression and the intakes of viscous fiber (P = 0.05) and pectin (P = 0.01). Correction for measurement error increased the magnitude of these estimated effects. The ratio of total to HDL cholesterol was inversely related to the intakes of total fiber (P = 0.01), viscous fiber (P = 0.05), and pectin (P = 0.01). The magnitude of the association between IMT progression and the intakes of viscous fiber and pectin was attenuated by adjustment for serum lipids.

Conclusions: The intake of viscous fiber, especially pectin, appears to protect against IMT progression. Serum lipids may act as a mediator between dietary fiber intake and IMT progression. Am J Clin Nutr 2003;78:1085–91.

KEY WORDS Dietary fiber, measurement error, atherosclerosis, intima-media thickness, serum lipid, cohort study

SUBJECTS AND METHODS

Study population

The Los Angeles Atherosclerosis Study is a prospective study designed to investigate the relation between potential etiologic factors and atherosclerosis progression. The cohort was described previously (22, 23). In brief, 269 women aged 45–60 y and 304 men aged 40–60 y who had no history of heart attack, angina, revascularization, or stroke at entry into the study were randomly sampled from strata in a large utility
company. The strata were age, ethnicity (Hispanic or non-Hispanic), and smoking status. Hispanics and smokers were oversampled. The participation rate among the sampled eligible employees was 85%, which resulted in a cohort of 573 subjects at the baseline examination. The baseline examination took place in 1995–1996. Two follow-up examinations were conducted at 1.5 and 3 y. Seventy-three subjects were excluded because of loss to follow-up, resulting in a longitudinal study sample of 500 participants. There were no significant differences in baseline characteristics between these participants and the 73 subjects who were not followed up. In the analysis of serum lipids, 53 subjects were excluded from the present analysis because of a nonfasting blood draw (last meal < 8 h before the draw) or a serum triacylglycerol concentration > 3.95 mmol/L, and 2 subjects were excluded because of missing lipid measurements. Five subjects were excluded because of large discrepancies between repeated measures of total cholesterol (TC) concentration (difference > 3.36 mmol/L). The protocol for this study was approved by the Institutional Review Board of the Keck School of Medicine of the University of Southern California. Written informed consent was obtained from all the participants.

Measurement of carotid intima-media thickness

The protocol for measurement of the common carotid intima-media thickness (IMT) that was used in this study was described previously (22). Briefly, a 1-cm segment of the far wall adjacent to the carotid bulb was analyzed by using automated software with an edge-detection algorithm developed at the Jet Propulsion Laboratory (Pasadena, CA) (24). Measurements were averaged over the left and right carotid artery in the supine and lateral positions. A reproducibility study of this protocol detected a mean absolute difference of 0.022 mm (CV of 2.8%) between repeated scans by 2 sonographers. Scan readers were blinded to dietary fiber intake. All measurements were conducted in a mobile unit located at the participant’s work site.

Dietary intake assessment

Dietary intake was assessed with the use of 24-h dietary recalls. Briefly, at visit 1, an experienced nurse obtained a 24-h dietary recall from each participant by oral interview. Vitamin use during the previous day was also assessed with a questionnaire. This first recall also served as a teaching experience for the participants. The second and third 24-h dietary recalls were obtained by telephone interview within 2 mo of the initial recall. The three 24-h recalls were collected on 2 weekdays and 1 weekend day. Measurement of dietary intakes was repeated with the same procedure at the 18-mo follow-up; thus, a total of up to 6 records per participant were obtained during the study. The recalls were collected by using the protocol and software provided by Nutrient Data System (Nutrition Coordinating Center, University of Minnesota, MN) (25, 26).

Serum lipid measurement

Blood samples were processed immediately after collection and were stored at −80 °C until analyzed. Serum TC, HDL-cholesterol, and triacylglycerol concentrations were measured by using an enzymatic method on an automated clinical chemistry analyzer in a laboratory at the University of Southern California. LDL-cholesterol concentrations were estimated from TC, HDL-cholesterol, and triacylglycerol concentrations by using the formula of DeLong (27).

Other measures

Ethnicity, alcohol intake, cigarette use, physical activity, medication use, and medical history were determined with the use of an interviewer-assisted questionnaire. Anthropometric measurements and blood pressure measurements were also collected by the study nurse or sonographer during the baseline and follow-up examinations.

