= Thrombophilia =

Thrombophilia (sometimes hypercoagulability or a prothrombotic state) is an abnormality of blood coagulation that increases the risk of thrombosis (blood clots in blood vessels) . Such abnormalities can be identified in 50 % of people who have an episode of thrombosis (such as deep vein thrombosis in the leg) that was not provoked by other causes . A significant proportion of the population has a detectable abnormality , but most of these only develop thrombosis in the presence of an additional risk factor .

There is no specific treatment for most thrombophilias , but recurrent episodes of thrombosis may be an indication for long @-@ term preventative anticoagulation . The first major form of thrombophilia , antithrombin deficiency , was identified in 1965 , while the most common abnormalities (including factor V Leiden) were described in the 1990s .

= = Signs and symptoms = =

The most common conditions associated with thrombophilia are deep vein thrombosis (DVT) and pulmonary embolism (PE) , which are referred to collectively as venous thromboembolism (VTE) . DVT usually occurs in the legs , and is characterized by pain , swelling and redness of the limb . It may lead to long @-@ term swelling and heaviness due to damage to valves in the veins . The clot may also break off and migrate (embolize) to arteries in the lungs . Depending on the size and the location of the clot , this may lead to sudden @-@ onset shortness of breath , chest pain , palpitations and may be complicated by collapse , shock and cardiac arrest .

Venous thrombosis may also occur in more unusual places : in the veins of the brain , liver (portal vein thrombosis and hepatic vein thrombosis) , mesenteric vein , kidney (renal vein thrombosis) and the veins of the arms . Whether thrombophilia also increases the risk of arterial thrombosis (which is the underlying cause of heart attacks and strokes) is less well established .

Thrombophilia has been linked to recurrent miscarriage , and possibly various complications of pregnancy such as intrauterine growth restriction , stillbirth , severe pre @-@ eclampsia and abruptio placentae .

Protein C deficiency may cause purpura fulminans , a severe clotting disorder in the newborn that leads to both tissue death and bleeding into the skin and other organs . The condition has also been described in adults . Protein C and protein S deficiency have also been associated with an increased risk of skin necrosis on commencing anticoagulant treatment with warfarin or related drugs .

= = Causes = =

Thrombophilia can be congenital or acquired . Congenital thrombophilia refers to inborn conditions (and usually hereditary , in which case " hereditary thrombophilia " may be used) that increase the tendency to develop thrombosis , while , on the other hand , acquired thrombophilia refers to conditions that arise later in life .

= = = Congenital = = =

The most common types of congenital thrombophilia are those that arise as a result of overactivity of coagulation factors . They are relatively mild , and are therefore classified as " type II " defects . The most common ones are factor V Leiden (a mutation in the F5 gene at position 1691) and prothrombin G20210A , a mutation in prothrombin (at position 20210 in the 3 ' untranslated region of the gene) .

The rare forms of congenital thrombophilia are typically caused by a deficiency of natural anticoagulants . They are classified as " type I " and are more severe in their propensity to cause thrombosis . The main ones are antithrombin III deficiency , protein C deficiency and protein S deficiency . Milder rare congenital thrombophilias are factor XIII mutation and familial

dysfibrinogenemia (an abnormal fibrinogen) . It is unclear whether congenital disorders of fibrinolysis (the system that destroys clots) are major contributors to thrombosis risk . Congenital deficiency of plasminogen , for instance , mainly causes eye symptoms and sometimes problems in other organs , but the link with thrombosis has been more uncertain .

Blood group determines thrombosis risk to a significant extent . Those with blood groups other than type O are at a two- to fourfold relative risk . O blood group is associated with reduced levels of von Willebrand factor ? because of increased clearance ? and factor VIII , which is related to thrombotic risk .

= = = Acquired = = =

A number of acquired conditions augment the risk of thrombosis . A prominent example is antiphospholipid syndrome , which is caused by antibodies against constituents of the cell membrane , particularly lupus anticoagulant (first found in people with the disease systemic lupus erythematosus but often detected in people without the disease) , anti @-@ cardiolipin antibodies , and anti @-@ ?2 @-@ glycoprotein 1 antibodies ; it is therefore regarded as an autoimmune disease . In some cases antiphospholipid syndrome can cause arterial as well as venous thrombosis . It is also more strongly associated with miscarriage , and can cause a number of other symptoms (such as livedo reticularis of the skin and migraine) .

Heparin @-@ induced thrombocytopenia (HIT) is due to an immune system reaction against the anticoagulant drug heparin (or its derivatives) . Though it is named for associated low platelet counts , HIT is strongly associated with risk of venous and arterial thrombosis . Paroxysmal nocturnal hemoglobinuria (PNH) is a rare condition resulting from acquired alterations in the PIGA gene , which plays a role in the protection of blood cells from the complement system . PNH increases the risk of venous thrombosis but is also associated with hemolytic anemia (anemia resulting from destruction of red blood cells) . Both HIT and PNH require particular treatment .

