Fibrinogen Test Overview

**Introductory Information**

The fibrinogen test has been traditionally performed when abnormal blood clotting is present, particularly if there is excessive bleeding. More recently, fibrinogen has been related to the risk for cardiovascular disease through its relationship to the inflammatory process of developing vascular pathology; the greater the amount of fibrinogen in the bloodstream, the greater the risk of clotting. The importance and relevance of the fibrinogen level in modern healthcare has been established through considerable current research.

The cardiovascular inflammatory paradigm relates to the repair mechanism for damage to the arterial linings leading to formation of plaque. Associated elements include lipids, homocysteine, monocytes, free calcium, glucose, and in many cases, insulin and its role in Syndrome X. There are a number of other components that may correlate to individual cases of vascular disease, but the overall concept is one of damage-related inflammation and repair with interrelated risk factors.

In cases of deviated fibrinogen we may encounter bleeding disorders. Prothrombin time or partial thromboplastin time is often used to monitor this situation as well as gauging need for blood thinners such as coumedin.

Hypertension has been called the “Silent Killer” – unless blood pressure is tested, we may not know it is a danger until a major cardiovascular event takes place. The same can be said for fibrinogen and other serum elements: we may not know there is a problem until testing discloses the possible risk or until heart attack or stroke provides an obvious after-the-fact alert.

We will examine research on the implications of fibrinogen deviations and possibilities for resolution in this issue of the PCS newsletter.

*From Medline Plus Medical Encyclopedia...*

Fibrinogen is a protein produced by the liver. Fibrinogen helps stop bleeding by helping blood clots to form. During normal blood clotting:

- Fibrinogen is broken down by an enzyme called thrombin into short fragments of fibrin. Thrombin also activates a substance called Factor XIII.
- Factor XIII helps weave the fibrin fragments into a complex lattice, closing off injured blood-vessel walls.
- Blood platelets attach to the fibrin fragments, clumping together to form blood clots and stop bleeding.

Fibrinogen associated problems:

- Lack of fibrinogen production (acquired or congenital)
- Excessive fibrinogen utilization (as in disseminated intravascular coagulation)
- Fibrinolysis, or abnormal breakdown of fibrinogen (either primary or secondary)
- Hemorrhage, with transfusion of blood products deficient in fibrinogen

**Fibrinogen, Quantitative**

**Optimal Value**: 215 - 300 mg/dL

**Ordering Code**: 001610  **CPT Code**: 86141

*Excerpts From Lab Corp’s Directory of Services…*

**Reference Range**: 215-519 mg/dL

Test is used to identify congenital afibrinogenemia, disseminated intravascular coagulation, and fibrinolytic activity. Increased in patients on oral contraceptives. Interpretations of results may be limited if patient is receiving anticoagulant therapy. Fibrinogen is a complex polypeptide, which upon enzyme action (physiologically by thrombin but pathologically by other substances such as occur in snake venom), is converted to fibrin that forms along with platelets the meshwork of the common blood clot.

Fibrinogen levels are decreased with hereditary afibrinogenemia, intravascular coagulation, primary and secondary fibrinolysis, and liver disease.

Increased levels may be seen with inflammation, pregnancy, and in women taking oral contraceptives.

Fibrinogen, while of primary importance as a coagulation protein, is also an acute-phase protein reactant. As such, it is increased in disease processes involving tissue damage/inflammation.

**NOTE**: If there is an acute event when fibrinogen is tested, the high level may be an acute-phase reaction and should be confirmed by secondary testing.

Fibrinogen is one of the major determinants of the ESR (sedimentation rate) phenomenon. Changes in fibrinogen may impair the reliability of erythrocyte sedimentation measurements.

There is evidence that increase in dietary fish oils results in decreased fibrinogen levels. Measurement of CRP by high sensitivity CRP assays may add to the predictive value of other markers used to assess the risk of cardiovascular and peripheral vascular disease.

**Related Laboratory Tests**

Serum amyloid A [SAA] (an inflammatory protein associated with lipid behavior); Prothrombin Time (PT) and INR, Activated Partial Thromboplastin Time (PTT), homocysteine, Lipoprotein(a), CRP, Sed Rate (ESR), triglycerides, cholesterol, and insulin.

There are various components of the blood coagulation system that can be tested in disorders involving clotting mechanism, with Factor I being fibrinogen and Factor II, prothrombin. There are a total of 13 factors and all are available through PCS.

