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Effect of long term low-fat dietary intervention on change in hemostatic factors: Results from the Women's Health Initiative

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Abstract

Low-fat diet may play a role in prevention of cardiovascular disease (CVD) by altering the levels of hemostatic factors. There are yet limited data on the effects of low-fat diet on the circulating levels of these factors and existing studies are limited by small sample size and short duration of follow-up. We conducted an analysis in a subset of women (active arm = 723; control arm = 1,036) within the Women's Health Initiative Dietary Modification Trial to investigate the long-term effect of a low-fat diet on circulating levels of fibrinogen, factor VII concentration and factor VII activity among postmenopausal women aged 50-79 years. Using linear mixed effects model with random intercept and data from three follow-up visits (years 1, 3 and 6) we evaluated the change in each factor over time. Overall, the changes in these factors were small (less than 5%) in both the arms of the trials at the end of intervention and there was no significant difference in mean change between the two arms. Our results indicate that the low-fat dietary intervention was not associated with significant changes in hemostatic factors among postmenopausal women.

Epidemiological data have suggested a role for low-fat diet in the prevention of cardiovascular disease (CVD). Although high circulating levels of hemostatic factors are associated with increased CVD risk (1,2), there are limited data on the effects of low-fat dietary interventions on the circulating levels of these biochemical markers (3-5). A few of these studies suggested a benefit of low-fat diet on coagulation profile. For example, in a cross-over study among 21 healthy middle-aged individuals, a low-fat dietary intervention (28% of energy) for 2 weeks resulted in lowering of plasma factor VII activity (88 vs. 96%, p=0.002) while raising plasma fibrinolytic activity (4). In another study among healthy young men, a similar low-fat (26% of energy) diet for 8 months also was associated with a significant increase in systemic fibrinolytic activity but found no significant change in plasma levels of fibrinogen, t-PA antigen, or plasminogen activator inhibitor type I antigen

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(3). These existing studies, however, are limited by small sample sizes and short duration of follow-up, generally less than one year. Hence, we conducted an analysis within a subset of a participants of a large randomized clinical trial to investigate the effect of a longer-term (over 6 years) low-fat dietary intervention on the circulating levels of hemostatic factors including fibrinogen, factor VII and factor VII activity (%) among postmenopausal women aged 50-79 years.

The Women's Health Initiative enrolled 48,835 women aged 50-79 in the Dietary Modification (DM) Trial to evaluate the effect of a low-fat, and high fruit, vegetable, and grain diet on breast cancer, colorectal cancer, and heart disease in postmenopausal women. The method and the primary findings of the DM trial have been reported earlier (6,7). In brief, the DM intervention was designed to reduce total fat intake to 20% of total energy while increasing consumption of vegetables and fruits to at least 5 servings per day and grains to at least 6 servings per day. The intervention did not include total energy reduction or weight-loss goals. It has been previously reported that there were no meaningful changes from baseline observed in any of the dietary factors in the comparison group (6). Compared with the control group, however, the intervention group reported significant changes in several nutrients and resulted in an 8.2% lower mean total fat intake, and a 2.9% lower mean saturated fat intake, as well as reduced intakes of *trans*, monounsaturated, and polyunsaturated fat and increased intakes of fiber, vegetables and fruits, total and whole grains, and soya at the end of 6 years.

The current study was conducted among 1,759 women (active arm = 723; control arm = 1,036) within the randomly selected 2,171 women with repeated blood sample collections with measurements on hemostatic factors baseline and at the end of year 1, 3 and 6. Hemostatic factors were measured in citrated plasma. Fibrinogen is measured on a MLA ELECTRA 1400C (Medical Laboratory Automation Inc., Mt. Vernon, NY) using a clot-based turbidometric detection system. Factor VII activity was measured on a MLA ELECTRA 1400C (Medical Laboratory Instrumentation Inc., Mt. Vernon, NY) using a turbidometric detection. Factor VII antigen was measured using a sandwich ELISA assay (Asserchrom VIIag, Diagnostica Stago, France). Based on the sample size and the standard deviation of each biomarkers estimated from our data, we had 80% power to detect a difference in mean change between intervention and control group of 7.5 mg/dl for fibrinogen, 4.3% for factor VII activity and 3.9% factor VII antigen concentration.

All analyses were conducted using the intention-to-treat approach. That is, data from each study participant were analyzed as per her initial assignment to a treatment or control arm. We used linear mixed effects model with data on all the follow-up visits together to evaluate change in each hemostatic factor over time with a random intercept to account for correlations between repeated observations for the same woman. Time since randomization was included in the model as a categorical variable (years 1, 3 and 6). An interaction term between time since randomization and intervention group was also included to allow the effect of intervention to be different at each follow-up time. Wald test was used to assess if the intervention effect were statistically significant. The baseline level of each marker was included as a covariate to account for a potential effect due to “regression to the mean” (8).

