TRENDS IN INTERPROFESSIONAL CARE MANAGEMENT IN HEALTHCARE

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CONTENTS

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PREFACE

Dr. Emral GÜLÇEK……..1

CHAPTER 1

DIABETES NURSING

Lecturer Dr. Emral GÜLÇEK……..…….3

CHAPTER 2

CHRONIC NURSING IN HOSPITALS

Lecturer Dr. Emral GÜLÇEK…….....19

CHAPTER 3

THE IMPORTANCE OF SPHINGOLIPIDS IN HUMAN DISEASES

Assist. Prof. Ferah CÖMERT ÖNDER, Sevil KALIN…….....33

CHAPTER 4

CYTOKINES

Spc. Dr. Mehmet ÖZDİN……....65

CHAPTER 5

RELATIONSHİP OF PARAOXONASE WITH CARDIOVASCULAR DISEASES

Spc. Dr. Mehmet ÖZDİN……....79

CHAPTER 6

TELE-NURSING DURING COVID-19 OUTBREAK

Assist. Prof. Dr. Mustafa DURMUŞ

Lecturer Yusuf DURMUŞ.....89

CHAPTER 7

COVID-19, NURSING CARE AND ETHICS

Assist. Prof. Dr. Mustafa DURMUŞ

Lecturer Yusuf DURMUŞ.....103

CHAPTER 8

EFFECTS OF STRESS ON MALE REPRODUCTION

Assoc. Prof. Dr. Saadet BELHAN.....121

CHAPTER 9

WOMEN WITH EPILEPSY, PREGNANCY, BIRTH AND POSTPARTURE

Dr. Sümeyye BARUT……...141

CHAPTER 10

OBESITY AND MIDWIFERY CARE DURING PREGNANCY

Dr. Sümeyye BARUT……..153

CHAPTER 11

NEW VARIANTS OF SARS-CoV-2

Assist. Prof. Dr. Ahmet Melih SAHIN

Spc. Dr. Ayşe AKTEMUR……..……..165

CHAPTER 12

PATIENT SAFETY AND THE ROLE OF THE NURSE IN SURGERY

Assist. Prof. Dr. Kezban KORAŞ SÖZEN……...191

CHAPTER 13

NON-PHARMACOLOGICAL METHODS USED FOR NIPPLE TRAUMA IN LACTATING WOMEN

R.A. Feride ÇEVİK, R.A. Ebru ERTAŞ……...205

CHAPTER 14

EVALUATION OF STROKE

Spc. Dr. Hüseyin GÜRBÜZ, Prof. Dr. Hülya ÇİÇEK……..225

PREFACE

New competences are required for organizing decisional intergroup conflict resolution in health care settings for more functionality and higher performance. Identifying barriers and facilitators of negotiation between caregivers for current applications and future prospects is related to readiness to change. Exploring ınterpersonal skills and building more interpersonal trust between service users and professionals might one of an optimum promoter on the way to that target. Performance of health care professionals, job satisfaction in long-term care and making better health-related decisions at homes might be improved by participatory mixed methods protocol. Analysing the roles of leaders deeper for the adoption of different approaches, processes, issues and implications is also essential. Benefits of participatory governance and leadership are prooved individual and organizational factors influencing of work context. Increasing cooperation in health systems is a highly productive area for better public health status of nations especially in the more and more complicating medical age.

Dr. Emral GÜLÇEK

CHAPTER 1

DIABETES NURSING

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1. Introduction

Diabetes is an emerging epidemic with cumulative impact on every country, age and economy in the world. In 2015, approximately 415 million people were suffering from diabetes and is expected to exceed 640 million by the year 2040 in the world. It is estimated that half of diabetes patients are unaware of the disease and more prone to diabetic complications (Papatheodorou et al., 2018). Uncontrolled diabetes during the perioperative period can result in a variety of adverse postoperative outcomes (Mott et al., 2018).

Delivering high quality primary care for patients with chronic diseases has potential to reduce non-elective hospital admissions. More research are needed for organisation and delivery of diabetes care services in general practice to better understand the impact of the different staffing applications on patient outcomes (Griffiths et al., 2010). Primary care has changed significantly with chronic disease growth rate. Nurse case managers assist with this chronic disease by providing if not significantly better care, than equivalent care to that provided by usual primary care providers. Chronic disease management requires patient-centered skills and tools, such as registries, panel management, review of home data, communicating with patients outside of face-to-face care, and coordinating multiple services. Registered nurse care managers perform many actions required for diabetes chronic disease management including initiation and titration of medications with similar or improved physiologic and patient satisfaction outcomes over usual care providers. Selection and training of the nurse case managers

is of utmost importance for implementation of a successful chronic disease management program (Watts & Lucatorto, 2014).

Patients are generally confident in nurse prescribing. Confidence in nurse prescribing is inspired by nurses' specialist knowledge, experience, trusting relationship, thorough consultation and benefits of nurse prescribing. Communication between nurses and doctors about patient care, awareness by nurses of their area of competence, training and experience, specialist diabetes knowledge and access to training updates are important for safe prescribing (Courtenay et al., 2010). Positive psychological characteristics, such as optimism, self-efficacy and resilience is increasingly associated with better outcomes in ill individuals. In people with diabetes, positive psychological characteristics are significantly associated with improved glycemic control, fewer complications, and reduced rates of mortality. Potential mechanisms mediating these associations include behavioral factors (improved treatment adherence etc.), reduced inflammation, improved neuroendocrine and improved autonomic functioning (Celano et al., 2013).

Ginzburg et al., (2021) assessed long-term diabetes management and control in a central multidisciplinary primary care clinic, following a brief intervention conducted by a community nurse. Randomly 100 people with diabetes was followed-up during 10 years, following a brief intervention managed by a community nurse. During the period, 18 participants were died. HbA1c dropped significantly after intervention and remained low. LDL and Systolic Blood pressure decreased and

continued to decrease during the long-term follow-up. While the number of nurse visits per year increased, physician and dietician visits decreased. Annual foot examinations and ophthalmologist visits, which increased following the intervention, remained high. Diabetes-related hospitalizations also decreased from the point of intervention.

2. Infection spread

Patients of diabetes are at a greater risk of hospitalization and mortality resulting from viral, bacterial, and fungal infections (Erener, 2020). Several studies have shown that people with diabetes are vulnerable to infection (Kim et al., 2019). Urinary tract infection frequency and severity in patients with diabetes mellitus is increasing (Fünfstück et al., 2012). Hospital-acquired infections are infections developing after 48 hours of hospitalization or stay at a healthcare facility that were not present or incubating at the time of admission (Kelly & Monson, 2012). These infections include catheter-associated urinary tract infections, surgical site infections, central line-associated bloodstream infections, hospital-acquired pneumonia, ventilator-associated pneumonia and *Clostridium difficile* infections. Symptoms that favor an infection include productive cough, abdominal pain, shortness of breath, rebound tenderness, palpitations, altered mental status, suprapubic pain, dysuria, polyuria, and costovertebral angle tenderness. Nurses play a vital role in prevention as they are often the first to encounter infected patients. Washing hands and ensuring that everyone follows the established rules for infection prevention are key (Monegro et al., 2020).

