James L. Holly, M.D.

Plasminogen Activator Inhibitor I: Why Should I Care?
James L. Holly M.D.
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This morning I saw a young patient who obviously has significantly increased cardiovascular risk factors as demonstrated by a brief chart review, which showed:

- Diabetes Mellitus – which is by itself and independent risk factor for heart disease
- PVD – disease in the arteries of the legs which points to heart disease
- Hgb A1C 8.5 – an indication that the patients blood sugar is poorly controlled
- CRP of 3.45 – C-reactive protein is an inflammatory marker which represents an increased risk of the development of heart disease.
- HDL 24 – HDL is the good cholesterol and 24 is a very low value which represents a significant risk for heart disease.

As a result, I ordered the following tests:

- hsCRP – this is an inflammatory marker which measures the same molecule as the CRP mentioned above but is more sensitive to levels between 0-10 while the CRP is typically used in patients with conditions which could reflect an acute CRP from 10-100.
- Homocystiene – this is another inflammatory marker which reflects risk for cardiovascular disease.
- Ferritin – this is another inflammatory marker
- Fibrinogin – this is another inflammatory marker
- Plasminogen activator Inhibitor 1 (PAI-1) – see below
- Magnesium and
- Calcium – the Calcium/Magnesium ratio reflects whether a person has a tendency for the blood to clot or not. A Calcium/Magnesium ratio above 4 indicates a higher risk for the blood clotting which is a risk for heart disease.

What do some of these less well known tests mean? For your body to function properly there has to be a proper balance in many different systems of the body:

1. Between the amount of glucose (sugar) your liver produces and the level of the glucose in your blood.
2. Between the amount of fluid in your arteries and veins and the amount of water which is excreted by your kidneys.
3. Between the amount of carbon dioxide which is produce by your normal metabolism and the air exchange in your lungs where oxygen is absorbed and carbon dioxide is released into the air.
4. Between the amount of blood which arrives at your heart and the amount of blood which is pushed out of the heart back into the circulation.

There are literally hundreds if not thousands of these "balancing acts" which are constantly taking place in your body which are essential for your health. Most illnesses are caused by the loss of balance in one or more of these systems. The balance in all of these and other systems are created by signals which turn one thing on and turn another thing off. These signals are chemicals or proteins which are produced in the body and which regulate bodily functions.

Fibrinolysis

A system upon which we rely constantly but which we don't think about often is that of our blood's ability to clot in order to keep us from bleeding to death if we cut ourselves. This clotting ability must be balanced, however, with the ability of our blood not to clot in order for blood to flow smoothly through our arteries, veins, heart and tissues.

The former, the ability of our blood to clot is called "coagulation" and the latter the ability of our blood not to clot involves what is called "fibrinolysis." Fibrin is one of the first elements of the bloods clotting. "Lysis" means to "dissolve, loosen or to disintegrate." The balance between clotting and dissolving a clot is critical to health and well being as the loss of one, or the other, or the out-of-balance dominance of one over the other is disastrous.

Research has demonstrated that decreased fibrinolytic activity - the anti-clotting function of your blood -- is associated with heart and vascular (arteries) disease which is called atherosclerotic cardiovascular disease or “hardening of the arteries.” The arteries become stiff and are more susceptible to break or being blocked.

While a detailed discussion of the fibrinolytic pathway is beyond the scope of this presentation, it is important to know that "clot busting" is initiated when a substance called “plasminogen” is acted upon by another substance called "tissue-type plasminogen activator." (tPA)

Likewise, in order to keep you from bleeding to death when you are injured, there is a substance called Plasminogen Activator Inhibitor-1 - referred to as PAI-1 (pronounced as "pie one"). PAI-1 promotes blood clotting and inhibits the lysis (destruction) of clots. PAI-1 is found in abnormally elevated levels in heart attacks and it is found in low levels in patients with low incidences of strokes and heart attacks.

Tissue-type Plasminogen Activator (tPA) circulates in your blood in a 1-1 ratio with PAI-1. It is when the PAI-1 is elevated that problems develop. But how does it become elevated?

Fat is an Endocrine Gland

Adipose tissue (fat) is now accepted as an endocrine organ that produces and secretes a variety of cytokines, hormones, and other metabolites such as plasminogen activator

inhibitor-1 (PAI-1). PAI-1, the primary physiological inhibitor of plasminogen activation, plays a pivotal role in the balance of the fibrinolytic system. Thus, elevated levels of PAI-1 are closely related to blood clots in the heart and arteries. Increased PAI-1 acts as a cardiovascular risk factor, particularly in insulin-resistant patients.

The fat cells around your waist are a prominent source of (PAI-1). Increased plasma levels of PAI-1 strongly correlate with body mass index (BMI). The higher your BMI, the higher your PAI-1 and the higher your risk of developing a blood clot, heart attack or stroke.

Obesity, an increasing burden worldwide, particularly in Western industrialized countries, is often associated with insulin resistance, development of type 2 diabetes, and other metabolic disorders of the insulin resistance syndrome (IRS), which is now called the Cardiometabolic Risk Syndrome. Obese patients are at higher risk of developing cardiovascular diseases, and studies suggest obesity as an independent risk factor for heart disease. The American Heart Association identifies obesity and lack of exercise as major, independent risk factors for heart disease, while the American College of Cardiology identifies them as "predisposing risk factors" for heart disease.

