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Fiber Intake and PAI-1 in type 2 diabetes: Look AHEAD Trial Findings at Baseline and Year 1

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Abstract

Plasminogen Activator Inhibitor 1 (PAI-1) is elevated in obese individuals with type 2 diabetes (T2DM) and may contribute, independently of traditional factors, to increased cardiovascular disease (CVD) risk. Fiber intake may decrease PAI-1 levels. We examined the associations of fiber intake and its changes with PAI-1, before and during an intensive lifestyle intervention for weight loss (ILI) in 1,701 Look AHEAD participants with dietary, fitness and PAI-1 data at baseline and 1-year. Look AHEAD was a randomized CVD trial in 5,145 overweight/obese subjects with T2DM, comparing ILI (goal of ≥7% reduction in baseline weight) with a control arm of diabetes support and education (DSE). ILI participants were encouraged to consume vegetables, fruits and grain products low in sugar and fat. At baseline, median fiber intake was 17.9 g/d. Each 8.3 g/day higher fiber intake was associated with a 9.2% lower PAI-1 level (p=0.008); this association persisted after weight and fitness adjustments (p=0.03). Higher baseline intake of fruit (p=0.019) and high-fiber grain and cereal (p=0.029) were related to lower PAI-1 levels. Although successful in improving weight and physical fitness at 1-year, ILI in Look AHEAD resulted in small increases in fiber intake (4.1g/day, compared with -2.35 g/day with DSE), which were not related to PAI-1 change (p=0.34). Only 31.3% of ILI participants (39.8% of women; 19.1% of men) met daily fiber intake recommendations. Increasing fiber intake in overweight/obese individuals with diabetes interested in weight loss is challenging. Future studies evaluating changes in fiber consumption during weight loss interventions are warranted.

Keywords

lifestyle intervention; weight loss; fiber; diabetes; plasminogen activator inhibitor-1; cardiovascular disease risk; Look AHEAD; coagulation balance; fibrinolysis; diabetes; obesity

Introduction

Plasminogen activator-inhibitor-1 (PAI-1) is an inhibitor of fibrinolysis, and its levels are high in individuals with type 2 diabetes (T2DM).[1] PAI-1 is associated with elevated cardiovascular disease (CVD) risk.[2,3] Unlike hypertension and hypercholesterolemia, elevated PAI-1 levels do not benefit from specific pharmacological therapy. Interventions that decrease PAI-1 could further decrease CVD in diabetes by modifying pathways not targeted by standard preventive therapy. PAI-1 is synthesized in multiple tissues, with adipose in the presence of obesity, constituting a major source. [4,5] Lifestyle interventions that achieve weight loss have been associated with lower PAI-1 levels. [1,6,7] Lower levels of PAI-1 have also been observed with higher intake of fiber in individuals without diabetes.[7]

Previous studies, including work from Look AHEAD, have shown that fiber intake in adults with T2DM is low, particularly in those interested in losing weight.[8-10] The effects of increased fiber intake on PAI-1 levels in overweight/obese individuals with diabetes is uncertain, and it is unclear whether greater fiber consumption would lead, in addition to weight loss, to further PAI-1 reduction. Given our previous observations that in individuals with diabetes other factors, including increased fitness and improved glucose control, were associated with lower PAI-1 levels independently of weight loss,[1] we hypothesized that higher intake of fiber and of fiber-rich foods (vegetables and legumes, fruits, whole grains and cereals) would be associated with lower PAI-1 levels, independently of baseline or 1-year changes in adiposity and physical fitness. To test our hypothesis, we examined the associations at baseline of fiber intake, and the consumption of foods generally considered to be high in fiber, with PAI-1 levels, before and after adjusting for adiposity and physical fitness; we assessed the effects of the intensive lifestyle intervention for weight loss (ILI) on fiber intake at 1-year, and evaluated the association of fiber changes with PAI-1 change in a subset of Look AHEAD participants with dietary data at baseline and 1 year. Look AHEAD is the largest and longest randomized study to date (9.6 years of median follow-up) to evaluate the effects of ILI in overweight/obese persons with diabetes.[11] Weight loss and fitness changes with ILI were greatest at 1-year, when the behavioral intervention was most intense.[12]