Reducing nurse burnout by just 10% could prevent thousands of hospital-acquired infections and reduce costs. Increased workload increases certain infections (Potera et al., 2012). Each year, nearly 7 million hospitalized patients acquire infections while being treated for other conditions. Nurse staffing has been implicated in the spread of infection within hospitals. But little evidence explain this association. Cimiotti et al., (2012) linked nurse survey data to the Pennsylvania Health Care Cost Containment Council report on hospital infections and the American Hospital Association Annual Survey. They examined surgical site and urinary tract infection which are the most prevalent infections reported on any unit within a hospital. There was a significant association between patient-to-nurse ratio and urinary tract infection and surgical site infection. Only nurse burnout remained significantly associated with urinary tract infection and surgical site infection infection. Hospitals in which burnout was reduced by 30% had a total of 6,239 fewer infections, for an annual cost saving of up to $68 million. Reducing burnout in registered nurses is a promising strategy to help control infections in acute care facilities.

The quality of medical services can be regarded as an indication of the changes being implemented at a given moment. At the same time, improving the care quality remains essential, regardless of the current situation. This makes upgrading employees' skills a necessity, for instance by preventing undesired events, like hospital acquired infections which are quite common (Dziewa et al., 2015). Nurses are central in hospital efforts to improve quality care (Ceballos et al., 2013).

3. Nurse staffing

Studies during past decades was shown an association between nurse staffing and patient outcomes (Penoyer, 2010). Better hospital nurse staffing, more educated nurses and improved nurse work environments have been shown to be associated with lower hospital mortality. Positive effect of increasing percentages of Bachelors of Science in Nursing Degree nurses is consistent across all hospitals. Also lowering patient-to-nurse ratios significantly improves patient outcomes in hospitals with good work environments, slightly improves them in hospitals with average environments, and has no effect in hospitals with poor environments (Aiken et al., 2012).

Diabetes nursing continues to progress with specialist nurses providing high quality evidence based practice. During last decade, diabetes 'scene' has become even more complex with the advent of new technologies, complex therapies, structured diabetes education programmes and a greater need to reduce costs. Training and continuing education for providing care and support is essential to people with diabetes (Mackinnon, 2012). Nurses are the largest component of the health workforce worldwide and numerous models and profile of workforce allocation were implemented. These include changes in skill mix, grade mix or qualification mix, staff-allocation models, staffing levels, nursing shifts, or nurses' work patterns (Butler et al., 2019).

Glucose monitoring is an essential component of type 1 diabetes treatment. Continuous glucose monitoring systems measure glucose levels every few minutes and provide valuable trend information about

the direction and speed glucose levels are change. Use of continuous glucose monitoring is increasing rapidly in youth with type 1 diabetes and consistent use of continuous glucose monitoring is associated with improved glycemic control. School nurses are a vital part of the care team for a student with type 1 diabetes, and therefore, must be comfortable using continuous glucose monitoring to support their students at school (Berget & Wyckoff, 2020).

Diabetes is strongly associated with healthy eating knowledge and is effectively controlled by dietary modification. Nutrition education is effective to increase knowledge about dietary management of diabetes among nursing students (Saeed et al., 2016).

4. Other subjects

Tight blood glucose control in critically ill patients is difficult and labor intensive, resulting in poor efficacy of glycemic control and increased hypoglycemia rate (Van Herpe et al., 2013). Most type 2 diabetes patients have glycaemic levels outside of target. Insulin is effective in improving glycaemia and most people with type 2 diabetes eventually need this. Despite this, transition to insulin therapy is often delayed in primary care (Furler et al., 2014).

Failure to achieve and maintain glycemic targets in patients with type 2 diabetes (T2D) is a major clinical issue but for effectively combating the barriers, key roles are at nurse practitioners. In patients receiving insulin therapy not achieving targets despite dose titration, a change in insulin regimen may be necessary to achieve clinical targets while minimizing hypoglycemia and weight gain. Whichever strategy is

initiated first must be tailored to the individual and include on-going monitoring to manage both hyperglycemia and hypoglycemia. In addition to considerations of glycemic control, the timing and method of insulin intensification will depend on patient willingness, overall health status, meal patterns and routines, and risk of hypoglycemia. Common patient barriers to insulin intensification include regimen complexity and increased risk of hypoglycemia and weight gain (Kruger, 2012).

A glucose tolerance test is used to determine a person's ability to handle a glucose load. The test can show whether a person can metabolize a standardized measured amount of glucose. The results can be classified as normal, impaired, or abnormal. A glucose tolerance test may be used to diagnose type 1 diabetes mellitus, type 2 diabetes mellitus, and gestational diabetes mellitus. It is a blood test that involves taking multiple blood samples over time, usually 2 hours (Wei et al., 2019).

A glucose tolerance test is typically ordered by a medical doctor or advanced nurse practitioner. Interprofessional collaboration is required for the correct administration of the test. The provider or the nurse must ensure to give the patient adequate instructions to prepare for the test and for what to expect at the test (Huhn et al., 2018). Nurses, medical assistants, or phlebotomists may perform the test. There must be clear communication on order from the provider on the type of test, the length of time, and the number of samples ordered. The personnel administering the test should be aware of the requirements of the test including the fasting requirement and the pre-test dietary carbohydrate

requirement. It is important to collaborate with laboratory personnel to ensure timely processing of the specimens, as well as proper storage and shipping (Eyth et al., 2020).

Proper injection techniques are crucial for appropriate diabetes management. Such injections should ensure achievement of the desired action profile of the insulin and avoid any potential adverse effects of the injection. Training practitioners of proper administration is one of the tasks of diabetes educators (Gu et al., 2010). Evaluation of the insulin knowledge of nurse practitioners is especially important (Kuo et al., 2015).

Hypoglycemia due to inadequate carbohydrate intake is a frequent complication of insulin treatment of diabetic patients. Marelli et al., (2015) assessed the effectiveness of a nurse-managed protocol to prevent hypoglycemia during subcutaneous insulin treatment. A nurse-managed protocol focusing on carbohydrate intake was found reduced the incidence of hypoglycemia in patients with diabetes receiving subcutaneous insulin in hospital.

The use of hypoglycaemic drugs was associated with poor health outcomes in nursing home residents. Therefore, more attention must be paid to adapting anti-diabetic treatment in this complex population (de Souto Barreto et al., 2014).

Yoga has a greater effect on patients with type 2 diabetes mellitus and peripheral vascular disease, up to 80%. Combined with the experimental data, it is analyzed that the two kinds of exercise therapy, yoga and walking, are relatively good, and the use of yoga exercise

therapy is as high as 53%. The results show that exercise therapy is important for patients with type 2 diabetes and peripheral vascular disease. Role, nursing intervention plays a corresponding auxiliary role (Zhou & Mao, 2020).

5. Conclusions

There is a need for more research into the organisation and delivery of diabetes care services in general practice, preferably using patient level data; in order to better understand the impact of the different staffing configurations on patient outcomes.

Patients of diabetes are at a greater risk of hospitalization and mortality resulting from viral, bacterial, and fungal infections. Increased nurse workload and burnout increases certain infections; tight blood glucose control in critically ill patients is difficult and labor intensive; failure to achieve and maintain glycemic targets in patients with type 2 diabetes is a major clinical issue and hypoglycemia due to inadequate carbohydrate intake is a frequent complication of insulin treatment of diabetic patients.

Communication between nurses and doctors about patient care, awareness by nurses of their area of competence, training and experience, specialist diabetes knowledge and access to training updates are important for safe prescribing. Better hospital nurse staffing, more educated nurses and improved nurse work environments have been shown to be associated with lower hospital mortality.