Hematologic conditions associated with sluggish blood flow can increase risk for thrombosis . For example , sickle @-@ cell disease (caused by mutations of hemoglobin) is regarded as a mild prothrombotic state induced by impaired flow . Similarly , myeloproliferative disorders , in which the bone marrow produces too many blood cells , predispose to thrombosis , particularly in polycythemia vera (excess red blood cells) and essential thrombocytosis (excess platelets) . Again , these conditions usually warrant specific treatment when identified .

Cancer , particularly when metastatic (spread to other places in the body) , is a recognised risk factor for thrombosis . A number of mechanisms have been proposed , such as activation of the coagulation system by cancer cells or secretion of procoagulant substances . Furthermore , particular cancer treatments (such as the use of central venous catheters for chemotherapy) may increase the risk of thrombosis further .

Nephrotic syndrome , in which protein from the bloodstream is released into the urine due to kidney diseases , can predispose to thrombosis ; this is particularly the case in more severe cases (as indicated by blood levels of albumin below 25 g / l) and if the syndrome is caused by the condition membranous nephropathy . Inflammatory bowel disease (ulcerative colitis and Crohn 's disease) predispose to thrombosis , particularly when the disease is active . Various mechanisms have been proposed .

Pregnancy is associated with an increased risk of thrombosis . This probably results from a physiological hypercoagulability in pregnancy that protects against postpartum hemorrhage .

The female hormone estrogen , when used in the combined oral contraceptive pill and in perimenopausal hormone replacement therapy , has been associated with a two- to sixfold increased risk of venous thrombosis . The risk depends on the type of hormones used , the dose of estrogen , and the presence of other thrombophilic risk factors . Various mechanisms , such as deficiency of protein S and tissue factor pathway inhibitor , are said to be responsible .

Obesity has long been regarded as a risk factor for venous thrombosis . It more than doubles the risk in numerous studies , particularly in combination with the use of oral contraceptives or in the period after surgery . Various coagulation abnormalities have been described in the obese .

Plasminogen activator inhibitor @-@ 1 , an inhibitor of fibrinolysis , is present in higher levels in people with obesity . Obese people also have larger numbers of circulating microvesicles (fragments of damaged cells) that bear tissue factor . Platelet aggregation may be increased , and there are higher levels of coagulation proteins such as von Willebrand factor , fibrinogen , factor VII and factor VIII . Obesity also increases the risk of recurrence after an initial episode of thrombosis .

= = = Unclear = = =

A number of conditions that have been linked with venous thrombosis are possibly genetic and possibly acquired . These include : elevated levels of factor VIII , factor IX , factor XI , fibrinogen and thrombin @-@ activatable fibrinolysis inhibitor , and decreased levels of tissue factor pathway inhibitor . Activated protein C resistance that is not attributable to factor V mutations is probably caused by other factors and remains a risk factor for thrombosis .

There is an association between the blood levels of homocysteine and thrombosis , although this has not been reported consistently in all studies . Homocysteine levels are determined by mutations in the MTHFR and CBS genes , but also by levels of folic acid , vitamin B6 and vitamin B12 , which depend on diet .

= = Mechanism = =

Thrombosis is a multifactorial problem because there are often multiple reasons why a person might develop thrombosis . These risk factors may include any combination of abnormalities in the blood vessel wall , abnormalities in the blood flow (as in immobilization) , and abnormalities in the consistency of the blood . Thrombophilia is caused by abnormalities in blood consistency , which is determined by the levels of coagulation factors and other circulating blood proteins that participate in the " coagulation cascade " .

Normal coagulation is initiated by the release of tissue factor from damaged tissue . Tissue factor binds to circulating factor VIIa . The combination activates factor X to factor Xa and factor IX to factor IXa . Factor Xa (in the presence of factor V) activates prothrombin into thrombin . Thrombin is a central enzyme in the coagulation process : it generates fibrin from fibrinogen , and activates a number of other enzymes and cofactors (factor XIII , factor XI , factor V and factor VIII , TAFI) that enhance the fibrin clot . The process is inhibited by TFPI (which inactivates the first step catalyzed by factor VIIa / tissue factor) , antithrombin (which inactivates thrombin , factor IXa , Xa and XIa) , protein C (which inhibits factors Va and VIIIa in the presence of protein S) , and protein Z (which inhibits factor Xa) .

In thrombophilia , the balance between " procoagulant " and " anticoagulant " activity is disturbed . The severity of the imbalance determines the likelihood that someone develops thrombosis . Even small perturbances of proteins , such as the reduction of antithrombin to only 70 ? 80 % of the normal level , can increase the thrombosis risk ; this is in contrast with hemophilia , which only arises if levels of coagulation factors are markedly decreased .