Subjects and Methods

Study Design

Look AHEAD enrolled 5,145 overweight/obese subjects with T2DM to test whether ILI would reduce CVD events and overall mortality when compared with a control arm of diabetes support and education (DSE).[11] Dietary information was collected on approximately half of participants at each clinic site. This ancillary study obtained consent for biomarker measurements from 15 of 16 study sites (Online supplemental Figure 1) and included 1,701 participants with dietary, fitness and PAI-1 data at baseline and 1-year. Participants were randomized to ILI, aiming for a 7% weight loss from baseline, or to DSE, as previously described.[11,13] During the first year, ILI participants attended three group sessions and one individual monthly encounter (initial six months), followed by two group and one individual monthly appointments aimed at supporting behavioral change to increase physical activity to 175 weekly minutes of moderate-intensity exercise and reduce caloric intake. The activity program relied on at-home exercise, mostly brisk walking. The energy intake goal was 1200–1500 kcal/day if body weight <114 kg and 1500–1800 kcal/day if weight ≥114 kg. ILI participants were taught how to identify legumes, grains or products made from whole grains and how to increase intake of low-fat fiber-containing foods in their diet by making dips, adding them to soups, meat dishes or salads, or using them as desserts or snacks. ILI participants were instructed to start at least 5 of their 6 meals with vegetables, legumes, or a fruit, as a way of lowering the overall caloric density of their diet, and were also encouraged to try new recipes that included fiber-containing foods. Fiber supplement use was not promoted. Subjects completed dietary self-evaluation forms and reviewed and discussed them with co-participants and dietitians. DSE participants received 3 group health information sessions during the year. All participants continued care with their primary providers. The institutional review boards of the participating centers approved Look AHEAD and this ancillary study.

Laboratory, Anthropometric and Fitness Determinations

PAI-1 was measured, in duplicate, in platelet-free plasma by ELISA (Stago, Parsippany, NJ, Asserachrom # 00249), as previously described.[1,14] This assay is sensitive to all plasma forms of PAI-1 and had an average interassay coefficient of variation (CV) of 8.9% over 8 different control materials. Determination of fitness using submaximal effort on a graded exercise stress test and expressed in Metabolic Equivalents of Task (METs), and procedures for obtaining anthropometric measures, HbA1c, glucose and lipids in Look AHEAD have been reported.[12]

Nutritional Assessment

Dietary data was obtained by self-report on a semi-quantitative ethnically-sensitive, validated food frequency questionnaire (FFQ),[8,15] completed with minimal staff participation (limited to instruction and verification of completion). The Look AHEAD FFQ (LA-FFQ) was adapted from that used in the Diabetes Prevention Program,[16] shortening the recall period to six months and adding a line item for meal replacements.[8] The 134-line item self-administered LA-FFQ examined frequency and portion size of food and beverage consumption during the recall period and was given to approximately the first half of randomized Look AHEAD participants (n=2,500). Information on supplement use was not collected. Dietary analysis was done with the National Cancer Institute Health Habits and History Questionnaire/DietSys program (version 3.0, 1993, National Cancer Institute, Rockville, MD). Quality control and dietary data interpretation have been previously reported.[8] The Look AHEAD Diet Assessment Center (LA-DAC) in South Carolina implemented and managed the nutrition assessment for the study, and performed editing and quality control checks, including internal consistency and range. Primary diet interviewers were certified annually by the LA-DAC to ensure uniformity in LA-FFQ instructions to participants and in editing of the completed questionnaire.

Statistical Analysis

Variable distribution was examined and median and interquartile range (IQR) were used to describe non-normally distributed variables. Non-linear associations were excluded and Spearman's correlation coefficients were determined prior to constructing the regression models; the latter to evaluate colinearity and select the adiposity change measure (body mass index [BMI], waist or weight) to include in the models. Given similar correlation coefficients, we used BMI at baseline to facilitate comparison with other studies and change in total body weight in our change models. Type I error rate was fixed at 0.05 and two-tailed for all analyses. Analyses were performed using SAS 9.2 (SAS Institute, Cary, NC).