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CHAPTER 2

CHRONIC NURSING IN HOSPITALS

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1. Introduction

Chronic diseases are diseases of long duration with slow progression. Main chronic diseases are cardiovascular diseases, cancers, chronic respiratory diseases and diabetes. The related epidemiological data is alarming at global scale (Domnariu, 2011). The prevalence of chronic diseases has increased during last decades (Wilkins et al., 2019). Chronic diseases such as heart disease, cancer and diabet are the leading cause of death worldwide and are emerging as 'epidemic of the twentyfirst century'. For nursing students and health professionals, acquiring the knowledge and skills needed to work with people with a chronic illness and/or disability is vital to providing quality competent care (Chang & Johnson, 2014). Heart disease, stroke, diabetes, cancer, chronic respiratory disease are often comorbid with mental illness. Comorbid mental illness and physical illness worsens health compared to alone or any of the chronic diseases alone. Self-management and self-righting are now being considered integral to reduce the negative impact of mental illness. Personal characteristics associated with resilience comprise optimism, an active or adaptable coping style and the ability toelicit social support. Existing resilience factors can be assessed forby nurses and optimised through interventions when patients with chronic conditions are in care. Representing over 70% of the global health workforce, nurses are well positioned to enact such practice enhancements to facilitate better outcomes for patients (Edward, 2013).

As the prevalence of chronic diseases continues to increase, attention is paid on the progresses on primary care strategies which enhance healthcare. Chronic disease management strategy implementation is not uniform across primary care practices where nurses work. There is the potential to optimize and standardize the nursing role within primary care and improve the implementation of chronic disease management strategies (Lukewich et al., 2014). Current models of chronic disease management within general practice are not meeting the needs of the community (Young et al., 2016).

The global response to the rise in prevalence of chronic disease is a focus on the way services are managed and delivered, in which nurses are seen as central in shaping patient experience (Wilson et al., 2012). Nurses in primary care organizations play a central role for patients with chronic disease. Lack of clarity in role description may be associated with underutilization of nurse competencies that could benefit the growing population of patients with chronic disease (Poitras et al., 2018). Roles of nurses in clinical nurse specialist are well positioned and ideally suited to the needs of a growing population with chronic diseases. Clinical nurse specialists with master's-level preparation provide high-quality and cost-effective care to patients with chronic diseases (Moore & McQuestion, 2012).

In the decision-making environment of evidence-based practice, the following three sources of information must be integrated: research evidence of the intervention, clinical expertise, and the patient's values. In reality, evidence-based practice usually focuses on research evidence

and clinical expertise without considering the individual patient's values. The shared decision-making model seems to be helpful in the integration of the individual patient's values in evidence-based practice. A skilled nurse with a positive attitude towards shared decision making, integrated with evidence-based practice, can facilitate the shared decision-making process (Friesen-Storms et al., 2015).

Nurses with additional skills, training, or scope of practice may help improve the primary care of patients with chronic diseases. Specialized nurses working on their own could achieve health outcomes that were similar to doctors. Specialized nurses working with doctors can reduce hospital visits and improve patient outcomes related to diabetes. Patients recieved nurse-led care are more satisfied and tended to receive more tests and medications. But it is unclear if specialized nurses improve quality of life or doctor workload (Health Quality Ontario, 2013).

Community nurse in a multidisciplinary team for chronic conditioned clients has six key role: advocate, supporter, coordinator, educator, team member and assessor. The six key role domains reaffirm the generic role and centrality of the community nurse in the team. Community nurses working in multidisciplinary teams caring for clients with chronic conditions can define their role as a team member. The working relationship of the community nurse with other health professionals in the multidisciplinary enables increased understanding and build stronger and more effective care teams (Wilkes et al., 2014).

2. Pallative and preventive care

Palliative care nursing provides care for the pain and suffering of a patient's chronic or serious illness. Hospital-based nurses need to be equipped with palliative care nursing knowledge to provide optimal care for patients and their families to improve the quality of life. Lack of education in pain and symptom management and communication can result in an inefficient and costly care. Palliative nursing education is needed to be included in education for nurses (Balicas, 2018). Clinical nursing process recording is an effective tool to facilitate teaching and learning in nursing (Chao & Chiang, 2017).

Self-management is a chronic pain treatment modality and mainly provided in the primary care. Nurses are optimally suited to facilitate self-management in primary care (Lukewich et al., 2015). Primary health care nurses provide an increasing amount of chronic disease management and preventive lifestyle advice. Lifestyle interventions delivered by nurses in primary health care positively affect blood pressure, weight, cholesterol, dietary behaviours, physical activity behaviours, readiness for change, patient satisfaction and quality of life (Sargent et al., 2012).

The expansion of primary care and community-based service delivery systems meet emerging needs, reduce hospital-based ambulatory care costs and prevent avoidable hospital use. Many studies were determined that nurses promote health and deliver preventive programs more compared to other health professionals within primary care (Massimi et al., 2017). Health promotion plays an important role in the

management of diabetes and chronic kidney disease (Pham & Ziegert, 2016). However, organizational barriers such as poor practice environments prevent nurse practitioner from delivering high quality care. Efforts should be implemented to improve nurse practitioner practice environment to potentially improve care quality (Poghosyan et al., 2018).

3. Readmissions and skilled nursing facilities

Rehospitalization after discharge may load financial penalties to hospitals (Schoenfeld et al., 2016). Patients with chronic diseases often readmit to hospitals within 30 days of discharge. Studies revealed that one-third of this discharges from the hospital are not following up with their primary care provider. Identifying barriers can help to reduce rate of readmissions (Ward, 2016). Readmission within 30 days of discharge is a quality parameter representing potentially preventable adverse outcome. Many readmission reduction program were proposed and implemented in past. Coordination of care can play a major role to lower readmissions. A hospital-based skilled nursing facility in a hospital help improving care for patients needing short-term skilled nursing or rehabilitation services. Higher skilled nursing facility to hospitals ratio in the region was associated with lower readmission rates in the study of Gupta et al., (2019). Skilled nursing facilities approach may reduce excess thirty-day readmissions and avoid penalties and costs (McHugh et al., 2017). The goal of the skilled nursing facility is to help clients to stabilize their medical conditions and attain their therapy goals so that they can return home. Patients discharged to a

skilled nursing facility for post-acute care have a high risk of hospital readmission (Chandra et al., 2019). Specially trained nurses can provide care at least equivalent to care provided by physicians at chronic diseases for process of care (Martínez-Gonzalez et al., 2015).

4. Stigmatization

Understanding the social utility of stigmatization in preserving social cohesion and protecting the social order is an important function. However, this process can be harmful when applied to persons with chronic illness, such as HIV-AIDS, and psychiatric illness. These individuals often become shamed, ostracized, isolated, discredited, and socially and economically marginalized. Recent theoretical work on stigma has identified several issues and patient responses that may have implications in many other chronic conditions. Stigma is based on visible or nonvisible health conditions and can be both externally imposed or perceived in a process of self-stigma. Understanding stigma can aid clinicians in providing supportive help for patients with chronic illness. Recognizing the underlying social factors has potential use in health-promoting behaviors. Sensitivity to stigma allows health professionals to critically reflect on ways the healthcare environment may add to stigma for their patients (Engebretson, 2013).

Cancer patients' pain is related to the tumor, to diagnostic and therapeutic procedures and to the terminality of the disease; however health professionals, especially nursing teams, still have difficulties in evaluating and managing pain. As from experience in hospitals, it was noticed that nursing teams face barriers, which is intensified in case of

cancer patients, marked by the "incurable" cancer pain stigma (Oliveira et al., 2016).

5. Patient monitoring

Recommendations for rheumatology nursing management of chronic inflammatory arthritis from European League Against Rheumatism states that nurses should take part in the monitoring patients' disease and therapy in order to achieve cost savings. This could free resources for more intensive monitoring of patients early in the disease or patients with high disease activity (Larsson et al., 2015).

