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Fibrin degradation product and Haemorrhage

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Abstract

Fibrin degradation products (FDP) are substances that remain in your bloodstream after your body dissolves a blood clot. Your fibrinolytic system manages and regulates clot dissolving. Platelets in your blood gather together and stick to the injury site to form a plug or clot. The formation of the plug or clot is called the clotting cascade. Fibrin is a protein that aids in clotting. When there is haemorrhage the blood coagulation system is activated and the inactive plasma protein prothrombin is converted by thromboplastin to thrombin, which in turn brings about the conversion of the soluble protein fibrinogen to insoluble fibrin. The fibrinolytic system has a similar basic structure plasminogen, an inert plasma globulin, is converted by activators to plasmin, a proteolytic enzyme which digests fibrin and releases soluble smaller molecular weight fragments of this protein called fibrin degradation products (FDP). After fibrin or fibrinogen is digested by plasmin certain fragments are released which retain antigenic determinants of the parent fibrinogen which remains in the blood stream, these fragments are called fibrin degradation product. The fibrinolytic system manages and regulates clot dissolving.

Keywords: fibrin degradation product, haemorrhage, fibrin, fibrinogen, plaminogen fibrinolytix system

Introduction

Haemorrhage is also known as bleeding or simply blood loss, it's the process of blood escaping from the circulatory system from damaged blood vessels (Healthline, 2011).Bleeding can occur internally, or externally either through a natural opening such as the mouth, nose, ear, urethra, vagina or anus, or through a wound in the skin. It's classified into four categories depending on the level of blood loss (Healthline, 2011; Okoroiwu *et al.,I 2021;* Okoroiwu *et al.,* 2014; Ifeanyi *et al.,* 2020; Obeagu and Obeagu, 2015; Nwovu *et al.,* 2018; Obeagu; 2022; Obeagu *et al.,* 2022*).*

Fibrin degradation products (FDP) are substances that remain in your bloodstream after your body dissolves a blood clot. Your fibrinolytic (clot-busting) system manages and regulates clot dissolving. Platelets in your blood gather together and stick to the injury site to form a plug or clot. The formation of the plug or clot is called the clotting cascade. Fibrin is a protein that aids in clotting. Clotting, also called coagulation, at the wound site produces a mass of fibrin threads called a net. The net remains in place until the cut is healed. As the cut heals, the clotting slows down. Eventually the clot breaks down and dissolves. When the clot and fibrin net dissolve, fragments of protein are released into the body. These fragments are fibrin degradation products (FDPs). If your body is unable to dissolve a clot, you may have abnormal levels of FDPs. Blood tests can measure your level of FDPs to see if you have a clotting disorder. The fibrin degradation products test is a specific test that determines the amount of FDPs in your blood. The test is also known as the fibrin split products (FSPs) test, or the fibrin breakdown products test (Healthline 2011).

A mechanically stable clot is necessary to prevent haemorrhage (stopping bleeding is called hemostasis) and to promote wound healing. Fibrin clots are dissolved by the fibrinolytic system, acting in a series of enzymatic reactions with positive and negative feedback(Wei *et al*., 2009).In vivo, there is a careful balance between clotting, the conversion of fibrinogen to fibrin, and fibrinolysis, the proteolytic dissolution of the clot. Imbalance in one direction (prevalence of fibrinolysis) can lead to bleeding while the opposite imbalance (prevalence of clotting) can cause thrombosis, or formation of a clot that blocks the flow of blood through a vessel (called a thrombus). Thrombosis, often resulting from atherosclerosis or many other pathological processes, is the most common cause of myocardial infarction, ischemic stroke, deep vein thrombosis, and other cardiovascular diseases (Bridge *et al*., 2014).