We examined the association of PAI-1 with fiber intake (grams per day) and, when significant ($p<0.05$), proceeded to explore the association between the consumption of foods generally considered to be relatively high in fiber[17] and whose intake was encouraged by ILI (fruits without fruit juices, high-fiber whole grains and cereals, and vegetables and legumes in servings/day), with PAI-1 levels or their changes. PAI-1 levels were log-transformed to enhance normality of the distribution. Weight and fitness were added to fiber intake in separate models and combined in a full model to determine their effects on the association of fiber intake with PAI-1 levels. Regression models were analyzed independently and adjusted for demographics (age, gender, race/ethnicity, clinic site), medical history (history of CVD, diabetes duration, current smoking; use of insulin, thiazolidinediones, statins and hormone replacement in women) and metabolic variables (HbA1c, HDL-cholesterol and triglycerides). Intake of total kilocalories, alcohol, protein, saturated and other fat were adjusted for in the models using the standard multiple variable regression approach, with fiber and all other dietary variables examined as continuous variables. Models examining the relation of nutrient intake with PAI-1 using the nutrient residual method[18] provided similar results. We chose the standard multivariable approach without conversion to residuals, due to its ease of interpretation.[18] Baseline models tested for the following interactions: fiber* gender, fiber * race/ethnicity and fiber*BMI.

Differences in 1-year variable changes between ILI and DSE were evaluated using the two-sample t-test or the Wilcoxon rank sum test. To address our question of whether fiber change with ILI added to the effects of improved fitness and/or weight loss, we examined separate regression models looking at the effect of adding fiber change to a model with either change in fitness or change in weight, and to a full model including both. Change models were adjusted for baseline PAI-1 levels, changes in metabolic and dietary variables and for demographics and medical history as described for the baseline models. The significance of the following interactions were assessed in the change models: ILI*gender, baseline BMI* change in fiber intake, baseline fiber intake* fiber change, intake of liquid meal replacement products * fiber change.

Results

Baseline

Participants in this ancillary study were obese and sedentary (Table 1), as were those in the overall Look AHEAD cohort.[13] PAI-1 levels were elevated (median [IQR] of 45.1 [25.0, 75.2] ng/mL), as previously reported.[1] Age eligibility criteria in Look AHEAD was changed after the second year of recruitment and our subjects were on average two years younger, more likely to be Caucasian, and had a slightly shorter duration of diabetes and a lower prevalence of CVD and statin use than the remainder of study participants (Online supplemental Table 1). As in the entire Look AHEAD cohort with dietary data,[8] the intake of fiber in our participants with T2DM was low at baseline, with a median intake of 17.9 g/day (18.9 and 16.9 g of fiber/day in men and women, respectively). Median intake of fiber food sources was lowest for high-fiber grains and cereals at less than 1 serving per day; fruit intake (excluding fruit juices) was a little over half of recommended levels, whereas intake of vegetables and legumes was closest to recommendations.[17]

Higher fiber intake was associated with lower PAI-1 levels at baseline after adjusting for demographics, medical history, medication use and other dietary variables; an 8.3 g/day (1 standard deviation) higher intake of fiber was associated with 9.2% lower PAI-1 levels (p=0.0076, Table 2, Model A). The association remained significant after adjusting for both adiposity and fitness (Table 2, Model C, p=0.031). When we investigated the relationship between fiber food sources and PAI-1 levels (Table 2, Model A′), we found that intake of fruits (p=0.019) and high-fiber grains and cereals (p= 0.029), but not that of vegetables and legumes (p= 0.53), contributed to the favorable association. Increased consumption of fruit (p=0.019), but not fruit juice (p=0.90), was associated with lower PAI-1 levels. The model with fiber alone (Table 2, Model A), and that with fiber food sources (Table 2, Model A′), each accounted for ∼17% of the variance in PAI-1 levels. The inverse association of PAI-1 levels with fruit intake remained significant after accounting for adiposity and fitness (Table 2, Model C′, p=0.045), and was attenuated for high-fiber grains and cereals when BMI (Table 2, Model B′, p=0.10) or BMI and fitness (Table 2, Model C′, p=0.11) were in the model. Interestingly, Spearman correlation coefficients between total daily intake of dietary fiber and consumption of these fiber-rich foods in servings per day, was highest for vegetables and legumes (0.73) and lower for fruits (0.52), and for grains and cereals (0.43).