**Research Information**

**Coronary Artery Disease (CAD)**

Patients with CAD tended to have higher fibrinogen levels than those without the disease. Of the patients whose fibrinogen levels fell within the two highest quartiles (>331 mg/dL), about 75% of men and 50% of women were diagnosed with clinical CAD. A previous history of heart attack in the group with CAD was also associated with significantly higher average levels of fibrinogen.

*Acevedo M et al (Am Heart J 2002;143:277-82)*

**Comment**: Values associated with significant risk are well within the reference range! This is not a “normal” range as it is based on the values of all patients tested, many of whom had some diagnosed condition. There is nothing normal about a fibrinogen of 500.

**Fibrinogen and Stroke**

This analysis of the EUROSTROKE project indicates "fibrinogen is a powerful predictor of stroke" - including fatal and nonfatal strokes, first time strokes, and hemorrhagic and ischemic strokes.

*J Epidemiol Community Health 2002;56(Suppl I):i14-i18*

**Higher Fibrinogen, Higher Mortality**

Of 111 men who died during a long-term study involving 3092 men, 54.4% of the mortality was attributed to CHD. Mean baseline plasma
fibrinogen levels were 29.4 mg/dL higher in patients who died than in the survivors. All-cause and CHD mortality rates increased with increasing fibrinogen levels 1 SD of plasma fibrinogen level (75 mg/dL) was found to increase risk of CHD and all-cause mortality 29% 

Fibrinogen is a predictor of mortality in coronary heart disease patients. Arterioscler Thromb Vasc Biol 1996 Mar;16(3):351-6

Related to other diseases
Elevated fibrinogen levels have also been associated with a number of other diseases, including cancer, diabetes and hypertension. N Engl J Med, 1987, 317: 521; The Framingham Study. JAMA, 1987, 258: 1183

Top 3 causes of death
Statistics for death in the U.S. form 2001 from the CDC:
Total Number of deaths: 2,416,425
Heart disease: 700,142
Cancer: 553,768
Stroke: 163,538

Higher risks for Blacks
One in three African Americans has high blood pressure or hypertension.
Nearly 40% of blacks suffer from heart disease.
African Americans aged 45-55 years have four to five times the stroke death rates of whites.
Congressional Black Caucus Foundation

Statins and fibrinogen
If your blood fibrinogen level is checked and is high, Zocor lowers it, while Lipitor can raise it even higher.
AM. J. Cardiol. 2001; 87:338-340
Comment: wonder how many patients on statins are monitored for fibrinogen?

Diabetes and Fibrinogen
The current study demonstrates substantial differences in the effect of insulin on fibrinogen production in type 2 diabetic and non-diabetic subjects. During maintenance of basal plasma glucose and amino acid concentrations, physiological hyperinsulinemia markedly increased fibrinogen production in type 2 diabetic but not in non-diabetic control subjects.

Diabetes, July, 2003, by Rocco Barazzoni, Edward Kiwanuka, Michela Zanetti, Michela Cristini, Monica Vettore, Paolo Tessari

Comment: Since hyperinsulinemia is part of Syndrome X it seems reasonable that further research will demonstrate a link here as well.

Flax, Fibrinogen and Mental Stress
A flax strain, Linola 989, high in lignan and low in alpha-linolenic acid was associated with the least increase in peripheral resistance during stress, the greatest reduction in plasma cortisol during stress and the smallest increase in plasma fibrinogen during mental stress.

Flax seed contains large quantities of a phytoestrogen precursor, secoisolariciresinol diglucoside (SDG),
It has been previously shown that the rise in blood pressure during mental stress is a strong predictor of atherosclerosis progression.
The effect of flax seed cultivars with differing content of alpha-linolenic acid and lignans on responses to mental stress.

Weight Gain
A follow-up of the Atherosclerosis Risk in Communities (ARIC) study reported that a large weight gain was more common in subjects with elevated fibrinogen and other inflammatory markers.
Increased fibrinogen may precede substantial weight gain.
It has been suggested that activation of the hypothalamic-pituitary-adrenal (HPA) axis followed by hypercortisolemia and sympathethic activation cause obesity and other features of the metabolic syndrome. Chronic inflammation is also associated with inhibition of the growth hormone secretion, which could further increase abdominal obesity.

We conclude that elevated ISP (inflammation sensitive protein) levels, including fibrinogen, haptoglobin and ceruloplasmin, predict weight gain in middle-aged men. This relation could contribute to the relations between inflammation, Syndrome X, and cardiovascular disease.