6. Conclusions

Skills are needed at health professionals to work with people with a chronic illness. Nurses with additional skills, training, or scope of practice may help improve the primary care of patients with chronic diseases. Palliative care nursing provides care for the pain and suffering of a patient's chronic or serious illness. Nurses are optimally suited to facilitate self-management in primary care. Nurses promote health and deliver preventive programs more compared to other health professionals within primary care. Skilled nursing facilities approach may reduce excess thirty-day readmissions and avoid penalties and costs. Nurses should take part in the monitoring patients' disease and therapy in order to achieve cost savings.

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CHAPTER 3

THE IMPORTANCE OF SPHINGOLIPIDS IN HUMAN DISEASES

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INTRODUCTION

The plasma membrane found in all cells (eukaryote, prokaryote, viruses) which provides separated from external environment and determined boundaries. Lipids are macromolecules one of the members of the plasma membrane. Cellular structure, generate energy, provide signal transmission are protected by the lipids in all cells (Bal et al., 2018). According to the International Lipid Classification and Nomenclature Committee, eight categories for lipids including sphingolipids, glycerolipids, glycerophospholipids, fatty acids, prenol lipids, saccharolipids, polyketides, and sterol lipids can be given (Fahy et al., 2009). Sphingolipids are a subclass of lipids and are widely studied in human diseases. In addition, sphingolipids that play a role in protecting the membrane structure, are known as building blocks of eukaryotic membranes. (Bal et al., 2018). The characterization of sphingolipids is supplied with a sphingoid base of the hydrophobic part of the molecule. Sphingolipids are amphipathic molecules. They have various hydrophilic and hydrophobic parts. The hydrophobic part consists of 18 carbon long, sphingoid base attaches to the fatty acid via an amide bond, while the hydrophilic part consists of the hydroxy group, phosphate, alcohol groups or sugars take a part in the more complex sphingolipids. (Coant et al., 2017).

Sphingolipid mechanism has several metabolites such as ceramide, sphingosine 1 phosphate, sphingosine, sphingomyelin etc.. Furthermore, sphingolipid metabolites have appeared as intermediaries of significant signaling chains liable for the regulation

of diverse cellular processes (Gupta et al., 2019). Ceramide, sphingosine-1-phosphate (S1P), and sphingosine are main components between the sphingosine metabolites (Ponnusamy et al., 2010; Gupta et al., 2019). Ceramide and sphingosine are pro-apoptotic molecules which are induced apoptosis and mediating molecule for stopped the cell cycle (Saddoughi et al., 2008; Hait and Maiti, 2017). On the other hand, S1P supports cell proliferation and survival. Sphingolipid-rheostat is formed by a balance via intracellular levels and opposite sphingosine metabolites (Gupta et al., 2019; Haass et al., 2017). Modulation of rheostat to promote the levels of ceramide or sphingosine could be accepted as a therapeutic strategy. Sphingosine kinase (SphK) is known as main regulators of this rheostat as it produces S1P from sphingosine and thus reduces sphingosine and ceramide levels (Gupta et al., 2019; Haass et al., 2017). The alterations in sphingolipid metabolism and changing their rheostat give rise many of human diseases. (Wendeler et al., 2005). In addition to the importance of sphingolipids in membrane structure, they also act as signaling molecules (Chalfant et al., 2011).

In summary, sphingolipids are significant components to straighten a broad spectrum of cellular processes that is widely seen as one of the main advantages over the past 20 years. Thus, this chapter introduce to the sphingolipid metabolism and includes the importance of sphingolipids on some human diseases such as cancer, neurodegenerative diseases, lysosomal storage diseases, viral infection.

1. THE UNDERSTANDING OF SPHINGOLIPID MECHANISMS

Sphingolipid metabolism is an important cellular event and a highly coordinated process. It is evidence that sphingolipid metabolism is linked to various diseases. Sphingolipid metabolism and their intermediate metabolites are closely related to the bioactivities of sphingolipids (Wang et al., 2021). Ceramides that regulate key metabolic functions are known as central of sphingolipid metabolism (Custodia et al., 2021). All sphingolipids such as Cer, S1P and C1P are related to natural sphingolipids or bioactive metabolites that are important for cell signaling and pathological functions. Great progress has been played a role in elucidating sphingolipid metabolism in physiology and disease. Especially, many advantages have been obtained in identifying the related enzymes in sphingolipid metabolism, their structures, and action mechanisms in recent years (Hannun and Obeid, 2008). The structures of some sphingolipids are given in Figure 1.

Throughout the structures, sphingosine and sphingosine-1-phosphate have 18 carbons on the structure and they include hydroxy and phosphate groups, respectively, as well as amine group. In contrast to these molecules, ceramide contains a sphingosine backbone and fatty acid, that has saturated group. Therefore, a main class of molecules is called as ceramide. When sugar ring is added to the structure, it is termed as glycoceramides. In sphingomyelin structure, there is a phosphorylcholine moiety is linked to the terminal hydroxyl group of

ceramide.

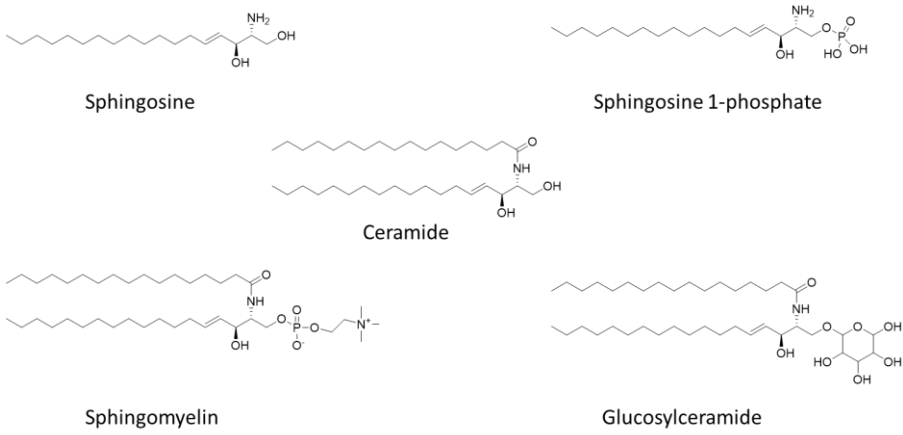

Figure 1. The structures of some sphingolipids (redrawn from Beckmann and Becker, 2021)

According to the sphingolipid mechanism, ceramide synthesis occurs in several pathways. De novo synthesis of ceramide is accomplished by the addition of serine and palmitoyl CoA. Ceramide can turn to other bioactive molecules including sphingosine, sphingosine-1-phosphate, and glycoceramide via related enzymes. Ceramide uses acyltransferase to obtain acylceramide. Ceramide-1-phosphate (CP1) and sphingomyelin are produced from ceramide by reversible mechanism. As is seen, ceramide, sphingosine, and sphingosine-1-phosphate are bioactive components to be used in several cellular processes (Wu et al., 2021). The sphingolipid metabolism is given in Figure 2.

