

Blood Coagulation

☒ Introduction:-

- **In normal situation** there is a delicate balance that prevents thrombosis and hemorrhage.
- **Disorders of coagulation** can lead to an increased risk of bleeding (hemorrhage) or obstructive clotting (thrombosis).
- **Inside the vascular system** the blood must be remain fluid but when exposed to non-endothelial surface outside the vascular system, it clots quickly as in case of vascular injury. When intravascular thrombi occur, a system of fibrinolysis is activated to restore fluidity.

☐ Main Steps of Clot Formation:-

1. **Vasoconstriction (VC)**; to decrease blood flow in injured area.
2. **Platelet adheres** to macromolecules in the subendothelial regions of the injured blood vessels.
3. **Release of intracellular granules** containing chemical mediators.
4. **Platelets aggregate** to form the primary haemostatic plug.
5. **Activation of plasma coagulation factors**, leading to generation of thrombin which catalysis the conversion of fibrinogen to fibrin.

☒ Overview of Platelet Physiology:-

❖ Introduction;

- Platelets were discovered by Giulio Bizzozero in 1882.
- They are primarily associated with hemostasis, which is to initiate blood coagulation, but hemostasis or blood coagulation is not the sole function of platelets.
- Platelet activity is associated with the initiation of coagulation cascades.
- Damage in blood vessel makes the subendothelial surface the primary target site of platelet action, where it establishes the hemostasis.

❖ Structure;

- Platelet plasma membrane (phospholipid bilayer); is the site of expression of various surface receptors and lipid rafts which helps in signalling and intracellular trafficking.
- Platelets have two major storage granules; α and dense granules;
 1. **α granules**; which play a role in multiple functions; coagulation, inflammation, atherosclerosis, antimicrobial host defence, angiogenesis, wound repair and tumorigenesis. a granule contains proteins (e.g., Glycoprotein IIb/IIIa; GPIIbIIIa, fibrinogen and Von Willebrand factor; vWf) which initiate the coagulation cascades.
 2. **Dense granules** or **delta (δ) granules**; which are secreted during platelet activation; these include catecholamines, serotonin, calcium, adenosine diphosphate (ADP) and adenosine triphosphate (ATP). ADP is a weak platelet agonist, triggering platelet shape change, granule release and aggregation.

☒ Platelet Response to Vascular Injury;

1. Resting Platelets:

- Platelets act as vascular sentries, monitoring the integrity of the vascular endothelium.
- In the absence of injury, resting platelets circulate freely, because the balance of chemical signals indicates that the vascular system is not damaged

2. Platelet Adhesion:

- When the endothelium is injured: Glycoprotein Ib/V/IX Complex and subendothelial compounds like Von Willebrand factor (vWf) and collagen interact with each other to platelet adhesion to exposed subendothelial surface of damaged endothelium.

3. Platelets Activation;

- Receptors on the surface of the adhering platelets are activated by the collagen.
- This causes morphologic changes in platelets (from spherical to stellate) and the release of platelet granules containing chemical mediators, such as: - Adenosine diphosphate (ADP), serotonin, platelet-activating factor (PAF), Von Willebrand factor (vWf), platelet factor 4 and thromboxane A2 (TXA2).
- These signaling molecules bind to receptors in the outer membrane of resting platelets circulating nearby □ platelets become activated and start to aggregate.
- During shape change, platelet fibrinogen receptors (GPIIb/IIIa) are exposed and activated and platelet-platelet aggregation is initiated.

4. Platelet Aggregation;

- The chemical mediator activate a G-protein (Gg) receptor, □ increase intracellular Ca^{2+} .
- The Ca^{+} activates protein kinase C □ which activates phospholipase A2 (PLA2).
- PLA2 then modifies the integrin membrane glycoprotein IIb/IIIa, increasing its affinity to bind fibrinogen □ platelets aggregate.

Notes;

- o Arachidonic acid-thromboxane (TXA2) pathway is an important platelet activation pathway.
- o Adenosine diphosphate (ADP) is another important platelet activator. P2Y₁₂, an ADP specific receptor, which can activate GPIIb/IIIa receptor, leads to platelet aggregation.
- o Prostacyclin and nitric oxide, are synthesized by endothelial cells and act as inhibitors of platelet aggregation.
 - Prostacyclin (PGI₂) acts by binding to platelet membrane receptors □ increase cyclic adenosine monophosphate (cAMP) □ decrease intracellular Ca^{2+} □ decrease platelet activation.
 - Damaged endothelial cells synthesize less prostacyclin than □ increase platelet activation.

❏ Coagulation Cascade:-

- The coagulation cascade (secondary hemostasis) has three pathways which lead to fibrin

Formation : extrinsic, intrinsic and common pathway.

A. Tissue Factor Pathway (Extrinsic);

- Tissue factor (TF); is a protein present in subendothelial tissue.
- The main role of the tissue factor pathway is to generate a minor amount of thrombin.
- TF itself has no enzymatic function, but serves as a cofactor and facilitates rapid auto-activation of factor VII.
- The process includes the following steps:
 - 1) After damage of blood vessel; Factor VII (FVII) leaves the circulation and comes into contact with tissue factor (TF) forming an activated complex (TF-FVIIa).
 - 2) TF-FVIIa activates factor IX (FIX) and factor X (FX) to FIXa and FXa.
 - 3) FXa and its co-factor FVa, activates prothrombin to thrombin.
 - 4) Thrombin then activates other components of the coagulation cascade.