Inflammation-sensitive plasma proteins are associated with future weight gain.
(Pathophysiology).
Diabetes, August, 2003
Comment: It isn’t the most far-fetched idea that the weight problems of many may actually be in part due to a response to inflammation. Sam Queen has explained in his lectures and newsletters that fat soluble toxins can cause serum lipid deviations as a protective measure. Anyone in your practice had a difficult time losing weight? If you had an angry pit bull in a cage would you let him loose or try to keep him contained? Detoxification anyone?

**Fibrinogen Deficiency**

Hypofibrinogenemia (< 100 mg / dl) should be replaced.

Methods of Fibrinogen Replacement:

1. Fresh Frozen Plasma: - Used when volume is needed - Approximately 1 gram of Fibrinogen / unit. Should raise fibrinogen by 30 - 40 mg / dl per unit.
2. Cryoprecipitate: - Low Volume: Should be used if significant hypofibrinogenemia treated - Approximately 0.25 gm Fibrinogen per unit. - One unit raises fibrinogen 7 - 10 mg / dl.

(Example: The fibrinogen level is 30 mg / dl. How many units of cryoprecipitate needed to raise level to 150 mg / dl? Answer: 12)

Cryoprecipitate is a human blood component obtained from fresh frozen plasma

*University of Kentucky Chandler Medical Center website.*

**“Benefits” of Birth Control**

CRP increases during oral contraceptive use were associated with changes in some other acute-phase proteins (fibrinogen, ceruloplasmin, von Willebrand factor [vWF]) originating from the liver and vessel wall, but not in others (interleukin-6 [IL-6], serum amyloid A [SAA]). The results demonstrate an increase in a specific set of acute-phase reactants caused by oestrogen-containing preparations. It is proposed that the pro-inflammatory effect of oestrogens should be checked for a relationship with the increased risk of thromboembolism for both oral contraceptive and HRT.


**Smoking Cigarettes**

Studies suggest a primary role for increased synthesis in producing the hyperfibrinogenaemia associated with smoking. Moreover, abstention from smoking for a period of only 2 weeks induces a significant decrease in the rate of fibrinogen synthesis by the liver, with a concomitant reduction in the plasma fibrinogen concentration.

*Effects of smoking and abstention from smoking on fibrinogen synthesis in humans Clinical Science (2001) 100, 459–465 (Printed in Great Britain)*

**Seasonal Variation in Fibrinogen**

Fibrinogen levels are highest in winter. The seasonal variation of fibrinogen is more pronounced in the elderly. Outdoor temperature does not seem to play a role in the seasonal variation of fibrinogen. Seasonal variation of fibrinogen may partly explain the increased cardiovascular disease mortality in winter.


**Fibrinogen and Menopause**

Coagulation balance is not altered significantly with menopause because a counterbalance of changes occurs; some procoagulation factors increase (factor VII, fibrinogen), but also certain fibrinolytic factors such as antithrombin III and plasminogen.

*Menopause Management for the Millennium CME Author: Rogerio A. Lobo, MD WebMD’s Medscape*
**Fibrinogen Related Nutrients**

**Lumbrokinase**
A strong fibrinolytic enzyme was readily obtained in saline extracts of the earthworm. In the treatment group, KPTT was prolonged, t-PA activity and D-dimer level increased, while the content of fibrinogen decreased significantly. There were no significant changes of PT and PAI activity in both groups. It is concluded that lumbrokinase is beneficial to the treatment of cerebral infarction. The effect of lumbrokinase is related to the inhibition of intrinsic coagulation pathway and the activation of fibrinolysis via an increase of t-PA activity.


**Vitamin C**
In human studies, vitamin C in doses ranging from 1 to 2 grams per day has been shown to hinder platelet aggregation and adhesion, reduce the level of an oxidation by-product in platelets, and increase fibrinolytic activity, which may help to clear arteries. Animal studies have found that vitamin C can prevent or reverse the plaque formation caused by a high-cholesterol diet, reduce platelet aggregation by stimulating the production of prostacyclin, and interfere in the platelet release mechanism, thereby reducing platelet activity


**Beer, fibrinogen and clotting**
Downing a beer a day alters the structure of fibrinogen, a blood protein active in clotting. Shela Gorinstein of the Hebrew University-Hadassah Medical School in Jerusalem and her colleagues recruited 48 men who had just recovered from coronary-artery-bypass surgery. Half received 12 ounces of pale lager every day for a month; the rest got an equivalent amount of mineral water. Not only did about 10 percent of their clot-promoting fibrinogen disappear, but more detailed analyses also revealed that much of the remaining fibrinogen underwent structural changes that compromise the clotting process. Earlier work by the group suggests that at least some of the newfound fibrinogen effects trace to polyphenols—pigmented antioxidant compounds in beer, tea, wine, and fruit juices. Moreover, the team’s earlier studies of people with high cholesterol showed that regular, moderate beer drinking lowered their total cholesterol by about 25 percent and their low-density (bad) cholesterol by more than 27 percent.