Change in Fiber intake and reductions of PAI-1 levels with ILI

At 1-year, ILI resulted in significant weight loss, improved fitness and lower PAI-1 levels, when compared with DSE, as previously reported.[1] Fiber intake increased by a mean of 4 g/day in ILI participants, and decreased with DSE (-2.35 g/day, p<0.001; Table 3). When evaluating PAI-1changes in response to the intervention, change in fiber intake did not appear to add to the beneficial effects of weight loss or fitness change. Once fitness and weight changes were accounted for, change in fiber intake was not significantly associated with PAI-1 change (Table 4, Models A′ and B′, p= 0.53 and 0.80, respectively). We then examined if fiber change would be related to PAI-1 change without accounting for weight and fitness changes and found that the association did not reach significance (p=0.34, Model C). Despite the correlation between baseline fiber and fiber change (Pearson correlation coefficient=0.51), the interaction of baseline fiber intake * fiber change, was non-significant (p=0.92). Only 31.3% of ILI participants (11.9% in the DSE arm) achieved fiber intake at 1-year within recommended levels (Table 5).[17]

Discussion

Our study in overweight/obese individuals with T2DM shows that higher fiber intake was associated with lower PAI-1 levels at baseline, independently of adiposity and fitness. The favorable association of fiber with PAI-1 was explained by higher intake of fruits, whole grains and high-fiber cereals, but not of fruit juices, or of vegetables and legumes. Low baseline fiber intake increased with ILI, relative to DSE; however, only 31.3% of ILI participants reached daily recommendations for fiber intake at 1-year. The modest increase in fiber intake with ILI was not significantly associated with PAI-1 change, before or after accounting for the effects of weight and fitness changes.

Longitudinal studies have found that high fiber intake is related to lower CVD, [17, 19-22] the main cause of death in people with diabetes. Studies investigating changes in fiber intake on markers of metabolic and CVD have yielded conflicting results, [17] some partly accounted for by fiber type heterogeneity within analyzed foods. There are few reports from clinical trials looking at changes in fiber intake and PAI-1, the majority small and of short duration. [23-26] The largest study reported to date, in 321 Finnish adults without diabetes, found a significant association between higher fiber intake and lower PAI-1 levels with lifestyle intervention, before but not after accounting for changes in weight.[7] The mean increase in fiber intake (3.1 g/1000 kcal) in the Finnish study was slightly smaller than that observed in our ILI participants (4.3 g/1000 kcal), and weight loss was about half (-4.7% from baseline) of that observed in Look AHEAD.

Our results, together with those from the Finnish study[7] could be interpreted to suggest that the effects of fiber change on PAI-1 are related to mechanisms associated with weight loss. Fiber intake, mainly of soluble viscous fiber, may contribute to weight loss by decreasing the absorption of nutrients and inducing satiety.[17] In addition, soluble fiber fermentation in the colon promotes the growth of organisms, such as lactobacillus,[17] which modulate triglyceride deposition in adipose tissue.[27,28] Fiber fermentation also leads to the production of short chain fatty acids, including propionate and acetate. These fatty acids activate G protein-coupled receptors (Gpr 41 and 43) resulting in the production of gut peptides that modulate intestinal transit time, reduce caloric extraction from foods and modify adipose tissue secretion.[29]

Despite the low intake of fruits in our overweight/obese participants with diabetes at baseline, the association of fruit intake with lower PAI-1 levels was robust and persisted after adjusting for adiposity and fitness, whereas no association was present for fruit juice. There was also an inverse association between whole grains and high-fiber cereals with PAI-1. Fruits, and less so whole grains and high-fiber cereals, contain soluble fiber, which, as noted above, may contribute to weight loss.[17] It is also reasonable to speculate that the fermentable fiber in fruit could, via effects on gut microflora and short chain fatty acid signaling, lead to weight-independent changes on PAI-1. Our finding that the intake of vegetables and legumes was not associated with PAI-1 levels, despite a higher correlation with fiber than that of fruits and high-fiber grains and cereals, may suggest that the type of fiber, and/or differences in micronutrients present in these foods, could be more important in relation to PAI-1 than the amount of fiber alone.