Statistical analysis

The characteristics of the participants at baseline were analyzed for linear trend across quintiles of total dietary fiber intake by using logistic regression for categorical variables and general linear regression for continuous variables. Relations between the progression of IMT and other factors were modeled with 2 repeated-measures regression models. Quintiles of components of dietary fiber intake (total dietary fiber, nonviscous fiber, viscous fiber, and pectin) were used to assess the relation between fiber and IMT progression. Tests of trend across quintiles were derived from models using dietary intakes as continuous variables. Model 1 was adjusted for age, sex, and total energy intake. Model 2 was further adjusted for ethnicity; smoking status; alcohol intake; vigorous physical activity; work-related psychological stress; treatment with cholesterol-lowering or antihypertension medication; diabetes; use of vitamin C or E supplements; systolic blood pressure; body mass index; intake of vegetables, fruit, saturated fat, magnesium, and potassium; and the interaction of dietary fiber and sex as covariates. Model 3 was further adjusted for serum lipids. Dietary fiber intake was adjusted for total energy intake by including total energy in the model as a covariate.

The influence of measurement error in dietary variables was investigated by incorporating a measurement model into a regression model. In the measurement model, latent variables for viscous fiber and pectin were indicated by the intakes from 2 examinations (baseline and 18-mo follow-up). The attenuation of slopes that occurs when predictor variables are measured with error is sometimes referred to as “regression dilution bias” (28). The model estimates the slope of the dependent variable regressed on the long-term average intake, which is unobserved, by assuming that the errors of measurement at each examination are random (29). The estimates of slope were adjusted for the same confounders as in model 2 above. Relations between dietary fiber intake and serum lipids were analyzed with Pearson correlation coefficients.

Regression equations with measurement models were estimated by maximum likelihood by using AMOS software, version 4 (SmallWaters Corporation, Chicago). Only continuous variable models were estimated with correction for measurement error. Other repeated-measures models, including those with quintiles, were estimated by maximum likelihood by using the MIXED procedure in SAS, version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS

Quintiles of total dietary fiber intake were generated by using the average total dietary fiber intake from the 2 exams.
Asians (P higher quintiles. Fiber intake also differed significantly across more prevalent in the lower quintiles of fiber intake than in the P 8), with lower intakes among current smokers (P higher intakes among those who had never smoked (P never smokers (P never smokers (P 15.1 μmol/L) and the men (10.7 ± 16.5 μmol/L). Because no significant interaction between sex and dietary fiber intake was observed, the data from the men and the women were pooled for analyses.

IMT progression tended to decline across intake quintiles for each of the 4 dietary fiber groups (Table 2). This inverse association was significant for viscous fiber (P for trend = 0.05) and pectin (P = 0.01), marginally significant for total fiber (P = 0.06), but not significant for nonviscous fiber (P = 0.26) after multivariate adjustment. Because vegetables and fruit are 2 major foods that are rich in dietary fiber in general and viscous fiber in particular and because they also contain many other antiatherogenic constituents, the multivariate model was further adjusted for vegetable and fruit intake. The results indicated that controlling for vegetable and fruit intake did not attenuate the magnitude of the inverse association between IMT progression and the intake of viscous fiber or pectin: the P values were still significant [10% and 8% de-
Progression in intima-media thickness of the common carotid arteries by quintile of energy-adjusted dietary fiber intake among participants in the Los Angeles Atherosclerosis Study (1995–1999)\textsuperscript{1}

