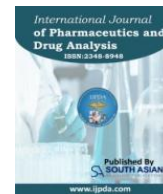




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ADVANCEMENTS IN UNDERSTANDING AND MANAGING DEEP VEIN THROMBOSIS: A CONTEMPORARY PERSPECTIVE

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Abstract

Deep vein thrombosis (DVT) refers to the formation of blood clots within the deep veins, typically affecting those in the pelvis or lower extremities, including the calf, femoral, and popliteal veins. DVT poses a significant global healthcare challenge due to its potential to cause life-threatening complications like pulmonary embolism. Recent years have seen substantial progress in comprehending the pathophysiology of DVT and in enhancing strategies for its prevention and management. This review article presents a contemporary viewpoint on the progress made in understanding and addressing DVT, focusing on advancements in epidemiology, risk factors, diagnosis, treatment, and preventive measures.

Keywords: Deep vein thrombosis, pathogenesis, pulmonary embolism.

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Introduction

1. Overview

Deep vein thrombosis (DVT) is the occurrence of blood clot formation within the deep veins of the pelvis or lower extremities, as highlighted in recent studies [1]. In severe cases, it can lead to pulmonary embolism (PE), where blood clots migrate from deep veins to the lungs via the bloodstream, impeding blood flow and heightening the probability of clot formation [2]. Early detection of DVT is imperative for timely intervention, as PE can have fatal consequences in certain instances [3]. Nevertheless, diagnosing DVT early poses challenges due to its inexplicit symptoms, which may even manifest asymptotically. In the past decade, novel techniques have emerged for the rapidly diagnosing DVT in elevated-risk individuals, marking significant advancements in medical practice.

2. Epidemiology

Epidemiological data underscore the widespread prevalence of DVT, affecting individuals across diverse

demographic groups and geographical regions. While certain risk factors, such as ageing, obesity, inactivity, and amputation, have long been recognized as predisposing factors for DVT, recent research has identified additional contributors, including genetic predispositions, hormonal influences, and environmental factors. Deep vein thrombosis (DVT) plays a substantial role in the overall healthcare burden worldwide. Reports indicate that the yearly occurrence of this disease is approximately 100 cases per 1 lakh humans [4]. Nevertheless, the occurrence of DVT increases with advancing age, and males have a higher likelihood than females of developing DVT and witnessing its subsequent occurrence [5-7]. Ageing of the vessels is key susceptibility factor for the origination of the disease. Furthermore, it is hypothesized that kids have a diminished ability to produce thrombin, an increased ability to have anti-thrombin in the walls of their blood vessels, and a stronger potential for α -2-macroglobulin to obstruct thrombin [8]. There is also substantial data indicating a correlation between the utilization of contraceptives, the postpartum period, pregnancy, and caesarean sections with an elevated susceptibility to deep vein thrombosis (DVT) [9].

3. Factors increasing the likelihood of developing DVT

The likelihood factors can be categorized into three main groups: acquired, inherited, and situational [10].

3.1. Acquired Risk Factors:

3.1.1. Prolonged Immobility: Prolonged periods of inactivity, such as during extended travel, being hospitalized, or being confined to bed, can result in the stagnation of blood flow, which raises the likelihood of developing deep vein thrombosis (DVT) [11,12].

3.1.2. Orthopedic Surgery: Major surgical procedures, particularly those involving the lower extremities or pelvis, can disrupt normal blood flow and lead to endothelial injury, predisposing individuals to DVT. Patients who have undergone significant orthopedic surgery or have sustained injuries to their lower limbs have enhanced chances of developing this disease. There are researches suggesting that DVT in these patients is associated with artery wall deterioration, a lack of motion and stimulated coagulation cascades [13].

3.1.3. Cancer: Individuals diagnosed with malignancy have a greater incidence of DVT, with the particular occurrence of it varying based on the physiological characteristics of the cancer. Further evidence of an elevated risk for DVT in cancer victims receiving intensive therapy, such as chemotherapy, has been found [14,15]. This may be because the plasma functioning of protein C and S are hindered. Malignant tumors, such as those seen in the pancreas, ovaries, and brain, are linked to an enhanced likelihood of developing DVT due to multiple factors. These factors include the physical pressure exerted by tumors on veins and the blood clot-promoting activities of cancer cells.