Overall, the changes in fibrinogen, factor VII activity and factor VIIC were small (less than 5%) in both the arms of the trials at the end of 6 years of intervention. Furthermore, the between-group (intervention vs. control) differences in mean change of these markers from baseline were not statistically significant at any timepoint (Table 2). Further, these changes in hemostatic factors were not related to changes in the BMI (6 year mean change intervention group: -0.3±2.5 kg/m^2 and control group: 0.2 ± 3.2 kg/m^2). As in the case of any clinical trial, our study is also limited by any bias due to non-compliance to study

intervention. In this trial, dietary adherence rates, defined based on participation in trial activities, were 87% at year 3 and 75% at year 6, while the corresponding rates in the intervention group were 57% and 31%.

Our results indicate that the low-fat dietary intervention was not associated with significant changes in several hemostatic factors among postmenopausal women and hence the potential benefit of a low-fat diet on CVD risk is likely to be mediated through other important mechanisms.

References

1. Folsom AR. Hemostatic risk factors for atherothrombotic disease: an epidemiologic view. Thromb Haemost. 2001 Jul; 86(1):366–73. [PubMed: 11487026]
2. Tracy RP. Hemostatic and inflammatory markers as risk factors for coronary disease in the elderly. Am J Geriatr Cardiol. 2002 Mar-Apr; 11(2):93–100. 7. [PubMed: 11872967]
3. Marckmann P, Sandstrom B, Jespersen J. Favorable long-term effect of a low-fat/high-fiber diet on human blood coagulation and fibrinolysis. Arterioscler Thromb. 1993 Apr; 13(4):505–11. [PubMed: 8385479]
4. Marckmann P, Sandstrom B, Jespersen J. Low-fat, high-fiber diet favorably affects several independent risk markers of ischemic heart disease: observations on blood lipids, coagulation, and fibrinolysis from a trial of middle-aged Danes. Am J Clin Nutr. 1994 Apr; 59(4):935–9. [PubMed: 8147341]
5. Junker R, Pieke B, Schulte H, Nofer R, Neufeld M, Assmann G, et al. Changes in hemostasis during treatment of hypertriglyceridemia with a diet rich in monounsaturated and n-3 polyunsaturated fatty acids in comparison with a low-fat diet. Thromb Res. 2001 Mar 1; 101(5):355–66. [PubMed: 11297752]
6. Howard BV, Van Horn L, Hsia J, Manson JE, Stefanick ML, Wassertheil-Smoller S, et al. Low-fat dietary pattern and risk of cardiovascular disease: the Women's Health Initiative Randomized Controlled Dietary Modification Trial. Jama. 2006 Feb 8; 295(6):655–66. [PubMed: 16467234]
7. Design of the Women's Health Initiative clinical trial and observational study. The Women's Health Initiative Study Group. Control Clin Trials. 1998 Feb; 19(1):61–109. [PubMed: 9492970]
8. Barnett AG, Van Der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. Int J Epidemiol. 2004 Aug 27.

Table 1

Mean levels and change in hemostatic factors at different time points of the DM trial

	Fibrinogen, (mg/dl)	Factor VII activity, %	Factor VII concentration, %
MEAN			
Intervention			
Baseline	305.0 ± 61.1	127.2 ± 33.2	126.1 ± 31.7
Year 1	306.8 ± 62.6	123.7 ± 32.3	122.0 ± 30.0
Year 3	293.9 ± 62.2	126.9 ± 34.0	125.9 ± 34.8
Year 6	291.8 ± 61.6	121.4 ± 30.0	132.7 ± 37.1
Control			
Baseline	300.8 ± 63.2	126.7 ± 31.4	126.0 ± 28.8
Year 1	300.1 ± 62.7	125.4 ± 31.2	123.9 ± 28.6
Year 3	293.1 ± 60.1	127.1 ± 30.9	128.1 ± 32.1
Year 6	291.5 ± 61.3	121.7 ± 38.1	132.2 ± 33.0
MEAN CHANGE			
Intervention			
Year 1 – baseline	1.1 ± 47.9	-3.4 ± 20.7	-4.0 ± 23.5
Year 3 – baseline	-7.5 ± 49.8	-1.8 ± 28.3	-1.5 ± 27.9
Year 6 – baseline	-11.4 ± 54.6	-6.9 ± 27.0	5.3 ± 28.8
Control			
Year 1 – baseline	-2.1± 49.0	-1.6 ± 20.1	-1.7 ± 18.3
Year 3 – baseline	-8.3 ± 50.9	-1.1 ± 26.2	1.5 ± 26.6
Year 6 – baseline	-8.6 ± 57.2	-6.1 ± 38.3	5.6 ± 29.0

Table 2

Results from linear mixed effects model for change in hemostatic factors the between-group (intervention vs. control)

	Year 1		Year 2		Year 3	
	β	p-value	β	p-value	β	p-value
Fibrinogen	4.36	0.086	0.23	0.931	-2.40	0.381
Factor VII activity	-1.83	0.179	-0.35	0.812	-0.99	0.504
Factor VII C	-1.74	0.185	-2.07	0.137	0.17	0.905