<table>
<thead>
<tr>
<th>Model\textsuperscript{2}</th>
<th>Quintile</th>
<th>( \mu m/y )</th>
<th>( P ) for trend</th>
<th>Change in slope\textsuperscript{3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dietary fiber</td>
<td>1 (lowest)</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Adjustment for age, sex, and energy</td>
<td>10.00 ± 1.89</td>
<td>11.02 ± 1.66</td>
<td>8.51 ± 1.64</td>
<td>10.74 ± 1.74</td>
</tr>
<tr>
<td>Multivariate</td>
<td>12.86 ± 2.73</td>
<td>12.24 ± 1.94</td>
<td>8.41 ± 1.88</td>
<td>9.96 ± 1.98</td>
</tr>
<tr>
<td>Adjustment for lipids</td>
<td>10.24 ± 2.65</td>
<td>12.74 ± 1.93</td>
<td>7.64 ± 1.86</td>
<td>10.17 ± 1.93</td>
</tr>
<tr>
<td>Nonviscous fiber</td>
<td>10.98 ± 1.87</td>
<td>7.69 ± 1.67</td>
<td>10.87 ± 1.64</td>
<td>10.37 ± 1.70</td>
</tr>
<tr>
<td>Adjustment for age, sex, and energy</td>
<td>11.87 ± 2.60</td>
<td>9.79 ± 1.98</td>
<td>10.48 ± 1.91</td>
<td>10.80 ± 2.02</td>
</tr>
<tr>
<td>Adjustment for lipids</td>
<td>10.02 ± 2.57</td>
<td>10.59 ± 1.93</td>
<td>9.87 ± 1.88</td>
<td>10.71 ± 1.97</td>
</tr>
<tr>
<td>Viscous fiber</td>
<td>9.57 ± 1.87</td>
<td>12.05 ± 1.63</td>
<td>7.96 ± 1.68</td>
<td>11.05 ± 1.64</td>
</tr>
<tr>
<td>Adjustment for age, sex, and energy</td>
<td>11.12 ± 2.76</td>
<td>13.39 ± 1.97</td>
<td>8.52 ± 1.81</td>
<td>9.68 ± 1.92</td>
</tr>
<tr>
<td>Multivariate</td>
<td>10.64 ± 2.70</td>
<td>13.72 ± 1.95</td>
<td>8.78 ± 1.78</td>
<td>10.30 ± 1.89</td>
</tr>
<tr>
<td>Pectin</td>
<td>11.12 ± 1.71</td>
<td>11.25 ± 1.65</td>
<td>9.44 ± 1.70</td>
<td>7.64 ± 1.59</td>
</tr>
<tr>
<td>Adjustment for age, sex, and energy</td>
<td>12.27 ± 2.12</td>
<td>12.25 ± 1.94</td>
<td>10.18 ± 1.90</td>
<td>7.10 ± 1.89</td>
</tr>
<tr>
<td>Multivariate</td>
<td>11.73 ± 2.09</td>
<td>12.28 ± 1.87</td>
<td>11.02 ± 1.87</td>
<td>6.99 ± 1.85</td>
</tr>
</tbody>
</table>

\textsuperscript{1} \( \bar{x} \pm \text{SEM}; n = 100 \) in each quartile.
\textsuperscript{2} The multivariate model added adjustments for ethnicity, smoking status, physical activity, stress, use of cholesterol-lowering medication or antihypertension medication, diabetes, supplementation with vitamins C and E, BMI, systolic blood pressure, and intake of vegetables, fruit, saturated fat, magnesium, and potassium. The lipids-adjusted model added adjustments for HDL, LDL, and triacylglycerol.
\textsuperscript{3} Between the lipid-adjusted model and the multivariate model.

The regression dilution bias increases in slope for viscous fiber (\( P = 0.05 \)) and pectin (\( P = 0.01 \)), respectively]. However, the magnitude of the association was attenuated after adjustment for serum lipids; the slope decreased 32\% for viscous fiber and 15\% for pectin (Table 2).

Correction for measurement error in dietary variables increased the magnitude of the regression coefficients relating IMT progression to dietary fiber intake (Table 3). When the measurement of dietary fiber intake only from exam 1 was used, the regression coefficient of fiber intake on IMT progression was \( -1.33 \) for viscous fiber and \( -2.73 \) for pectin. Averaging the measures of dietary fiber intake from the 2 exams, but not correcting the measurement error, improved the regression coefficient for viscous fiber (from \( -1.33 \) to \( -1.57 \)) but not for pectin (from \( -2.73 \) to \( -2.22 \)). However, relative to the average of the six 24-h recalls from the 2 examinations, the modeling of measurement error increased the magnitude of the association by \( \geq 2 \) times for pectin intake and by 1.6 times for viscous fiber intake.

We further examined the relation between dietary fiber intake and serum lipids by using correlation statistics. Small but significant inverse correlations of the ratio of TC to HDL cholesterol were observed with total fiber and viscous fiber (Table 4). Conversely, HDL cholesterol was positively related to total fiber (\( P = 0.03 \)), viscous fiber (\( P = 0.01 \)), and pectin (\( P = 0.04 \)) (Table 4). These associations were not corrected for attenuation due to measurement error in the dietary and lipid variables.

**DISCUSSION**

Cohort studies of CVD events found inverse associations with the intake of fiber-rich foods, such as fruit, vegetables, whole grains, and cereals (6, 12, 30). However, these fiber-rich foods also contain many antioxidants, minerals, and other nutrients that may be associated with CVD (31). The present study observed a significant protective association of viscous fiber and pectin intake with IMT progression after adjustment for other known atherosclerosis risk factors and suspected dietary factors (31). These findings are consistent with those

**TABLE 3**

Influence of measurement error on estimates of regression slope relating progression of intima-media thickness of the common carotid arteries to dietary fiber intake among participants in the Los Angeles Atherosclerosis Study (1995–1999)