Cardiometabolic Risk Syndrome

The prediabetic conditions of impaired fasting glucose (IFG - a blood sugar between 100-125 after a 12-hour fast) and impaired glucose tolerance (IGT - a blood sugar between 140-200 two hours after a 75 gram carbohydrate loading dose) are associated with the insulin resistance syndrome, previously called the metabolic syndrome and now referred to as the Cardiometabolic Risk Syndrome, which consists of:

- insulin resistance,
- compensatory increase in blood levels of insulin to control blood sugar when your body does not respond properly to insulin.
- obesity (especially abdominal or visceral obesity),
- dyslipidemia of the high-triglyceride and/or low-HDL type
- hypertension

The cardiometabolic risk syndrome includes increased plasminogen activator inhibitor-1 (PAI-1) levels which is a cardiovascular risk factor probably because it inhibits fibrinoloysis. Thus, the reason the insulin resistance syndrome or metabolic synderome's name was changed to the cardiometabolic risk syndrome is that it contains many features that increase cardiovascular risk.

Too Much Pie Produces too Much PAI-1

Recent studies have shown that adipose tissue (fat), abundant in the IRS, produces substantial amounts of PAI-1, and plasma levels of PAI-1 strongly correlate with body mass index BMI). Moreover, weight loss due to calorie restriction or surgery is associated with reduced PAI-1 activity. Therefore, if you eat too much pie, and gain

excessive weight, you will increase your production of PAI-1 and increase your risk of a heart attack.

Both environmental (dietary and activity level) and genetic factors determine plasma PAI-1 activity. PAI-1 is associated with other established risk indicators for coronary heart disease such as Very Low Density Lipoproteins (VLDL). There is a strong positive correlation between the plasma VLDL and PAI-1 activity levels. Obesity, a sedentary lifestyle, diabetes and a high non-fibrous carbohydrate (mashed potatoes, bread, pasta, pie, alcohol, etc) diet increase triglycerides and VLDL and contribute to elevated PAI-1 levels.

Balance between clotting and non-clotting

The fibrinolytic defense system counteracts clot formation caused by fibrin deposits on the vessel endothelium (vessel wall). Plasminogen is activated to plasmin by tissue-type plasminogen activator (tPA), which is made by the cells which line the arteries (endothelial cells). PAI-1, which is also produced by endothelial cells, inhibits the activity of tPA and the fibrinolytic process. A low level of fibrinolytic activity has been shown to be a cause of ischemic heart disease in younger men, and increased concentrations of PAI-1 have been found in patients with myocardial infarction. Conversely, low levels of PAI-1 activity have been reported in a population with an apparent absence of ischemic heart disease.

Altered Fibrinolytic Activity as a Vascular Risk Factor

Increased fibrinolytic activity reduces the risk of thrombus (clot) formation, and the level of PAI-1 activity has been reported to be low in a population with an apparent absence of stroke and ischemic heart disease. A low level of fibrinolytic activity may be a risk factor for vascular disease. The Northwick Park Heart Study of 1382 men aged 40 to 64 years found the level of fibrinolytic activity to be low in 179 individuals with subsequent ischemic heart disease.

Practical Implications – PAI-1 makes treatment more difficult

A study published in Clinical Cardiology reviewed one of the most effective ways of treating an acute heart attack which is with a substance called streptokinase (STK). This study showed that streptokinase therapy was successful when blood flow to the damaged heart muscle was restored; it failed when restoring blood flow was delayed and/or re-infarction developed. The study showed that fibrinolysis with STK failed significantly in patients with elevated pretreatment PAI-1 levels, especially with levels >4.0 U/ml. The pretreatment PAI-1 level was significantly higher in unsuccessfully treated patients. The study concluded that elevated PAI-1 activity was the most significant independent risk factor of failed fibrinolysis with STK.

Treating PAI-1

It appears, at present, that PAI-1 levels are the cause and not the result of vascular disease and injury. The reduction of other major risk factors for heart disease and strokes also reduce PAI-1 levels. PAI-1 is decreased by:

1. Weight loss
2. Exercise - apparently this is principally beneficial when it results in weight loss.
3. Insulin sensitizing medications called TZDs such as Actos and Avandia.
4. Diabetes medications such as Metformin (Glucophage)
5. Triglyceride lowering medications, Fibrates, particularly Lopid, Gemcor and clofibric acid
6. Angiotensin Converting Enzyme medications such as Altace, Prinivil, Captopril, etc, which are commonly used for treating high blood pressure and which help protect the kidney from damage in diabetes.

Present recommendations do not warrant screening patients for PAI-1 levels and treatment recommendations do not yet include PAI-1 as a target for reduction. However, it is probable that in the near future, PAI-1 will be an accepted and valuable risk marker for risk of future cardiovascular disease and reducing PAI-1 levels will be a part of a global cardiovascular risk reduction strategy.

It is possible to find out what your PAI-1 levels are. Your insurance will not pay for it at present, but it is your life and it is your health.