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Review

Dietary fiber, inflammation, and cardiovascular disease

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The role of dietary fiber in the prevention of cardiovascular disease has received increasing attention as data have accumulated. Recent cohort studies have found a consistent protective effect of dietary fiber on cardiovascular disease outcomes, prompting many leading organizations to recommend increased fiber in the daily diet. However, the biologic mechanisms explaining how a fiber influences the cardiovascular system have yet to be fully elucidated. Recent research in large national sample in the USA has demonstrated an association between dietary fiber and levels of C-reactive protein (CRP), a clinical indicator of inflammation. Epidemiologic evidence demonstrating that high-fiber diets are beneficial, coupled with this newer evidence of a possible metabolic effect on inflammatory markers, suggest that inflammation may be an important mediator in the association between dietary fiber and cardiovascular disease (CVD). This paper reviews the evidence for the connections among inflammation, CRP, dietary fiber, and CVD, and recommends further clinical studies using fiber supplementation to isolate and prospectively confirm these important relationships.

Keywords: Cardiovascular disease / C-reactive protein / Dietary fiber / Fiber / Inflammation / Review

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Contents

1 Introduction

The role of dietary fiber in the prevention of cardiovascular disease has been the subject of considerable attention in recent years. No fewer than ten cohort studies addressing this topic were included in a recent pooled analysis [1]. The consistent finding of a protective effect of dietary fiber on cardiovascular disease outcomes has prompted many leading organizations to recommend increased fiber in the daily diet, and has prompted some to go a step further to endorse vegetarian diets [2]. The available evidence indicates that persons who consume foods high in dietary fiber (whole-grain cereals, fruits and vegetables) have a lower prevalence of important risk factors for cardiovascular disease (CVD), including hypertension, obesity, and type 2 diabetes mellitus [3, 4]. Recent large, prospective studies also show a direct inverse association between high fiber food intake and the development of coronary heart disease and stroke [5]. While several etiologies have been considered, the biologic mechanisms whereby a diet of high-fiber foods may exert beneficial cardiovascular effects are not entirely known.

Recent evidence suggests that inflammation may be an important mediator in the association between consumption of dietary fiber and CVD. The latest research has demonstrated an association between dietary fiber and levels of C-reactive protein (CRP), a clinical indicator of inflammation [6]. These findings in a large USA sample were maintained

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Abbreviations: BMI, body mass index; **CHF**, congestive heart failure; **CRP**, c-reactive protein; **CVD**, cardiovascular disease; **IL-6**, interleukin-6; **LDL**, low-density lipoprotein; **MI**, myocardial infarction; **RR**, relative risk

after controlling for age, gender, race, education, smoking, physical activity, body mass index (BMI), total energy consumed, and fat intake. The likelihood of having elevated CRP in the highest fiber group was significantly lower than in the lowest fiber intake group. The findings were particularly marked in middle-aged adults, an age group with a high prevalence of cardiovascular risk factors. This association is a strong indicator that the effect of dietary fiber on the risk of CVD may be mediated in part by the inflammatory process. This paper will review the current status of research on the association of inflammation and CVD, with particular attention to the connection with dietary fiber.

2 Inflammation and atherosclerosis

Research in the last several years has supported that inflammation plays an important role in the atherosclerotic process. Animal models provided some of the early evidence for the connection and continue to provide support for the concept. For example, in a strain of apolipoprotein E (apoE)-deficient mice, in which atherosclerosis spontaneously develops, inflammatory cytokines, such as intercellular adhesion molecule (ICAM)-1, have been found at lesion sites [7]. More recent studies also demonstrate elevated levels of the pro-inflammatory cytokine tumor necrosis factor α (TNF-α) and the acute phase reactant fibrinogen in the livers of apoE-deficient mice [8]. A dramatic reduction in atherosclerosis can be demonstrated when IL-10 (an anti-inflammatory cytokine) deficient mice are given interleukin-10 (IL-10) [9].

In the human clinical research setting, evidence for the inflammation/atherosclerosis link has continued to accumulate. Plaque rupture and other types of endothelial injury appear to be vascular inflammatory processes, and are provoked by many inflammatory factors, including smoking and others that are not as obviously inflammatory (hyperglycemia) [3, 7, 10, 11]. Evidence that endothelial injury is essentially an inflammatory process also stems from the fact that the prominence of production of inflammatory cells and proteins by atherogenic processes. These include leukocyte soluble adhesion molecules, increased monocyte chemoattractant protein, oxidation products, and plasminogen activator inhibitor I (PAI-1) [12 – 14]. Further evidence of the interaction between inflammation and atherosclerosis is provided by the strong links between CRP and the major cell types and proteins involved in the vascular inflammatory process, including monophils, neutrophils, lipoproteins, and the complement system [15]. For example, Deveraj [16] examined endothelial cells from the human aorta and found that CRP induces expression of PAI-1, a marker of atherothrombosis in vascular cells. The effects were time- and dose-dependent, further supporting the validity of the findings. Overall, atherosclerosis is now understood to be a condition of heightened oxidative stress, characterized by inflammation and lipid and protein activation in the vascular wall [17]. The inflammation may be caused by a response to oxidized low-density lipoproteins, chronic infection, or other factors. Markers of this inflammatory process, such as CRP, may be useful to predict an increased risk of cardiovascular disease [18].

