

## Natural Remedies Lower Elevated Fibrinogen Levels in the Prevention of Atherosclerosis

Atil Narayan\*

Natural Wonders Healthcare, La Puente, CA 91744, USA

### Abstract

Cardiovascular Disease (CVD), which includes heart attack and stroke, is the number one cause of death in the United States. Data gathered from certain lab tests utilized as part of an early detection and prevention strategy can be used to gauge the efficacy of preventative measures in an effort to halt or slow the progression of CVD. Acute phase reactant tests, Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Fibrinogen, and Ferritin are the most clinically relevant to detection. Acute phase reactants are proteins that increase or decrease in the presence of inflammatory stimuli. Of the four tests, the most widely used in conventional medicine are ESR and CRP. Fibrinogen tests are underutilized in conventional medicine. Fibrinogen, which originates in the liver, is a fibrous glycoprotein in vertebrates that helps in the formation of blood clots. Fibrinogen levels rise in the following conditions: Inflammation, tissue damage/trauma, infection, cancer, acute coronary syndrome, strokes, and inflammatory diseases. Fibrinogen tests are often used after a cardiovascular incident has occurred or if symptoms are severe enough to warrant a test. However, there is sufficient evidence which shows that fibrinogen levels slowly begin to rise long before a heart attack or stroke and may even be reflective of the severity of subclinical atherosclerotic conditions. Traditional Chinese Medicine (TCM) and other preventative natural medical systems have treatments which reduce or normalize Fibrinogen levels, thereby, preventing the progression of symptoms that can lead to more serious cardiovascular occurrences in the future. This article will review published studies that show how natural remedies can effectively lower elevated plasma fibrinogen levels.

**Keywords:** Fibrinogen; Atherosclerosis; Prevention; Natural; Exercise; Nattokinase; Fibrin; Omega 3; Fish oil; Stress; Vitamin K independent

### Introduction

The purpose of this paper is to present evidence that elevated plasma fibrinogen not only causes intravascular inflammation, but is a result of inflammation, and is part of the clotting factor contributing to CVD [1-8]. The secondary purpose of this review is to show elevated fibrinogen levels are an early predictor of future CVD. The final purpose of this report is to discuss natural remedies that can lower fibrinogen levels in the prevention of CVD via a Vitamin K independent pathway.

### Fibrinogen overview

Fibrinogen is one of 12 blood clotting factors in the human body. Fibrinogen proteins are soluble proteins that get converted to fibrin, an insoluble protein. The presence of elevated fibrinogen in blood plasma indicates acute and/or chronic inflammation in various parts of the body, most notably, in the cardiovascular system [2]. Fibrinogen appears as a result of inflammation and is a predictor of CVD severity [2].

Endothelial cells line the entire structure of the innermost parts of arteries, veins, and capillaries. The Tunica Intima, made up of endothelial cells, and the Tunica Media comprised of smooth muscle, line the entire inside structure of arteries and veins. The thickness of the Tunica Intima and the Tunica Media of the carotid artery (Intima Media Thickness-IMT) are reliable indicators of the presence and severity of CVD [9,10]. Chronic high plasma fibrinogen levels have a strong relationship with the severity of IMT [11].

Fibrinogen levels also rise in the acute phase of post ischemic stroke [5]. Fibrinogen levels that continue to rise in post ischemic stroke result in a poor prognosis [3]. Therefore, fibrinogen testing is done when CVD is suspected and when a cardiovascular incident has occurred. However, fibrinogen testing can also be an early predictor of future CVD. Evidence suggests that fibrinogen levels begin to rise many months, even years, before cardiovascular disease is fully present

as part of the slow progressive clotting patho-physiology associated with vascular diseases [7]. The presence of fibrinogen levels in ages 27 to 35 has been singularly linked to IMT 13 years later in the CARDIA study [7].

Fibrinogen and CRP are both proteins that make up plaque. The CRP test is a sensitive test for inflammation and is more predictive of cardiovascular risk than fibrinogen as suggested by many research papers [2]. Therefore, CRP is the test primarily given to patients. Fibrinogen is part of the clotting factor and there is growing evidence suggesting that its presence is equally as revealing as the CRP. Combining the CRP and the fibrinogen test results in what is called CRP/Fibrinogen ratio, which has been shown to be more sensitive and a better predictor of CVD risk than each of these test used alone because of their higher level of sensitivity in detecting Disseminating Intravascular Coagulation (DVI), a condition where fibrin ultimately causes excessive clots leading to multiple organ failure [12].