ILI surpassed its goal to reduce mean weight from baseline by more than 7%, and led to moderate improvement in fitness at 1-year. Fiber intake, on the other hand, increased modestly (4 g/day) with ILI. Our results show that significant weight and fitness changes, such as those seen in Look AHEAD, may improve PAI-1 levels independently of changes in fiber intake. It may be possible that if a greater consumption in fiber had been obtained, particularly with fruits and high-fiber grains and cereals, an even greater reduction in PAI-1 levels could have been achieved.

Strengths of this study include its large sample size within a randomized weight loss intervention trial with dietary and fitness data. Our analysis with continuous dietary variables reduces the risk of misclassification seen in studies that convert continuous estimates to categorical data. However, our results need to be interpreted with caution, are exploratory, and should not be taken to represent causal relationships between intake of fiber or of examined food fiber sources with PAI-1 levels. Look AHEAD was a weight loss intervention study and fiber consumption, although encouraged, was not the target of the study; our analyses of fiber intake are therefore observational and subject to the limitations of dietary self-selection, self-report and unrecognized confounding. Furthermore, the ability to detect subtle differences in fiber intake may be limited given that the LA-FFQ dataset was not specifically constructed for fiber intake analysis. Liquid meal replacement was encouraged in ILI participants during the first year of the trial, potentially modifying the associations under study; however, the interaction of intake of liquid meal replacement products* fiber change was examined and found to be non-significant, suggesting that this dietary component does not alter our results. Our study does not exclude the potential effect on PAI-1 levels of other dietary constituents known to be present in fiber-rich foods, such as anti-oxidants and other phytochemicals. Future studies in Look AHEAD using calibration on dietary data may improve the ability to assess how dietary intake is related to biomarkers and to disease indices. Finally, although total PAI-1 measurement is not specific for the active form, this limitation may be minor since PAI-1 antigen and activity are highly correlated and the former is used in much of the epidemiological data linking PAI-1 to CVD. [1,3,30]

Conclusion

Higher intake of fiber was associated with lower PAI-1 levels at baseline, independently of adiposity and fitness, a finding that supports the consumption of fiber rich foods in individuals with T2DM. Changes in fiber intake during the weight loss intervention were small and the association of fiber change and PAI-1 change did not reach statistical significance. Studies evaluating interventions that directly modify fiber intake are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Baseline characteristics of a subset of Look AHEAD participants with diet and PAI-1 data

VARIABLE	ILI (n=881)	DSE (n=820)	OVERALL (n=1701)
Age (years)	57.2 (7.3)	57.5 (7.3)	57.3 (7.3)
Females (%)	59%	59%	59%
White (%)*	68%	68%	68%
Diabetes Duration (years)*	6.5 (6.0)	6.6 (6.2)	6.5 (6.1)
History of CVD (%)*	12%	11%	12%
Current Tobacco use (%)*	4%	3%	4%
Statin Therapy (%)	41%	39%	40%
Thiazolidinedione Therapy (%)	26%	27%	27%
Insulin Therapy (%)	15%	15%	15%
Estrogen replacement in women (%)	55%	59%	57%
Weight (kg)	101.8 (20.0)	101.5 (19.3)	101.7 (19.7)
BMI (kg/m^2)	36.2 (6.3)	36.2 (6.1)	36.2 (6.2)
Waist Circumference (cm)	114.5 (15.0)	114.6 (14.6)	114.5 (14.8)
Fitness (submaximal, METs)	5.2 (1.5)	5.2 (1.6)	5.2 (1.5)
Hemoglobin A1c (%)	7.3 (1.2)	7.4 (1.2)	7.3 (1.2)
LDL cholesterol (mg/dL)	113 (31.5)	112.8 (32.3)	112.9 (31.9)
HDL cholesterol (mg/dL)	42.6 (11.2)	42.6 (11.6)	42.6 (11.4)
Triglycerides (mg/dL)†	157 (111, 229)	150 (107, 218)	154 (109, 223)
PAI-1 (ng/mL)†	46.2 (26.1, 75.1)	43.9 (23.4, 75.3)	45.1 (25.0, 75.2)
Dietary fiber (g/day)† g/1000Kcal	17.7 (13.0, 23.3) 9.8 (3.1)	18.2 (13.7, 23.6) 10.0 (3.2)	17.9 (13.3, 23.4) 9.9 (3.1)
High fiber grain and cereals (servings/day) †	0.6 (0.3,1.0)	0.6 (0.2,1.1)	0.6 (0.3,1.1)
Vegetables and legumes (servings/day) †	2.8 (1.9, 4.0)	3.0 (2.1, 4.1)	2.9 (2.0, 4.1)
Fruits (servings/day) †	1.3 (0.7, 2.1)	1.4 (0.7, 2.2)	1.3 (0.7, 2.1)
Fruit juices (servings/day) †	0.15 (0.02, 0.53)	0.14 (0.02, 0.50)	0.14 (0.02, 0.52)
Total calories (kcal/day) †	1838 (1391, 2447)	1871 (1420, 2453)	1852 (1401, 2452)
Dietary fat (g/day) †	80.2 (57.7, 110.0)	81.0 (57.3, 114.1)	80.5 (57.3, 111.1)
Dietary saturated fat (g/day) †	26.1 (18.4, 38.1)	26.8 (18.3, 38.6)	26.4 (18.3, 38.3)
Dietary carbohydrates (g/day) †	203.7 (151.9, 262.8)	203.1(152.4, 264.3)	203.3 (152.3, 263.6)
Dietary protein (g/day) †	78.2 (59.1,103.3)	79.7 (59.8,105.2)	79.0 (59.4,103.9)