3 Inflammation measures and CVD

Several inflammatory products are produced in the course of atherogenesis and are potentially useful as measurements of the occurrence and intensity of the inflammatory process. These include total white blood cell count, lymphocyte counts, fibrinogen levels, IL levels, and CRP. Many of these cells and proteins, including CRP, have been related to an increased risk of cardiovascular events [19 – 22]. Abdelmouttaleb [23] found elevated CRP levels among patients with unstable angina compared to normal healthy controls. Epidemiologic data have documented the association between elevation of CRP levels and cardiovascular risk in people with and without a history of heart disease [24, 25]. Elevated white blood cell count and fibrinogen have been reported as independent risk factors for ischemic heart disease [19, 20]. IL-6 is associated with higher mortality in the elderly independent of age, sex, BMI, and history of smoking, diabetes, and cardiovascular disease [26]. In the same study, people who had elevations of both CRP and IL-6 were more than twice as likely to die over 4 years as people in the control group who had low levels of both markers. Elevations of IL-6 and CRP also have recently been associated with an increased risk of congestive heart failure (CHF) among Framingham study participants with no previous history of myocardial infarction or CHF [27].

The inflammatory proteins and cells involved in the vascular atherogenesis are elevated in many types of systemic inflammation, thus measurement of them may not be specific enough for clinical cardiovascular risk assessment [22, 28]. Further, many of the molecules are unstable or are assayed using techniques with limited availability, such as intracellular adhesion molecule-1 or IL-6. White blood cell count, complement levels, and fibrinogen are available widely in the clinical setting, but are not specific for endothelial inflammation, and are elevated with virtually any inflammatory process, from coronary syndromes to arthritis to infection. In addition, while average white blood cell counts may be statistically higher in people with more advanced atherosclerosis, there is considerable overlap with the normal population, and no measurement threshold that would make the measure useful. The most available, specific, and clinically useful measure is high sensitivity C-reac-

tive protein (hsCRP), which has been correlated with atherogenic processes and subsequent cardiovascular events in numerous studies [18, 22, 29].

4 CRP measurement and risk levels

CRP is currently measured using a highly sensitive latex-enhanced assay technique. The latex method has been validated against the original ELISA technique developed by researchers at Harvard, which had been used in studies that found CRP to be predictive of future cardiovascular events [30]. The ultrasensitive assay, which can detect CRP to 0.007 mg/L, has helped to extend the capabilities of previous CRP tests that could only be used to detect infection, exacerbations of arthritis, or stratify cardiac risk in people with already existing coronary syndromes. The newer technique is more sensitive and can be used to stratify risk in people who are asymptomatic. In addition, CRP has a long half-life, exhibits relatively stable levels in individuals free of acute inflammation or infection, and has negligible circadian variation [31].

CRP is produced in the liver, and in the local endothelium in response to certain cytokines, including IL-6. The presence of CRP, in addition to being a marker of the inflammatory process, appears to further induce inflammatory processes. Such processes include recruitment of monocytes into blood vessel walls, elevate levels of cell adhesion molecules, and mediate low-density lipoprotein (LDL) cholesterol uptake by endothelial macrophages [12, 32, 33]. The measurability of CRP and its prominence as an inducer of the vascular inflammatory response, make it not only a key inflammatory marker, but a potentially key target for reducing inflammation that leads to cardiovascular disease [34].

The American Heart Association and the Centers for Disease Control and Prevention in the USA issued a joint statement regarding the public health and clinical utility of new information regarding markers of inflammation and their relationship with CVD [22]. The statement confirmed that CRP is the best and most clinically useful of the markers of inflammation available. The group established the following cut-points for assessing CVD risk using CRP: low risk (CRP < 1.0 mg/L), average risk (1.0–3.0 mg/L), and high risk (>3.0 mg/L).

5 Elevated CRP and risk of CVD

An increased risk of CVD associated with elevated CRP has been documented for people with and without pre-existing CVD. One of the initial studies documenting this risk was in a population of over 1000 healthy men participating in the Physicians Health Study [35]. This study showed that higher baseline concentrations of CRP were associated with increased risk of both myocardial infarction (MI) ($p < 0.001$) and stroke ($p < 0.02$). The relative risk of MI for men in the highest quartile of CRP compared to the lowest quartile was 2.9 ($p < 0.001$). In a more recent study, Ridker and colleagues [36] evaluated the same association in women. They examined data from the Women's Health Study that tracked 28 000 women for 8 years, and found that CRP was a better predictor of later CVD than LDL (relative risk (RR) 2.3, $p < 0.001$).

