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EDITORS

PROF. DR. ENGİN ŞAHNA

PROF. DR. HASAN AKGÜL

PROF. DR. ZELİHA SELAMOĞLU

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web: www.seruvenyayinevi.com
e-mail: seruvenyayinevi@gmail.com

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CONTENTS

Chapter 1

MEDICAL TREATMENT OF DEEP VEIN THROMBOSIS

Abdullah GÜNER[1]

1 Uzm. Dr. Abdullah Güner, Kurumu: Konya Şehir Hastanesi Kalp ve Damar Cerrahisi Anabilim Dalı

INTRODUCTION

Deep vein thrombosis (DVT), which describes the formation of a blood clot in deep veins, is part of the spectrum of venous thromboembolic (VTE) diseases, which also includes pulmonary embolism (PE) (Hardy & Bevis, 2019). Venous thromboembolism is one of the most common causes of hospital mortality and ranks third among the causes of death from cardiovascular disease (Mahan, Holdsworth, Welch, Borrego, & Spyropoulos, 2011).

Deep vein thrombosis usually describes thrombus formation in the deep veins of the lower extremities. The disease often becomes symptomatic when the thrombus spreads to the popliteal, femoral or other proximal veins. The severity of symptoms depends on the extent of the thrombus, the adequacy of collateral vessels, vascular occlusion and the degree of inflammation. The most important cause of mortality is PE with detachment of the thrombus from the vein (Hardy & Bevis, 2019). The most common long-term complication is post-thrombotic syndrome (PTS) (Mazzolai et al., 2018). Treatment of deep vein thrombosis aims to prevent the development of complications related to DVT in the acute and chronic periods (Kearon et al., 2016).

Epidemiology

The mean annual incidence of newly diagnosed DVT is around 5 per 10,000 per year, and in addition, PE and DVT occur together in 1-2 per 10,000 per year (Fowkes, Price, & Fowkes, 2003). DVT alone is observed in two thirds of VTE cases and 80% of DVT cases are in the proximal segments (Mazzolai et al., 2018). The incidence of VTE increases significantly with age. While the incidence of VTE is higher in fertile women, the incidence is higher in men after the age of 45 (Heit, 2015). While the mean annual incidence in the 30-49 age range is around 2-3 people per 10.000 per year, this rate increases to 20 people per 10.000 per year in the 70-79 age range (Fowkes et al., 2003).

Despite medical treatment, the recurrence rate of VTE and PE in patients with proximal DVT within 5 years is 26.4% and 3.6%, respectively (Baglin et al., 2010). In patients who do not receive treatment, the mortality rate within 30 days is 3% for DVT and 31% for PE (Søgaard, Schmidt, Pedersen, Horváth–Puhó, & Sørensen, 2014).

Etiology

In the pathophysiology of venous thromboembolism, the Virchow triad (venous stasis, hypercoagulability and endothelial damage) has been valid since the 19th century. In recent years, the effects of coagulation-fibrinolytic systems, vascular endothelial functions and prothrombotic conditions caused by inflammatory response have been better understood (Fuchs, Brill, & Wagner, 2012).

Risk Factors

Deep vein thrombosis is called "primary or idiopathic" if it occurs without risk factors and "secondary" if it occurs in the presence of risk factors. The use of terminologies such as "provoked" or "unprovoked" VTE is not recommended in recent guidelines because it is potentially misleading and does not help in decision-making regarding the duration of anticoagulation. Risk factors in the development of venous thromboembolism are divided into three groups as high (odds ratio > 10), moderate (odds ratio = 2-9) and poor (odds ratio < 2) according to the European Society of Cardiology (ESC) guidelines (Konstantinides et al., 2020).

Clinic and Diagnosis

Clinical signs and symptoms, while forming the basis of the diagnostic approach, are highly variable and lack specificity. Signs of deep vein thrombosis (DVT) in the legs encompass pain, swelling, redness, calf pain, tenderness, and the presence of collateral superficial veins. The clinical presentation of DVT ranges from incidental findings to a pale, swollen, painful leg (phlegmasia alba dolens). In cases where the thrombus extends into venous and capillary vessels, causing secondary acute arterial insufficiency, the leg may appear cyanotic (phlegmasia caerulea dolens). Differential diagnosis considerations include cellulitis, bleeding into calf muscles in anticoagulated patients, calf muscle tear, and ruptured Baker's cyst.

Relying solely on clinical findings for venous thromboembolism diagnosis isn't reliable due to the poor specificity of symptoms and signs. Clinical indicators like Homans' sign may be detected in only 30-80% of patients. For individuals clinically suspected of DVT or pulmonary embolism, the disease prevalence is approximately twenty percent. Consequently, clinical probability scores have been developed to guide treatment decisions, with DVT probability assessment being the initial diagnostic step.

Treatment

The main aim of DVT treatment is to prevent progression to post-thrombotic syndrome (PTS), to prevent recurrence of VTE and to prevent death that may develop due to PE. In addition to anticoagulation, compression stockings and other medical therapies, interventions such as catheter-mediated thrombolytic therapy, pharmacomechanical thrombolytic therapy or aspiration thrombectomy can be performed for specific patient groups in the treatment of DVT. Anticoagulation therapy constitutes the basic treatment for patients with DVT unless there is a contraindication (Kearon et al., 2016).

Indications for Anticoagulant Therapy

Anticoagulation is used in all patients with proximal DVT (DVT in popliteal, femoral or iliac veins) and some patients with distal DVT (DVT in calf

veins) who have no contraindication for anticoagulation, regardless of the presence of symptoms. Anticoagulation treatment should be administered by evaluating the profit-loss relationship against the patient's risk of bleeding (Mazzolai et al., 2018).

The effectiveness and safety of anticoagulant therapy in asymptomatic or incidental proximal vein DVT compared with symptomatic DVT is unclear. However, due to the high risk of proximal DVT embolization and evidence showing a reduced risk of recurrence with anticoagulation in symptomatic proximal DVT patients, it is recommended that anticoagulant therapy be administered similarly to symptomatic cases.

Isolated distal DVT located in the calf veins below the knee (excluding the popliteal vein) is primarily found in the posterior tibial and peroneal veins, with the anterior tibial and muscular veins rarely affected. Routine proximal vein compression ultrasonography may not detect isolated distal DVT, requiring whole leg ultrasonography. Therefore, to overcome this disadvantage, serial proximal USG can be used to detect thrombus extending into the proximal veins. The management of isolated distal DVT varies between centres and clinicians. While some specialists prefer anticoagulation in all patients with isolated distal DVT, some specialists avoid anticoagulation treatment (Lip & Hull, 2015). The American College of Chest Physicians (CHEST) guideline recommends follow-up of thrombus with serial USG repetition for patients with asymptomatic isolated distal DVT and 3 months of anticoagulation therapy in patients with symptomatic isolated distal DVT (Kearon et al., 2016). The ESC guideline recommends anticoagulation for at least 3 months in patients with high-risk isolated distal DVT (Mazzolai et al., 2018).

Current guidelines recommend different anticoagulation treatment strategies for pregnant patients, those with active cancer, or individuals with severely impaired renal function. In cases where anticoagulation is absolutely contraindicated, the consideration of inferior vena cava filter application may be appropriate for patients with newly diagnosed proximal deep vein thrombosis (DVT).

Thrombocytopenia doesn't always preclude anticoagulation. Patients with platelet counts greater than 50,000/microL may be candidates for anticoagulation. There might be instances where anticoagulation is utilized in patients with a history of previous intracranial hemorrhage; however, the decision should be individualized, considering the patient-specific cost-benefit ratio.

Stages of Anticoagulant Therapy

Treatment of deep vein thrombosis involves three stages: initial, long-term, and extended treatment. Delaying treatment may heighten the risk of potentially life-threatening embolization, underscoring the importance of

initiating anticoagulation promptly. The risk of recurrent thrombosis and embolization is most pronounced in the initial days and weeks post-diagnosis. Administering anticoagulation promptly within the first several days (i.e., 0-10 days) is pivotal for averting recurrence and VTE-related fatalities. Planning treatment during this window and continuing with long-term anticoagulation is paramount. Initial and long-term treatment is advised for all patients with proximal DVT.

Interruption in anticoagulation therapy should be minimised. In some patients, the same drugs may be selected for initial and long-term treatment, while in others different drugs may be selected. In these cases, it is necessary to switch from one drug to another appropriately.

Treatment options for DVT include unfractionated heparin (UFH), low molecular weight heparin (DMAH), fondaparinux, oral factor Xa inhibitors (e.g. rivaroxaban, apixaban, edoxaban), direct thrombin inhibitors (e.g. dabigatran), vitamin K antagonists (e.g. warfarin).

Initial period treatment:

It covers the period of 5-21 days following the diagnosis of deep vein thrombosis (DVT). Anticoagulant treatment is an option at this stage;

1. Low molecular weight heparins (DMAH) and vitamin K antagonists (VKA),
2. DMAH followed by direct thrombin (IIa) inhibitors or oral factor Xa inhibitors
3. Oral factor Xa inhibitors are available.

Initial treatment involves systemic anticoagulation administered over several days. During this phase, patients receive parenteral therapy, and the decision to continue treatment with either vitamin K antagonists (VKA) or direct oral anticoagulants (DOACs) is assessed.

Warfarin, a vitamin K antagonist, cannot be administered alone in the initial treatment of DVT due to the delay in depleting vitamin K-dependent coagulation factors. Rivaroxaban or apixaban may be administered as monotherapy from the onset of treatment.

Hospitalization for systemic anticoagulation may not be necessary for all patients with acute DVT. The decision to treat DVT on an outpatient basis should consider the patient's risk-benefit ratio, preferences, and clinical condition. Outpatient treatment compared to hospitalization shows no significant difference in major or minor bleeding events and mortality.

While factors determining hospitalization for DVT patients are not clearly defined, they may include:

Massive DVT (e.g., iliofemoral DVT, phlegmasia cerulea dolens)

Concurrent symptomatic pulmonary embolism

High risk of bleeding under anticoagulant therapy

Cases where outpatient treatment is not recommended due to comorbid conditions or other factors necessitating hospital care.

Long-term treatment:

Long-term anticoagulant therapy covers the duration of treatment following the initial treatment, which usually extends for 3-6 months and in some cases up to 12 months (Mazzolai et al., 2018).Long-term anticoagulation options encompass oral or subcutaneous medications.

Extended period treatment:

Long-term anticoagulant therapy covers the duration of treatment that extends beyond 3-6 months following the initial treatment and in some cases, lifelong treatment (Mazzolai et al., 2018).

The risk of VTE recurrence in the years after anticoagulation is stopped is around 30% (Boutitie et al., 2011). Prolonged anticoagulation therapy protects against recurrence, but exposes the patient to the risk of unpredictable bleeding complications. Continuation of anticoagulation therapy is based on a balance of profit and loss. Patient compliance, profit-loss and risk assessment should be performed regularly at least once a year in patients receiving extended period treatment (Mazzolai et al., 2018).

Unfractionated Heparin (UFH)

Antithrombin III (AT3) peptide inhibits many coagulation factors. Unfractionated heparin (UFH) binds to AT3 and increases its activity, thus inhibiting factors Xa and IIa. In addition, it also has an inhibitory effect on factor IXa, XIa and XIIa (Hirsh et al., 2008). Plasma half-life varies between 30 minutes and three hours depending on the dose. It is administered by intravenous infusion or subcutaneous injection.

Intravenous unfractionated heparin (UFH) is preferred for patients with severe renal impairment (CrCl <30 mL/min) and patients with a high bleeding risk where there is a possibility of neutralisation of acute anticoagulation, haemodynamically unstable patients or patients with a large clot burden (phlegmasia cerulae dolens). It has a short half-life and can be neutralised with protamine sulphate (Mazzolai et al., 2018).

The therapeutic dose of subcutaneous and intravenous (IV) UFH is adjusted according to the weight of the patient and no dose adjustment is required in renal failure. The CHEST guideline recommends the dose of IV heparin as 80 U/kg bolus followed by 18 U/kg/hour infusion (Hirsh et al.,

2008). The biggest disadvantage of UFH is that it requires laboratory monitoring and dose adjustment shows interindividual variability; active partial thromboplastin time is monitored by aPTT, anti- factor Xa activity or active clotting time (ACT). aPTT value is aimed to be between 1.5-2.5 times the control range (Mazzolai et al., 2018).

Another side effect other than bleeding is that it may cause heparin-induced thrombocytopenia (HIT).

Low Molecular Weight Heparins (DMAH)

Low molecular weight heparins also bind to AT3 like anfractionated heparins. They have lower molecular weights and act on factor Xa at a higher rate than factor IIa (Hirsh et al., 2008). The half-life of DMAHs is dose independent and 2-4 times longer than UFH. Follow-up does not require laboratory tests. They are not recommended in patients with advanced chronic renal failure (CRF) with creatine clearance<30 ml/min and require dose adjustment in patients with mid- term CRF. There are no specific antidotes.

Low molecular weight heparins are preferred for the treatment of DVT in patients with active cancer, pregnant patients and patients who cannot receive oral therapy. DMAHs are preferred over warfarin because the INR (international normalised ratio) may increase in chronic liver failure and monitoring is more difficult. DMAHs are preferred in the transition treatment given before the planned treatment for patients in whom warfarin, dabigatran or edoxaban will be selected for long-term treatment (Kearon et al., 2016). DMAH therapeutic dose varies according to the active substance. The dose is basically adjusted according to the weight of the patient and all of them are administered subcutaneously.

Fondaparinux

Fondaparinux is a synthetic pentasaccharide applied subcutaneously and inhibits activated factor Xa by acting indirectly via antithrombin (Hardy & Bevis, 2019). Its half-life is 15-20 hours and a single dose can be administered daily. Dose adjustment and laboratory tests are not required.

DMAH is an alternative anticoagulant for most newly diagnosed non-pregnant patients. Not recommended in patients with advanced CRF. They are preferred in patients with HIT and a history of HIT. There is no specific antidote.

Fondaparinux is usually administered as 5 mg (100 kg) once daily according to patient weight (Blick, Orman, Wagstaff, & Scott, 2008).

Warfarin

Warfarin, a vitamin K antagonist (VKA), inhibits coagulation by blocking an enzyme called vitamin K epoxide reductase, which reactivates vitamin

K. Lack of sufficient active vitamin K reduces the synthesis of factors II, VII, IX and X. Warfarin also inhibits protein C and protein S at lower rates (Kearon et al., 2016).