Haemorrhage

This is also known as bleeding or simply blood loss, it's the process ofblood escaping from the circulatory system from damaged blood vessels (Healthline, 2011). Bleeding can occur internally, or externally either through a natural opening such as the mouth, nose, ear, urethra, vagina or anus, or through a wound in the skin. Hypovolemia is a massive decrease in blood volume, and death by excessive loss of blood is referred to as exsanguination (Healthline, 2011). Typically, a healthy person can endure a loss of 10–15% of the total blood volume without serious medical difficulties (by comparison, blood donation typically takes 8–10% of the donor's blood volume). The stopping or controlling of bleeding is called hemostasis.

Classification of haemorrhage

Hemorrhaging is broken down into four classes by the American College of Surgeons' advanced trauma life support (ATLS) (***Manning***, 2008).

1. Class I Hemorrhage: This involves up to 15% of blood volume. There is typically no change in vital signs and fluid resuscitation is not usually necessary.

2. Class II Hemorrhage: This involves 15-30% of total blood volume. A patient is often tachycardic (rapid heartbeat) with a reduction in the difference between the systolic and diastolic blood pressures. The body attempts to compensate with peripheral vasoconstriction. Skin may start to look pale and be cool to the touch.

3. Class III Hemorrhage involves loss of 30-40% of circulating blood volume. The patient's blood pressure drops, the heart rate increases, peripheral hypoperfusion (shock) with diminished capillary refill occurs, and the mental status worsens. Fluid resuscitation with crystalloid and blood transfusion are usually necessary.

4. Class IV Hemorrhage involves loss of >40% of circulating blood volume. The limit of the body's compensation is reached and aggressive resuscitation is required to prevent death.

Causes of haemorrhage

1. Traumatic injury: Traumatic bleeding is caused by some type of injury. There are different types of wounds which may cause traumatic bleeding. These include: Abrasion, Excoriation, Hematoma, Laceration, Incision, Puncture Wound, Contusion, Crushing Injuries, Ballistic Trauma.

2. Medical condition: Medical bleeding denotes hemorrhage as a result of an underlying medical condition (i.e. causes of bleeding that are not directly due to trauma). Blood can escape from blood vessels as a result of 3 basic patterns of injury: Intravascular changes, Intramural changes and extravascular changes.

Fibrinogen

Fibrinogen and fibrin are essential for hemostasis and are major factors in thrombosis, wound healing, and several other biological functions and pathological conditions. Fibrinogen is a soluble macromolecule, but forms an insoluble clot or gel on conversion to fibrin by the action of the serine protease thrombin, which is activated by a cascade of enzymatic reactions triggered by vessel wall injury, activated blood cells, or a foreign surface (Coller, 2011). A mechanically stable clot is necessary to prevent blood loss (stopping bleeding is called hemostasis) and to promote wound healing. Fibrin clots are dissolved by the fibrinolytic system, acting in a series of enzymatic reactions with positive and negative feedback. In vivo, there is a careful balance between clotting, the conversion of fibrinogen to fibrin, and fibrinolysis, the proteolytic dissolution of the clot. Imbalance in one direction (prevalence of fibrinolysis) can lead to bleeding while the opposite imbalance (prevalence of clotting) can cause thrombosis, or formation of a clot that blocks the flow of blood through a vessel (called a thrombus) (Coller and Shattil, 2008). Thrombosis, often resulting from atherosclerosis or many other pathological processes, is the most common cause of myocardial infarction, ischemic stroke, deep vein thrombosis, and other cardiovascular diseases. In addition to fibrin clot formation, fibrinogen is also necessary for an earlier step in hemostasis (called “primary hemostasis”), the aggregation of platelets leading to formation of a platelet “plug” at the site of vessel wall injury. The bivalent fibrinogen molecules act as bridges to link activated platelets, since the ends of rod-like fibrinogen bind with high affinity to the major adhesive receptor on platelets, the integrin αIIbβ3(Wei et al. 2009).