Two separate meta-analyses of prospective population based cohort studies observed increased risk of major coronary events in subjects who had elevated CRP [37]. Other population based cohort studies, such as the MONICA (MONItoring trends and determinants in CArdiovascular disease) Augsberg Center in Germany, the Atherosclerosis Risk in Communities Study, and the Honolulu Heart Study have shown a positive correlation between CRP and the occurrence of coronary artery disease [38–40]. In other population-based cohort studies, even when adjusted by stratification or multivariable statistical analysis for such traditional (CVD) factors as age, smoking, elevated cholesterol, obesity, family history, and diabetes, CRP remains an independent risk factor for CVD [25, 36].

As further evidence of the utility of CRP as a risk marker, researchers have demonstrated that CRP also is useful in predicting outcomes in patients with known coronary artery disease including angina. In one prospective cohort study of patients with unstable angina, elevated CRP levels predicted increased rates of recurrent ischemic events, higher rates of progression to myocardial infarction and revascularization when compared to those with lower levels of CRP [41]. In another study of 825 patients with known coronary disease, CRP was found to independently predict cardiovascular events at one year [42].

6 Diet, dietary fiber, and CVD

Several studies document the significant association between diet and CVD. Epidemiologic studies have found an association between higher saturated fat intake and higher rates of cardiovascular disease [43]. Randomized clinical trials have documented that lowering saturated fat reduces coronary events and reduces cholesterol, and that a Mediterranean diet (high in fiber, olive oil, fish, and <30% fat) improves survival [44–48]. Fung *et al.* [48] evaluated the association between dietary patterns and plasma biomarkers and found that a North American diet pattern (higher in red meat, high-fat dairy products, and refined grains and low in fiber) was positively correlated with higher CRP. However, the prudent diet pattern in the same

study was not correlated with lower CRP. The study also had some limitations, including that the study included only men, and the results did not evaluate any other inflammatory markers.

Dietary fiber intake from a variety of sources has been associated with a significantly decreased risk of coronary heart disease. In the Nurses Health Study, women in the highest quintile of fiber intake (median 22.9 g/day) had an age-adjusted relative risk for major coronary events that was 47% lower than women in the lowest quintile (11.5 g/day) [49]. Another study also showed that higher fiber intake of over 20 g/day is associated with lower risk of coronary heart disease among women [50]. Further, a cohort of over 39 000 women examined by Liu and colleagues [51] over a 7 year period demonstrated an inverse association between fiber consumption and CVD risk. However, the association was not significant after adjusting for other CV risk factors (RR 0.79, 95% confidence interval 0.58 – 1.09 for total CVD). Liu's study provides important additional information, but it was not specifically designed to evaluate the association of fiber and CVD, but rather the effect of low-dose aspirin and vitamin E on cardiovascular risk.

Further, large cohort studies have demonstrated an inverse relationship between fiber intake and CVD rates [52, 53]. In the study by Rimm and colleagues, each 10 g increment in dietary fiber corresponded to a significant 19% reduction in (CVD) risk. A further analysis of effects of fiber on vascular outcomes suggested that cereal fiber was most strongly associated with reduced risk of MI and that fruit and vegetable intake significantly correlated with a decreased stroke risk [54]. Knoops [47] has demonstrated that the Mediterranean diet, which is notably high in fiber, is associated with a 29% reduction in mortality from CVD over 10 years.

7 Dietary fiber and lipids

Several studies have evaluated dietary fiber in relation to intermediate vascular markers such as cholesterol. A recent comprehensive meta-analysis suggests that 3 g soluble fiber from oats (three servings of oatmeal, 28 g each) can decrease total cholesterol and LDL by 5 mg/dL [55]. A clinical study in 59 subjects with elevated LDL (131 – 191 mg/dL) already on a step I cholesterol-lowering diet (American Heart Association) showed that daily intake of 20 g of fiber, predominantly as water-soluble guar gum and pectin, lowered LDL 9% over 1 year of treatment [56]. These studies demonstrate the well-known effects of fiber consumption on lipids, particularly LDL. However, they also serve to counter the notion that fiber is metabolically "inert" and thus unlikely to exert significant effects on bodily metabolic processes.