In addition to its effects on thrombosis , hypercoagulable states may accelerate the development of atherosclerosis , the arterial disease that underlies myocardial infarction and other forms of cardiovascular disease .

= = Diagnosis = =

Tests for thrombophilia include complete blood count (with examination of the blood film) , prothrombin time , partial thromboplastin time , thrombodynamics test , thrombin time and reptilase time , lupus anticoagulant , anti @-@ cardiolipin antibody , anti @-@ ?2 glycoprotein 1 antibody , activated protein C resistance , fibrinogen tests , factor V Leiden and prothrombin mutation , and basal homocysteine levels . Testing may be more or less extensive depending on clinical judgement and abnormalities detected on initial evaluation .

= = Screening = =

There are divergent views as to whether everyone with an unprovoked episode of thrombosis should be investigated for thrombophilia . Even those with a form of thrombophilia may not necessarily be at risk of further thrombosis , while recurrent thrombosis is more likely in those who have had previous thrombosis even in those who have no detectable thrombophilic abnormalities . Recurrent thromboembolism , or thrombosis in unusual sites (e.g. the hepatic vein in Budd @-@ Chiari syndrome) , is a generally accepted indication for screening . It is more likely to be cost @-@ effective in people with a strong personal or family history of thrombosis . In contrast , the combination of thrombophilia with other risk factors may provide an indication for preventative treatment , which is why thrombophilia testing may be performed even in those who would not meet the strict criteria for these tests . Searching for a coagulation abnormality is not normally undertaken in patients in whom thrombosis has an obvious trigger . For example , if the thrombosis is due to immobilization after recent orthopedic surgery , it is regarded as " provoked " by the immobilization and the surgery and it is less likely that investigations will yield clinically important results .

When venous thromboembolism occurs when a patient is experiencing transient major risk factors such as prolonged immobility , surgery , or trauma , testing for thrombophilia is not appropriate because the outcome of the test would not change a patient 's indicated treatment . In 2013 , the American Society of Hematology , as part of recommendations in the Choosing Wisely campaign , cautioned against overuse of thrombophilia screening ; false positive results of testing would lead to people inappropriately being labeled as having thrombophilia , and being treated with anticoagulants without clinical need

In the United Kingdom , professional guidelines give specific indications for thrombophilia testing . It is recommended that testing be done only after appropriate counseling , and hence the investigations are usually not performed at the time when thrombosis is diagnosed but at a later time . In particular situations , such as retinal vein thrombosis , testing is discouraged altogether because thrombophilia is not regarded as a major risk factor . In other rare conditions generally linked with hypercoagulability , such as cerebral venous thrombosis and portal vein thrombosis , there is insufficient data to state for certain whether thrombophilia screening is helpful , and decisions on thrombophilia screening in these conditions are therefore not regarded as evidence @-@ based . If cost @-@ effectiveness (quality @-@ adjusted life years in return for expenditure) is taken as a guide , it is generally unclear whether thrombophilia investigations justify the often high cost , unless the testing is restricted to selected situations .

Recurrent miscarriage is an indication for thrombophilia screening , particularly antiphospholipid antibodies (anti @-@ cardiolipin IgG and IgM , as well as lupus anticoagulant) , factor V Leiden and prothrombin mutation , activated protein C resistance and a general assessment of coagulation through an investigation known as thromboelastography .

Women who are planning to use oral contraceptives do not benefit from routine screening for thrombophilias , as the absolute risk of thrombotic events is low . If either the woman or a first @-@ degree relative has suffered from thrombosis , the risk of developing thrombosis is increased . Screening this selected group may be beneficial , but even when negative may still indicate residual risk . Professional guidelines therefore suggest that alternative forms of contraception be used rather than relying on screening .

Thrombophilia screening in people with arterial thrombosis is generally regarded unrewarding and is generally discouraged , except possibly for unusually young patients (especially when precipitated by smoking or use of estrogen @-@ containing hormonal contraceptives) and those in whom revascularization , such as coronary arterial bypass , fails because of rapid occlusion of the graft .

= = Treatment = =

There is no specific treatment for thrombophilia , unless it is caused by an underlying medical illness (such as nephrotic syndrome) , where the treatment of the underlying disease is needed . In

those with unprovoked and / or recurrent thrombosis , or those with a high @-@ risk form of thrombophilia , the most important decision is whether to use anticoagulation medications , such as warfarin , on a long @-@ term basis to reduce the risk of further episodes . This risk needs to weighed against the risk that the treatment will cause significant bleeding , as the reported risk of major bleeding is over 3 % per year , and 11 % of those with major bleeding may die as a result .