Warfarin treatment is primarily favored when Factor Xa and direct thrombin inhibitors are not accessible or in patients with chronic renal failure (CRF). However, its use is not recommended during pregnancy. In cases of antiphospholipid syndrome, other oral anticoagulants are not considered alternatives to warfarin for treating venous thromboembolism (VTE); instead, warfarin is recommended as the oral anticoagulant treatment.

Regular INR monitoring is required. The target INR value of patients receiving VKA in the treatment of VTE is 2.5 and it is recommended to keep the INR between 2-3 (Kearon et al., 2016).

During the initial days of warfarin therapy, prolonged prothrombin time (PT) indicates a decrease in factor VII, which has a short half-life. However, this does not signify sufficient anticoagulation as other vitamin K-dependent factors have not yet decreased adequately. Additionally, the decrease in protein C and S shortly after initiating warfarin therapy heightens susceptibility to clotting and increases the risk of thrombosis. Depleting all vitamin K-dependent factors (factors II, VII, IX, and X) during warfarin treatment takes several days, and premature discontinuation of heparin without achieving a therapeutic INR value, preferably for two days, may lead to inadequate protection against thrombosis.

Warfarin has more accessible antidotes compared to other oral anticoagulants. In case of bleeding, vitamin K analogues, fresh frozen plasma or prothrombin complex concentrates may be given.

New Generation Oral Anticoagulants

The difficulties in the use of traditional anticoagulants have necessitated the search for new treatments. The most important advantages of new generation oral anticoagulants are their rapid onset of action, no need for monitoring and low drug and food interactions. New generation oral anticoagulants with clinical use are: factor Xa inhibitors; apixaban, edoxaban, rivaroxaban and direct thrombin inhibitor; dabigatran. Since these drugs bind directly to specific coagulation factors, they are also defined as “DOAC” in terminology, which means direct oral anticoagulant.

Direct oral anticoagulants (DOACs) have demonstrated comparable efficacy and safety to parenteral drugs and vitamin K antagonists. Meta-analyses have revealed similar rates of venous thromboembolism (VTE) recurrence between patients receiving DOACs and those on conventional therapy (2.0% vs. 2.2%; relative risk 0.90). Furthermore, patients treated with DOACs experienced significantly lower rates of major bleeding (relative risk 0.61), fa-

tal bleeding (relative risk 0.36), intracranial bleeding (relative risk 0.37), and clinically relevant non-major bleeding (relative risk 0.73) compared to those on conventional therapy (Mazzolai et al., 2018; van Es, Coppens, Schulman, Middeldorp, & Büller, 2014).

In the treatment of DVT, they are primarily preferred in non-pregnant and haemodynamically stable patients who do not have active cancer, chronic liver failure or chronic renal failure (Mazzolai et al., 2018).

The elimination half-life of new-generation oral anticoagulants exceeds that of direct-acting oral anticoagulants and heparin. Excretion from the body may be prolonged in patients with chronic renal failure (CRF) with creatinine clearance of 30 ml/min or in those with chronic liver disease with Child-Pugh class B or C hepatic function. Patients with renal or hepatic dysfunction, pregnant or lactating women, and those with thrombocytopenia are typically excluded from Phase III studies of DOACs. Patients with active cancer are rarely included in studies; thus, DOACs are not recommended for use in these patients (Mazzolai et al., 2018).

DOACs may not be suitable for managing hemodynamically unstable pulmonary embolism or massive iliofemoral deep vein thrombosis due to insufficient study of their efficacy in these conditions. Additionally, their use could potentially interfere with thrombolytic therapy or surgical embolectomy.

Routine laboratory analyses are not required for follow-up. These agents reach their peak efficacy within a few hours after oral intake and do not require a long period of transition treatment. However, anticoagulant treatment with heparin should not be postponed if the drug cannot be obtained immediately when deciding to treat with one of these agents (Mazzolai et al., 2018).

Typically, treatment with DOACs commences upon cessation of unfractionated heparin (UFH) infusion or instead of the next therapeutic DMAH dose. Factor Xa or direct thrombin inhibitors are generally administered within 6 to 12 hours after the last dose of twice-daily subcutaneous DMAH therapy or within 12 to 24 hours after the last dose for once-daily treatments. Factor Xa and direct thrombin inhibitors can be initiated immediately after discontinuing intravenous UFH infusion.

Factor Xa Inhibitors

The factor Xa inhibitors in clinical use are apixaban, rivaroxaban and edoxaban. These drugs bind directly to the active site of factor Xa in a dose-dependent manner and inhibit the coagulation cascade (Samama, 2011).

Rivaroxaban and apixaban are anticoagulant options that can be used without UFH or DMAH, including acute treatment. They can be used alone in initial anticoagulant treatment (Investigators, 2010). For patients receiving

edoxaban treatment, parenteral anticoagulation treatment should be administered for 5-10 days before the start of treatment (Mazzolai et al., 2018).

Andexanate alpha is a trap protein that binds directly to factor Xa inhibitors and reverses the effect in life-threatening uncontrolled haemorrhages (Connolly et al., 2016).

Rivaroxaban: Reaches maximum plasma concentration 2-4 hours after oral administration. In the treatment of VTE, rivaroxaban 15 mg twice daily for the first three weeks, followed by long-term treatment with 20 mg once daily. The therapeutic dose range is adjusted according to creatinine clearance. Patients with creatinine clearance>50 ml/min receive a dose of 20 mg/day; patients with creatinine clearance<50 ml/min receive a dose of 15 ml/day.

Since there are not enough studies on its use in pregnancy, it is not recommended in these patients. Similar results to DMAH have been reported in recent studies on cancer (Dong et al., 2019).

Apixaban: It selectively and reversibly inhibits factor Xa and prothrombinase activity. It is recommended as 10 mg twice daily for the first seven days in VTE treatment and 5 mg twice daily in long-term treatment (Mazzolai et al., 2018). It has been observed to be as effective as standard treatment in the acute period and to cause less major bleeding compared to warfarin in long-term maintenance treatment (Agnelli et al., 2013).

Apixaban has been studied in thromboprophylaxis in patients with cancer; patients on apixaban had significantly lower VTE complications compared with placebo, but a significantly increased risk of major bleeding events (Carrier et al., 2019).

Edoxaban: This oral medication is a direct factor Xa inhibitor with an elimination half-life of 8-10 hours. Edoxaban is typically prescribed at a dosage of 60 mg once daily (and 30 mg once daily in patients weighing less than 60 kg) following the initial 5-10 days of parenteral anticoagulation treatment. The risk of developing recurrent VTE was compared with warfarin and found to be significantly lower in the edoxaban group. It was observed to have similar bleeding complications with warfarin (Raskob et al., 2016).

Direct Thrombin Inhibitors

Direct thrombin inhibitors inhibit the internal activity of thrombin without the need for another factor. Direct thrombin inhibitors used parenterally include argatroban and bivalirudin. Oral direct thrombin inhibitor with clinical use is dabigatran.

Dabigatran etexilate: It is an oral direct thrombin inhibitor. It reaches maximum concentration 1-2 hours after ingestion and its half-life is 12-17 hours. Its efficacy in VTE prophylaxis and treatment has been shown to be

similar to warfarin and superior to warfarin in terms of major bleeding. It is recommended to use parenteral anticoagulation in the first 5-10 days of treatment before initiating dabigatran treatment in VTE and to use dabigatran after parenteral treatment. It is used as 150 mg twice a day. Idarucizumab is the antidote of dabigatran and has clinical use (Mazzolai et al., 2018).

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Chapter 2

THE ROLE OF SEROTONERGIC DYSFUNCTION IN THE PATHOPHYSIOLOGY OF PARKINSON'S DISEASE NON-MOTOR SYMPTOMS

Ercan OZDEMİR[1]

1 Dr., Department of Physiology, Faculty of Medicine, Sivas Cumhuriyet University, eozdemir@cumhuriyet.edu.tr., ercan_ozdemir@hotmail.com, ORCID: 0000-0001-8231-1053

Introduction

Parkinson's disease (PD) is known as a common neurodegenerative disease characterized by the progressive loss of dopaminergic neurons in the substantia nigra compacta (SNc) (Muñoz et al., 2020; Obeso et al., 2017). Clinically, motor dysfunctions such as bradykinesia, muscle stiffness, akinesia, resting tremor and postural instability are observed in patients. Apart from this, non-motor symptoms are also present, including depression, psychological changes, sleep disturbance, autonomic dysfunctions, sensory symptoms, and pain (Pinna et al., 2023; Mantovani et al., 2023).

Genetic, environmental and immunological factors such as genetic susceptibility, toxins and the aging process play a role in the etiopathogenesis of PD (Obeso et al., 2017). Beyond this, residues of α-synuclein, the main protein component of Lewy bodies, oxidative stress, mitochondrial dysfunction, excitotoxicity and neuroinflammation are factors that play an important role in dopaminergic neuron loss (Scapira and Jenner, 2011); Pang et al., 2019). These pathological processes have a progressive character, causing dopaminergic neuron degeneration and having negative effects on the success of current PD treatment. Moreover, it has been observed that neuron loss causes changes in neurotransmitters such as glutamate, noradrenaline, acetylcholine, adenosine and serotonin (5-HT), which contribute to the symptomatology of PD (Jellinger et al., 2015).

The first drug treatment used in PD is L-DOPA, a dopamine precursor (Muñoz et al., 2020). However, long-term use of L-DOPA in the treatment of PD reportedly leads to the development of motor and non-motor symptoms. These different symptoms indicate that the pathological process also affects other neurotransmitter systems, such as the serotonergic system (Espay et al., 2018).

The majority of the 5-HT neurotransmitter is produced by dorsal raphe nucleus (DRN) neurons. Changes in DRN function cause various neuropsychiatric diseases and movement disorders (Huot et al., 2011). Current studies have shown dense serotonergic innervation in the basal ganglia and SNc (Muzerelle et al., 2016; Huang et al., 2019a). Furthermore, a large body of evidence indicates that the serotonergic activity may play a role in the pathology of non-motor symptoms such as depression, sleep disorders, fatigue, autonomic dysfunctions (Tang et al., 2015).

The serotonergic system is involved in the regulation of many physiological functions, including the regulation of cognition, emotion, sleep, and nutrition (Huot et al., 2011; Ohno et al., 2015). Therefore, dysfunction of the serotonergic system may be responsible for non-motor symptoms as well as motor symptoms observed in PD patients (Chaudhuri and Schapira, 2009; Schapira et al., 2017).

In a clinical study, 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) levels in the cerebrospinal fluid (CSF) were found to be significantly lower in PD

patients than in controls (Olivola et al., 2014). Biochemical evidence has shown that the serotonergic system plays important roles in the pathophysiology of non-motor symptoms, such as sleep disorders, depression, autonomic dysfunction, fatigue, and pain (Politis et al., 2012; Politis and Loane, 2011).

This review explains from a broad perspective the role of serotonergic dysfunction in the pathophysiology of non-motor symptoms of Parkinson's disease.

Serotonin and Dopaminergic System

5-HT is synthesized from the essential amino acid tryptophan. Tryptophan hydroxylase type 2 (TPH2) hydroxylates typtophan to 5-hydroxytryptophan (5-HTP). In the next step, the enzyme l-aromatic acid decarboxylase (AADC) converts 5-HTP to 5-HT (Sahu et al., 2018) (**Figure 1**).

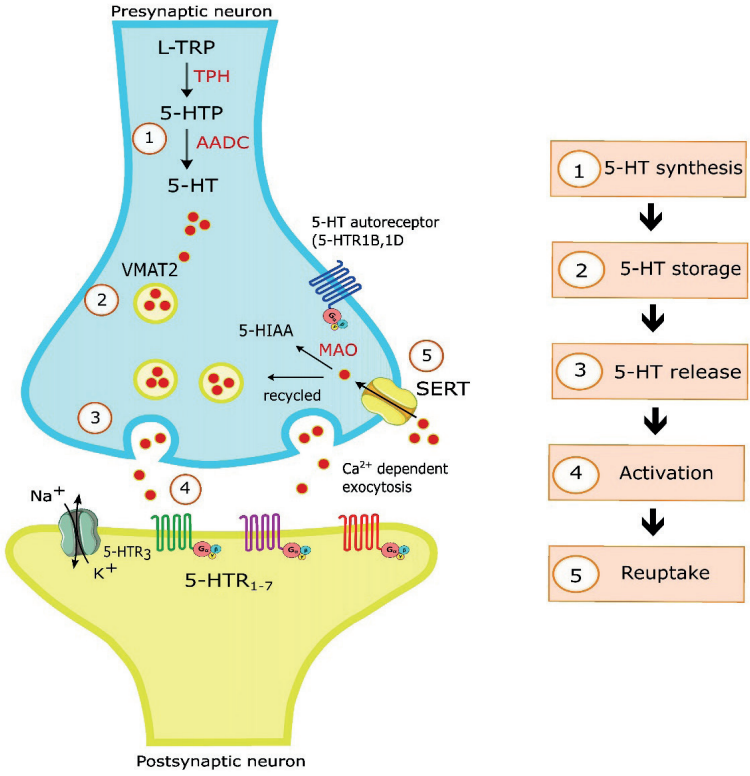

Figure 1. *Synthesis of serotonin (5-HT) from tryptophan. 5-HT is synthesized from tryptophan, an essential amino acid, in two steps. In the first step, tryptophan is hydroxylated by tryptophan hydroxylase (TPH) and is formed 5-hydroxytryptophan (5-HTP). The resulting 5-hydroxytryptophan is decarboxylated by the aromatic-L-amino acid decarboxylase enzyme to form 5-hydroxytryptamine (5-HT). 5-HT is metabolized by the monoamine oxidase (MAO) enzyme by converting it to 5-hydroxy-indole-acetaldehyde. L-TRP, L-tryptophan; SERT, serotonin transporter; MAO, monoamine oxidase; VMAT2, vesicular monoamine transporter 2; 5-HIAA, 5-Hydroxyindolacetic Acid. AADC, aromatic-L-amino acid decarboxylase.*

There are 7 classes of 5-HT receptors (5-HT_{1-7}) and 15 receptor subtypes that mediate the effects of 5-HT (Hannon and Hoyer, 2008; Ozdemir, 2024). It has been determined that 5-HT_{2C}, 5-HT_6 and 5-HT_7 receptors have a structural activity that is associated with pathophysiological conditions (De Deurwaerdere et al., 2020). In particular, 5-$HT_{1A/1B}$ and 5-HT_{2A} receptors are importance for PD (Huot and Fox, 2013) (**Table 1**).