3.1.4. Obesity: Excess adipose tissue can contribute to venous stasis and inflammation, promoting the development of DVT [11,12].

3.1.5. Hormonal Factors: The impact on coagulation pathways by estrogen-containing medicines (e.g., pill-based contraceptives and substitute hormonal medication), gestation period, and the postpartum phase might increase the risk of deep vein thrombosis (DVT) [11,12].

3.2. Inherited Risk Factors:

3.2.1 Factor V Leiden Mutation: This genetic variant confers resistance to the blood thinning properties of activated protein C, hence elevating the likelihood of developing clotting [16].

3.2.2 Prothrombin Gene Mutation (Factor II Mutation): Individuals with this mutation have elevated levels of prothrombin, a clotting protein, increasing their susceptibility to thrombosis [17].

3.2.3 Insufficiency or lack of antithrombin, protein C, and protein S: Deficiencies in these natural anticoagulant proteins can predispose individuals to excessive clotting and increase the risk of DVT [18].

3.3. Situational Risk Factors:

3.3.1 Advanced Age: The risk of DVT increases with age, with older adults being more susceptible due to factors such as reduced mobility and comorbidities. It is found to be least prevalent in the childhood [19].

3.3.2 Individuals who have previously had venous thromboembolism have a greater chance of reliving these incidents. [11,12].

3.3.3 Varicose veins [20,21], especially when accompanied by venous insufficiency, can disrupt normal blood flow and increase the risk of DVT [22].

4. Pathogenesis

Distally, the formation of thrombus expands primarily within the valve compartments of the calf vein, a phenomenon particularly observed in individuals post-surgical procedures [23]. While some thrombi develop within days, weeks, or months after surgery, the majority initiate during the surgical procedure itself. Recent hypotheses propose that the reduction in Von Willebrand factor (vWF) levels and elevated levels of thrombomodulin (TM) and endothelial protein C receptor (EPCR) in valve sinus endothelium in contrast to vein luminal endothelium grants backing to the notion that thrombus emerged in valve pockets. This suggests a decrease in procoagulant (vWF) levels and an increase in anticoagulants (EPCR, TM) in valvular sinus endothelium [24].

The primary constituents of thrombus are red blood cells and fibrin. Distinguishing vein thrombus from a postmortem clot at autopsy is essential. Typically not linked to the underlying wall, postmortem emboli have a yellow precipitate like melted chicken fat and a dark red dependent component with a gelatinous texture. Venous thrombi, on the other hand, are more resilient and nearly invariably adhere to the vessel wall, exposing hazy strands of pale gray fibrin [25].

Lower limb DVT can be classified as proximal, affecting the popliteal vein or thigh veins, or distal, affecting the calf veins. Proximal vein thrombosis is clinically relevant, associated with significant chronic conditions like congestive heart failure, advanced age, active malignancy, and respiratory issues, while distal vein thrombosis is more commonly linked to risk factors such as immobilization and recent orthopedic surgery. Proximal DVT is significantly more prone to causing fatal pulmonary embolism (PE) [26]. One year post-DVT, post-thrombotic syndrome—an enduring, potentially disabling condition characterized by limb edema, pain, venous dilation, and skin hardening—affects 17% to 50% of cases [27].

An unusual symptom of venous thromboembolism (VTE) is acute widespread venous thrombosis, which blocks the distal venous drainage channel. This includes ailments such as phlegmasia alba and cerulea dolens, and venous gangrene. Only the main deep venous conduits in the afflicted extremity experience thrombosis in phlegmasia alba dolens; collateral veins remain unharmed. Nevertheless, thrombosis spreads to collateral veins in phlegmasia cerulea dolens, resulting in more severe edema and fluid buildup.

5. Clinical Manifestation

Recognition of DVT with a history and clinical examination is not a dependable method [28]. DVT in the lower limbs may or may not cause symptoms. It's common for persons

with lower extremity DVT to show up without any erythema, discomfort, warmth, edema, or soreness. Calf discomfort, lower extremity edema, and lower extremity pain are common symptoms in proximal DVT patients [29,30]. In DVT, Homans' sign could be observable. Since the majority of these characteristics lack specificity, a clinical evaluation typically suggests that additional testing is necessary. When it comes to acute major venous thrombosis and venous thrombosis during pregnancy, the left leg is most frequently affected. This could be as a result of May-Thurner syndrome [31].