### Conventional anticoagulant therapy and long term limitations

Warfarin (Coumadin) is an anticoagulant and a common drug of choice in patients with thrombosis [13]. Warfarin reduces the clotting factor by functioning as a Vitamin K antagonist [14]. Vitamin K is part of the blood clotting process and Vitamin K antagonists play a role in clot formation by reducing its ability to form clots. However, one of the other primary functions of Vitamin K is to inhibit vascular calcification

\*Corresponding author: Atil Narayan, Board Certified Acupuncturist, Natural Wonders Healthcare, La Puente, CA 91744, USA, Tel: (626) 377-0753; E-mail: [naturalwondershealthcare@gmail.com](mailto:naturalwondershealthcare@gmail.com)

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[15]. It has been suggested that long term use of Vitamin K antagonists promote arterial calcification and increases IMT by reducing the function of Vitamin K to prevent calcification [13,14]. In a longitudinal study by Lip GY et al., Warfarin elevated fibrinogen levels 0.36 g/L [16]. This side effect of Vitamin K antagonist class of drugs warrants other means of preventing and reversing atherosclerotic coagulation.

## Methods

This article is a review of published, peer reviewed scientific papers that support the reliability of fibrinogen as an indicator of existing and future CVD risks and natural remedies shown to be effective in reducing elevated plasma fibrinogen levels. The studies range from double-blind, scientific review, retrospective study, cohort study, and meta-analysis papers.

There are many laboratory testing methods of assessing the presence of fibrinogen in blood plasma. The Clauss method is a fairly common one. In reviewing literature relevant to fibrinogen, it became evident that many researchers did not mention the specific fibrinogen detecting test; rather, they simply mentioned the test results. The reference range for fibrinogen is generally between 1.5-4.0 g/L [17]. This paper will present effective methods used to lower elevated plasma fibrinogen measured in g/L and percent reduction relative to base levels identified in each specific study.

Various non-pharmaceutical methods of intervention exist in the prevention of CVD by reducing plasma fibrinogen levels. These methods can be organized into herbal and lifestyle treatments. Many of these modalities are often combined in a treatment plan by natural health practitioners from various health systems including naturopathy, Ayurveda, and TCM.

### Intervention 1

**Herbs:** There are many natural herbal remedies that are beneficial in ameliorating high fibrinogen levels. This report includes a small sampling of a few common remedies often prescribed by natural health practitioners. Most of these herbs appear to reduce high plasma fibrinogen levels using different physiological pathways than the vitamin K dependent means of Warfarin (Coumadin) [13].

**Fish oil:** Vanschoonbeek et al. studied the hypocoagulant effects of 3.0 g of omega 3 fish oil on 25 healthy, borderline overweight, male volunteers for 4 weeks [18]. Their data suggested fibrinogen levels were significantly reduced  $-4.1 \pm 3.1\%$ . In addition, they showed a causal relationship between the lowering of fibrinogen levels and a lowering of thrombin. The hypocoagulant effect was achieved independent of Vitamin K [18].

Hartweg et al. reviewed 24 studies on omega 3 fish oils from 1966 to 2008 [19]. They studied the data of 1533 participants who took 2.4g of omega 3 fish oils for 24 weeks [19]. Compared to the control groups, their data revealed that fibrinogen levels were reduced by 10% [19].

Mita et al. studied 60 Japanese type 2 diabetic patients who took 1800 mg of eicosapentaenoic acid (EPA) fish oils per day for 2.1+/-0.2 years [20]. Their data revealed a significant annual decrease of Carotid IMT compared to the control group (mean IMT,  $-0.029 \pm 0.112$  mm versus  $0.016 \pm 0.109$  mm) [20].

Hostmark et al. conducted a double blind study of 64 men between the ages of 35-40 for 6 weeks divided into two groups. Their data revealed that within 3 weeks of 14 g of omega 3 fish oil intake there was a significant reduction of plasma fibrinogen of 13.2% compared to the

control group of participants that took 14g of olive oil capsules per day who showed no significant fibrinogen lowering effect [21].

**Nattokinase:** Hsia et al. conducted a study of 3 groups of participants (Healthy Group, Cardiovascular Group, Dialysis Group) who took 2 capsules of nattokinase orally (2000 fibrinolysis units per capsule) for 2 months daily. Their data showed that fibrinogen decreased by 9% in the Healthy Group, 7% in the Cardiovascular Group, and 10% in the Dialysis Group [22].