B. Contact Activation Pathway (Intrinsic);

- The contact activation pathway begins with formation of the primary complex on collagen by high-molecular-weight kininogen (HMWK), Prekallikrein and FXIIa.
- prekallikrein is converted to kallikrein and FXII becomes FXIIa.
- FXIIa converts FXI into FXIa.
- Factor XIa activates FIX, which activates FX to FXa.

C. Common Pathway;

- Formation of FXa to the formation of active thrombin from prothrombin.
- Thrombin converts fibrinogen to fibrin.
- Fibrin monomers bind together to form a gel of network □ Collect blood cells to form clot.

📌 Fibrinolysis:-

- **Fibrinolysis**; is a critical hemostatic process that regulates control of clot dissolution and hence wound repair, also plays key roles in inflammation, neoplastic and other biological processes.
- The major components of fibrinolysis are plasminogen activators, plasminogen, plasmin, fibrinogen, fibrin, Factor XIII, alpha-2 antiplasmin and plasminogen activator inhibitor.
- Tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA) circulate in plasma as a reversible complex with plasminogen activator inhibitor-1 (PAI-1)
- t-PA and u-PA are the agents that convert plasminogen to the active plasmin □ fibrinolysis.
- t-PA and plasminogen activator inhibitor-1 (PAI-1 and PAI-2).
- Alpha 2-antiplasmin and alpha 2-macroglobulin inactivate plasmin.

📌 Definition:-

- **Venous thromboembolism (VTE)** is the formation of blood clots in the vein.
 - When a clot forms in a deep vein, usually in the leg, it is called;
Deep Vein Thrombosis (DVT).
 - If that clot breaks loose and travels to the lungs, it is called;

Pulmonary Embolism (PE).

- Together, DVT and PE are known as VTE.

- **Venous thromboembolism (VTE);** is a disease that includes both deep vein thrombosis (DVT) and pulmonary embolism (PE).
- **Deep Vein Thrombosis (DVT);** a blood clot that forms in a deep vein (usually in the leg).
- **Pulmonary Embolism (PE);** a blood clot in the lungs.
 - PE occurs when a DVT breaks free from a vein wall, travels to the lungs and blocks some or all of the blood supply to the lungs. PE can often be fatal.

☐ **Prevalence:-**

- Venous thromboembolism is the third most common cardiovascular illness after acute coronary syndrome and stroke.
- It is believed that there are approximately 1 million cases in the United States each year.
- Nearly two thirds of all VTE events result from hospitalization and approximately 300,000 of these patients die.
- DVT and PE is low, and much lower than awareness of other diseases like heart attack, stroke, hypertension, breast cancer, prostate cancer and AIDS.

☐ **Risk Factors:-**

- VTE affects people of all ages, races and ethnicities and occurs in both men and women.
- Certain factors and situations can increase the risk of developing potentially deadly blood clots.
 - During surgery (especially hip, knee and cancer-related surgery).
 - Not moving for long periods of time (e.g. long-duration travel).
 - Age (> 60).
 - Family history of blood clots.
 - Cancer chemotherapy.
 - Estrogen-based medication (e.g., oral contraceptives).
 - Obesity.
 - Pregnancy or recent birth.
 - Smoking.
 - Alcohol consumption.

☒ **Symptoms:-**

Deep Vein Thrombosis (DVT)	Pulmonary Embolism (PE)
- Pain or tenderness, often starting in the calf. - Swelling, including the ankle or foot. - Redness or noticeable discoloration. - Warmth.	- Unexplained shortness of breath. - Rapid breathing. - Chest pain (may be worse upon deep breath). - Rapid heart rate. - Light headedness or passing out.

□ **Diagnosis:-**

Deep Vein Thrombosis (DVT)	Pulmonary Embolism (PE)
1. Ultrasound; a clot may be visible in the image. 2. D-dimer test. (blood test); almost all people who develop severe deep vein thrombosis have an elevated blood level of a clot- dissolving substance called D-dimer. 3. Venography; If the results of a D-dimer test and ultrasound scan cannot confirm a diagnosis of DVT, a venogram might be used. A dye (contrast agent) is injected into a large vein in the foot or ankle. An X-ray procedure creates an image of the veins in the legs and feet, to look for clots. 4. CT or MRI scans. Both computerized tomography (CT) scan and magnetic resonance imaging (MRI) can provide a visual images of the veins and may show a clot.	1) Ultrasound. 2) D-dimer test 3) Pulmonary Angiogram; a flexible tube (catheter) is inserted into a large vein (usually in groin) and threaded through into the heart and on into the pulmonary arteries. A special dye is then injected into the catheter, and X-rays are taken as the dye travels along the arteries in the lungs. 4) Chest X-ray; Although X-rays can't diagnose pulmonary embolism and may even appear normal when pulmonary embolism exists, they can rule out conditions that mimic the disease. 5) CT or MRI scans. 6) Lung ventilation/perfusion scan (VQ scan); radioactive substance to show how well oxygen and blood are flowing to all areas of the lungs.

⊠ **Treatments:-**

- **Medications;** thrombolytics and anticoagulants (see next topics).
- **Surgical and other procedures;** clot removal or vein filter.