Table 1. *Serotonin receptor subtypes and mechanisms of action*

Receptor subtype	Signal transduction	Effect	Mechanism
5-HT_1	G-protein coupled	Inhibitory	Decreasing cellular levels of cAMP
5-HT_2	G-protein coupled	Excitatory	Increasing cellular levels of IP3 and DAG
5-HT_3	Na^+ - K^+ ion channel	Excitatory	Depolarising plasma membrane
5-HT_4	G-protein coupled	Excitatory	Increasing cellular levels of cAMP
5-HT_5	G-protein coupled	Inhibitory	Decreasing cellular levels of cAMP
5-HT_6	G-protein coupled	Excitatory	Increasing cellular levels of cAMP
5-HT_7	G-protein coupled	Excitatory	Increasing cellular levels of cAMP

It has long been known that there are important interactions between serotonin and dopamine. However, the role of the serotonergic system in modulating the functions of dopaminergic neurons has not yet been fully elucidated (Ogawa et al., 2018). Studies have shown that serotonergic neuron signals have an inhibitory effect on dopamine-secreting neurons (Arborelius et al., 1993). Chronic 5-HT transporter (SERT) inhibition in patients using serotonin selective reuptake inhibitors (SSRIs) attenuates dopamine levels and causes basal ganglia dysfunction (Morelli et al., 2011). However, different studies have shown that experimentally created DRN lesions do not affect SNc activity (Kelland et al., 1990). Furthermore, 5-HT deficiency in tryptophan hydroxylase 2 knockout mice did not produce changes in the functions of dopaminergic neurons (Gutknecht et al., 2018). Genetic studies have revealed important interactions between 5-HT and dopamine systems at the ventral tegmental area level in the control of motivation (Browne et al., 2019). Furthermore, activation of serotonergic neuron triggers dopamine release from serotonergic terminals following L-DOPA treatment, resulting in loss of 5-HT-mediated synaptic transmission (Gantz et al., 2015). It has been found that striatal 5-HT levels are significantly reduced in the brains of PD patients with dopaminergic lesions (Rylander et al., 2010). Additionally, sprouting of striatal serotonergic neurons has been found after lesion of dopaminergic neurons in adult rats (Maeda et al., 2003).

It has been determined that there are significant decreases in serotonergic signal transmission due to DRN degeneration in the advanced stages of PD (Kerenyi et al., 2003). Moreover, the concentration of 5-HT and the expression

of its metabolite 5-HIAA and the SERT were found to be reduced in some basal ganglia nuclei (Kish et al., 2008; De Natale et al., 2021).

Important interactions between serotonergic and dopaminergic neurons have also been identified during neurological development (Lauder, 1990). Decreasing 5-HT levels in mesencephalic precursor cells in rats increased the differentiation of dopaminergic neurons. In contrast, activation of 5-HT_4 and 5-HT_7 receptors caused a decrease in the formation of dopaminergic neurons from mesencephalic precursors (Parga et al., 2007).

Recent evidence has shown that long-term exposure to dopamine therapy may alter serotonergic system functions in Parkinson's disease. A clinical study found a significant decrease in plasma 5-HT in Parkinson's patients receiving L-DOPA therapy (Chia et al., 1993). Moreover, in experimentally induced Parkinson's disease mice, chronic L-DOPA treatment significantly reduced the striatal levels of 5-HT and 5-HIAA (Carta et al., 2007). Neurochemical studies revealed that basal 5-HT release were significantly reduced in rats treated with therapeutic doses of L-DOPA (Navailles et al., 2011).

Serotonergic System and Parkinson's Disease

Lewy bodies have been detected in serotonergic neurons along with neuron degeneration in PD patients and PD animal models (Huot and Fox, 2013). Beyond this, decreases in 5-HT levels and SERT expression have been observed in many serotonergic nuclei in PD (Rylander et al., 2010). However, several lines of evidence suggest that SERT reduction is not associated with PD duration (Politis and Loane, 2011). An increase in 5-HT_{2C} receptor expression and a decrease in 5-HT_{1A} receptor level were observed in the basal ganglia of PD patients with depression (Ballanger et al., 2012). At the same time, it has been observed that noradrenergic signaling impairment along with serotonergic dysfunction in PD patients causes non-motor symptoms such as depression, sleep disorders, and fatigue (Vermeiren and De deyn, 2017). Recent evidence has revealed that administering the 5-HT precursor 5-hydroxytryptophan to Parkinson's patients results in significant reductions in depressive symptoms (Meloni et al., 2020).

Lewy bodies in serotonergic DRN neurons are detected early in PD and cause limbic symptoms such as depression (Braak et al., 2003). Depression in PD often occurs in the period leading up to the onset of motor symptoms. Therefore, impaired serotonergic neurotransmission causes depressive symptoms to occur frequently in patients with Parkinson's disease (Reinders et al., 2008). Positron emission tomography (PET) in PD patients have revealed that dopamine conduction disorder as well as serotonergic dysfunction plays a significant role in the formation of non-motor symptoms along with rest tremor, and that this is not improved by dopamine treatment (Doder et al., 2003; Pasquini et al., 2018). Additionally, PET imaging has provided findings

indicating that dysfunction of serotonergic neurotransmission plays a role in the development of non-motor symptoms and complications in PD (Politis and Niccolini, 2015). Therefore, as the disease progresses, dopamine decrease in the putamen and serotonergic transmission disorder in the raphe nucleus may further contribute to the emergence of Parkinson's tremor. In these patients, serotonergic agonist drugs may provide useful treatments in PD patients where tremor is associated with raphe dominant dysfunction (Pasquini et al., 2018).

The Role of the Serotonergic System in Non-Motor Symptoms of Parkinson's Disease

Depression

Depression is seen as one of the frequently detected non-motor symptoms in Parkinson's patients. Symptoms of depression occur in approximately 35% of Parkinson's patients, and approximately 17% of these symptoms meet criteria for major depressive disorder (Reinders et al., 2008). Numerous studies show that early developing serotoninergic dysfunction in PD patients causes the emergence of depressive symptoms (Politis and Niccolini, 2015).

Depressive symptoms such as passivity or withdrawal, fatigue, difficulty in making decisions, loss of appetite, and slowing of cognitive processes are commonly detected in PD patients (Schapira et al., 2017). It is stated that approximately 25% of patients diagnosed with depression receive effective antidepressant drug treatment (Ahmad et al., 2023; Mueller et al., 2018). Beyond this, 25% of PD patients suffer from depression before motor symptoms appear, and 40–50% of PD carriers show depressive symptoms throughout the disease (Ahmad et al., 2023). Evidence shows that depression occurs up to 20 years before PD diagnosis and its incidence increases in the 3-6 years before PD diagnosis (Kalinderi et al., 2024). However, studies have suggested that patients with depression and previous chronic use of antidepressants increase the likelihood of developing PD (Mueller et al., 2018). Other neurotransmitters such as 5-HT and noradrenaline have been reported to be reduced in Parkinson's disease-related depression (Ahmad et al., 2023; Braak et al., 2017).

Depression is a risk factor for the development of neurodegenerative diseases such as PD in general and is a common symptom of other chronic diseases (Ahmad et al., 2023). Although depression frequently occurs in elderly patients, depression appears to be more common in Parkinson's patients than in people of the same age group. Depression is the disorder that most affects the quality of life and daily activities of Parkinson's patients and is most frequently associated with Parkinson's disease (Mueller et al., 2018). In a clinical study, plasma 5-HT and 5-HIAA levels of PD patients were found to be lower than control individuals. Additionally, this study reported that decreased plasma 5-HT levels correlated with depression and pain severity (Tang et al.,

2015). Serotonergic dysfunction contributes to non-motor symptoms in Parkinson's patients.

In Braak's staging system, it has been shown that in the early stages of PD, Lewy body and Lewy neurite deposition occurs in the median and caudal Raphe nuclei, gigantocellular reticular nucleus, and coeruleus complex (Braak et al., 2003). These neurons perform important functions in the control of mood, food intake, alertness, and the sleep-wake cycle (Klimek et al., 1997). In Parkinson's disease, changes in 5-HT levels may occur as a result of decreased synthesis and increased catabolism. Additionally, L-DOPA may reduce 5-HT synthesis by inhibiting tryptophan hydroxylase and via aromatic amino acid decarboxylase (Hashiguti et al., 1993).

It has been shown that there is a close relationship between the intensity of serotonergic neuron degeneration and depressive behaviors in PD patients. Evidence has revealed that PD patients with depression have a more pronounced decrease in Rape nucleus echogenicity than non-depressed individuals (Berg et al., 1999). Some study results have shown that there is a positive correlation between symptoms such as depression, apathy and anxiety seen in Parkinson's patients and the intensity of serotonergic lesions in the nucleus accumbens (Maillet et al., 2016). In addition, PET examination performed in depressed Parkinson's patients revealed significant decreases in postsynaptic 5-HT_{1A} receptor density in limbic structures and the serotonergic metabolite 5-HIAA in the CSF (Ballanger et al., 2012).

The monoaminergic hypothesis, which includes monoamines (5-HT, dopamine, and noradrenaline), is one of the most accepted hypotheses in the pathophysiology of depression associated with PD (Ahmad et al., 2023). Damage to locus coeruleus (LC) neurons leads to important enhances in proinflammatory cytokine release as a result of the decrease in the antiinflammatory effect of noradrenaline on glial cells. This increases 5-HT reuptake, causing serious impairments in serotonergic signal transmission. Serotonergic and noradrenergic signaling disorders lead to depressive symptoms in the early stages of PD (Sampio et al., 2024) (**Figure 2**).

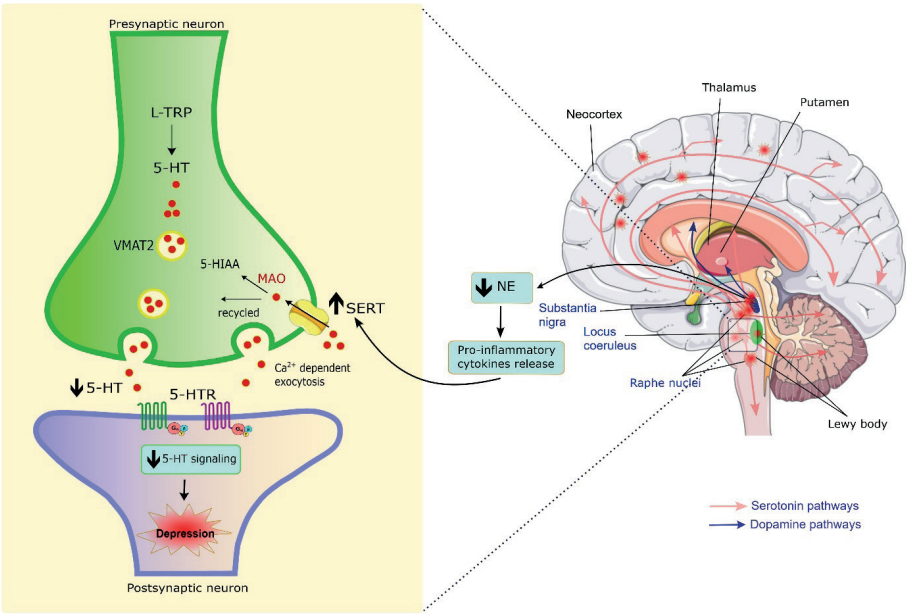

Figure 2. *Pathophysiological mechanism of depression in PD. Neurodegeneration in locus coeruleus (LC) neurons in PD leads to increases in pro-inflammatory cytokine release as a result of the decrease in the anti-inflammatory effect of noradrenaline on glial cells. Cytokines activate serotonin reuptake via the 5-HT transporter and cause disruptions in serotonergic signal transmission. In conclusion, noradrenergic and serotonergic signaling disorders lead to depressive symptoms in the early stages of Parkinson's disease. 5-HTR, serotonin receptor; NE, norepinephrine.*

Psychosis

PD begins with severe motor symptoms as a result of the accumulation of α-synuclein-containing Lewy bodies in the SNc, which subsequently causes psychotic symptoms such as hallucinations, called PD psychosis (PDP), in more than half of the patients (Kordower et al., 2013; Cummings, 1991). Different theories are put forward for the psychosis that occurs in Parkinson's. The most accepted theory is related to the accumulation of Lewy bodies in the CNS (Chang and Fox, 2016; Goldman et al., 2014). It is thought that the accumulation of Lewy bodies in the cerebral cortex causes the visual hallucinations that are characteristic findings of PDP. Early phase accumulation of Lewy bodies in the substantia nigra is associated with dementia (Wirdefeldt et al., 2001; Ballard et al., 2013). In Parkinson's disease, Lewy body accumulation in the cerebral cortex that causes psychosis may progress to cortical synucleinopathy (Cummings, 1991; Chang and Fox, 2016).

In the early stages of Parkinson's disease, the harmony between 5-HT and dopamine is disrupted due to the loss of substantia nigra projections in

the dorsal striatum. As a result of the disruption of this balance, the effect of dopamine deficiency leads to the classic motor symptoms of PD (Kordower et al., 2013; Stahl, 2016a; Ravina et al., 2012). Evidence suggests that concurrent with the onset of the disease, 5-HT neurons in the Rafe nucleus also degenerate with loss of 5-HT (Halliday, 1990). However, these neuron degenerations are less obvious and are probably linked to non-motor symptoms.

In some Parkinson's patients, Lewy bodies accumulate in the CNS in the later stages and degeneration is observed in pyramidal neurons containing 5-HT receptors. This results in significant increases in the number of $5HT_{2A}$ receptors with an upregulation in other pyramidal neurons of the cerebral cortex (Ballanger et al., 2010). Increases in $5HT_{2A}$ receptor concentration occur especially in the visual/temporal and prefrontal cortex areas of patients with psychosis (Cheng et al., 1991). Additionally, in Parkinson's psychosis, an increase in 5-HT levels in Raphe nucleus neurons has been observed, probably due to increased 5-HT turnover as a result of loss of serotonergic Raphe neurons (Birmayer et al., 1974). Increases in the activity of upregulated $5HT_{2A}$ receptors occur in the temporal and visual visual pathways. It is assumed that this increased serotonergic activity causes visual hallucinations (Ballanger et al., 2010; Huot et al., 2010). Hallucinogenic drugs (stimulate $5HT_{2A}$ receptors) are known to cause distinct visual hallucinations (Kometer et al., 2013). In contrast, the $5HT_{2A}$ receptor antagonists pimavanserin and clozapine have been shown to reduce visual hallucinations (Stahl, 2016b; Zahodne and Fernandez, 2008). Pimavanserin is a drug that does not have any D_2 dopamine antagonist effects and is a potent antagonist of $5HT_{2A}$ receptors. Therefore, it is the first agent with proven antipsychotic effects for PD (Stahl, 2016b; Cummings et al., 2014). Studies indicate that the serotonergic pathway play a crucial role in the development of psychiatric side effects due to dopaminergic treatment (Redensek et al., 2022).