<table>
<thead>
<tr>
<th>Model</th>
<th>Regression slope\textsuperscript{4}</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viscous fiber</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exam 1\textsuperscript{2}</td>
<td>(-1.33 \pm 0.60)</td>
<td>0.03</td>
</tr>
<tr>
<td>Exam 2\textsuperscript{2}</td>
<td>(-0.90 \pm 0.62)</td>
<td>0.15</td>
</tr>
<tr>
<td>Average of 2 exams\textsuperscript{2}</td>
<td>(-1.57 \pm 0.62)</td>
<td>0.03</td>
</tr>
<tr>
<td>Measurement error corrected\textsuperscript{3}</td>
<td>(-2.52 \pm 1.11)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pectin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exam 1\textsuperscript{2}</td>
<td>(-2.73 \pm 1.26)</td>
<td>0.03</td>
</tr>
<tr>
<td>Exam 2\textsuperscript{2}</td>
<td>(-1.95 \pm 1.31)</td>
<td>0.12</td>
</tr>
<tr>
<td>Average of 2 exams\textsuperscript{2}</td>
<td>(-2.22 \pm 1.05)</td>
<td>0.04</td>
</tr>
<tr>
<td>Measurement error corrected\textsuperscript{3}</td>
<td>(-5.87 \pm 2.34)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

\textsuperscript{1} Regression coefficient in the structural model.
\textsuperscript{2} Average of three 24-h recalls at the baseline examination.
\textsuperscript{3} Average of three 24-h recalls at exam 2 (18-mo follow-up).
\textsuperscript{4} Average intake of dietary fiber from the 2 examinations (total of 6 recalls).

\textsuperscript{4} From a latent variable model in which unobservable long-term average intake of dietary fiber is indicated by observable intake at 2 examinations. If the observable measures are estimates of the long-term average plus a random error, then estimation of slopes unattenuated by measurement error (or “regression dilution bias”) is possible.
from studies using clinical events as endpoints (6, 10, 32). For example, Pietinen et al (6) observed that only viscous fiber remained significantly associated with CVD events after adjustment for known risk factors and dietary variables similar to those included in our analysis. Liu et al (32) recently reported a weak inverse association between dietary fiber intake and coronary events in a cohort with an 8.1-g difference in median total dietary fiber intake between the highest and the lowest quintile. In contrast, this value was 12.9 g in our cohort. This higher variation in dietary fiber intake, or improved measurement of fiber intake, might have provided more power to detect an association. As a continuous variable measured during the preclinical stage of atherosclerosis, IMT progression may provide more power to detect associations than do clinical events. For example, in a small study of volunteers with established coronary artery disease (n = 94), viscous fiber intake decreased in subjects with IMT progression and increased in subjects with IMT regression (33).

The present study showed a significant inverse association between IMT progression and pectin intake (Tables 2 and 3). Pectin, as the major part of viscous fiber, exists mainly in fruit and vegetables. The physiologic effects of dietary fiber are known to depend on the properties of pectin. For example, water-holding capacity, which is an important property of viscous fiber, is much higher in vegetables and fruit than in cereals or bran (34). Several mechanistic studies showed that pectin has significant effects on lipid metabolism (35). However, epidemiologic data on this issue are still lacking.

It has been suggested that dietary fiber intake might displace saturated fat intake and thus reduce CVD events (36). However, adjustment for saturated fat intake in the present study did not significantly diminish the association, which supports the previous conclusion that dietary fiber has beneficial cardiovascular effects independent of saturated fat (37, 38). It is also plausible that fiber intake is confounded with other constituents of fruit and vegetables, but we found the inverse association between pectin or pectin intake and IMT progression to be independent of fruit and vegetable intake.

Because of insufficient data, the American Heart Association currently has no recommendation for a specific fiber intake target for risk reduction in its Dietary Guidelines (39). Complexity of food composition is a natural obstacle to causal inference from epidemiologic studies (40, 41), and lack of high-quality measurement of intakes probably leads to inconsistent findings across studies of dietary intakes (4, 32).

Measurement error in dietary assessment has limited the evaluation of dietary effects on disease processes because of the loss of statistical power and the bias both in estimates of dietary effects and in statistical significance in multivariate analyses (42). Correction of bias due to measurement error in the present study increased the magnitude of the regression coefficient for regression of IMT progression on viscous fiber and pectin intake by > 100%. This provides support for a stronger protective effect of dietary fiber against atherosclerosis than has been observed in previous studies. With the exception of the Nurses’ Health Study (13), epidemiologic studies examining the possible effects of fiber intake on CVD estimated dietary intake from a single measurement. In a study on the association between dietary fiber and plasma lipids, Tillotson et al (21) also found that 4 or 5 measurements of dietary fiber intake produced larger regression coefficients than did a single measurement at baseline, reflecting the greater reliability of multiple measurements.