Data shown as mean (SD), unless indicated otherwise.

*By self-report;

†Median (interquartile range).

CVD: Cardiovascular disease (self-reported prior myocardial infarction, stroke, transient ischemic attack, angioplasty/stent, coronary artery bypass graft, carotid endarterectomy, abdominal aortic aneurysm, or heart failure). DSE: diabetes support and education; ILI: intensive lifestyle intervention; BMI: Body mass index; METs: metabolic equivalents of task; PAI-1: plasminogen activator inhibitor-1.

Table 2

Association of PAI-1 levels with fiber intake at baseline in a subset of Look AHEAD participants with diet and PAI-1 data

	PAI-1 (ng/mL) †						
Model *	***B (log scale)***	**1 SD**	**B for 1 SD**	**95th%**	**C.I.**	**p-value**	**R^2**
Model A							
Fiber (g/day)	-0.010	8.3	0.92	0.86	0.98	0.0076	0.17
Saturated fat (g/day)	0.001	17.0	1.01	0.91	1.12	0.86	
Protein (g/day)	-0.002	39.3	0.93	0.84	1.02	0.12	
Model B							
Fiber (g/day)	-0.008	8.3	0.93	0.87	0.99	0.027	0.19
Saturated fat (g/day)	0.001	17.0	1.00	0.91	1.11	0.94	
Protein (g/day)	-0.002	39.3	0.93	0.84	1.02	0.12	
BMI (kg/m^2)	0.021	6.2	1.14	1.10	1.18	<.0001	
Model C							
Fiber (g/day)	-0.008	8.3	0.93	0.88	0.99	0.031	0.19
Saturated fat (g/day)	0.001	17.0	1.00	0.90	1.11	0.99	
Protein (g/day)	-0.002	39.3	0.93	0.84	1.02	0.12	
BMI (kg/m^2)	0.020	6.2	1.13	1.09	1.17	<.0001	
Fitness (METs)	-0.016	1.5	0.98	0.94	1.02	0.23	
Model A′							
Grains/Cereals (servings/day)	-0.060	0.7	0.96	0.92	1.00	0.029	0.17
Vegetables/legumes (servings/day)	-0.009	1.7	0.99	0.94	1.03	0.53	
Fruits (servings/day)	-0.042	1.2	0.95	0.91	0.99	0.019	
Fruit juices (servings/day)	-0.004	0.6	1.00	0.96	1.04	0.90	
Saturated fat (g/day)	0.001	17.0	1.02	0.92	1.13	0.76	
Protein (g/day)	-0.002	39.3	0.92	0.83	1.02	0.13	
Model B′							
Grains/Cereals (servings/day)	-0.045	0.7	0.97	0.93	1.01	0.10	0.19
Vegetables/legumes (servings/day)	-0.008	1.7	0.99	0.94	1.03	0.54	
Fruits (servings/day)	-0.036	1.2	0.96	0.92	1.00	0.045	