Apathy

Apathy is considered one of the common non-motor symptoms of PD, which generally precedes the onset of motor symptoms (Pont-Sunyer et al., 2015). It is reported that apathy symptoms are detected in approximately 20-36% of drug-naive Parkinson's patients in the early stages of the disease (Barone et al., 2009; Santangelo et al., 2014). Early use of dopaminergic drugs in PD patients demonstrates significant reductions in apathy symptoms. However, after 5-10 years, the prevalence of apathy in Parkinson's patients with dementia is 60%, while it is 40% in those without dementia (Aarsland et al., 2007; Kulisevksy et al., 2009).

Recent data indicate that PD apathy is mainly caused by mesolimbic and mesocortical dopaminergic degeneration (Thobois et al., 2013; Sierra et al., 2015). However, the role of serotonergic neuron impairment in PD is not ful-

ly understood. Furthermore, a study indicated the pathophysiological role of the serotonergic neurons in the development of apathy in PD, independent of dopaminergic systems (Maillet et al 2016). Researchers found that apathetic patients with PD had greater degeneration of serotonergic neurons in their basal ganglia compared with patients without apathy using PET imaging and detailed clinical evaluation (Meloni et al., 2020).

However, the use of antidepressant medications for apathy in PD is controversial. It has been reported that apathetic symptoms occurring after subthalamic deep brain stimulation are resistant to tricyclic antidepressants, 5-HT receptor agonists and combined serotonin-norepinephrine reuptake inhibitors. However, applying dopaminergic treatment to these patients resulted in a positive response (Houeto et al., 2002; Funkiewiez et al., 2004).

Anxiety

Anxiety is one of the early non-motor symptoms of PD associated with serotonergic neurotransmission disorder (Chen and Marsh, 2014). Theories put forward regarding the pathogenesis of anxiety are quite contradictory. One of the mechanisms of anxiety disorder suggests low serotonergic input in the amygdala (Curran and Chalasanii 2012). Another theory also suggests that increased 5-HT release in both raphe nuclei and amygdala contributes to the state of serotonergic hyperactivity (Näslund et al., 2015). When considered independently of these mechanisms, it shows that altered serotonergic status is one of the factors underlying anxiety disorder (Curran and Chalasanii 2012; Liu et al., 2019). Therefore, the emergence of anxiety symptoms in the early stages of PD reveals that brain areas involved in 5-HT production may be affected early as the disease progresses.

Gastrointestinal Dysfunction

Gastrointestinal dysfunction in PD may result from both motor and non-motor (dysautonomic) pathology. Researchers have reported that intestinal dysfunction is frequently encountered in Parkinson's patients (Pfeiffer, 2018). Approximately 60% to 80% of PD patients consult a doctor with findings due to bowel dysfunction (Poirier et al., 2016). Intestinal dysfunctions such as dysphagia, weight loss, sialorrhea, hypogeusia, delayed gastric emptying and dyschezia are frequent symptoms in the early stages of PD (Sung et al., 2014).

Constipation is one of the most frequent non-motor gastrointestinal symptoms in Parkinson's patients (Klingelhoefer et al., 2015). A cohort study revealed that as the complaint of constipation increases in individuals, the incidence of Parkinson's disease also increases (Lin et al., 2014). Prolonged constipation may participate in or induce PH pathogenesis (Savica et al., 2009). Recent evidence suggests that the microbiota-gut-brain axis may play a role in

the pathogenesis of PD. It has been found that dysbiotic changes in the intestinal microbiome are frequently observed in PD patients (Keshavarzian et al., 2015; Pietrucci et al., 2019; Nishiwaki et al., 2020).

The change in intestinal microbiota in Parkinson's patients appears to be associated with constipation, motor phenotype and inflammation (Scheperjans et al., 2015; Huang et al., 2019b). Altering the gut microbiota in Parkinson's patients through antibiotics, probiotics, diet, and fecal microbiota transplantation causes intestinal inflammation, intestinal dysfunction, and neuropathological changes. In one study, oral administration of Proteus mirabilis caused activation of microglia in the SNpc and striatum, as well as loss of dopaminergic neurons and aggravated motor impairment in PD mice (Choi et al., 2018). Applying probiotic treatment to Parkinson's patients was effective in improving constipation (Tan et al., 2021).

Several studies have suggested that serotonergic receptors regulate gastrointestinal motor movements in PD (Freitas et al., 2018; Cui et al., 2023). Among these, 5-HT_4 receptors are one of the most important targets for the treatment of intestinal motility disorder in Parkinson's disease (Bianco et al., 2016). 5-HT_4 receptor activators provide significant improvements on enteric neurons, which can be regulated by the intestinal microbiota (De Vadder et al., 2018; Wang et al., 2022). In Parkinson's patients, 5-HT_4 receptors exert important effects by regulating the intestinal microbiota, inflammation and neuronal survival, most likely through the gut-brain axis. Application of 5-HT_4 receptor antagonist (GR 125487) to mice PD model prolonged the gastrointestinal transit time of feces and caused the intestinal microbiota composition to change. Consequently, increased neuroinflammation aggravated MPTP-induced striatal neurodegenerative processes (Cui et al., 2023). However, the application of 5-HT_4 receptor agonists improves gastrointestinal motility and increases bowel movement frequency in PD patients through its effect on the enteric nervous system (Freitas et al., 2018; Liu et al., 2005).

The serotonergic system is the main regulator of gastrointestinal motility and fluid secretion, but it is one of the earliest structures affected by α-synuclein pathology in Parkinson's disease (Scheperjans et al., 2015). Additionally, a large body of evidence has suggested that 5-HT_4 receptors are required for the survival and neurogenesis of many neurons in the enteric nervous system (Wang et al., 2022; Liu et al., 2009). Another important symptom related to the gastrointestinal system seen in Parkinson's patients is decreased intestinal motility, and this symptom is one of the earliest symptoms in PD (Yu et al., 2018). Researchers consider this phenomenon as an autonomic dysfunction and state that 5-HT receptors play an important role in intestinal motility. Additionally, the serotonergic system modulates sympathetic activity and plays critical roles in the etioptatogenesis of gastrointestinal symptoms in PD (Kim and Sung, 2015; Margolis, 2017).

Sleep impairment

Among the non-motor symptoms, sleep is detected in approximately 70% of Parkinson's patients (Goetz et al., 2005; Jahan et al., 2009). Sleep symptoms are one of the earliest symptoms seen in Parkinson's patients and begin approximately 5-10 years before motor symptoms appear. This indicates that there is an early impairment in sleep-related signaling pathways in patients. The most prominent sleep disorders are insomnia, increased micro-arousals, and rapid eye movement (REM) sleep disruption (Goetz et al., 2005).

Numerous studies of the serotonergic system exist to explain many of the poorly understood early symptoms of PD. Many of the early non-motor symptoms of PD appear to be associated to some degree with a state of serotonergic hyperactivity. It has been reported that sleep disturbance is associated with impaired serotonergic activity in PD (Fox et al., 2009). Accumulating evidence has shown that serotonergic neurons in the DRN play a role in sleep-wake cycle disorders observed in Parkinson's patients. An increase in 5-HT neuron firing causes arousal, while a decrease causes sleep (McGinty and Harper, 1976). PD patients often experience REM sleep disorder, which is associated with 5-HT dysfunction in this disease.

An experimental study showed that REM sleep expression and motor activity increased as a result of increased serotonergic dorsal raphe nucleus activity in cats with REM sleep disorder through lesion of the pontine tegmentum (Trulson and Jacobs, 1979). Apart from this, the lack of muscle atonia and increased motor activity seen during REM sleep in Parkinson's patients may be an indicator of serotonergic dysfunction (Gagnon et al., 2002).

Studies indicate that obstructive sleep apnea has a prevalence as high as 20-60% in Parkinson's patients. The cause of obstructive apnea in PD is the degeneration of the peripheral nerves innervating the oropharyngeal muscles and the accumulation of α-synuclein in the vagus nerve innervating the laryngeal, pharyngeal muscles and episodic upper muscles. In addition, airway movement disorders caused by dyskinesia that begins at night contribute to the development of obstructive sleep apnea (Kumareson and Khan, 2021).

Pain

Stimulation of serotonergic raphe neurons leads to a decrease in pain responses via the descending inhibitory pathway in the dorsal horn of the spinal cord (Ozdemir, 2017; Lee te al., 2015). At the same time, the antinociceptive effectiveness of 5-HT reuptake inhibitors was determined in tail-flick pain tests in experimental pain studies (Ozdemir et al., 2011; Li et al., 2024; Ozdemir et al., 2012). It has been reported that there is a significant relationship between plasma levels of 5-HT markers and pain severity in PD patients (Tong et al., 2015). Additionally, abnormal functional connections in raphe nuclei in Par-

kinson's disease may partially play a role in the pathophysiological mechanism of pain (Shen et al., 2022).

It has been shown that degeneration of the serotonergic system, especially the dorsal and median raphe nuclei, in Parkinson's disease causes many non-motor symptoms such as pain (Wang et al., 2023). Data from an animal study revealed decreased 5-HT content in the contralateral ventrobasal thalamus and raphe magnus nucleus in rat neuropathic pain models (Politis et al., 2010). A clinical neuroimaging study showed that apomorphine had no effect compared to placebo on pain thresholds or pain-induced cerebral activity in Parkinson's patients. This result provided important evidence for the involvement of other non-dopaminergic systems, such as norepinephrine and 5-HT, in pain in Parkinson's patients (Dellapina et al., 2011). It has been shown that the use of duloxetine, a selective 5-HT reuptake inhibitor, is beneficial in improving pain in Parkinson's patients (Djaldetti et al., 2007). These findings proved the role of the serotonergic system in pain modulation in PD.

Conclusions

Studies of animal models of PD and evidence from patients suggest an important role of the serotonergic system in the pathophysiology of non-motor symptoms such as depression, anxiety, sleep disturbance, apathy, gastrointestinal disturbance and pain. In advanced stages of PD, a decrease in serotonergic neurotransmission is observed due to degeneration of the dorsal raphe nuclei. Damage to LC neurons in Parkinson's disease suppresses the anti-inflammatory effect of noradrenaline on glial cells, resulting in increased pro-inflammatory cytokine release. This condition disrupts serotonergic signal transmission and leads to depression. During the development of PD, Lewy bodies are detected early in the raphe neurons and are characterized by limbic symptoms such as anxiety. It has been determined that sleep disturbance seen in Parkinson's disease is associated with altered serotonergic activity. Evidence shows that administration of 5-HT_4 receptor agonists improves gastrointestinal motility and reduces constipation in PD patients. Abnormal functional connections in raphe nuclei in Parkinson's disease partially explain the pathophysiological mechanism of pain. In light of all this information, further studies are needed to better understand the role of the serotonergic system in improving the non-motor symptoms seen in Prakinson's disease.

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Chapter 3

CHILD HEALTH AND HEALTH LITERACY

Çiğdem Müge HAYLI[1]
Dilek DEMİR KÖSEM[2]
Mehmet Zeki AVCI[3]

1 Assistant Professor Doctor
Hakkari University, Faculty of Health Sciences, Department of Nursing, Hakkari, Turkey,
orcid number: 0000-0001-7630 -9619, mail: mugehayli@hakkari.edu.tr
2Assistant Professor Doctor
Hakkari University, Faculty of Health Sciences, Department of Nursing, Hakkari, Turkey,
orcid number: 0000-0001-9914-8299, mail: dilekdemir@hakkari.edu.tr
3 Professor Doctor
Cyprus Science University, Faculty of Health Sciences, Kyrenia, TRNC,
orcid number: 0000-0001-6614-9447, mail: mehmetavci@csu.edu.tr

Introduction

One of the most important development indicators of a country is child health. Today's health system is important in terms of adopting practices to protect and improve children's health, obtaining information about health services, making correct and effective decisions about their own health, and taking responsibilities regarding the health of individuals. In all these processes, health literacy of individuals emerges as another important factor in searching and understanding health information and communicating with those who provide health information and services (Birru et.al., 2004).

With low health literacy in children, the incidence of negative health behaviors increases. Developmental level of the child it can affect the level of knowledge and skills regarding care and health literacy.

The Concept Of Health Literacy

American Academy of Pediatrics 2005 It was reported that policies adopted to increase health literacy in adults should be adapted to children and families. In this regard, a guide has been created to improve the health literacy of children and families (Chang et.al., 2015).

Health literacy; is associated with general literacy and in daily life related to healthcare, disease prevention and health promotion to maintain or improve quality of life throughout life. People's knowledge, motivation and ability to access, understand, evaluate and apply health information to make decisions and make judgments.

It has a scope and framework that requires their involvement (Betz et.al., 2008; David et.al., 2006). According to the World Health Organization (WHO), health literacy is about maintaining well-being and these are the cognitive and social skills of individuals regarding their ability and desire to access, understand and use health information in order to improve their health (David et.al., 1999).

The Importance Of Health Literacy

Studies conducted in developed and developing countries have found that the level of health literacy is low. For example, in America, adults. Approximately 50% of the population has difficulty understanding and implementing health information (Dewalt et.al., 2006). Inadequate health literacy; inadequate health information, failure to implement preventive health services, inadequacy in accessing and using health services, errors in disease management and medication use.

It is stated that it is associated with serious health consequences that may cause an increase in the incidence of chronic diseases and mortality rates (Fleary et.al., 2018; Fiksda et.al., 2014).

Health Literacy in Children

In recent decades, the concept of health literacy in children has become increasingly important and the need for the development and understanding of this concept has increased. The age has increased (Chang et. Al., 2015). Health literacy education should begin in childhood, as children's healthy lifestyle behaviors may be affected in later years. When we look at the literature, it is seen that child-centered health education is

It is reported that the child should be given according to age and developmental characteristics (Jacobs et.al., 2016; Hsu et.al., 2014; Jimenez-Marroquin et.al. 2014). Inadequate health literacy levels in children negatively affect child health. In a study examining the health literacy of adolescents, 200 adolescents were studied in Australia and low health literacy levels were examined. It has been found that cigarette and alcohol consumption is higher in adolescents with lower literacy levels (Kann et.al., 2007). In another study conducted with 350 adolescents in the USA, it was observed that children with low health literacy exhibited negative behaviors such as carrying weapons and peer bullying (Kickbusch et.al., 2021). Sharif (2010) reported that low health literacy level is one of the factors that determine body mass index after the child's age, gender and eating habits (Sharif and Blank, 2010).