8 Dietary fiber and CRP

Recently, researchers have begun to evaluate the possibility of a link between diet and inflammation, and more specifically, the impact of dietary fiber [6, 57]. Because of the established connection between dietary fiber and CVD, and the relatively modest effect of fiber on lipids, it is intriguing to consider that there may be other mechanisms at work in reducing CVD, namely an anti-inflammatory effect of fiber. For example, a recent study evaluated the Mediterranean diet in relation to markers of inflammation and endothelial dysfunction among people with the metabolic syndrome [57]. The study randomized 180 patients to receive either the Mediterranean diet or a "prudent diet" low in fat (50 – 60% carbohydrates, 15 – 20% protein, < 30% fat) and followed them for 2 years. Consumption of fiber among the people on the Mediterranean diet increased from 14 to 32 g/day, a significantly greater increase than the control group ($p < 0.001$). The level of CRP decreased from 2.8 to 1.7 mg/L ($p < 0.01$) in the intervention group, while the level did not change in controls. While this study demonstrates the impact of the Mediterranean diet on inflammatory markers, it was not designed to isolate the impact of fiber alone. Whether the beneficial influence on CRP was due to fiber or other factors in the diet (increased olive oil, decreased calories, weight loss) cannot be determined. Information regarding which nutrient is responsible would greatly improve our understanding of the interaction between diet and inflammation, and ultimately how to better prevent CVD.

Because this area of investigation is relatively new, there are few studies to support a direct link between dietary fiber and markers of inflammation. Our recent study relating dietary fiber consumption to CRP levels among people who took part in the U.S. National Health and Nutrition Examination Survey (NHANES 99-00) was one of the first to demonstrate a specific link between dietary fiber and inflammation in a nationally representative sample [6]. In our analysis, among 4900 adults age 40 – 65, the likelihood of elevation of CRP was significantly lower for people in the highest fiber quartile compared to the lowest (odds ratio (OR) 0.51, 95% confidence interval (CI) 0.27 – 0.95). Similar trends were evident regardless of age. The same findings extended to all adults over age 40 who had a BMI > 25 (OR 0.53, 95% CI 0.30 – 0.95). Among current or past smokers, the association between fiber and elevated CRP also was very strong (OR 0.58, 95% CI 0.38 – 0.88).

It is also important to point out that the study did not show a relationship between total fat, saturated fat, or cholesterol intake and CRP levels. Further, neither fish intake nor total protein intake were associated with CRP elevation. Fiber remained the sole major nutritional component associated with CRP levels, and remained significant after controlling

for important confounders, including age, race, sex, BMI, exercise, total calories, alcohol, and smoking. Thus the findings, while cross-sectional, point to a clearer and more specific association between fiber intake and the likelihood of elevation of CRP than has been demonstrated previously.

To translate these findings into clinical and public health benefit would require significant dietary changes in the USA. Motivating citizens through the stages of change to alter their diet behavior can be challenging [58]. Diet is often slow to change, and a Mediterranean diet (or other heart healthy) may not easily be adopted by everyone, for reasons of cooking traditions, taste, or personal preferences.

While diet and CVD are clearly related, which specific components of the diet that can be manipulated to have the most impact on lowering CVD has not been completely elucidated. Further, compliance with diets over the long term is often difficult [59, 60]. If dietary supplementation with fiber, which may be easier to comply with than more radical diet change, can lower CRP and subsequent CV risk, a new and significant strategy for prevention of CV disease can be designed.

Our research group at the Medical University of South Carolina has begun a prospective clinical trial to evaluate whether fiber supplementation can reduce markers of inflammation (trial to reduce inflammatory markers (TRIM). In this study, funded by the National Heart Lung and Blood Institute (NHLBI), we are randomizing 180 participants age 40 – 65 to receive one of two different doses of a fiber supplement (7 g or 14 g/day), or control. Over a 12-week period, we will examine the impact of fiber supplementation on CRP and other markers. Study participants will be instructed not to change their regular eating habits during the study. This trial, along with a companion study of a strictly controlled high-fiber diet, will provide important information to isolate the impact of fiber on inflammation as well as lipids and oxidative markers.

This review has focused on new research that indicates an important role for dietary fiber in inflammation and in the prevention of CVD. We may someday soon be touting the "anti-inflammatory" properties of high-fiber foods, and encouraging greater intake of anti-inflammatory (fiber) supplements in the general population. Research is needed to confirm the association of dietary fiber with inflammation in people with diabetes, hypertension or obesity, people who are at increased risk of CVD. Establishing a causal relationship between dietary fiber and CVD would require a large sample, over a long period of time, and would be very costly. However, shorter-term clinical trials, focusing on important intermediaries such as inflammation (*e.g.*, the TRIM study), will be very helpful in evaluating the beneficial effect of dietary fiber on inflammation, which has a well-evidenced link with CVD. I look forward with anticipation to seeing further developments in our knowledge regarding the relationship of diet, fiber, and CVD.

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