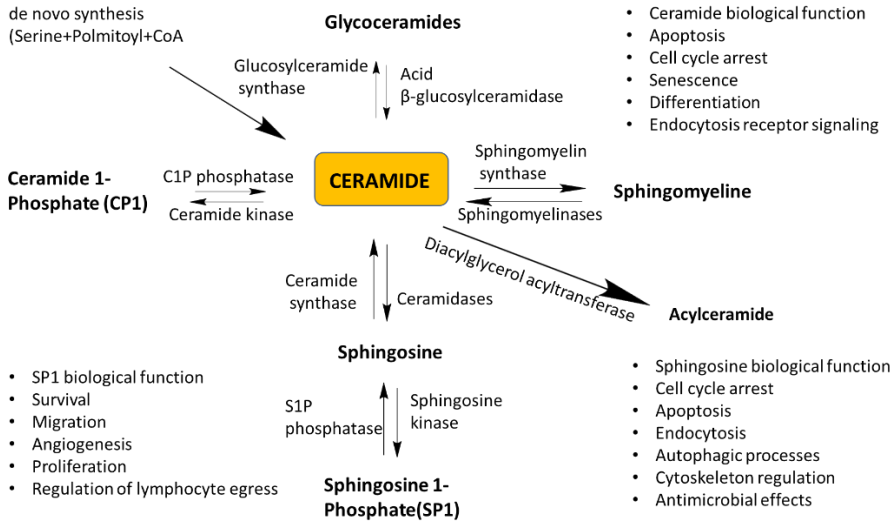

Figure 2. Sphingolipid metabolism and their biological functions.

2. THE ROLE OF SPHINGOLIPIDS IN HUMAN DISEASES

2.1. Sphingolipids in Neurodegenerative Diseases (ND)

Lipids possess a crucial role in various diseases including neurodegeneration and neuroinflammation. Sphingolipids that are conserved were discovered in the brain a century ago. Therefore, their names such as gangliosides, sphingomyelins, and cerebrosides were derived from original resource to isolation. Due to the abundance of sphingolipids in the brain where the specificity of cell type depends on aging and pathological alterations in the brain, the unbalance in levels of sphingolipid is regarded with diseases. It was reported that the metabolic modifications of gangliosides were associated with neurodegeneration. According to the recent studies, ceramide and S1P that are bioactive metabolic intermediate of ganglioside and sphingomyelin, play an important role to maintenance of brain health

(van Kruining et al., 2020). For instance, it was showed that the brain malformations were depended on inborn mutated S1P-lyase. (Bamborschke et al., 2018). S1P is generated by sphingosine phosphorylation such as two kinases sphingosine kinases 1 and 2 (SK1 and SK2). When SK2 is mislocalization, it results with neurodegenerative diseases (Dominguez et al., 2018).

Taken together, neurodegenerative diseases including alzheimer's disease (AD), Parkinson's disease, Huntington's disease are main problems affecting human health. There has been an increasing interest to sphingolipid metabolism and neurological diseases thus, modern techniques can help o measure sphingolipids with high specificity in the brain (van Kruining et al., 2020).

2.1.1. Alzheimer's Disease (AD)

Alzheimer's disease (AD) is a neurodegenerative disorder and known as a widespread form of dementia (Hirbod et al., 2017). AD is observed on more than 15 million people in the worldwide and it is estimated that this number may increase concerning with life span (Tehrani et al., 2019). The recent studies showed that AD is affected abnormal sphingolipid metabolism. On the other hand, Aβ production in neurons speeds with increased de novo synthesis for ceramide and thus it is resulted with the high amounts of ceramide in the brain. In addition, the connection between plasma ceramides and dementia is reported with clinical studies (Mielke et al., 2017 and Bouscary et al., 2021). Hippocampal volume loss is associated with the high plasma

ceramides in some of the studies. According to these, brain and the levels of plasma ceramides change at early stage of AD. (Kim et al., 2017). Moreover, in sphingolipid metabolism, potential targets including sphingomyelin, sphingosine, sphingomyelinase, SK1 are found and given in Table 1.

Table 1. Brain Sphingolipid Level Changes in Neurodegenerative Diseases.

Sphingolipids	**Hungtington's Disease**	**Alzhemimer's Disease**	**Parkinson's Disease**
Sphingosine	**NA**	**Up** He et al., 2010	**NA**
Sphingosine 1-phosphate	**Down** Di Pardo et al., 2017a	**Down** He et al., 2010	**Down** Sivasubramanian et al., 2015
Ceramides	**Up** Di Pardo et al., 2017a	**Up** Cutler et al., 2004	Down Abbott et al., 2014
Sphingomyelin	**NA**	**Down** He et al., 2010	**Down** Abbott et al., 2014
Ganglioside GM 1	**Down** Alpaugh et al., 2017	**Up** Kracun et al.,2002	**Down** Wu et al., 2012
Ganglioside GM 3	**NA**	**Up** Kracun et al., 2002	**NA**
Sphingolipids Enzymes			
Sphingosine kinase 1(SK 1)	**Down** Di Pardo et al., 2017a	**Down** Ceccom et al., 2014	**Down** Motyl and Strosznajder, 2018
Sphingosine kinase 2(SK 2)	**Unchanged** Di Pardo et al., 2017a	**Down** Dominguez et al., 2018	**Down** Sivasubramanian et al., 2015

*Up: upregulated; Down: downregulated; NA: Not available

For instance, the activity of γ-secretase is inhibited by the high levels of sphingomyelin and thus, Aβ accumulation decreases (Zinser et al., 2007). Sphingomyelinase activity is supported by Aβ in AD to cause ceramide increase in the brain. Even though ceramide turn to sphingosine, increased levels of sphingosine is detected in the brain. (He et al., 2010).

Gangliosides are formed 6% of the total lipids and in AD the levels of ganglioside GM1 increase and affect Aβ-plaques (Grimm et al., 2012). Gangliosides contain a sphingoid base (18-20 carbon). C18 and C20 gangliosides are found the nervous system and localized within the central nervous system (CNS), respectively (van Kruining et al., 2020). The researchers have been indicated that alterations of diseases in brain concentration in the animal and human models. It can be understood that the abnormalities in lipid metabolism in AD are studied by useful tools mouse models (Chan et al., 2012).

2.1.2. Parkinson's Disease (PD)

PD that contains the symptoms such as loss of postural reflexes, bradykinesia, rigidity, tremor, and cognitive decline, is a widespread encoured neurogenerative disease after AD. PD affects the population over 60 years of age with a higher risk in males (Custodia et al., 2021). On the contrary, PD is comparatively new to subtlety lipids. The researchers have been focused on α-synuclein and the effect of its toxicity. The results show that lipid homeostasis is affected and observed neurotoxicity (Fanning et al. 2019 and Lin et al., 2019).

Sphingolipids have a role for the development of PD. Glucocerebrosidase has been associated with Lewy body dementia and sporadic PD. In addition, ceramide and sphingomyelin exhibit unusual metabolism in PD autopsy brain tissue and increased various ceramide species has been observed in the PD patient's plasma (Abbott et al., 2014). The reduced levels of gangliosides (GM1) have been determined in the disease. Fingolimod that affects to S1P receptor, can be a modulator for PD patients (van Kruining et al., 2020). According to five-year open study, long-term application of GM1 has been approved for its safety in humans (Schneider et al., 2010). As a result, there is a need to understand the role of sphingolipids.