Fibrin formation, structure, and stability

During coagulation, fibrinogen is converted into insoluble fibrin. Fibrin formation involves thrombin-mediated proteolytic cleavage and removal of N-terminal fibrinopeptides from the Aα and Bβ chains. Insertion of these newly exposed α- and β-knobs into a- and b-holes in the γC and βC regions of the D nodule, respectively, on another fibrin monomer permits the half-staggered association of fibrin monomers into protofibrils. Subsequent aggregation of protofibrils into fibers yields a fibrin meshwork that is essential for blood clot stability. This process has been extensively reviewed (Lord, 2011).

Clot formation, structure, and stability are strongly influenced by the conditions present during fibrin generation. These include the concentrations of procoagulants, anticoagulants, fibrin(ogen)-binding proteins, molecules (Smith *et al*., 2015) and metal ions (Henderson *et al*., 2016) as well as contributions of blood and vascular cells, cell-derived microvesicles and presence of blood flow. The contribution of thrombin concentration to fibrin formation and structure has received considerable attention. High thrombin concentrations produce dense networks of highly branched fibrin fibers, and these clots are relatively resistant to fibrinolysis. In contrast, low thrombin concentrations produce coarse networks of relatively unbranched fibrin fibers, and these clots are relatively susceptible to fibrinolysis (Wolberg *et al*., 2009).

Fibrin crosslinking

Covalent crosslinking of fibrin chains is a critical determinant of fibrin stability. Crosslinking is mediated predominantly by transglutaminase factor XIII (FXIII) found in plasma and platelets. Plasma FXIII is a 320-kDa heterotetrameric zymogen (FXIII-A2B2) composed of 2 catalytic subunits (FXIII-A2) tightly associated (Kd≈10−10 mol/L) (Katona*et al*., 2014) with 2 noncatalytic subunits (FXIII-B2). FXIII-A2B2 circulates at ≈70 nmol/L (14–28 µg/mL)98 in complex with fibrinogen. Although early data suggested that FXIII-A2B2 preferentially binds the alternatively spliced fibrinogen γ′ chain, more recent studies have localized binding to γ-chain residues 390 to 396 with additional contributions from the Aα-chain (Byrnes *et al*., 2016). Catalytically active FXIII (FXIIIa) introduces ε-N-(γglutamyl)-lysyl crosslinks between glutamine and lysine residues on fibrin γ- and α-chains, yielding γ-γ dimers and high molecular weight species (γ-multimers, α-polymers, and αγ-hybrids). FXIII can also crosslink other plasma proteins (eg, α2-antiplasmin and fibronectin) to fibrin. Covalent crosslinking of α2-antiplasmin to fibrin prevents expulsion of α2-antiplasmin from the clot during clot compression or contraction102 and is essential for clot stability.

Clot contraction

An essential function during coagulation is the platelet-mediated consolidation of clots in a process known as clot contraction (or retraction). This process involves fibrin(ogen) binding to platelet integrin receptor αIIbB3 and is influenced by both platelet and fibrin(ogen) concentrations (Tutwiler *et al*., 2016).

Fibrin degradation product

Fibrin degradation products (FDP) are substances that remain in your bloodstream after your body dissolves a blood clot. The fibrinolytic (clot-busting) system manages and regulates clot dissolving. When you cut yourself, the injured blood vessel constricts to stop bleeding and promote healing. This process is called hemostasis. Platelets in your blood gather together and stick to the injury site to form a plug or clot. The formation of the plug or clot is called the clotting cascade. Fibrin is a protein that aids in clotting. Clotting, also called coagulation, at the wound site produces a mass of fibrin threads called a net. The net remains in place until the cut is healed. As the cut heals, the clotting slows down. Eventually the clot breaks down and dissolves. When the clot and fibrin net dissolve, fragments of protein are released into the body. These fragments are fibrin degradation products (FDPs). If your body is unable to dissolve a clot, you may have abnormal levels of FDPs. Blood tests can measure your level of FDPs to see if you have a clotting disorder. The fibrin degradation products test is a specific test that determines the amount of FDPs in your blood. The test is also known as the fibrin split products (FSPs) test, or the fibrin breakdown products test (Healthline 2011).

