**Study Material: Pathophysiology of Coagulation and Thrombosis**

**Learning Objectives**

By the end of this topic, you should be able to:

* Understand the physiological process of **hemostasis**.
* Describe the **coagulation cascade** and its regulation.
* Differentiate between normal clotting and **thrombosis**.
* Recognize **pathological mechanisms** that lead to thrombus formation.
* Understand clinical consequences and therapeutic targets in coagulation disorders.

**I. Introduction to Coagulation**

**Coagulation** is a tightly regulated process that ensures:

* Bleeding is stopped (hemostasis) following injury.
* Clotting does **not** occur inappropriately within intact vessels.

When unbalanced, it can result in:

* **Hemorrhage** – too little clotting
* **Thrombosis** – too much clotting

**II. Phases of Hemostasis**

Hemostasis is divided into **3 coordinated stages**:

**1. Vascular Phase**

* Vasoconstriction limits blood loss.
* Endothelial cells release factors to promote clotting (e.g., endothelin).

**2. Platelet Phase (Primary Hemostasis)**

* Platelet adhesion to exposed subendothelial collagen (via vWF).
* Activation and aggregation form the **platelet plug**.

**3. Coagulation Phase (Secondary Hemostasis)**

* Cascade of enzymatic reactions activates fibrin formation.
* Stabilizes platelet plug into a **fibrin clot**.

**III. The Coagulation Cascade**

The coagulation system involves a cascade of inactive plasma proteins (zymogens) that become activated in a sequence.

**Two Pathways Initiate Coagulation:**

| **Intrinsic Pathway** | **Extrinsic Pathway** |
| --- | --- |
| Triggered by trauma **within** the vascular system | Triggered by **external** trauma (e.g., tissue injury) |
| Slower and involves many factors | Rapid response |
| Involves Factors: XII, XI, IX, VIII | Involves Factor: VII, Tissue Factor (TF) |

➡ Both pathways converge at the **common pathway** involving:

* **Factor X** → Xa
* Xa converts **Prothrombin (II)** → **Thrombin (IIa)**
* Thrombin converts **Fibrinogen (I)** → **Fibrin (Ia)**
* Fibrin stabilizes the clot

**IV. Regulation of Coagulation**

To prevent excessive clotting, the body uses **natural anticoagulants**, including:

* **Antithrombin III** – inhibits thrombin and other clotting factors
* **Protein C and S** – degrade Factors Va and VIIIa
* **Tissue Factor Pathway Inhibitor (TFPI)** – blocks early steps in extrinsic pathway
* **Plasminogen/Plasmin system** – dissolves clots (fibrinolysis)

**V. Pathophysiology of Thrombosis**

**Definition:**

Thrombosis = Pathological clot formation within intact blood vessels.

**Virchow’s Triad – 3 major contributors:**

1. **Endothelial Injury**
   * From trauma, surgery, hypertension, atherosclerosis
2. **Hypercoagulability**
   * Genetic: Factor V Leiden, Protein C/S deficiency
   * Acquired: Cancer, pregnancy, oral contraceptives
3. **Stasis of Blood Flow**
   * Immobilization, atrial fibrillation, varicose veins

**VI. Types of Thrombi**

| **Type** | **Location** | **Composition** |
| --- | --- | --- |
| Arterial thrombus | High flow (arteries) | Platelet-rich (“white clot”) |
| Venous thrombus | Low flow (veins) | Fibrin-rich (“red clot”) |

**VII. Clinical Consequences**

* **Deep Vein Thrombosis (DVT)** – clots in deep veins, often legs
* **Pulmonary Embolism (PE)** – clot travels to lungs
* **Myocardial Infarction (MI)** – arterial thrombosis in coronary arteries
* **Ischemic Stroke** – thromboembolism in cerebral arteries

**VIII. Therapeutic Approaches**

| **Drug Class** | **Examples** | **Mechanism** |
| --- | --- | --- |
| **Antiplatelets** | Aspirin, Clopidogrel | Inhibit platelet aggregation |
| **Anticoagulants** | Heparin, Warfarin, DOACs | Inhibit clotting factors |
| **Fibrinolytics** | Alteplase (tPA) | Dissolve fibrin clots |

**Summary**

* Coagulation is a **life-saving process** but must be **carefully regulated**.
* Thrombosis occurs when **clotting exceeds normal limits**, leading to serious disease.
* Understanding clotting mechanisms aids in **diagnosis, prevention, and treatment** of thrombotic disorders.