Kurasawa et al. conducted a double blind, placebo controlled study on 12 healthy males who took a single dose of 2,000 fibrinolysis units of nattokinase. Blood samples were taken from each group at 2, 4, 6, and 8 hours and various blood coagulation parameters were measured including fibrinogen levels. The placebo group had the following fibrinogen levels: baseline  $191.4 \pm 6.6$  mg/dL, 2 hours  $191.1 \pm 7.9$  mg/dL, 4 hours  $191.4 \pm 7.7$  mg/dL, 6 hours  $195.9 \pm 7.1$  mg/dL, 8 hours  $196.1 \pm 7.5$  mg/dL. The nattokinase group had statistically lower fibrinogen levels: baseline  $192.7 \pm 7.7$  mg/dL, 2 hours  $191.7 \pm 7.8$  mg/dL, 4 hours  $192.4 \pm 7.3$  mg/dL, 6 hours  $195.4 \pm 7.4$  mg/dL, 8 hours  $189.8 \pm 6.5$  mg/dL [23].

**XueFu ZhuYu decoction:** Wang et al. conducted a meta-analysis study of XueFu ZhuYu Decoction (XZD), a Chinese herbal formula prescribed for blood coagulation disorders [24]. Their data, from a study of 62 participants in the XZD group and 62 participants in the conventional antihypertensive medicine group, showed that XZD lowered plasma fibrinogen  $-0.56$  g/L and improved IMT  $-0.40$  mm [25]. The study did not indicate a specific dosage of XZD.

### Intervention 2

**Exercise:** Data in a few studies on exercise and fibrinogen levels have shown that mild to moderate exercise can lower fibrinogen levels [26-29].

Connely et al. conducted a cross sectional survey of 3,967 male participants and found that strenuous exercise, which included jogging, cycling, and fast swimming lowered fibrinogen levels [26].

Gomez-Marcos et al. studied 1,284 participants with elevated fibrinogen levels. They showed a decrease of plasma fibrinogen was causally related to physical activity. Physical activity was measured by the 7-Day PAR (Physical Activity Recall) method where subjects that performed 30 minutes of moderate activity five days a week or a minimum of 20 minutes of hard activity for 3 days a week reduced plasma fibrinogen levels by  $-0.162$  mg/dl [29].

Elwood et al. performed a cross sectional study of 2,398 men between the ages 50-64 years [28]. Their data showed a strong correlation between high intensity leisure activities (jogging, soccer) and lower fibrinogen concentration by  $0.24$  g/l in the third of men who were most active in leisure activities [28].

**Chronic stress and elevated fibrinogen:** There is a strong statistical correlation between moderate to high levels of chronic psychological stress over extended periods, elevated plasma fibrinogen concentration, and CVD in various studies [30-33].

Ellins et al. studied 155 healthy men and women who performed standardized behavioral tasks that induced acute psychological and physiological stress resulting in an inflammatory response evident in blood test measuring plasma fibrinogen, tumor necrosis factor (TNF) alpha and interleukin (IL) 6 [32]. Individuals presented with higher plasma fibrinogen concentrations had increased carotid artery stiffness 3 years later [32].

Step toe et al. show a similar correlation between psychological stress, inflammatory response, increased fibrinogen, and increased risk of hypertension after an 8 year period [31]. The study focused on the relationship between psychological stress and hypertension along with the biological impact of acute stress on cardiovascular function and concluded that women had the greater risk [31].

Wolff et al., in a larger study involving 2,164 participants, showed that high psychological strain did not predict IMT (Intima Media Thickness); however, the data revealed a linear relationship to plaque buildup [33].

Lippi et al. studied the morning serum cortisol and fibrinogen levels in 302 patients and found a strong statistical relationship between elevated levels of both inflammatory markers [30]. They found morning cortisol levels that were higher on the reference parameters equated with higher fibrinogen levels [33].

## Conclusion

The high prevalence of CVD and side effects of conventional medical treatments warrant multimodal methods of intervention. Inflammatory markers like fibrinogen and CRP along with the measurement of IMT has clinically been shown to be a viable means of assessing present and future CVD risks. Natural remedies show promise in helping to ameliorate symptoms and inflammatory markers such as fibrinogen, CRP, and IMT associated with CVD. This paper presents evidence that some natural remedies play a role in reducing elevated plasma fibrinogens, which is associated with the prevention and treatment of CVD. Natural remedies should, therefore, continue to be further explored scientifically and integrated into mainstream CVD treatment strategies.

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