Apart from the abovementioned forms of thrombophilia , the risk of recurrence after an episode of thrombosis is determined by factors such as the extent and severity of the original thrombosis , whether it was provoked (such as by immobilization or pregnancy) , the number of previous thrombotic events , male sex , the presence of an inferior vena cava filter , the presence of cancer , symptoms of post @-@ thrombotic syndrome , and obesity . These factors tend to be more important in the decision than the presence or absence of a detectable thrombophilia .

Those with antiphospholipid syndrome may be offered long @-@ term anticoagulation after a first unprovoked episode of thrombosis . The risk is determined by the subtype of antibody detected , by the antibody titer (amount of antibodies) , whether multiple antibodies are detected , and whether it is detected repeatedly or only on a single occasion .

Women with a thrombophilia who are contemplating pregnancy or are pregnant usually require alternatives to warfarin during pregnancy , especially in the first 13 weeks , when it may produce abnormalities in the unborn child . Low molecular weight heparin (LMWH , such as enoxaparin) is generally used as an alternative . Warfarin and LMWH may safely be used in breastfeeding .

When women experience recurrent pregnancy loss secondary to thrombophilia , some studies have suggested that low molecular weight heparin reduces the risk of miscarriage . When the results of all studies are analysed together , no statistically signifiant benefit could be demonstrated .

= = Prognosis = =

In people without a detectable thrombophilia , the cumulative risk of developing thrombosis by the age of 60 is about 12 % . About 60 % of people who are deficient in antithrombin will have experienced thrombosis at least once by age 60 , as will about 50 % of people with protein C deficiency and about a third of those with protein S deficiency . People with activated protein C resistance (usually resulting from factor V Leiden) , in contrast , have a slightly raised absolute risk of thrombosis , with 15 % having had at least one thrombotic event by the age of sixty . In general , men are more likely than women to experience repeated episodes of venous thrombosis .

People with factor V Leiden are at a relatively low risk of thrombosis , but may develop thrombosis in the presence of an additional risk factor , such as immobilization . Most people with the prothrombin mutation (G20210A) never develop thrombosis .

= = Epidemiology = =

The major (" type 1 ") thrombophilias are rare . Antithrombin deficiency is present in 0 @.@ 2 % of the general population and 0 @.@ 5 ? 7 @.@ 5 % of people with venous thrombosis . Protein C deficiency , too , is present in 0 @.@ 2 % of the population , and can be found in 2 @.@ 5 ? 6 % of people with thrombosis . The exact prevalence of protein S deficiency in the population is unknown ; it is found 1 @.@ 3 ? 5 % of people with thrombosis .

The minor (" type 2 ") thrombophilias are much more common . Factor V Leiden is present in 5 % of the population of Northern European descent , but much rarer in those of Asian or African extraction . In people with thrombosis , 10 % have factor V Leiden . In those who are referred for thrombophilia testing , 30 ? 50 % have the defect . The prothrombin mutation occurs at rates of 1 ? 4 % in the general population , 5 ? 10 % of people with thrombosis , and 15 % of people referred for thrombophilia testing . Like factor V Leiden , this abnormality is uncommon in Africans and Asians .

The exact prevalence of antiphospholipid syndrome is not well known , as different studies employ different definitions of the condition . Antiphospholipid antibodies are detected in 24 % of those referred to thrombophilia testing .

= = History = =

German physician Rudolf Virchow categorized abnormalities in the consistency of the blood as a factor in the development of thrombosis in 1856 . The exact nature of these abnormalities remained elusive until the first form of thrombophilia , antithrombin deficiency , was recognized in 1965 by the Norwegian hematologist Olav Egeberg . Protein C deficiency followed in 1981 , when described by researchers from the Scripps Research Institute and the U.S. Centers of Disease Control . Protein S deficiency followed in 1984 , described by researchers at the University of Oklahoma .

Antiphospholipid syndrome was described in full in the 1980s , after various previous reports of specific antibodies in people with systemic lupus erythematosus and thrombosis . The syndrome is often attributed to the British rheumatologist Graham R.V. Hughes , and is often referred to as Hughes syndrome for that reason .

The more common genetic thrombophilias were described in the 1990s . Many studies had previously indicated that many people with thrombosis showed resistance activated protein C. In 1994 a group in Leiden , The Netherlands , identified the most common underlying defect ? a mutation in factor V that made it resistant to the action of activated protein C. The defect was called factor V Leiden , as genetic abnormalities are typically named after the place where they are discovered . Two years later , the same group described a common mutation in the prothrombin gene that caused elevation of prothrombin levels and a mild increase in thrombosis risk .

It is suspected that other genetic abnormalities underlying familial thrombosis will in future be discovered through studies of the entire genetic code , looking for small alternations in genes .