Phlegmasia cerulea dolens is a condition where there is painful blue inflammation that starts from the farthest areas and progresses towards the closer areas, accompanied by the formation of blisters or bullae. On the other hand, phlegmasia alba dolens is a condition characterized by swelling, discomfort, and whitening of the affected area, without the presence of cyanosis.

6. Clinical Assessment

Although untreated thrombi may lead to potentially catastrophic consequences such as PE, prompt and accurate diagnosis of DVT is crucial. However, anticoagulation might be dangerous even in the absence of thrombosis. The thorough assessment that combines comprehensive medical risk factors, signs and symptoms, and indicators is the most extensively recognized research-based methodology for identifying deep vein thrombosis or venous thrombus embolism.

Assessing the patient's clinical aspects (medical history, physical examination, etc.) to ascertain their risk of DVT is a crucial initial step. For patient categorization, numerous standardized clinical likelihood evaluation techniques have been offered; nevertheless, because of its extensive study and popular use, the Wells score [32] is the most often recommended model.

Individuals identified with DVT were categorized into 3 groups (low, moderate, and high-probability group) in the original Wells score model. based on medical presentation and risk factors; these groups were estimated to have an 85%, 33%, and 5% risk for DVT, respectively. Nevertheless, Wells et al. divided patients into two groups in a subsequent trial, further developing an easy-to-understand version of the evaluation measures: improbable to suffer from the disease when the diagnostic score is ≤ 1 , and likely to possess the disease when the diagnostic score is > 1 . [33].

6.1 Wells Scoring System

The elements of the scoring system is displayed in Table 1 (34). A score of ≥ 2 increases a person's risk of developing DVT by 28%, whereas a score of < 2 increases that risk by 6%. Based on their Wells scores, participants may be categorized into three groups: low-likelihood (score < 1), moderate-likelihood (score = 1-2), and high-likelihood (score > 2). The likelihood for acquiring Deep vein thrombosis is 53%, 17%, and 5%, respectively.

TABLE 1: WELLS Scoring System for DVT Probability Analysis and Evaluation

WELLS SCORING SYSTEM	
Variables	Points Allocated
Receiving cancer treatment currently or within the past 6 months, or undergoing hospice treatment	+1
Paralysis or weakness in the lower extremity, or recent use of plaster casts for immobilization.	+1
Recently confined to bed for three days or underwent significant surgery within the past three months, necessitating either general or regional anesthesia.	+1
Sensitivity observed in specific regions corresponding to the distribution of deep veins.	+1
Swelling in the entire lower limb	+1
Swelling in the calf exceeding 3 cm on the side without symptoms (measured 10 cm below the tibial tuberosity).	+1
Pitting edema observed unilaterally, confined to the leg experiencing symptoms.	+1
Expansion of superficial veins without varicosities, noted in the leg experiencing symptoms.	+1
DVT diagnosis was established in the past.	+1
A substitute diagnosis is as likely as, or more likely than, deep vein thrombosis.	-2

6.2 D-dimer

D-dimer is a tiny protein that is created when fibrinolysis ruptures apart blood clots. It gets its name from the structure it possesses, which is made up of two linked segments of fibrin protein D. Its bloodstream presence suggests that fibrinolysis and clot formation have been widely stimulated [35]. A number of clinical situations where coagulation of blood might form, including post-operative care, trauma, cancer, severe infections, and bleeding episodes, can result in elevated D-dimer levels, especially in those receiving medical care [36]. Interestingly, there is a higher chance of deep vein thrombosis (DVT) with these disorders. D-dimer values usually stay elevated for around a week in people with DVT. D-dimer values, however, might be lower in individuals who arrive later in the course of the illness, after blood clots have been established and stuck. Comparably, people with DVT in the calf vein might have a lower clot burden and, as a result, lower D-dimer levels, which might be below the diagnostic assay's susceptibility threshold. The decreased efficacy of D-dimer tests in cases of confirmed DVT may be explained by this variable.