It has been proposed that a protective effect of dietary fiber against CVD is mediated through direct or indirect effects on serum lipids (43). The significant associations of dietary fiber with plasma lipids, together with the attenuation of the relation between dietary fiber intake and IMT progression when serum lipids were included in the regression model, support this hypothesis. However, LDL cholesterol did not play an important mediating role in the present study. Tillotson et al (21) reported similar findings. The association between dietary fiber and HDL cholesterol observed in our study suggests a possible up-regulation of HDL cholesterol by dietary fiber. Results from other investigations support this hypothesis (21).

Elevation of HDL cholesterol has been linked to weight loss, increased exercise, and smoking cessation (44, 45). However, the mechanisms regulating the increase in HDL cholesterol by these factors are still not clear. In the present study, the significantly lower triacylglycerol concentrations in the highest intake quintile for total fiber, nonviscous fiber, and pectin than in the lower intake quintiles suggests a beneficial effect of dietary fiber on CVD. However, a review of studies assessing the effect of dietary fiber on triacylglycerol concentrations found inconsistency across studies (46).

The ratio of TC to HDL cholesterol showed the strongest association with dietary fiber intake. A significant response of the ratio of TC to HDL cholesterol to diet manipulation has also been observed in intervention studies. For example, one study using a low-fat diet compared the effect on various lipid indicators and found the strongest effect on the ratio of TC to HDL cholesterol. The ratio of TC to HDL cholesterol was proposed as the best metabolic predictor for the effectiveness of intervention for CVD (47). The ratio of TC to HDL cholesterol has also been reported to be the strongest prospective predictor of CVD events in numerous studies (40, 48). Thus, the association of the ratio of TC to HDL cholesterol with dietary fiber in the present study suggests a significant influ-

### Table 4

<table>
<thead>
<tr>
<th>Dietary Fiber</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>LDL-C/HDL-C</th>
<th>TC/HDL-C</th>
<th>Triacylglycerol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fiber</td>
<td>−0.032</td>
<td>0.091</td>
<td>−0.078</td>
<td>−0.094</td>
<td>−0.077</td>
</tr>
<tr>
<td>Nonviscous fiber</td>
<td>−0.024</td>
<td>0.075</td>
<td>−0.065</td>
<td>−0.079</td>
<td>−0.076</td>
</tr>
<tr>
<td>Viscous fiber</td>
<td>−0.038</td>
<td>0.114</td>
<td>−0.091</td>
<td>−0.105</td>
<td>−0.062</td>
</tr>
<tr>
<td>Pectin</td>
<td>−0.016</td>
<td>0.089</td>
<td>−0.082</td>
<td>−0.074</td>
<td>−0.083</td>
</tr>
</tbody>
</table>

1 Pearson correlation coefficient; P in parentheses. Correlations were adjusted for age, sex, smoking status, diabetes, use of cholesterol-lowering medication, use of antihypertension medication, systolic blood pressure, BMI, and intake of saturated fat and cholesterol. LDL-C, LDL cholesterol; HDL-C, HDL cholesterol; TC, total cholesterol.
ence of dietary fiber on lipid metabolism relevant to the pathogenesis of atherosclerosis and thrombotic events. It is likely that some food constituents, such as vitamins, trace elements, phenolic compounds, and phytoestrogens, found in fiber-rich foods also affect CVD risk and operate via pathways other than the lipid-regulating pathway (49).

Although increasing the intake of dietary fiber has been recommended as a safe and practical approach for cholesterol reduction (50), several other mechanisms may underlie the cardiovascular benefits of dietary fiber. These mechanisms include improvement in postprandial glucose and insulin responses and lowering of blood pressure and body weight (51–53). The small correlation coefficients (r values) obtained in the present study also indicated that the regulation of serum lipids by dietary fiber intake was not strong, which reflects the existence of multiple pathways for serum lipid regulation. Thus, the present study suggests that increased dietary fiber intake has significant cardiovascular benefit and that the regulation of serum lipids by dietary fiber may be partially involved in the process of slowing the progression of atherosclerosis.

HW, ZF, and AS contributed to data analysis and manuscript preparation. KMD contributed to the study design and manuscript preparation. JF contributed to data analysis. JHD contributed to the study design, data analysis, and manuscript preparation. None of the authors had any financial or personal interest, including advisory board affiliations, in any company or organization sponsoring the research.

REFERENCES