Health Literacy in Child Health Determinatıon Methods

There are very few scales developed to assess health literacy in child health. Most of the tools used to measure health literacy are inadequate because they only measure word recognition or reading ability. Rapid Estimate of Adolescent Literacy in Medicine, a health literacy measurement tool used in adolescents REALM Teen) is valid for children aged 10-19; uses a word list to measure reading ability, but does not include reading comprehension and quantification. Does not measure yeast (Tokuda et. al., 2009). Other health literacy tools used in adolescents are The Test of Functional Health Literacy in Adults (TOFHLA) and the New Vital Signs Scale. (Newest Vital Sign, NVS) are the most commonly used measurement tools (Simovsk et.al., 2010).

New measures of health literacy in child health should take into account the developmental status of child health care and the specific health needs of children. Health literacy skills from childhood to adulthood. Measurement tools should take into account the age and developmental stage of the children being assessed, as the range of children varies along a developmental continuum. Additionally, pediatric health literacy measurements are tailored to child health needs must be specific (Sleath et.al., 2003).

Health Literacy and School-Based Health Education

Health is vital to education. Education is also vital to health. Healthier students, families, and society are better academically is successful and more

productive in the following years. Studies on education play a major role in developing and strengthening health literacy (Spadaro, 2003).

Most studies of health literacy in the educational setting use the National Health Education Standards (NHES) as a framework for research and discussion uses. NHES is a functionally healthy literate, school-aged child who is considered essential to the development and maintenance of the individual and emphasizes specific competencies for adolescents. According to NHES, these qualifications are;

(1) critical thinking and problem solving,

(2) responsibility and productivity,

(3) self-management

(4) effective communication (Sorensen et.al., 2012). Seven National Health Education Standards developed by the joint committee on National Health Education Standards. The standard describes what students should and can do as a result of school health education and indicates the direction of development of the program.

As a result, the following approaches are recommended to increase the level of health literacy in children and develop health awareness.

1. The foundations of health literacy should be laid by taking into account childhood.

2. Health-enhancing school approaches should be developed and supported.

Conclussion

Health literacy should be part of an effective framework for improving the delivery of quality child health care. However, health literacy education should begin in childhood. Studies in the literature address the relationship between health literacy and child health outcomes and the most effective interventions for health literacy in the pediatric setting. The basics that children need to manage themselves.

Establish a better curriculum for health literacy skills in primary and secondary schools for clinician education.

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Chapter 4

SYSTEMIC INFLAMMATORY MARKERS: A NEW PARADIGM IN THE TREATMENT OF TUBO-OVARIAN ABSCESS

Güzide Ece Akıncı[1]

Teymur Bornaun[2]

Hamit Zafer Güven[3]

1 Dr. Department of Obstetrics and Gynecology, Istanbul University Health Sciences Istanbul Bagcilar Training and Research Hospital, egeeceakinci@gmail.com, https://orcid.org/0000-0003-2782-1143

2 Op. Dr., Department of Obstetrics and Gynecology, Istanbul University Health Sciences Istanbul Bagcilar Training and Research Hospital, https://orcid.org/0009-0007-8081-8003

3 MD, Department of Obstetrics and Gynecology, Istanbul University Health Sciences Istanbul Bagcilar Training and Research Hospital, https://orcid.org/0009-002-7217-7318

1. Introduction

Tubo-Ovarian Abscess (TOA) represents a significant clinical challenge within the spectrum of pelvic inflammatory disease (PID), carrying a considerable risk for both acute systemic complications and long-term reproductive morbidity. Traditionally, the cornerstone of TOA management has involved a combination of broad-spectrum antibiotics, with surgical intervention reserved for cases unresponsive to medical treatment or those presenting with acute complications, such as abscess rupture or peritonitis (1). However, this conventional approach does not fully address the complexity of TOA pathophysiology or the nuanced interplay between host immune response and infection dynamics.

Recent advancements in our understanding of inflammatory processes and their central role in the pathogenesis and progression of TOAs have highlighted the potential of systemic inflammatory markers as both diagnostic tools and predictors of treatment response. Markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count (WBC) have gained prominence for their ability to reflect the severity of the inflammatory response and provide actionable insights into disease severity, prognosis, and the likelihood of treatment success (2).

The role of CRP, a sensitive and dynamic acute-phase reactant, has been particularly emphasized in recent literature. Elevated CRP levels have been associated with increased TOA size and severity, offering a quantitative measure that correlates with clinical outcomes (3). Similarly, ESR and WBC, while less specific, contribute valuable information regarding the systemic impact of the infection and the body's response to therapeutic inter00ventions.

Emerging evidence suggests that these inflammatory markers can guide the decision-making process in TOA management, aiding in the differentiation between patients who may benefit from conservative management and those requiring surgical intervention. For instance, studies have shown that patients with markedly elevated CRP levels are less likely to respond to antibiotic therapy alone, indicating a need for more aggressive treatment approaches (4).

Moreover, the dynamic changes in systemic inflammatory markers during treatment provide clinicians with a real-time assessment of therapeutic efficacy. A significant decrease in these markers often precedes clinical improvement, serving as an early indicator of response to treatment and allowing for timely adjustments in management strategies (5).

In light of these findings, systemic inflammatory markers have emerged as a critical component of the modern management paradigm for TOA. By integrating these markers into the diagnostic and therapeutic algorithm, clinicians can achieve a more personalized approach to TOA management, optimizing treatment outcomes while minimizing unnecessary interventions.

This evolving paradigm underscores the necessity of reevaluating traditional approaches to TOA treatment in favor of a more nuanced understanding of the disease process. As we continue to unravel the complexities of TOA pathophysiology and the systemic inflammatory response, the incorporation of systemic inflammatory markers into clinical practice offers a promising avenue for enhancing patient care and improving outcomes in this challenging clinical entity.

The objective of this book chapter is to elucidate the burgeoning role of systemic inflammatory markers in revolutionizing the management strategy of Tubo-Ovarian Abscess (TOA). This chapter seeks to bridge the gap between traditional management practices, which predominantly rely on empirical antibiotic therapy and surgical intervention, and a more nuanced approach that incorporates the assessment of systemic inflammatory markers. By doing so, it aims to foster a deeper understanding of the pathophysiological underpinnings of TOA and leverage this knowledge towards optimizing patient outcomes.

The significance of this chapter lies in its potential to redefine clinical practice by introducing a novel paradigm that emphasizes the utility of inflammatory markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count (WBC) in the diagnostic, prognostic, and therapeutic realms of TOA management. These markers not only provide insights into the severity of the infection and the body's response but also offer a means to tailor treatment strategies more effectively. For instance, elevated levels of these markers could indicate a poor response to conservative treatment, thereby necessitating a more aggressive or surgical approach. Conversely, a significant reduction in these markers could signal an effective response to treatment, thus guiding clinicians in decision-making processes regarding the continuation or adjustment of therapy.

Furthermore, this chapter underscores the importance of adopting a patient-centric approach in the management of TOA, advocating for the use of systemic inflammatory markers as a tool for personalized medicine. By integrating these markers into the clinical workflow, healthcare professionals can make informed decisions that are specifically tailored to the individual patient's condition, thus avoiding unnecessary interventions and enhancing the quality of care.

In an era where precision medicine is increasingly becoming the cornerstone of healthcare, the exploration of systemic inflammatory markers in the context of TOA management represents a significant advance. This chapter aims to catalyze a paradigm shift in the treatment of TOA, paving the way for more effective, efficient, and personalized therapeutic interventions. It is an invitation to healthcare professionals, researchers, and stakeholders to reevaluate and enrich their clinical practices by integrating the insights garnered

from the study of systemic inflammatory markers, thereby contributing to the evolution of patient care in gynecological infectious diseases.

2. Background

2.1. Pelvic Inflammatory Disease (PID)

Pelvic Inflammatory Disease (PID) represents a prevalent infection affecting the female reproductive system worldwide, involving the upper genital tract, including the uterus, fallopian tubes, and ovaries. Primarily resulting from the ascent of sexually transmitted infections from the lower to the upper genital tract, PID diagnosis heavily relies on clinical presentation and patient history. Patients typically present with lower abdominal or pelvic pain and tenderness in the genital area, prompting clinical suspicion of PID (6).

2.1.1. Epidemiology and Risk Factors

PID predominantly affects women of reproductive age. A study conducted in the United States reported that between 4-12% of women encounter PID at least once during their reproductive years (7). Considering the often asymptomatic or vague symptomatology of PID, its true prevalence is likely higher. According to data from the Centers for Disease Control and Prevention (CDC), about 88,000 women aged 15-44 were diagnosed with PID in 2021 (Table 1) (8). Risk factors for PID include sexual intercourse, especially with a new or multiple partners, a history of sexually transmitted infections (STIs), being younger than 25, previous episodes of PID, use of intrauterine devices (IUDs), lower socioeconomic status, and immunosuppression. Interestingly, the use of barrier and hormonal contraceptives is associated with a reduced risk of PID, highlighting their protective effect against ascending infections (9).

Table 1. CDC 2021 Diagnostic Criteria for Pelvic Inflammatory Disease (PID)

Criteria Type	Criteria Detail
Minimum Clinical Criteria	- Pelvic or lower abdominal pain and tenderness - Adnexal tenderness - Cervical motion tenderness in bimanual examination
Additional Criteria	- Oral body temperature > 38.3°C - Abnormal cervical mucopurulent discharge or cervical friability - Presence of numerous white blood cells in saline microscopy of vaginal fluid - High erythrocyte sedimentation rate (ESR) - High C-reactive protein (CRP) - Confirmed cervical infection with N. gonorrhoeae or C. trachomatis
Definitive Criteria	- Histological diagnosis of endometritis in endometrial biopsy - Detection of tubo-ovarian abscess (TOA) by USG or other radiological imaging methods - Verification of PID through laparoscopy

Table 1 summarizes the diagnostic criteria for PID as outlined by the CDC in 2021, including the minimum clinical criteria necessary for a presumptive diagnosis, additional supportive criteria that enhance the diagnostic accuracy, and definitive criteria that confirm the diagnosis.

2.1.2. Microbiology and Pathogenesis

Approximately 85% of PID cases stem from sexually transmitted pathogens or organisms linked to bacterial vaginosis, with Neisseria gonorrhoeae and Chlamydia trachomatis being the most prevalent causative agents in sexually active premenopausal women. Anaerobic and facultative anaerobic bacteria also contribute to the condition (10). PID is approached as a polymicrobial infection, emphasizing the need for broad-spectrum therapeutic strategies. Notably, 15% of women with an endocervical N. gonorrhoeae infection may develop PID (11). Further, evidence suggests that these microorganisms do not directly cause pelvic abscesses but play a synergistic role with aerobic and anaerobic bacteria in abscess formation, supporting the polymicrobial pathogenesis model of PID and TOA (12). The pathogen's ascension to the upper genital tract can occur via several mechanisms, including the ascent of motile trichomonads, transportation by sperm, or passive transport due to negative intraperitoneal pressure created by uterine activity and respiration (13).

2.1.3. Imaging Techniques

Ultrasonography (US) is the first-line imaging modality for pelvic inflammatory disease (PID), favored for its affordability, accessibility, and absence of radiation risk. However, its sensitivity and specificity are limited in the early stages of PID. Transvaginal US is preferred when possible. Findings such as increased tubal wall thickness, fluid in the Douglas pouch, the cogwheel sign in the tube, polycystic-appearing ovaries, incomplete septa, and the presence of adnexal masses like a tubo-ovarian complex may suggest PID on ultrasonography (Table 2). A literature review in 2014 highlighted that the most sensitive finding was increased tubal wall thickness, followed by the cogwheel sign (6).

Doppler ultrasonography can assess increased blood flow, vasodilation, and angiogenesis in inflammatory tissue, but these are not distinctive for PID (7).

Computed Tomography (CT) is another useful diagnostic tool, especially in cases where ultrasonography's results are inconclusive. CT may not have high sensitivity and specificity for PID alone but is valuable for differential diagnosis and detecting complications (8).

Magnetic Resonance Imaging (MRI) is significant for its high soft tissue contrast and sensitivity to inflammation, making it crucial in diagnosing PID, particularly for identifying acute complications like pyosalpinx, tubo-ovarian abscess (TOA), and peritonitis (9).

Table 2. *Imaging Techniques*

Imaging Technique	Advantages	Disadvantages	Notable Findings in PID
Ultrasound (US)	Cost-effective, accessible, no radiation exposure	Lower sensitivity and specificity in early PID	Increased tubal wall thickness, fluid in Douglas space, cogwheel sign in tubes, polycystic appearance of ovaries, incomplete septa, and presence of adnexal masses
Computed Tomography (CT)	Useful in unclear clinical presentations, valuable in differential diagnosis and identifying complications	Exposure to radiation	Not typically the first choice but offers valuable information when US is inconclusive
Magnetic Resonance Imaging (MRI)	High soft tissue contrast, high sensitivity to inflammation	More expensive and less available than US and CT	Particularly useful in detecting PID complications like pyosalpinx, tubo-ovarian abscess, and peritonitis

2.1.4. Differential Diagnosis

The nonspecific clinical and laboratory findings of PID mean it can be confused with a variety of infectious or non-infectious intra-abdominal conditions. Gynecological issues such as adnexal masses, ovarian torsion, degenerating fibroids, ectopic pregnancy, endometriosis, septic abortion, and dysmenorrhea should be considered in differential diagnoses. Conditions involving the gastrointestinal system like appendicitis, diverticulitis, acute gastroenteritis, and inflammatory bowel disease can mimic the pain associated with PID. Urinary system infections like cystitis, pyelonephritis, and urethritis can also present similarly. A comprehensive diagnostic approach is essential to exclude all other potential causes of pelvic pain and correctly diagnose PID (10-15).

2.1.5. Treatment

The treatment regimes for PID typically involve antibiotics that are effective against primary pathogens like N. gonorrhoeae and C. trachomatis. Empirical treatment is recommended for mild and uncomplicated cases of PID. The chosen antibiotics should have a broad spectrum to cover sexually transmitted microorganisms, endogenous vaginal, and cervical flora. Initiating empirical treatment based on clinical suspicion is crucial to prevent late treatment complications of PID (16,17).

Outpatient and inpatient treatments are viable for PID cases. Different antibiotic regimens have been recommended in the 2017 European and 2021 CDC guidelines. Intramuscular or oral treatment recipients should be reevaluated within 72 hours to consider IV therapy (18).