2.1.3. Huntington's Disease (HD)

HD is a hereditary neurodegenerative disorder (Di Pardo and Maglione, 2018). It is resulted with the heart damage, pneumonia, and lifespan decline. HD occurs with CAG triplet repeat in Huntington (HTT) gene (Di Pardo et al., 2020). In contrast to AD and PD, recently, sphingolipid metabolism including gangliosides and S1P pathway in HD has been interested by the researchers. The up- and down-regulated levels of S1P Lyase1 and SK1 have been reported for advanced HD (Di Pardo et al., 2017a). Although the levels of ceramide and S1P Lyase 1 have been increased at early stage of HD, the expression of SK1 and SK2 has been not showed the differences. These results showed that S1P metabolism is affected in HD. Fingolimod has been used for therapeutic strategy in various studies

(Di Pardo et al., 2014). The alterations of S1P may be a potential drug target for further studies (Di Pardo and Maglione, 2018). In the previous studies, disturb ganglioside metabolism in HD has been reported (Alpaugh et al., 2017). Decreased levels of ganglioside GM1 has been determined in fibroblasts from HD patients (Maglione et al., 2010). According to the recently reported study, sphingolipid metabolism has been disrupted at the early phase of disease in HD mice intestinal tract and then, intestinal integrity and homeostasis are maintained by K6PC-5, a selective activator of the synthesis of S1P (Di Pardo et al., 2020). As a result, the alterations S1P metabolism and decreased level of S1P in brain tissue of animal models contribute to the pathogenesis and progression of the disease (Di Pardo and Maglione, 2018).

2.2. Multiple Sclerosis (MS)

MS is an inflammatory disease, is concerned with autoimmunity (Podbielska et al., 2018). It is estimated that this disease prominently affects women. According to the sphingolipid-based studies in MS, the roles of ceramides, sphingosine, and SP1 are investigated due to the myelination process (Podbielska et al., 2018). Although ceramide species take a part in neurodegenerative diseases like AD, sphingosine is related to MS. Sphingosine accumulate in MS brain. It has been proposed that the process of myelination is affected by the sphingolipids at the early stage of the development of the brain (van Kruining et al., 2020). Additionally, ceramide and sphingosine have a role in CNS demyelination process (Podbielska et al., 2018).

Otherwise, S1P receptors may be a substantial for de- and re-myelination. The hyperactivation of sphingomyelin/ceramide/ sphingosine/S1P pathway is proposed as fundamental mechanism resulted with the increased and decreased levels of phospholipids and sphingolipids, respectively, in MS (Wheeler et al., 2008). The most important property of MS is the breakdown of neuronal myelin sheets. Due to high amounts of sphingolipids in myelin sheets, there has been an interesting interest to understand the role of sphingolipids in demyelination. De novo sphingosine biosynthesis activation affects the toxicity of sphingosine in MS (van Kruining et al., 2020).

2.3. Lisosomal Storage Diseases

Approximately fifty lysosomal storage diseases are known and they are characterized by various lipids and sugars accumulation in the endolysosomal compartment. These diseases are generally named as sphingolipidoses that contain a main disease caused in sphingolipid degradation pathway. These diseases cause the degradation of membrane and thus, cell growth and survival like neural cells are affected. Consequently, neurodegeneration is an important feature for the most sphingolipidoses. In addition, sphingolipidoses show many clinical manifestations in various organ systems. For instance, some of these diseases are affected to cardiovascular system. GM1 gangliosidosis shows cardiovascular lesions and Fabry disease affects cardiovascular system (Rabbo et al., 2021). Fabry's, Gaucher's, Sandhoff's, and Tay-Sachs’ diseases can be exemplified as major sphingolipidoses. Besides Niemann-Pick (NP) family diseases belong

to this group. In these NP family, it was discovered in 1980 by Vanier and coworkers although sphingomyelinase activity is normal in Type C, Types A and B are resulted from defects in sphingomyelinase (Newton et al., 2018). Due to the build of sphingolipid metabolism and potency of bioactive metabolites including sphingosine-1-phosphate (S1P), sphingosine, and ceramide, that was proposed to discover of sphingolipids in NPC context to understand (Lloyd-Evans and Platt, 2010). Gaucher disease (GD) is a hereditary disorder. GBA1 gene mutations cause inadequate the activity of β-glucocerebrosidase and glucosylceramide accumulation (Brady et al., 1965). Farber's lipogranulomatosis is occurred by ASAH1 gene mutations that acid ceramidase is expressed. Ceramide is hydrolyzed by acid ceramidase with the help of SapC or SapD (Kolter and Sandhoff, 2006). The lack of enzyme cause to the accumulation of Cer. (Fabian et al., 2018). GM1-β-galactosidase (β-gal) is supported by GM2A or SapB to catalyze the obstruction of GM1 to GM2 (Kolter and Sandhoff, 2006). The deficiency of an enzyme can cause to GM1 gangliosidosis (Caciotti et al., 2011). For instance, because of the high amounts of containing sialic acid GM1 and GM2 in the brain, the neural dysfunction observes in GM1 and GM2 **(**Sandhoff and Harzer, 2013) (Vajn et al., 2013). Lysosomal disorders sphingolipidoses are given in below Table 2.

Table 2. Lysosomal Disorders Sphingolipidoses are Associated with Sphingolipids.

Lysosomal Disorders **Sphingolipidoses**	**Sphingolipids**	**References**
Gaucher disease	Glucosylceramide	Brady et al., 1965
Niemann-Pick disease	Sphingomyelinase (Type A and Type B)	Vanier et al., 1980
Niemann-Pick disease	Ceramide, sphingosine, S1P (Type C)	Lloyd-Evans and Platt, 2010
Fabry disease	Ceramide	Fabian et al., 2018
Gangliosidosis	Glycosphingolipids	Vajn et al., 2013

2.4. Sphingolipids and Cancer

Cancer disease is known as the second death cause in the worldwide after cardiovascular disease. Therefore, the researchers show an increasing interest to understand the mechanism of cancer. Aberrations in sphingolipids, S1P, gangliosides, and ceramide are related with many steps in cancer progression and response (Canals and Hannun, 2013). For instance, the alterations of phospholipids and sphingolipid composition attend to the progression and development of colon cancer. The lipid levels of various species have been determined to be changed in cancerous tissues. Alterations of sphingolipid levels in colon cancer have been obtained by *in vivo* and some clinical studies (Machala et al.,2019). In one of the studies, it is

indicated that cell growth and apoptosis are induced by ceramide and sphingosine and cell proliferation and survival are promoted by S1P (Gupta et al., 2021). The accumulation of ceramides in subcellular localization in mammalian cells may take a role in the motility, apoptosis (Birbes et al., 2002) and cell cycle arrest. Many cancer cells and models have been exemplified with important the changings in the enzymes taking a part in the generation or degradation of ceramide. Additionally, the alterations in sphingosine metabolism have been observed in cancer. Due to the sphingolipid metabolism take a part in multiple biological processes, that is reported it is reviewed to be crucial for the progression, development, and drug-resistance of ovarian cancer (Kreitzburg et al, 2018). S1P induces invasion, migration etc.. The related enzymes that catalyze S1P were determined with the high expression levels in various types of cancers (Canals and Hannun, 2013). The synthesis of S1P from sphingosine is catalyzed by sphingosine kinase (SphK) that is a key regulator of this balance called as sphingolipid rheostat. The cell cycle arrest is supported by the high levels of ceramide. SphK upregulation and the accumulation of S1P in the cells are related with various diseases such as diabetes, AD, atherosclerosis, cancer, and inflammatory disorders (Gupta et al., 2021). Miura and coworkers have been reported the relationship between sphingolipids and human hepatocellular carcinoma (HCC). The findings propose that S1P possess a significant role in HCC tumor progression compared to ceramide (Miura et al.,2021). The functions of glycosphingolipids contain cell adhesion and motility. Therefore, sphingolipids contribute to regulate cancer

cells and their enzymes are used as drug targets (Canals and Hannun, 2013).