	PAI-1 (ng/mL) †						
Model *	***B (log scale)***	**1 SD**	**B for 1 SD**	**95th%**	**C.I.**	**p-value**	**R^2**
Fruit juices (servings/day)	-0.011	0.6	0.99	0.96	1.03	0.75	
Saturated fat (g/day)	0.000	17.0	1.01	0.91	1.11	0.90	
Protein (g/day)	-0.002	39.3	0.93	0.84	1.03	0.14	
BMI (kg/m^2)	0.020	6.2	1.14	1.09	1.18	<.0001	
Model C′							
Grains/Cereals (servings/day)	-0.043	0.7	0.97	0.93	1.01	0.11	0.19
Vegetables/legumes (servings/day)	-0.009	1.7	0.98	0.94	1.03	0.51	
Fruits (servings/day)	-0.036	1.2	0.96	0.92	1.00	0.045	
Fruit juices (servings/day)	-0.011	0.6	0.99	0.95	1.03	0.74	
Saturated fat (g/day)	0.000	17.0	1.00	0.91	1.11	0.98	
Protein (g/day)	-0.002	39.3	0.93	0.84	1.03	0.15	
BMI (kg/m^2)	0.019	6.2	1.13	1.08	1.17	<.0001	
Fitness (METs)	-0.017	1.5	0.98	0.94	1.02	0.23	

† log-transformed;

* Each model was analyzed independently and adjusted for age, gender, race/ethnicity, clinic site, history of CVD (cardiovascular disease, including self-reported prior myocardial infarction, stroke, transient ischemic attack, angioplasty/stent, coronary artery bypass graft, carotid endarterectomy, abdominal aortic aneurysm, or heart failure), diabetes duration, current smoking and use of insulin, thiazolidinediones, statins, hormone replacement in women, total kilocalories, alcohol, other fat intake, hemoglobin A1c, high density lipoprotein-cholesterol and triglycerides.

PAI-1: plasminogen activator inhibitor-1; BMI: Body mass index; METs: metabolic equivalents of task. The interactions gender* fiber (p=0.86) and fiber*race/ethnicity (p=0.11) and fiber* BMI (p=0.07) were tested in Model A and found to be non-significant

Table 3

1-year changes in metabolic and dietary variables by treatment arm in a subset of Look AHEAD participants with diet and PAI-1 data

Variable*	ILI (n=881)	DSE (n=820)	p-value††
Δ Weight (kg)	-8.99 (7.60)	-0.81 (5.04)	<.0001
Δ Waist (cm)	-7.77 (9.38)	-0.99 (7.66)	<.0001
Δ Fitness (METs)	1.04 (1.40)	0.24 (1.09)	<.0001
Δ HbA1c (%)	-0.74 (0.98)	-0.19 (0.94)	<.0001
Δ LDL-C (mg/dL)	-3.85 (26.76)	-4.29 (27.25)	0.74
Δ Triglycerides (mg/dL)	-35.56 (118.81)	-11.98 (92.63)	<.0001
Δ HDL-C (mg/dL)	3.48 (6.97)	1.28 (6.61)	<.0001
Δ PAI-1 (ng/mL)	-18.17 (41.56)	-1.09 (40.64)	<.0001
Δ Total Fiber (g/day) (g/1000kcal)	4.05 (8.75) 4.35 (3.73)	-2.35 (7.26) 0.45 (3.15)	<.0001
Δ Grains/cereals (servings/day)	-0.24 (0.71)	-0.14 (0.74)	0.0037
Δ Vegetables/legumes (Servings/day)	0.17 (1.72)	-0.31 (1.48)	<.0001
Δ Fruit (servings/day)	0.36 (1.24)	-0.12 (1.10)	<.0001
Δ Fruit juice (servings/day)	-0.15 (0.59)	-0.04 (0.55)	0.0001
Δ Protein (g/day)	-9.95 (34.38)	-11.85 (34.13)	0.25
Δ Carbohydrate (g/day)	-6.99 (89.88)	-36.60 (85.61)	<.0001
Δ Total fat (g/day)	-25.63 (39.71)	-16.11 (39.28)	<.0001
Δ Saturated Fat (g/day)	-10.68 (14.24)	-5.55 (14.62)	<.0001

*All data shown as mean (standard deviation) since normally distributed. 1-year change (Δ) from baseline expressed as follow-up minus baseline values

††For difference between ILI and DSE.