Table 3. *Treatment*

Treatment Setting	2021 CDC Guidelines	2017 European Guidelines
Outpatient Regimens	- Ceftriaxone 250 mg IM once - Doxycycline 100 mg orally twice a day for 14 days - Metronidazole 500 mg orally twice a day for 14 days	- Ceftriaxone 500 mg IM once - Doxycycline 100 mg orally twice a day for 14 days - Metronidazole 500 mg orally twice a day for 14 days
Inpatient Regimens	- Cefotetan 2 g IV twice a day - Doxycycline 100 mg orally or IV twice a day - Followed by Doxycycline 100 mg orally twice a day + Metronidazole 500 mg orally twice a day to complete 14 days	- Ceftriaxone 1 g IV or IM - Doxycycline 100 mg IV twice a day - Followed by Doxycycline 100 mg orally twice a day + Metronidazole 500 mg orally twice a day to complete 14 days

2.1.7. Complications

Delayed and inadequate treatment of PID is associated with poor recovery outcomes and numerous complications. In the acute phase, these include sepsis, Fitz-Hugh-Curtis syndrome (FHCS), tubo-ovarian abscess (TOA), while chronic pelvic pain, infertility, and ectopic pregnancy are long-term complications. A study showed that 20-24-year-old PID patients had a 18% chance of chronic pelvic pain, 8.5% for ectopic pregnancy, and 16.8% for infertility (19).

FHCS, characterized by the intraperitoneal spread of PID leading to perihepatic inflammation and the formation of adhesions and fibrous bands, adds severe upper quadrant pain to the lower quadrant pain caused by PID (20).

Chronic complications such as pelvic pain are related to inflammation, scar tissue, and adhesions resulting from PID. The incidence of chronic pelvic pain is high in patients with a history of recurring PID. Regardless of symptomatic or asymptomatic progression, infertility can occur, especially due to damage in the tubes affecting ciliary function, which is also related to the development of ectopic pregnancies. Even if treated timely, long-term complications of PID can occur (21).

2.2. Tubo-Ovarian Abscess (TOA)

A tubo-ovarian abscess (TOA) can be defined as inflammatory masses involving not only the fallopian tubes and ovaries but also neighboring pelvic organs. TOA, typically presenting as a tubo-ovarian complex following the ascending progression of genital infections, is considered a complication of pelvic inflammatory disease (PID). The mortality and morbidity associated with TOA are significant. Prior to the advent of broad-spectrum antibiotic therapy and modern surgical treatments, abscess-related mortality rates approached 50%, while currently, sepsis develops in 10-20% of TOA patients. Therefore, to reduce mortality and morbidity, TOA must be aggressively treated(22).

2.2.1. Epidemiology and Risk Factors

Tubo-ovarian abscesses represent a complicated form of PID, with approximately 10-15% of PID cases progressing to a TOA presentation(23). These are predominantly seen in women of reproductive age, with the highest incidence rates between the ages of 20 and 40(24). Another factor influencing the incidence of TOA is the prevalence of sexually transmitted infections (STIs) within a community. Infections with *N. gonorrhoeae* and *C. Trachomatis*, in particular, significantly increase the risk of TOA. Genetic and immunological factors may also play a role in the development of TOA(25).

The prevalence of TOA varies worldwide, depending not only on the prevalence of STIs within a community but also on sexual behaviors and access to healthcare services. For instance, in the United States, the incidence of TOA is higher among African American women compared to White women. This disparity is attributed to the higher prevalence of N. gonorrhoeae and C. Trachomatis infections in this population and is related to socioeconomic status(26).

Risk factors for PID also apply to TOA. These include being sexually active under the age of 25, having multiple sexual partners, a history of PID, vaginal douching, the use of an intrauterine device (IUD), low socioeconomic status, immunosuppression, endometriosis, a history of pelvic inflammatory disease, and recurrent PID(27,28). Additionally, the presence of an IUD is considered a risk factor in many studies. Literature review on PID cases indicates a high rate of IUD usage among these patients. Studies have found that patients with an IUD present larger TOA sizes, and the duration of IUD use also independently increases the risk of medical treatment failure for TOA(29).

2.2.2. Microbiology and Pathogenesis

The pathogenesis of tubo-ovarian abscesses involves the ascending spread of microorganisms from the lower genital tract to the upper genital system and peritoneum, leading to infection. N. gonorrhoeae, *C. Trachomatis*, and *M. genitalium* are primarily responsible for this infectious condition. The infectious process spreading to the fallopian tubes can cause salpingitis, progressing to pelvic peritonitis and endometritis. Alternatively, it can result in an infectious complex involving the tubes and ovaries, namely a tubo-ovarian abscess.

Although the precise mechanism leading to abscess formation is not fully understood, it is believed to involve endothelial damage and edema causing tubal blockage and salpingitis. Microorganisms spread to the ovaries via contiguity, forming a complex and creating necrotic areas and abscess cavities. Ascending infections, as well as other intra-abdominal inflammatory processes such as inflammatory bowel disease, appendicitis, and adnexal surgeries, can contribute to the development of TOA.

Microorganisms associated with TOA are typically STI pathogens, though the lower genital tract flora can also be involved. Acute salpingitis caused by STI pathogens like N. gonorrhoeae and C. trachomatis plays a role in the pathogenesis. Prevotella species, Peptostreptococcus sp., Gardnerella vaginalis, Escherichia coli, and aerobic streptococci are also commonly found in TOAs(30). Additionally, the individual's immune response, the virulence of the bacteria, and existing sexually transmitted diseases can influence the development and severity of TOA(31)

2.2.3. Clinical and Laboratory Findings

Since TOA is a complication of PID, its clinical presentation is similar to that of PID. The typical presentation includes abdominal pain, fever, and vaginal discharge. This similarity can make diagnosing TOA challenging. The absence of fever, a hallmark of inflammatory processes, does not exclude a TOA diagnosis.

Sensitivity and warmth increase upon bimanual examination, similar to PID. A study encompassing 175 patients diagnosed with TOA found that 23% had normal WBC counts, 35% had no fever, and symptoms such as vaginal discharge, nausea, and irregular vaginal bleeding were reported in 28%, 26%, and 21% of patients, respectively(32). Therefore, emergency diagnostic evaluation should be considered in cases of clinical suspicion.

The rupture of an abscess is a gynecological emergency, presenting with severe pelvic pain and acute abdomen. Symptoms such as anorexia, nausea, and vomiting may accompany peritoneal irritation signs. Fever is typically above 38.3°C and can be a sign of sepsis. Hemodynamic instability and hypotension indicating sepsis require immediate medical intervention(33,34,35).

Laboratory analysis in TOA, although the related markers are not specific, can predict the severity of the disease. Commonly assessed laboratory markers include WBC, ESR, and CRP. While leukocytosis is not specific, elevated levels of ESR and CRP have greater diagnostic value(36). Studies have found that an ESR over 19.5 mm/hr and a CRP level above 11.5 mg/L indicate a high sensitivity and specificity for presumptive TOA diagnosis(37). Although elevated inflammatory markers can predict severe disease and longer hospital stays, they are not specific. A study involving 94 patients found that a CRP level above 49.3 mg/L could predict the presence of TOA in patients diagnosed with PID with high sensitivity and specificity(38).

2.2.4. Imaging Techniques

Ultrasound (US) or contrast-enhanced computed tomography (CT) can be used for TOA diagnosis. US is preferred due to its lack of radiation, while CT provides a global view and allows for detailed assessment of surrounding tissues, making it more valuable for differential diagnosis.

Literature indicates that transvaginal ultrasound (TVUS) is more sensitive than transabdominal ultrasound (TAUS) for detecting adnexal pathologies. A cross-sectional study involving 50 patients found TVUS to be more successful than TAUS in detecting tubo-ovarian masses. In cases where TVUS is superior to TAUS, features such as thick walls and increased echogenicity represent purulent material, and air foci can appear hypoechoic. The "cogwheel sign" is considered indicative of salpingitis. Fluid in the Douglas pouch can also be observed in TOA cases. Although TVUS has a higher sensitivity than TAUS, its sensitivity ranges between 75-90%. If a definitive diagnosis cannot be made with US alone, further imaging may be required(39).

When reviewing literature for TOA patients, the sensitivity of contrast-enhanced CT ranges from 78-100%, higher than that of US. The addition of IV and oral contrast to enhance sensitivity and specificity is debated. CT findings include increased abscess wall thickness, increased fluid density within the abscess, and multilocular fluid collections. CT can clearly show tubal thickening and fluid collection indicative of pyosalpinx, as well as bowel wall thickening, pelvic fat infiltration, and ascites(40).

Different from PID, magnetic resonance imaging (MRI) can be used in pregnant patients where US is insufficient. T1-weighted images show low signal intensity, while T2-weighted images show high signal intensity in masses, suggesting a TOA. The sensitivity of MRI for TOA diagnosis is around 95%, with a specificity of approximately 81%(41).

2.2.5. Differential Diagnosis

The differential diagnosis of TOA encompasses a wide range of pathologies causing lower abdominal and pelvic pain. All diseases considered in the differential diagnosis of PID should also be evaluated for TOA. Specifically looking at the reproductive system, conditions such as ovarian masses, cyst rupture, torsion, and ectopic pregnancy can present with a TOA-like clinical picture. Additionally, diseases affecting the gastrointestinal system, such as appendicitis, gastroenteritis, inflammatory bowel diseases, colorectal masses, and bowel perforation, as well as the urinary system, including cystitis, pyelonephritis, and urethritis, should be considered in the differential diagnosis of TOA(42-48).

2.2.6. Treatment

Although medical and surgical treatment options are available for TOA cases, the primary treatment is medical, with antibiotics being the first choice. However, the success rate is approximately 70%(49). For the 25-30% of cases where medical treatment fails, abscess drainage may be attempted for suitable patients, while surgical removal of the abscess and/or surrounding tissue may be considered either laparoscopically or via laparotomy(50). Parenteral antibiotic regimens are preferred initially. The CDC 2021 guidelines specify the

antibiotic therapy regimens used (see Table 4). Patients without clinical and laboratory improvement within the first 72 hours of treatment should be evaluated for medical treatment failure. Patients undergoing surgical treatment must receive complementary antibiotic therapy.

Patients considered for antibiotic therapy alone are those with stable hemodynamics, an abscess size below 7 cm, and no suspicion of rupture in premenopausal women. Studies have shown that the size of the abscess is directly related to the success of medical treatment(51). Although surgical intervention is considered primarily for patients with an abscess size over 7 cm, imaging-assisted drainage protocols may be considered in addition to antibiotic therapy for patients with suspected pelvic adhesions or those desiring fertility preservation and concerned about organ preservation(52,53,54).

Surgical exploration is more appropriate for postmenopausal TOAs due to the risk of malignancy. Studies evaluating postmenopausal TOA patients have found the incidence of gynecological cancer to be 44%, 25%, and 47%, respectively(55,56,57). Given these rates, surgical intervention in postmenopausal TOA patients and the use of frozen section examination during surgery are important to determine the need for an expanded procedure.

There is no different treatment protocol for immunosuppressed patients. However, there is no data supporting early surgical intervention in immunocompromised patients. Literature mentions only complicated clinical courses in HIV-positive patients, but no difference in treatment benefits between HIV and non-HIV patients has been found according to current treatment protocols(58).

Table 4. Tubo-Ovarian Abscess Treatment Regimens

	Recommended Parenteral Regimens	**Alternative Parenteral Regimens**
Antibiotic Regimen	Ceftriaxone 1g IV once daily + Doxycycline 100 mg IV twice daily + Metronidazole 500 mg IV or PO twice daily	Ampicillin-sulbactam 3g IV four times daily + Doxycycline 100 mg IV or PO twice daily
	or	**or**
	Cefotetan 2g IV twice daily + Doxycycline 100 mg IV or PO twice daily	Clindamycin 900 mg IV three times daily + Gentamicin loading dose IV or IM (2 mg/kg), followed by a maintenance dose three times daily (1.5 mg/kg). Single daily dosing (3-5 mg/kg) can be continued
	or	
	Cefoxitin 2g IV four times daily + Doxycycline 100 mg IV or PO twice daily	

Interventional treatment protocols can be analyzed in two main branches: drainage and operation. In patients given medical treatment, factors indicating the need for surgery include lack of biochemical and clinical

improvement within 72 hours, positive defense and rebound, new onset fever, signs of sepsis, and an increase in abscess diameter. Regardless, abscess rupture directly indicates the need for surgical treatment and presents clinically with signs of sepsis, such as hypotension, tachycardia, acidosis, and signs of acute abdomen. Even in the absence of sepsis signs, surgical exploration is indicated for abscesses larger than 9 cm and in patients suspected of sepsis(7,8,45).

Minimal invasive drainage has been attempted since the 1970s and literature reports success rates of 70-100%(58,59). It is especially recommended for patients with fertility expectations. With the assistance of imaging techniques like CT and US, percutaneous, transvaginal, transrectal, and transgluteal approaches can be used for drainage depending on the abscess location(47). Studies show that minimal invasive drainage procedures are more successful in small and unilocular abscesses(60-62). The success rate in patients treated with primary drainage and antibiotic therapy is 86-100%. In addition to medical success, quicker regression of clinical symptoms, shorter hospital stays, and cost-effectiveness compared to surgical procedures are apparent advantages(60,61).

Laparotomy is the most commonly preferred surgical method in the treatment of tubo-ovarian abscesses. The incision for laparotomy is chosen based on the abscess location, either median or Maylard/Pfannenstiel. Although laparotomy is still recommended for ruptured abscesses, laparoscopic approach is advised for non-ruptured abscesses. In cases of adnexal abscesses, laparoscopy along with intravenous antibiotic therapy is recommended as the first-line treatment in suitable patients(63).

The surgery has three main goals. First, confirming the diagnosis of TOA while completely removing the abscess and surrounding infectious and necrotic tissue is crucial. The third goal is to completely clean the peritoneal cavity of infectious material. A range of operations from cystectomy to hysterectomy and bilateral salpingo-oophorectomy can be planned. The patient's age, fertility expectations, abscess diameter, and spread to surrounding tissues play a significant role in this planning(47,53,62-64).

2.2.7. Complications

Despite rapid diagnosis and treatment reducing the risk of complications, recurring PID, infertility, ectopic pregnancy, and chronic pelvic pain are long-term complications in women who have had TOA. The main reason for the development of complications is the scarring and formation of adhesions as damaged tissues heal(47). Weström et al. found that 21% of 415 women with confirmed PID developed infertility. Moreover, the severity of initial PID was shown to result in infertility at rates of 2.6%, 13.1%, and 28.6% for mild, moderate, and severe disease, respectively. The same study showed that the frequency of ectopic pregnancy in the first pregnancy after PID was 7.8%, while it was 1.3% in women without a history of PID(65). Scar formation and adhe-

sions are also blamed for the development of chronic pelvic pain, which occurs in about one-third of women with a history of PID. Similar to the risks of infertility, recurring infections are determinant in the development of chronic pelvic pain, which occurs in about one-third of women with a history of PID. Similar to the risks of infertility, recurring infections are determinant in the development of chronic pelvic pain(48).