2.5. Sphingolipids and Viral Infection

Viruses that control and interact with the host, are intracellular pathogens and also, they use cell membranes and their components. In addition, the interaction with cell membranes plays a crucial role for the steps of viral replication cycle (Schneider-Schaulies et al., 2021). It is an important that lipid composition such as sphingolipids is effectively modulated by the viruses to complete of the viral life cycle. Due to the bioactive properties of some sphingolipids, they take a part in cellular signaling processes related to regulate viral replication. It is indicated that human immunodeficiency virus (HIV), sindbis virus (SINV), Ebola virus (EBOV), measles virus (MV), and rhinovirus display sphingolipid-dependent virus input that activate sphingomyelinases and use ceramides (Wu et al., 2021).

Viruses have often taken their place in the literature as a threat to human health, from the past to the present. Sphingolipid metabolism is important for viral infections like other diseases. For instance, inhibition of viral replication and prevent infection by targeting hepatitis C virus (HCV) sphingolipid metabolism was reported by Sakamoto et al for the first time (Sakamoto et al., 2005). Lipid metabolism is quite affected by Hepatitis C virus and according to the studies on patients, the quantification of serum sphingolipid alterations in acute HCV infected patients was reported that the levels

of sphingosine and sphinganine are highly upregulated (Sakamoto et al., 2005). It was reported for the first time that the spread of herpes simplex virus type 1 (HSV-1) that is an envelope DNA virus in macrophages was blocked (Lang et al., 2020). The restraint of HSV-1 reproduction was correlated with ceramidase (Karasneh and Shukla, 2011). The lack of ceramidase shows the HSV-1 uncontrolled replication.

Coronavirus disease (COVID-19) is a pandemic that started in 2019 in China caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (Torretta et al., 2021). Recently, some of the researchers have indicated that the role of lipid raft components that include cholesterol and sphingolipids to facilitate the interaction with the viral spike protein, in the infection of SARS-CoV-2 of host cells (Fantini et al., 2020; Sorice et al., 2020). Sphingosine has been reported against infection with SARS-CoV-2 in one of the important studies (Edwards et al., 2020). The interaction of low concentration sphingosine and ACE2 can be blocked when the cells are pretreated with exogenous sphingosine. Providing that sphingosine possess a direct antiviral effect on SARS-CoV-2 or HSV-1 is still unknown (Wu et al., 2021). The illustration of the interaction between sphingosine and SARS-CoV-2 is given in Figure 3. Also, related sphingolipids for viruses are given in Table 3.

Some of the studies showed that a sphingosine analog, fingolimod (FTY720) as sphingolipid-based drug may be used to prevent serious SARS-CoV-2 neurological side effects (Tasat and Yakisich, 2021).

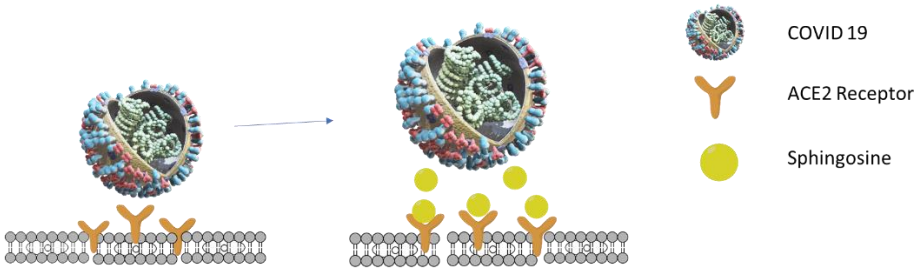

Figure 3. The illustration of sphingosine and SARS-CoV-2 infection

Table 3. Viruses Using Sphingolipids.

Viruses	**Sphingolipid metabolism**	**Reference**
Severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2)	ACE2 in lipid rafts	Lu et al., 2008
Hepatitis C virüs (HCV)	Viral sphingomyelin required for internalization	Aizaki et al., 2008
Norovirus GII.4	GalCer	Bally et al., 2012
Simian virüs 40 (SV40)	N-glycolyl GM1, GM1	Campanero-Rhodes et al., 2007
Rubella virus	SM and cholestrol	Otsuki et al., 2017
Human immunodefiency virüsType I (HIV-1)	GalCer, SMS2, GM3, Gb3	Hayashi et al., 2014
Ebola virüs (EBOV)	SM rich region	Miller et al., 2012
Influenza A virüs (IAV)	GalCer	Suzuki et al., 1996
Human parvovirus B19(B19V)	Gb4Cer	Quattrocchi et al., 2012
Rotavirus	Pentaosylceramides, GA1, GA2	Martinez et al.,2013
Rhinovirus	Ceramide-enriched platforms	Grassmé et al., 2005

CONCLUSION

Sphingolipid metabolism and bioactive metabolites have a great role in multiple cellular processes. According to the literature findings, the importance of sphingolipids for human health is clearly demonstrated. Therefore, sphingolipid metabolism may be an important candidate to become one of the major pathways of related human diseases. Although there are many studies on sphingolipids in the literature, we may recommend further studies to understand the sphingolipid-based action mechanisms in human diseases and to find new avenue and therapeutics.

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CHAPTER 4

CYTOKINES

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1. INTRODUCTION

Cytokines are small molecular weight (~5-20 kDa) soluble proteins that are released into the circulation by immune system cells and have specific effects on intercellular interplays and connections. Cytokine is a generic name, other names include lymphokine, monokine, chemokine, and interleukin. Cytokines can act on cells that secrete them, on in one's hearing cells, or in some cases on faraway cells. Cytokines are involved in the regulation of responses in the immune system. With these effects, they play a role in protective immune and inflammatory response and tissue healing against factors that cannot be noticed by the eye. The main types of cytokines; interleukins (IL), lymphokines, chemokines, tumor necrosis factor (TNF). There are also many types of cytokines that usually do not include hormones and growth factors. All of these types of cytokines are produced from B and T lymphocytes, macrophages and mast cells. It can also be produced by numerous cell groups, including immune cells as well as endothelial cells, fibroblasts and different stromal cells (1 -3). Cytokines are usually released in response to stimulation. They are not stored in the body. Cytokines show their effects by acting on the cells that give themselves to the circulation and the cells nearby. They can cause systemic effects that spread throughout the body in severe disease states where they are secreted in high amounts, called cytokine storm. The number of these receptors may decrease or increase depending on the state of the stimulus (4). The cytokines that are important in the inflammatory response are called "proinflammatory

cytokines". Innate immune system cells such as monocytes, macrophages and dendritic cells; such as TNF-α, IL-1, IL-6, IL-10, IL-12, IL-15, IL-18, IL-23, IL-27, type 1 interferons (IFN-α, IFN-β) and chemokines cytokines are released. IL-2, IL-5, IL-17, IFN-γ, TNF-α cytokines are secreted from acquired immune system cells (especially T lymphocytes). Chemokines are also from the family of cytokines, and they cause leukocytes and stem cells to perform chemotaxis in inflammation and homeostasis. Chemokines are heparin-binding proteins. Chemokines regulate leukocyte migration. In addition to these effects, they are also involved in the realization of processes such as leukocyte degranulation and angiogenesis. Chemokines have important effects on many biological processes occurring in the organism (5, 6). While the immune system creates an immune response against many microorganisms that enter the body, it does not respond to its own antigens. The fact that it does not form antibodies against its own antigens is a physiological feature and is the most important mechanism for the continuation of life. Autoimmune diseases; It occurs as a result of the body's immune system responding to its own antigenic structures. Cytokines; It is secreted by the cells of the natural and acquired immune system and cells in the tissue in the occurrence of these diseases and plays a role in intercellular communication (1).