*Science News, March 8, 2003*

**Comment:** We know there are benefits to red wine and beer. We’re now looking (real hard) for benefits of Bombay Sapphire and Cabo Wobo!

**Flax oil**
Flax significantly reduced blood pressure during mental stress induced by a frustrating cognitive task - the strain highest in lignan and lowest in alpha-linolenic acid was associated with the least increase in peripheral resistance during stress, the greatest reduction in plasma cortisol during stress and the smallest increase in plasma fibrinogen during mental stress.


**Comment:** Flax oil also inhibits platelet adhesiveness.

**Nattokinase Enzyme**
There is an interaction between subtilisin NAT (nattokinase), a profibrinolytic serine proteinase from *Bacillus subtilis*, and plasminogen activator inhibitor 1 (PAI-1). (evidence suggests that increased activity of plasma plasminogen activator inhibitor-1, an important component of the insulin resistance syndrome, plays a crucial role in the pathogenesis of atherosclerosis.) Subtilisin NAT dose dependently (0.06-1 nM) enhanced tissue-type plasminogen activator-induced fibrin clot lysis. Although subtilisin NAT was shown to enhance fibrinolysis, its precise mechanism is not known. It does not activate plasminogen but is reported to directly digest fibrin especially in its cross-linked form. In the present study we found a second mechanism by which subtilisin NAT enhances...
fibrinolysis through cleavage and inactivation of PAI-1. Because PAI-1 is the primary inhibitor of fibrinolysis and regulates total fibrinolytic activity by its relative ratio with tPA, its inactivation is directly related to the enhancement of fibrinolysis. Evidence suggests that increased activity of plasma plasminogen activator inhibitor type 1 (PAI-1) results in the effective enhancement of tPA-induced clot lysis of PAI-1-enriched fibrin.

**Mechanisms of Nattokinase**

Subtilisin NAT (nattokinase) appears to directly digest fibrin by limited proteolysis and also increases activity of a physiological inhibitor of fibrinolysis, plasminogen activator inhibitor type 1 (PAI-1) resulting in the effective enhancement of tPA-induced clot lysis of PAI-1-enriched fibrin.


**Serrapeptase**

The efficacy and tolerability of Serratia peptidase were evaluated in a multi-centre, double-blind, placebo-controlled study of 193 subjects suffering from acute or chronic ear, nose or throat disorders.

Tolerance was found to be very good and similar for both groups. It is concluded that Serratia peptidase has anti-inflammatory, anti-oedemic and fibrinolytic activity and acts rapidly on localized inflammation.


**Fibrinolytic herbs**

Garlic (inhibits platelet aggregation and increases fibrinolytic properties)

Feverfew (reduce platelet aggregation and increase fibrinolytic activity),

Bromelain, Capsicum (increase fibrinolytic activity), Cayenne (reduce platelet aggregation and increase fibrinolytic activity).

**Food and Fibrinogen**

This information is from a hospital website – in India! Maybe they could teach hospitals in other countries?

To lower the risk of blood clots the following foods and supplements are useful: garlic, ginger, raw onions, green chilies, capsicum, green tea, raw vegetables, flaxseed oil, dry red wine, fatty fish like salmon, mackerel and sardines, aspirin and vitamin E supplements.

In contrast, certain foods encourage clot formation namely high fat dairy products like milk, cheese, animal protein as in mutton, pork, steak, fried foods, maida-based fried snacks like samosa, kachoris, pizza, burgers and excessive alcohol intake.

http://www.puneheartbrigade.org/bloodthin.html

Note: maida is flour.

**Food Strategy for Clotting**

Crush garlic and cook it lightly with tomatoes in a teaspoon of olive or groundnut oil. Spread the paste on a slice of whole wheat bread or a whole wheat khakra (oil free) and have it for breakfast along with a glass of vegetable juice made from 1/2 raw onion, 2 carrots and 2 tomatoes (the anticoagulant compound called 'ajoene', present in garlic, is released in the presence of heat and acidic food like tomatoes).