D-dimer testing can help rule out DVT even though it cannot be used to definitively diagnose it. Patients with a low to moderate chance of DVT based on Wells score may find that typical D-dimer test findings are helpful in ruling out the condition(37). D-dimer testing, however, might not be enough in people who have significant Wells scores to

verify the medical condition; instead, compression ultrasonography and other diagnostic imaging procedures are recommended [38]. Thus, additional diagnostic procedures, including image processing, should be used if D-dimer levels are raised in order to either validate or exclude out DVT [39]. When calculating DVT, D-dimer has a high sensitivity (almost 97%) but a low specificity (about 35%) [40].

D-dimer can be used as an immediate evaluation technique if there is lower limb swelling in addition to negative results from diagnostic radiological exams, based on prior DVT diagnostic investigations. Serum D-dimer levels can be determined using one of three techniques: 1) Red blood cell whole-blood agglutination assay (simpliRED); 2) latex agglutination assay; and 3) enzyme-linked immunosorbent assay (ELISA). The features, sensitivity, and probability levels of these tests vary. For D-dimer tests, ELISA assays offer a relative rating system that helps determine susceptibility and negative likelihood ratios [3].

As per the recommendations of the American College of Chest Physicians, patients deemed to have a low likelihood of DVT should undergo a D-dimer test with moderate-to-high specificity, followed by an evaluation of the proximal veins using compression ultrasound [39]. In contrast, the UK National Institute for Health and Care Excellence advises that D-dimer levels be measured prior to conducting ultrasound imaging of the proximal veins [41]. For individuals with a moderate likelihood of DVT, NICE suggests prioritizing D-dimer testing with high specificity over whole-leg or compression vascular ultrasound [39]. NICE guidelines rely on a 2-point Wells score and focus on the moderate-probability category [41].

6.3 MRI (Magnetic resonance imaging)

MRI has many uses, such as phase-contrast venography and time-of-flight, which use blood flow to image instead of contrast medium. Vascular imaging is improved, nevertheless, by the introduction of contrast agents, such as IV gadolinium. To see veins in the lower extremities, contrast media can be injected through the dorsalis pedis or veins in the forearm [42].

MRI has the capability to identify DVT by directly imaging the thrombus, as it generates a robust signal due to the presence of red blood cells containing methemoglobin. Although MRI is a noninvasive technology that does not require contrast injections, it is not commonly used for DVT evaluation in most institutions.

6.4 Contrast Venography

Contrast venography is the primary method utilized in diagnosing DVT. This procedure entails injecting a contrast agent, typically non-iodinated such as Omnipaque, into the peripheral veins of the affected limb. X-ray imaging is subsequently employed to assess whether there are any impediments to venous blood flow (43). Identifying phlebothrombosis requires detecting regions within the vessel lumen where filling is

incomplete from various perspectives [44], as well as pinpointing an abrupt cessation of flow in a deep vein. This method is renowned for its high sensitivity and specificity, making it particularly effective in ascertaining the location and size of DVTs.

6.5 Venous ultrasonography

Venous ultrasonography is the favored diagnostic method for patients suspected of having DVT [45]. This approach is non-invasive, safe, readily available, and cost-effective. Venous ultrasonography comprises three variations: compressive ultrasound (solely B-mode scanning), duplex ultrasound (combining B-mode scanning with Doppler waveform analysis), and standalone color Doppler scanning.

During duplex ultrasonography, blood flow in a typical vein is pulsatile, synchronized with breathing, and can be increased by outside forces. A pulsed Doppler signal is used in color flow sonography to create pictures [46]. While duplex ultrasonography and color duplex are more commonly used to evaluate the calf and iliac veins, compression ultrasound is mostly used to examine the proximal deep veins, specifically the common femoral, femoral, and popliteal veins [47]. The main ultrasonographic marker for venous thrombosis detection is the vein lumen's inability to collapse when the probe is used to apply light pressure.