In the blood coagulation system the inactive plasma protein prothrombin is converted by thromboplastin to thrombin, which in turn brings about the conversion of the soluble protein fibrinogen to insoluble fibrin. The fibrinolytic system has a similar basic structure ; plasminogen, an inert plasma globulin, is converted by activators to plasmin, a proteolytic enzyme which digests fibrin and releases soluble smaller molecular weight fragments of this protein (F.D.P.). Plasminogen has a high affinity for fibrin, and when a clot forms, enough plasminogen is incorporated to mediate the subsequent lysis of the fibrin when plasminogen activator diffuses into the clot from the circulating plasma or surrounding endothelium. After fibrin or fibrinogen is digested by plasmin certain fragments are released which retain antigenic determinants of the parent fibrinogen (Nussenzweig *et al*., 2006). Such F.D.P. are incoagulable by thrombin and hence can be found in serum; F.D.P. are known to have pronounced antithrombin activity and to inhibit both fibrin polymerization and the aggregation of platelets (Wilson et al., 1968) for these reasons F.D.P. can produce a serious haemostatic defect.

During the proteolysis of fibrinogen and fibrin by the fibrinolytic enzyme plasmin several large fragments are released which are incapable of undergoing further digestion. Some of these fragments, with a molecular weight of approximately 88,000, contain an antigenic determinant which is identical to the parent fibrinogen (Nussenzweig *et al*., 2006). An accurate quantitative estimation of circulating fibrin/fibrinogen degradation products (F.D.P.) would be of considerable importance in investigations of physiological and pathological states of coagulation and fibrinolysis, for circulating F.D.P. represent a certain criterion that fibrinolysis is taking place. They play a significant part in the pathogenesis of certain bleeding disorders (Kopec *et al*., 2006); they may be of importance in the physiological control of the microcirculation (Buluk *et al*., 2006)

Fibrin D-Dimer

The antigen Fibrin D-dimer (DD) is the primary enzymatic degradation product of cross-linked fibrin by plasmin. Systemic values of DD are an index of fibrin turnover in the circulation and a single measurement may be adequate to assess the fibrinolytic status. Despite the implementation of clinical guideline, inappropriate DD testing is a significant problem. It is, consequently, valuable for emergency as well as intensive care physicians to be knowledgeable about the pathophysiological basis and limitations of DD testing to ensure its appropriate clinical use (Wakai *et al*., 2009).

Pathophysiology

Fibrin is the main component of a thrombus. It is formed by the activation of the coagulation system. Its production is followed by activation of the fibrinolytic system, resulting in plasmin generation and subsequent fibrin lysis. Plasmin, the fibrinolytic enzyme, derived from its inactive precursor, plasminogen, by the action of thrombin and plasminogen activator, that is tissue plasminogen activator (TPA) and prourokinase mainly. Plasmin is neutralized by Alfa 2 antiplasmin thereby restricting its fibrinogenolytic activity and localizing the fibrinolysis on the fibrin clot. Under the physiological conditions there is balance of the two opposing processes (Wakai *et al*., 2009).

Laboratory investigation of fibrin degradation product

The following methods can be used to assay fibrinogen and fibrin degradation product in the laboratory. The methods are as follows:

1. Tanned red cell hemaglutination inhibition immunoassay (TRCHII).
2. Staphylococcal clumping test.
3. Fi test.
4. Flocculation
5. Immunodiffusion and
6. Anticoagulant assay (Victor *et al*., 2007).

Reference range:

The result is normally less than 10mcg/ml (10mg/L).

Conclusion

When there is haemorrhage the blood coagulation system is activated and the inactive plasma protein prothrombin is converted by thromboplastin to thrombin, which in turn brings about the conversion of the soluble protein fibrinogen to insoluble fibrin.. After fibrin or fibrinogen is digested by plasmin certain fragments are released which retain antigenic determinants of the parent fibrinogen which remains in the blood stream, these fragmens are called fibrin degradation product. The fibrinolytic (clot-busting) system manages and regulates clot dissolving.

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