3) A regular intake of red wine (taken in moderation) or black grape juice seems to promote anticoagulant activity, discouraging heart disease.

4) Eat 1/2 an onion as part of the salad with each meal. This will help to keep the blood thin.

5) The 'garam masala' used in Indian cooking, discourages blood platelet clumping. Cloves and cumin seed powder used in it promote anti-clotting activity.

If you're interested in Indian food recipes, see this website- from New Zealand!

http://www.theindian.co.nz/testing/default.asp?page=495
Extras

**USING CANCER MARKERS**

These days everyone is concerned about cancer risk as they well should. Environmental toxins and emotional distress are omnipresent in this era. So do cancer markers provide comfort and safe harbor when the results are “normal”? Unfortunately, the answer is no. While it is good practice the look at these markers, they are really designed to monitor the progress of a known disease, especially after therapy, and not as screening tests. So why use them? We may find elevations in a percentage of people with no other signs and this would lead to intervention before symptoms may sound the alert.

Here is a list of symptoms that should not be ignored:

These can be remembered by thinking about the word **CAUTION**.

- **C**hange in bowel or bladder habits.
- **A**sore throat that does not heal.
- **U**nusual bleeding or discharge.
- **T**hickening or lump in breast or elsewhere.
- **I**ndigestion or difficulty in swallowing.
- **O**bvious change in wart or mole.
- **N**agging cough or hoarseness.

Please do not ignore any of these symptoms that persist more than two weeks. We should always seek the cause of such symptoms and using the various cancer markers would be appropriate as part of that goal. PCS does its best to keep the cost of these tests affordable.

Lab Corp is developing some new cancer markers with much greater sensitivity and we will notify our members when such tests are available. This has been in the works for sometime already and the process has been slow.

**CRP Follow-up**

“C-Reactive Protein and the Risk of Incident Colorectal Cancer”

Inflammation may play a role in the pathogenesis of colorectal cancer. Plasma CRP concentrations were higher among all colorectal cases combined than controls (median CRP, 2.44 vs 1.94 mg/L; \( P = .01 \)). Among rectal cancer cases, CRP concentrations were not significantly different from controls (median CRP, 1.79 vs 1.81 mg/L; \( P = .32 \)).

*Thomas P. Erlinger, MD, MPH; Elizabeth A. Platz, ScD, MPH; Nader Rifai, PhD; Kathy J. Helzlsouer, MD, MHS*

*JAMA. 2004;291:585-590.*

**Comment:** Even slight elevations in CRP can be meaningful and it is becoming more and more apparent that CRP testing is useful and necessary; this is one test we feel good about recommending for everyone.

**Free T-4 and Cardiovascular risk**

Study demonstrates that hsC-reactive protein is significantly negatively correlated with free thyroxine levels in non-smoker hyperlipidemic patients, suggesting that low thyroxine levels in euthyroid hyperlipidemic subjects constitute a new biomarker of elevated cardiovascular risk.

*Relationship of circulating C-reactive protein levels to thyroid status and cardiovascular risk in hyperlipidemic euthyroid subjects: low free thyroxine is associated with elevated hsCRP.*


**Another HRT trial stopped**

Scandinavian scientists announced Tuesday, Feb. 3, 2004 that they have called off a study of the effects of hormone replacement therapy for women with a history of breast cancer because early results showed an "unacceptably high" risk of recurrence.

HABITS (hormonal replacement therapy after breast cancer--is it safe?), study involved 345 women they had been following for an average of two years

In the HRT group, 26 women had a recurrence or a new case of breast cancer. That compared with seven women among those who took the other treatment.

*The Lancet, Volume 363 Issue 9406 Page 5000*

**Our new Price List**

We will be sending an updated price list by mail and email in the next few weeks. The format will be changed to an alphabetical one for ease of use and you’ll notice a number of new additions to the
test list. We think you may be pleasantly surprised! The prices will be updated on our website and we will begin archiving our newsletters there as well as listing seminars on blood chemistry from companies that support our co-op.

Next Topic: Insulin
This may be the most pervasive “new” issue in healthcare!

Your comments and suggestions are welcome and may be included in future newsletters.

Thank you!

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FDA has not commented on the above-mentioned studies or statements

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All in lower case with no spaces.