ILI: Intensive lifestyle intervention; DSE: diabetes support and education; PAI-1: plasminogen activator inhibitor-1; BMI: Body mass index; METs: metabolic equivalents of task

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Table 4

Association of changes in fitness, weight and fiber intake with PAI-1 at 1-year in a subset of Look AHEAD participants with diet and PAI-1 data

Model *	B	SE	p-value	Lower 95^{th}%	Higher 95^{th}%
Model A					
Δ in Fitness† (METs)	-2.78	0.682	<0.0001	-4.12	-1.44
ILI vs DSE	-11.08	1.882	<0.0001	-14.78	-7.39
Model A′					
Δ in Fitness (Mets, submax)	-2.75	0.684	<0.0001	-4.09	-1.41
Δ in Fiber (g/day)	-0.11	0.169	0.53	-0.44	0.23
ILI vs DSE	-10.68	1.986	<0.0001	-14.58	-6.79
Model B					
Δ in Weight (kg)	1.05	0.126	<0.0001	0.81	1.30
ILI vs DSE	-4.26	1.909	0.026	-8.00	-0.52
Model B′					
Δ in Weight (kg)	1.06	0.127	<0.0001	0.81	1.31
Δ in Fiber (g/day)	0.04	0.159	0.80	-0.27	0.35
ILI vs DSE	-4.38	1.970	0.026	-8.24	-0.52
Model C					
Δ in Fiber (g/day)	-0.15	0.16	0.34	-0.47	0.16
ILI vs DSE	-10.84	1.85	<.0001	-14.47	-7.22

* Each model was analyzed independently and adjusted for baseline PAI-1, age, gender, race/ethnicity, clinic site, history of CVD (cardiovascular disease, including self-reported prior myocardial infarction, stroke, transient ischemic attack, angioplasty/stent, coronary artery bypass graft, carotid endarterectomy, abdominal aortic aneurysm, or heart failure), diabetes duration, current smoking and use of insulin, thiazolidinediones, statins, hormone replacement in women, change in total kcal, alcohol, protein, saturated fat, other fat intake, and change in hemoglobin A1c, high density lipoprotein-cholesterol and triglycerides. n=1,636, except for Models A and A′, where n=1,485. The interactions ILI*gender (p=0.58), baseline BMI* change in fiber intake (0.49), baseline fiber intake* fiber change (0.92) and intake of liquid meal replacement products* fiber change (p= 0.45) were non-significant when checked in model with change in fiber (Model C). ILI vs DSE: treatment group indicator testing for treatment effect. PAI-1: plasminogen activator inhibitor-1; METs: metabolic equivalents of task

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Table 5

Fiber intake at 1-year in a subset of Look AHEAD participants with diet and PAI-1 data

Participants	Fiber intake at 1/year (g/day)*			% achieving recommended intake†		
	ILI	DSE	p-value	ILI	DSE	p-value
Overall	21.7 [16.4 – 28.4]	15.9 [11.6 – 20.5]	<.0001	31.3	11.9	<.0001
Men	23.5 [18.0 – 29.7]	16.8 [12.2 – 22.9]	<.0001	19.1	6.8	<.0001
Women	20.7 [15.8 – 26.8]	15.4 [10.9 – 19.4]	<.0001	39.8	15.7	<.0001

*Median (IQR);

†Recommended levels for men: age 31-50 years, ≥38 g/day of fiber, age > 50 years: ≥30 g/day for women: ≥25 g/day if age 31-50 years, ≥ 21 g/day if >50 yr age. [17] ILI: Intensive lifestyle intervention; DSE: diabetes support and education