Additional requirements for the ultrasonographic diagnosis of venous thrombosis include the lack of any color or spectrum Doppler signals coming from the vein lumen, the vein's reaction to the Valsalva maneuver or augmentation ultrasound, and the absence of a phasic pattern, which would indicate continuous flow [48]. Aside from avoiding radiation exposure, venous ultrasound has the advantage of being able to detect additional pathologies such as abscesses, femoral aneurysm, superficial thrombophlebitis, lymphadenopathy, and Baker's cysts.

Nevertheless, its main limitation lies in its reduced ability to detect thrombosis in distal areas [49]. Along with other immobilization methods hindering access to the limb, factors such as obesity, swelling, and tenderness in patients may also hinder venous compressibility. B-mode compression ultrasonography, with or without color, is employed for diagnostic purposes. Duplex imaging exhibits a sensitivity of 95% and specificity of 96% for detecting symptomatic proximal DVT [50].

Venous ultrasonography demonstrates a sensitivity of 73% for detecting DVT in the calf vein (51). In cases where the initial examination returns negative findings, it is advisable to conduct repeat or serial venous ultrasonography for symptomatic patients highly suspected of having DVT, especially when alternative imaging methods are not accessible or suitable. However, for patients with a negative D-dimer test result and a Wells score indicating a low likelihood of DVT, serial testing is deemed.

7. Prevention

Preventive strategies are essential in mitigating the risk of DVT, especially among groups with elevated chances of occurrence like hospitalized individuals undergoing surgery or extended periods of immobility.

Utilizing anticoagulants for pharmacological prophylaxis and employing mechanical interventions such as compression stockings and intermittent pneumatic compression devices have shown effectiveness in decreasing the occurrence of DVT and its related complications. A secure and cost efficient procedure described by Warwick et.al has been broadly accepted [52] Table 2.

TABLE 2 : Preventive measures that mitigate the risk of DVT

Procedure	Description
General Procedure [52]	
Anesthesia	Spinal or epidural anesthesia reduces the occurrence of DVT by approximately 50% by enhancing the blood circulation. Moreover, it is advisable to refrain from administering chemical prophylaxis and nerve anesthetic immediately after surgery to minimize the risk of spinal hematomas.
Surgical Procedure	Meticulous operative technique to minimize release of thromboplastins.
Mobilization	Early mobilization postoperatively recommended. Improves blood flow in veins.
Physical Methods	
Stockings with graduated compression	When compression stockings are woven accurately and fit snugly, they can halve the occurrence of DVT. Both above-knee and below-knee variations may offer comparable effectiveness [53].
Intermittent plantar venous compression	Weight-bearing activities facilitate adequate blood flow from the sole of the foot by exerting intermittent pressure on the venous plexus around the lateral plantar arteries, thereby enhancing venous blood circulation in the leg. In individuals confined to bed, a mechanical foot pump that mimics this natural process can intermittently compress the plantar venous plexus. Prior research has validated the efficacy of this apparatus in thrombo prophylaxis for individuals undergoing hip or knee arthroplasty, as well as those with hip fractures [53].
Intermittent	Due to its capacity to enhance blood

pneumatic compression of the lower limb	circulation in the lower leg's deep veins following surgery, this device has become widely utilized in the treatment of DVT and helps avoid venous stasis or sluggishness [54].
Chemical Methods	
Heparin	Unfractionated heparin poses risks for elderly patients, necessitating laboratory monitoring, whereas low molecular weight heparin offers a safe and economically viable alternative [55,56].
Pentasaccharide	While equally effective in preventing DVT, caution is advised in administering it shortly after surgery (within 6 to 8 hours) due to its potential to cause hemorrhagic complications. As this medication is metabolized by the liver and excreted by the kidneys, clinicians should be vigilant for any signs of hepatorenal dysfunction [3].
Dabigatran	Dabigatran, boasting a bioavailability of 5-6%, functions as thrombin's competitive inhibitor and swiftly absorbs from the gastrointestinal tract. With a plasma level peaking after two hours, its half-life is roughly eight hours for a single dosage and seventeen hours for consecutive doses [57]. Renal excretion serves as the primary elimination route for the drug. Given its low bioavailability, routine monitoring of coagulation function may not be warranted.
Warfarin	Warfarin, a common vitamin K antagonist, is effective in preventing DVT and can be utilized throughout the perioperative period [58]. However, it is not advisable for thrombo prophylaxis during pregnancy due to its ability to cross the placenta, potentially leading to teratogenic effects and fetal bleeding [59]. Maintaining an International normalized ratio of 2-3 is recommended during warfarin administration.