2.3. Systemic Immune-Inflammation Index (SII)

The Systemic Immune-Inflammation Index (SII) is an easily accessible and inexpensive inflammatory marker calculated from complete blood parameters. It is calculated using the formula platelet count x neutrophil count/ lymphocyte count (plt x N/L). It was first developed by Hu et al. during a retrospective study among patients with hepatocellular cancer between 2005-2006 and validated in a prospective study conducted between 2010-2011(12).

Although SII was primarily used as a prognostic marker in oncological cases, studies have also shown it to be a prognostic marker in inflammatory diseases(12-14,66). An increase in neutrophil count and lymphopenia is indicative of systemic inflammation. Additionally, platelets are known to play a role in the secretion of inflammatory mediators. Therefore, due to its formulation, SII can be used as a marker to indicate inflammation.

In cases of TOA, using SII as an indicator of the inflammatory process can assist in determining the need for surgery and preventing complications.

3. Conclusion

The exploration of systemic inflammatory markers in the management of Tubo-Ovarian Abscess (TOA) represents a significant leap forward in the approach to treating this complex condition. As detailed throughout this chapter, the integration of markers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell count (WBC) into the diagnostic and therapeutic algorithms for TOA offers a nuanced understanding of the disease process. This approach enables clinicians to tailor treatment strategies more effectively, optimizing outcomes while potentially reducing the need for invasive interventions.

The ability of these markers to provide real-time insights into the severity of inflammation, the body's response to treatment, and the prognosis of the disease underscores their value in the clinical setting. Elevated levels of these markers can signal a more severe infection and a lower likelihood of responding to conservative treatment measures, thus guiding clinicians towards more aggressive or surgical interventions. Conversely, a significant decrease in these markers can indicate a positive response to treatment, allowing for timely adjustments to the management plan.

This shift towards a more individualized treatment strategy, informed by systemic inflammatory markers, aligns with the broader movement in medicine towards precision and personalized care. By focusing on the specific physiological responses of each patient, healthcare providers can avoid one-size-fits-all approaches and instead opt for management plans that are specifically suited to the needs and conditions of individual patients.

However, the adoption of this approach also demands a reevaluation of current clinical guidelines and practices. It calls for increased awareness and education among healthcare professionals regarding the role of inflammatory markers in the management of TOA. Furthermore, there is a need for continued research to refine our understanding of these markers and their implications for treatment. This includes exploring new markers that may offer even more detailed insights into the inflammatory process and its impact on the progression and resolution of TOA.

In conclusion, the incorporation of systemic inflammatory markers into the management of Tubo-Ovarian Abscess represents a promising advancement in the field. It reflects a deeper understanding of the disease's pathophysiology and offers a more nuanced and effective approach to treatment. As we continue to explore the potential of these markers, it is imperative that we also consider the broader implications for clinical practice and patient care, with the ultimate goal of improving outcomes for individuals affected by this challenging condition.

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Chapter 5

PROTON PUMP INHIBITORS: CLINICAL APPLICATIONS, MECHANISMS, AND EMERGING CONCERNS

Ebru UĞRAŞ TİRYAKİ[1]

1 Uzm. Dr. Ebru Uğraş Tiryaki, Mamak District Health Directorate, Ankara, Türkiye, ebruugras@hotmail.com, https://orcid.org/0000-0002-5618-5265

1. Introduction

Proton Pump Inhibitors (PPIs) are pivotal in the management of acid-related gastrointestinal disorders. These include gastroesophageal reflux disease (GERD), peptic ulcer disease, and Zollinger-Ellison syndrome, which necessitate the suppression of gastric acid production for therapeutic success [1]. Since the introduction of the first PPI, omeprazole, in the late 1980s, the use of PPIs has expanded exponentially. They are now among the top 10 most commonly prescribed medications globally, reflecting their significance in clinical medicine [2].

The development of PPIs marked a significant pharmacological milestone. These drugs act by irreversibly binding to and inhibiting the H+/K+ ATPase pump in the gastric parietal cells, thus providing a more effective and prolonged reduction of stomach acid compared to histamine H2 receptor antagonists, which were the standard care before PPIs' introduction [3]. The profound impact of this mechanism was recognized with the awarding of the Nobel Prize in Physiology or Medicine in 1996 to the scientists who elucidated the genetic and mechanistic details of gastric acid secretion [4].

This chapter aims to comprehensively explore the broad spectrum of PPI applications from routine clinical practices to complex therapeutic regimes. It will delve into the nuanced pharmacokinetics and dynamic mechanisms of action of PPIs, elucidate their metabolic pathways, and discuss their systemic effects and interactions with other drugs. Furthermore, this text will examine the burgeoning body of research that has raised significant concerns over the long-term safety of PPIs. Recent studies suggest potential associations between extended PPI use and various adverse health outcomes, such as nutrient malabsorption, chronic kidney disease, increased susceptibility to infections, and a higher risk of certain cancers and neurodegenerative diseases [5,6].

In addition to addressing these potential risks, the chapter will also navigate through the controversies surrounding the overprescription of PPIs. It will assess the implications of emerging data for clinical guidelines and patient management strategies, emphasizing the importance of balancing efficacy with safety to optimize patient outcomes [7].

In light of these concerns, the final sections of the chapter will outline the current and future research directions. These include the development of novel PPIs with improved safety profiles, investigations into the molecular pathways influenced by PPIs, and the design of clinical trials to better understand their long-term effects. By bridging the gap between clinical practice and cutting-edge research, this chapter aims to provide a critical, evidence-based perspective on the role of PPIs in modern medicine [8].

2. Clinical Applications of PPIs

2.1. Indications for Use

Proton Pump Inhibitors (PPIs) are the mainstay of treatment for a variety of acid-related gastrointestinal disorders. The primary indication for PPI use is Gastroesophageal Reflux Disease (GERD), a condition characterized by frequent acid reflux that leads to symptoms such as heartburn and regurgitation, and potentially to esophagitis or Barrett's esophagus [9]. PPIs are also the treatment of choice for peptic ulcer disease, effectively promoting ulcer healing by reducing gastric acid secretion [10]. Furthermore, in patients with Zollinger-Ellison Syndrome—a rare disorder that causes tumors in the pancreas and duodenum to secrete excessive levels of gastrin, leading to severe acid hypersecretion—PPIs provide critical symptomatic relief and control of acid production [3].

Management of dyspepsia and other acid-related disorders is another significant indication for PPI therapy. These drugs are recommended for patients with persistent, unexplained dyspepsia where acid suppression is deemed beneficial, particularly when H2 receptor blockers are insufficient [11].

2.2. Dosage and Administration

The dosage of PPIs varies depending on the specific drug and the condition being treated. Typically, the initial treatment of GERD involves a once-daily dose of a PPI such as omeprazole 20 mg or esomeprazole 40 mg. For peptic ulcers, a similar dosing regimen may be applied, although treatment duration can vary from four to eight weeks depending on the severity and location of the ulcer [13]. In cases of Zollinger-Ellison Syndrome, higher doses may be necessary and treatment is often extended or maintained indefinitely to manage symptoms effectively [14-16].

Special populations, including elderly patients and those with hepatic impairment, often require adjusted dosing to reduce the risk of adverse effects due to slower drug metabolism and clearance. For example, it is recommended to start at a lower dose in elderly patients and adjust based on treatment response and tolerability [17].

2.3. Guidelines for Acute versus Maintenance Therapy

Acute therapy typically involves higher doses of PPIs to quickly reduce acid production and promote healing. Once the acute phase is managed, many conditions require maintenance therapy at a reduced dose to prevent recurrence. Guidelines suggest that maintenance therapy should be tailored to the individual, taking into account factors such as the severity of the disease and the patient's previous response to PPI treatment [18].

2.4. Comparative Efficacy

PPIs have been shown to be more effective than other antacids and H2 receptor blockers in managing symptoms and healing erosive damage in GERD and peptic ulcer disease. Studies comparing PPIs with other treatments, such as ranitidine, a commonly used H2 blocker, have consistently demonstrated PPIs' superior efficacy in reducing gastric acid output and improving clinical outcomes [19].

Case studies and clinical trial summaries further support the efficacy of PPIs. For example, a multicenter trial comparing esomeprazole with ranitidine in the treatment of acute GERD found that esomeprazole significantly improved healing rates and symptom relief over a 4-week period [20]. Another study highlighted the benefits of using lansoprazole in a maintenance setting, showing a substantially lower relapse rate of symptoms in patients with healed esophageal erosions [21].

3. Mechanism of Action

This section has highlighted the advanced understanding of the mechanism of action of PPIs, which has been crucial in optimizing their use in clinical practice. By understanding the specific interactions at the molecular level, researchers and clinicians can better predict the pharmacodynamic responses of different PPIs, tailoring treatment to achieve the best possible outcomes for patients with various acid-related disorders.

3.1. Biochemical Properties

Proton Pump Inhibitors (PPIs) possess a unique biochemical structure that allows them to effectively target and inhibit gastric acid secretion. The core structure of PPIs is a benzimidazole ring, which is crucial for their activity. This ring enables the conversion of the PPI into its active sulfenamide form within the acidic environment of the gastric parietal cells. This transformation is essential for the drug's ability to bind to and inhibit the proton pump [22].

Each PPI varies slightly in its molecular makeup, which can affect its stability, potency, and duration of action. For example, omeprazole, the prototypical PPI, and esomeprazole, its S-isomer, differ in terms of their pharmacokinetic properties and clinical efficacy, which can influence their suitability for different patient populations or conditions [23].

3.2. Structure and Active Sites of PPIs

The active site of PPIs is the gastric H+/K+ ATPase enzyme, also known as the proton pump. This enzyme is the terminal stage in the acid secretion pathway of the gastric parietal cells. PPIs are prodrugs – they require activation in the acidic conditions of the stomach. Once activated, they covalently bind to the cysteine residues in the proton pump via a process known as disulfide

bond formation. This binding is predominantly to the cysteine residues located at positions 813, 892, or 822 on the ATPase enzyme, which are critical for its enzymatic activity [24].

3.3. The Irreversible Inhibition of Gastric H+/K+ ATPase

Upon activation and binding, PPIs inhibit the H+/K+ ATPase irreversibly – meaning that the enzyme's function is disrupted until new enzymes are synthesized. This results in a prolonged duration of acid suppression, even after the plasma concentrations of the PPI have decreased. This mechanism underlies the superior efficacy of PPIs compared to other acid-suppressing medications that do not provide such a long-lasting effect [25].

The process begins with the PPI entering the acidic canaliculi of the parietal cell, where it is converted into the active tetracyclic sulfenamide form. This active form reacts with the sulfhydryl group of the cysteine residues on the ATPase, leading to the formation of a stable disulfide bond that effectively "shuts off" the acid pump. This inhibition is termed 'irreversible' because the enzyme remains inactive until it is degraded and replaced, a process which can take several days [26].

The unique ability of PPIs to irreversibly inhibit gastric acid secretion makes them particularly effective for conditions where reduction in gastric acidity is needed for an extended period. This includes treatment for erosive esophagitis, where prolonged acid suppression is necessary to allow healing of the esophageal mucosa, and in the management of Zollinger-Ellison syndrome, where excessive acid production must be controlled long-term [27].

3.4. Pharmacodynamics

Proton Pump Inhibitors (PPIs) are absorbed in the small intestine after oral administration. The absorption process is optimized by formulating PPIs as delayed-release capsules or tablets, protecting the drug from premature degradation by stomach acid. Once absorbed, PPIs are rapidly taken up by the liver, where they undergo extensive first-pass metabolism primarily via the cytochrome P450 system, predominantly involving the CYP2C19 and CYP3A4 isoenzymes [28].

The metabolism of PPIs significantly affects their systemic bioavailability and duration of action. For instance, genetic variations in the CYP2C19 enzyme can lead to differences in the metabolic rate among individuals, categorizing them as poor or extensive metabolizers. This variation can influence the clinical efficacy of PPIs and may necessitate dosage adjustments [29]. After metabolism, the remnants of PPIs are excreted primarily through the kidneys, with minor amounts eliminated via the feces [30].

Systemically, PPIs have been well-tolerated in most patient populations. However, because they significantly decrease gastric acid secretion, PPIs

can indirectly influence the absorption of other medications and nutrients that depend on an acidic environment for optimal absorption, such as iron, calcium, and vitamin B12. Over long-term use, this effect has been associated with an increased risk of deficiencies and related conditions such as anemia and osteoporosis [31].

3.5. Interaction with Gastric Mucosa and Acid Secretion Pathways

PPIs exert their primary pharmacological action by entering the acidic environment of the stomach, where they are converted into their active form. The active PPIs selectively accumulate in the parietal cells of the gastric mucosa, specifically targeting the secretory canaliculi where gastric acid is produced and secreted [32].

Once activated within the parietal cells, PPIs form a covalent bond with the cysteine residues on the gastric H+/K+ ATPase (proton pump), effectively blocking the final step in the acid production pathway. This bond results in the irreversible inhibition of acid secretion until new enzyme molecules are synthesized, which can take several days. This mechanism allows for sustained suppression of gastric acid, providing symptom relief and facilitating healing in acid-related disorders [33].

The profound decrease in gastric acidity due to PPIs also influences other components of gastric mucosal defense and digestive processes. For example, reduced acidity alters the gastric microbiome, which can lead to an increased risk of infections such as Clostridium difficile-associated diarrhea. Moreover, the inhibition of gastric acid secretion disrupts normal feedback mechanisms that regulate gastrin release. Chronic hypergastrinemia, as a result of long-term PPI use, has been implicated in various gastric pathologies, including enterochromaffin-like cell hyperplasia and increased risk of gastric neuroendocrine tumors [34].

4. Adverse Effects and Long-term Risks

4.1. Common Side Effects

While Proton Pump Inhibitors (PPIs) are generally safe and well-tolerated, they are not devoid of side effects. The most common short-term complications associated with PPIs include headaches, diarrhea, and nausea. These side effects are usually mild and transient, affecting a small proportion of patients. Headaches, for instance, are thought to result from the direct central nervous system action of the drug or from gastrointestinal changes that indirectly affect cerebral function [35]. Diarrhea may occur due to a shift in the stomach's pH balance, altering the gut microbiome and potentially leading to an overgrowth of certain bacteria like Clostridium difficile [36]. Nausea is another common complaint, which could be linked to altered gastric and gut motility influenced by acid suppression [37].