8. Treatment

When left untreated, DVT can lead to exacerbation of the condition by causing PE, with a significant risk of early recurrence [60]. There is also continuous rise in the recurrence rate and the development of post-thrombotic syndrome, pulmonary hypertension [61]. Early treatment for the prevention involves the administration of following

therapeutic components- unfractionated heparin(UFH), LMWH, or fondaparinux [3,62]. Treating DVT typically begins with administering the therapeutic components LMWH or unfractionated heparin, followed by long-term use of vitamin K antagonists (VKAs). In cases of moderate to high-risk cases, it's advisable to start consuming therapeutic components during the critical phase before conducting evaluation test [62].

LMWH is proved to be more efficacious than unfractionated heparin in the treatment of critical DVT. But as the kidneys are the primary organs responsible for excreting LMWH, UFH is recommended in individuals with severe renal failure. When the International normalized ratio reaches the estimated range of 2-3, after a minimum of 4-5 days, heparin is administered along with warfarin [3].

As emergency anticoagulation is accomplished, warfarin continues to be the recommended medication for prolonged therapeutic use to prevent the formation of clots. However, LMWH is recommended in an ongoing basis therapy in patients with malignancy and during pregnancy, as warfarin medication is not suitable for use [63].

Localization of Inferior Vena cava filters:

The American Heart Association's guidelines propose the following indications for the inferior vena cava filters localization: [64]:

- I. Critical PE or DVT with contraindication for the anticoagulant medication.
- II. Recurrent episodes of thromboembolism despite receiving anticoagulant therapy due to insufficient anticoagulation.
- III. Hemorrhage while on anticoagulant therapy that could potentially be fatal.
- IV. Presence of a massive, floating thrombus in the iliofemoral area in patients at extremely elevated risk.
- V. Iliofemoral thrombus is increasing in size despite anticoagulant therapy.

Placement of IVC filters further along the arteries to entrap clots and reduce venous congestion can help maintain normal blood flow in addition to avoiding the migration of clots larger than 4 mm. Although there are various different filters available, the Greenfield filter is still regarded as the industry standard due to its functionality proportions, which show recurrent embolism rates of < 5% and > 95%. Blood can fill emboli from the center without obstructing blood flow to the periphery due to its conical form.

Thrombolytic Therapy

Thrombolytic treatment indications are exceptionally rare due to the serious associated side effects, including cerebral hemorrhage and significant bleeding. However, patients with severe iliofemoral deep vein thrombosis (DVT) and minimal bleeding risk, along with circulatory compromise endangering the limbs and acute or subacute symptoms, may be considered for this treatment [65].

Individuals with iliofemoral DVT are frequently evaluated for endovascular treatments such thrombectomy (thrombi removal) and/or catheter-directed thrombolytic therapy (CDT).As per the available data, CDT appears to offer superior preventive measures against post-thrombotic syndrome (PTS) and DVT recurrence compared to systemic anticoagulation [66].

Conclusion

Deep Vein Thrombosis (DVT) is a significant healthcare issue due to its potential to cause life-threatening complications like pulmonary embolism and post-thrombotic syndrome. This illuminates the critical requirement for efficacious prevention, diagnosis, and treatment strategies. Advancements in diagnostic techniques such as ultrasound and D-dimer testing have revolutionized the timely detection of DVT, enabling swift initiation of treatment and reducing complication rates. In terms of treatment, there have been notable advancements, including implementation of anticoagulants for oral administration in direct form and the refinement of catheter-based interventions, leading to improved efficacy, safety, and patient convenience. Additionally, there is now a greater focus on personalized medicine approaches and managing complications like post-thrombotic syndrome, highlighting the importance of comprehensive patient care. Looking ahead, ongoing research efforts offer promise for further refining our understanding of DVT pathophysiology, identifying new therapeutic targets, and advancing precision medicine tailored to individual patient needs.

Conflict of Interest

The authors of the paper declare to have no conflict of interest in the publication of the paper.

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