4.2. Interaction with Other Medications

PPIs can interact with other medications primarily through their influence on gastric pH and by inhibiting enzymes involved in drug metabolism, specifically cytochrome P450 enzymes such as CYP2C19. The reduction in stomach acidity can affect the absorption of drugs that require an acidic environment to dissolve properly, such as ketoconazole, itraconazole, and atazanavir, leading to decreased efficacy of these medications [38]. Additionally, the inhibition of CYP2C19 by PPIs can slow the metabolism of drugs metabolized by this pathway, such as certain antidepressants and antiplatelet drugs like clopidogrel. This interaction is particularly significant as it may reduce the effectiveness of clopidogrel, a critical antiplatelet medication used in preventing cardiac events [39].

4.3. Long-term Health Concerns

The long-term use of PPIs has been associated with several potential health risks. One of the most significant concerns is the risk of mineral and vitamin deficiencies, particularly magnesium, calcium, and vitamin B12. These deficiencies occur due to diminished gastric acid secretion, which is essential for the absorption of these nutrients [40]. Chronic magnesium deficiency can lead to serious health issues such as muscle spasms, arrhythmias, and seizures. Similarly, decreased calcium absorption may contribute to the development of osteoporosis and an increased risk of fractures [41].

Another major concern is the potential for renal issues, including acute interstitial nephritis and chronic kidney disease. These conditions are thought to arise from long-term PPI use due to possible direct toxicity to kidney cells or through immune-mediated pathways [42].

Furthermore, there is growing evidence linking long-term PPI use with an increased risk of gastrointestinal infections and complications. As acid suppression alters the gut flora, the risk for infections such as Salmonella, Campylobacter, and Clostridium difficile increases [43]. There is also a potential association with an increased risk of certain types of gastrointestinal cancers, although the data are still being debated within the scientific community [44].

4.4. Mineral and Vitamin Deficiencies

Long-term PPI use has been clearly linked with deficiencies in essential minerals and vitamins, a consequence of reduced stomach acid production. Acid is crucial for the solubilization and absorption of minerals like magnesium and calcium, as well as vitamin B12. Prolonged acid suppression by PPIs can lead to significant reductions in the absorption of these nutrients. Magnesium deficiency, in particular, can manifest in severe neuromuscular symptoms, whereas calcium malabsorption has been associated with an increased risk of osteoporosis and bone fractures [45]. Furthermore, vitamin B12 deficiency

may result in megaloblastic anemia and neurologic disturbances, which can be particularly problematic in elderly patients [46].

4.5. Association with Increased Risk of Infections and Renal Complications

The alteration of gastric pH due to PPI use also impacts the gut flora, potentially leading to an increased susceptibility to gastrointestinal infections such as Clostridium difficile, Salmonella, and Campylobacter. These pathogens typically thrive in less acidic environments, and their overgrowth can lead to severe gastrointestinal distress and complications [47]. Additionally, there is evidence linking PPI use with an increased risk of developing acute interstitial nephritis, a condition that can progress to chronic kidney disease if not promptly managed. This risk is thought to arise either from a direct toxic effect of PPIs on renal tubules or from an immune-mediated response [48].

4.6. Potential Links to Dementia and Cardiovascular Issues

Recent studies have raised concerns about possible associations between long-term PPI use and an increased risk of dementia and cardiovascular problems. Some research suggests that PPIs may influence the metabolism of amyloid-beta in the brain, potentially leading to increased deposits, a hallmark of Alzheimer's disease, although these findings are still under investigation [49]. Regarding cardiovascular health, some evidence indicates that PPIs might interfere with the anti-clotting effects of clopidogrel, a drug used to prevent strokes and heart attacks, potentially increasing the risk of these events [50].

4.7. Cancer Risks

4.7.1. Epidemiological Evidence Linking PPI Use with Gastric and Esophageal Cancers

Several epidemiological studies have investigated the relationship between chronic PPI use and the risk of gastrointestinal cancers, particularly gastric and esophageal cancers. The data suggest a modest association, which may be due to the hypergastrinemia induced by long-term PPI use. Elevated gastrin levels have been shown to stimulate the growth of gastric mucosa, which could potentially lead to dysplastic changes and, subsequently, cancer [51]. However, it is essential to consider that these associations might also reflect underlying conditions necessitating PPI use, such as chronic gastroesophageal reflux, which itself is a risk factor for esophageal adenocarcinoma [52].

4.7.2. Mechanistic Insights into PPI-Induced Carcinogenesis

From a mechanistic perspective, the prolonged suppression of gastric acid by PPIs is thought to lead to an imbalance in the gastric environment. This can result in an overgrowth of bacteria and subsequent formation

of N-nitroso compounds, which are known carcinogens. Additionally, as previously mentioned, the long-term stimulation of gastrin secretion can promote the proliferation of enterochromaffin-like cells, potentially leading to malignant transformation [53].

5. Controversies and Debates

5.1. Debating PPI Overprescription

The debate over the overprescription of Proton Pump Inhibitors (PPIs) has gained significant attention in the medical community. Studies indicate that PPIs are often prescribed for inappropriate indications or are continued for longer durations than necessary without sufficient reevaluation of the patient's condition [54]. This overuse not only exposes patients to unnecessary risk of side effects and interactions but also significantly increases healthcare costs.

Many healthcare providers initiate PPI therapy for common, mild symptoms of dyspepsia or occasional heartburn that might be managed effectively with less potent drugs or lifestyle modifications. Moreover, once started, stopping PPIs can be challenging due to the rebound acid hypersecretion, which can temporarily worsen symptoms, leading to a cycle of continued use [55].

5.2. Discussion on the Necessity vs. Overuse of PPIs in Clinical Settings

The necessity of PPIs for certain conditions like GERD, peptic ulcer disease, and Zollinger-Ellison syndrome is well-documented and uncontested. However, the threshold for initiating PPI therapy is often lower than recommended by guidelines. There is a growing need for healthcare providers to adhere more strictly to these guidelines and to ensure that each prescription is based on a solid, evidence-based indication [56].

Clinical audits and educational interventions have been proposed as methods to reduce unnecessary PPI prescriptions. These initiatives can help physicians recognize when PPI use is appropriate and when alternative treatments might be equally or more effective without the risks associated with long-term acid suppression [57].

5.3. Alternatives to PPIs and Conservative Management Strategies

Given the concerns surrounding the overuse of PPIs, exploring alternatives is crucial. H2 receptor antagonists (H2RAs) are a potential alternative for managing conditions like GERD and peptic ulcers, especially where less potent acid suppression is sufficient. H2RAs have a shorter duration of action and a significantly lower risk profile, which may be preferable for managing intermittent symptoms [58].

Dietary and lifestyle modifications are also effective strategies for managing acid-related disorders and can reduce or eliminate the need for pharmacologic interventions. Simple changes such as avoiding late-night

meals, reducing fatty and spicy food intake, and elevating the head of the bed can significantly improve symptoms in many patients [59].

Furthermore, alginate-based formulations provide a mechanical barrier to gastroesophageal reflux and can be used as a first-line treatment in mild GERD cases or in combination with acid suppression therapy for added symptom control [60].

5.4. Regulatory and Safety Concerns

Regulatory bodies globally, including the Food and Drug Administration (FDA) in the United States, have expressed concerns regarding the safety profile of Proton Pump Inhibitors (PPIs) and have issued several warnings based on emerging evidence of their potential risks.

The FDA has issued multiple warnings about the risks associated with long-term or high-dose use of PPIs. These warnings include risks such as increased susceptibility to bacterial infections including Clostridium difficile, and a noted potential for nutrient malabsorption leading to magnesium deficiency, which could precipitate serious health issues such as arrhythmias and seizures. Moreover, the FDA has highlighted the possible increased risks of bone fractures, chronic kidney disease, and dementia associated with extended PPI use [61].

Internationally, regulatory bodies in Europe and Asia have followed suit, with similar advisories and the implementation of monitoring systems to track adverse reactions associated with PPIs. The European Medicines Agency (EMA) has recommended that PPIs should only be used in the lowest effective dose and for the shortest duration necessary to control symptoms, echoing the principle of minimizing exposure to mitigate risks [62].

Recent years have seen specific instances of PPI withdrawals due to safety concerns. For example, a particular formulation of a PPI was withdrawn from the market after studies confirmed that it caused adverse cardiac events when interacted with certain other medications. These interactions led to significant alterations in drug metabolism, posing severe risks to patients with existing cardiovascular conditions [63].

Additionally, safety alerts have been periodically issued as new research identifies potential new risks. For instance, alerts regarding the risk of acute interstitial nephritis, a condition that can lead to irreversible kidney damage if not diagnosed and managed promptly, have been widely disseminated to healthcare professionals. These alerts stress the importance of monitoring renal function in patients who are on long-term PPI therapy [64].

6. Future Directions in PPI Research

The ongoing challenges associated with the long-term use of Proton Pump Inhibitors (PPIs) have spurred significant interest in the development

of innovative drug designs. These advancements aim to retain the therapeutic efficacy of PPIs while minimizing their adverse effects.

6.1. Developing Safer, Reversible PPIs

One of the most promising areas of research is the development of safer, reversible PPIs. Unlike current PPIs, which irreversibly bind to and deactivate the gastric H+/K+ ATPase enzyme, reversible PPIs would allow for a temporary inhibition of acid secretion. This could significantly reduce the risk of complications associated with prolonged acid suppression, such as infections and nutrient malabsorption. Researchers are exploring molecular structures that can effectively compete with the natural substrates of the proton pump but dissociate after a controlled period, thus restoring enzyme activity more quickly [65].

6.2. Targeted Delivery Systems to Minimize Systemic Exposure

Another innovative approach is the creation of targeted delivery systems that can localize the drug's action to the stomach, thereby reducing systemic exposure and potential side effects. These systems could involve drug formulations that are activated only in the acidic environment of the stomach or encapsulation techniques that prevent the drug from being absorbed into the bloodstream until it reaches the gastric tissue. Such targeted delivery would not only enhance the effectiveness of the treatment but also reduce the impact on other bodily systems [66].

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A key aspect of improving PPI therapy involves identifying high-risk populations who may be more vulnerable to the adverse effects of these drugs. This includes patients with genetic predispositions that affect drug metabolism, such as variations in the CYP2C19 gene, which can alter the metabolic rate of PPIs and hence their pharmacokinetics and pharmacodynamics [67].

Advanced genetic screening and personalized medicine approaches could enable clinicians to predict which patients are likely to experience severe side effects or may require alternative treatments. Furthermore, understanding the specific risk factors that predispose individuals to PPI complications can guide more tailored and effective treatment strategies, potentially involving lower dosages or combination therapies [68].

The field of PPI research is also moving towards more comprehensive clinical trials that not only assess the efficacy and safety of new PPI formulations but also explore their long-term impacts on health, particularly in terms of chronic diseases and microbiome health. These studies are crucial for developing guidelines that can better manage the risks associated with acid suppression therapies [69].

Moreover, ongoing research into the gut-brain axis could illuminate the potential neurological effects of chronic PPI use, guiding future formulations to avoid these risks. This research is particularly significant given the tentative links between PPI use and conditions such as dementia [70].

6.4. Ongoing and Upcoming Research Focusing on Long-term Impacts

As the use of Proton Pump Inhibitors (PPIs) continues to be widespread, ongoing and upcoming research is increasingly focusing on understanding the long-term impacts of these medications. This includes comprehensive studies aimed at exploring the extended consequences of chronic acid suppression on the digestive system, the microbiome, and overall metabolic health.

Longitudinal studies are crucial to ascertain the true extent of risks associated with prolonged PPI use, such as the potential development of chronic kidney disease, micronutrient deficiencies, and gastrointestinal malignancies. Researchers are also investigating the long-term effects of PPIs on the microbiota of the gastrointestinal tract, hypothesizing that changes in gut flora may contribute to obesity, Clostridium difficile infections, and even immune system function [71].

Another area of significant interest is the potential impact of long-term PPI use on cognitive health. With preliminary studies suggesting a possible

link between chronic PPI therapy and an increased risk of dementia, further research is needed to explore this relationship, considering confounding factors and underlying mechanisms [72].

6.5. The Need for Rigorous, Randomized Controlled Trials

To address the gaps in understanding the broader implications of PPI use, there is a pressing need for rigorous, randomized controlled trials (RCTs). These trials are essential to provide high-quality evidence that can inform clinical guidelines and patient care practices.

RCTs focusing on PPIs should ideally include diverse patient populations to assess differential impacts based on genetic background, underlying health conditions, and concurrent medications. This approach would help clarify which populations are at higher risk when using PPIs and who might benefit from alternative treatments or modified dosing regimens.

Moreover, trials designed to compare PPIs with newer or less traditional treatments, such as alginate-based therapies or dietary interventions, could offer valuable insights into effective alternatives to PPIs for managing acid-related disorders. Such studies could also explore the efficacy of step-down strategies, where patients transition from PPIs to H2 blockers or other less potent agents as their symptoms improve, minimizing long-term exposure to PPIs [69,71].

Conclusion

Throughout this chapter, we have thoroughly explored the many facets of Proton Pump Inhibitors (PPIs), from their clinical applications and mechanisms of action to the controversies, debates, and future directions in research. PPIs are integral in the management of acid-related disorders, offering relief and therapeutic benefits to countless patients suffering from conditions like GERD, peptic ulcers, and Zollinger-Ellison syndrome. However, the potential for overprescription and the array of side effects associated with long-term use necessitate a careful approach to their prescription and management.

The evidence underscores the need for a balanced perspective on the use of PPIs. While they are highly effective in reducing gastric acid production and alleviating symptoms of acid-related diseases, their long-term use is associated with significant risks, including mineral deficiencies, increased susceptibility to infections, and possible links to more serious conditions like chronic kidney disease, dementia, and certain cancers. The complexity of these risks highlights the critical importance of using PPIs judiciously, ensuring they are prescribed only when necessary and regularly reviewed to assess the ongoing need for therapy.

Given the ongoing concerns and emerging evidence of potential harms, there is a clear and urgent need for continued research into PPIs. Future

studies should aim to better understand the long-term impacts of these drugs, develop safer therapeutic alternatives, and refine strategies to minimize risks. Such research will be essential in guiding future clinical practices and in the development of new guidelines that ensure patient safety and optimal therapeutic outcomes.

As we move forward, it is imperative that healthcare providers stay informed about the latest developments in PPI research and adhere to evidence-based practices. By doing so, they can ensure that patients benefit from the therapeutic advantages of PPIs while minimizing their potential risks. This balanced approach, coupled with ongoing research and education, will be key to maximizing the clinical efficacy of PPIs and safeguarding the health and well-being of patients globally.

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