Main features of cytokines (7,8)

- They are effective in wound healing,

- They are effective in the development of the nervous system and embryogenesis,
- By activating the cells involved in inflammation, they enable these cells to come to the reaction area,
- They cause differentiation and proliferation of lymphatic system and some other cells,
- They provide hematopoietic regulation with their effect on the bone marrow,
- They show antiviral activity,
- They take part in the synthesis and release of some hormones secreted from the pituitary gland,
- While it causes shock and death at high concentrations, it causes general infection findings such as muscle pain, headache, fever and acute phase response at low concentrations.

Cytokines with Proinflammatory Effect

Proinflammatory cytokines; It consists of interferons, TNF, IL-1, and IL-6. It has many biological activities. Regulates many genes expressed in inflammation (9). IL-1 is synthesized by monocytes, macrophages, lymphocytes, neutrophils and fibroblasts and activated mononuclear phagocytes in the tissue. It can also be synthesized by many different cells when stimulated, including keratinocytes, endothelial cells (10).

Cytokines with Inflammatory Effect

IFN- α: Has anti-diabetogenic effect when applied systemically (11). IFN-β: Natural Killer (Nκ) causes innate immunity increase with cell and fibroblast activation. (12). IFN- γ: Causes immune response regulation, phagocytic cell activation and increased cellular immunity. Causes suppression of humoral immunity and inhibition of B lymphocytes (11). TNF- α and β: They constitute an important mediator of the acute response in cases of infection. It is a very important cytokine in gram (-) infections. Shock and Disseminated Intravascular Coagulation are seen with increased secretion of IL-1 and IL-6 (11).

Essential Anti-Inflammatory Cytokines (8, 13)

- IL-1: It causes fever and provides acute phase protein synthesis,
- IL-2: Natural Killer (Nκ) cytolytic activity increase,
- IL-3: Multi Colony stimulating factor,
- IL-4: Ig heavy chain class change in B lymphocyte,
- IL-5: Antihelminthic effect and eosinophilia,
- IL-6: B lymphocyte proliferation-differentiation, Ig production. Fever is most important in acute phase protein production,IL-10: Sitokin sentezini inhibe eden faktör
- IL-12: The strongest stimulus for Nκ,
- Growth factor in T lymphocytes,
- Transforming growth factor – α (TGF- α)

Chemokines (6, 14)

- They are generally made by leukocytes and cells in tissues,
- They allow leukocytes to collect at the infection site,
- They take part in allergic reactions, organ and tissue rejection,
- They take part in the prevention of metastases of tumor cells,
- IL-8: They cause chemotaxis by neutrophil activation,
- They cause inhibition of T and B lymphocytes,
- In T cells; are suppressive,
- They play a regulatory role from the production of lymphocytes in the bone marrow to secondary lymphoid organs.
- TGF- β : It shows anti-cytokine effect,
- They take part in immune response suppression,
- They are effective in wound healing with fibroblast proliferation,
- They take part in mucosal immunity with IgA antibody conversion,
- They cause endothelial cell proliferation,
- G-CSF (Granulocyte colony stimulating factor),
- GM-CSF: It causes the division of bone marrow cells and thus the formation of mature leukocytes.
- M-CSF (Macrophage colony stimulating factor)

Diseases Associated with Cytokines

- Cytokines; They are effective in intercellular communication, interaction of immune system cells, severity and direction of immune responses. In this way, the use of cytokines in cancer immunotherapy

is important in order to support and revitalize the immune responses that develop against the tumor. In some types of cancer, such as lymphoid and myeloid carcinoma, cytokines are secreted (15).

- Interleukins are now tested to establish the corporation, proliferation, and migration of breast cancer, affecting the invasive and metastatic profile of the disease, causing angiogenesis and tumor growth, moving as prognostic factors and even determining the survival rates of breast cancer (16).

- IL-1 is the prototypical pro-inflammatory cytokine. IL-1 was implicated as a cardiodepressant factor in septic shock, and subsequent pre-clinical and clinical staudy has defined critical roles for IL-1 in atherosclerosis, acute myocardial infarction, and heart failure. IL-1 promotes the genesis of the atherosclerotic plaque and facilitates its progression and complication (17).

- Suppression of IL-2 production during experimental Chagas' disease explaining at least in part for the comprehensive depressed situation of the immune system in infected mice (18).

- Cytokines are related in the pathogenesis of thyroid disorders working in both the immune system and directly targeting the thyroid follicular cells. Cytokines are concerned in the induction and effector phase of the immune reply and inflammation, playing a key role in the pathogenesis of autoimmune thyroid disorders (19).

- Cytokines are related in numerous physiological processes such as ovulation, menstruation and pregnancy. Evenly, they act an important role in circumstances such as preterm labour, pre-eclampsia, endometriosis and adhesion formation and reformation. Research into cytokines in normal reproductive processes as well as diseases is of circumstances importance as the likely health and therapeutic benefits are large. Observations in ovarian cancer are very interesting. In ovarian cancer, M-CSF, a cytokine, is a strong tumor marker (20, 21).

- Serum TGF-α levels of patients with hepatocellular carcinoma; shown to be higher when compared to patients with hepatitis or cirrhosis (22).

- IL-27 is a pleiotropic cytokine that can have immunomodulatory effects on atherosclerosis over interaction with manifold T cell subsets owing to STAT1/STAT3 pathways (23).

- Cachexia is the hypercatabolism of lipids and other carbon sources, especially proteins, in the organism and their use for their conversion into energy. Cachexia is induced by many pathological conditions, including cancers. Inflammatory responses that occur in the body against cancer include the synthesis of cytokines, including IL-6 and related cytokines (24).

- In a study of COVID-19 patients, they identified for the first time distinctive features of lymphocyte subgroups, cytokine profiles, and time-dependent variation of lymphopenia. They reported that a marked decrease in CD8+T lymphocyte counts and an increase in

cytokine levels (such as IL-6, IL-10) are specific to severe COVID-19 patients (2).

- Inflammatory responses in the central and peripheral nervous systems play a very important role in the emergence and persistence of many pathological pain conditions. Particular inflammatory cytokines in spinal cord, dorsal root ganglion, wrecked nerve or skin are conversant to be associated with pain actions and with the generation of abnormal spontaneous activity from injured nerve fibers or compressed/inflamed dorsal root ganglion neurons (3, 25).

- Cytokines and their receptors are produced in organisms under physiological and pathological conditions; They are closely related to breast cancer metastasis. It shows that cytokines and growth factors are important in the induction of breast cancer metastasis. TGF- α levels are almost always elevated in breast cancer, regardless of stage (26, 27).

2. CONCLUSION

The levels of cytokines increase in many diseases, especially in autoimmune and inflammatory diseases.

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CHAPTER 5

RELATIONSHİP OF PARAOXONASE WITH CARDIOVASCULAR DISEASES

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1. INTRODUCTION

Cardiovascular diseases (CVD) industry is more common in developed countries and ranks first among the causes of mortality. CVD causes millions of deaths each year. The main factor in the development of CVD is atherosclerosis. The most important feature of atherosclerosis is the thickening and loss of flexibility of the vessel wall. Plaque formation is seen in the first place in the development of atherosclerosis. Various metabolic, inflammatory, infectious or hemodynamic factors are involved in the activation of atherosclerosis. CVD; It is one of the leading causes of death worldwide, and it is shown as the most important cause of increasing mortality and morbidity all over the world, especially in developed countries. It is known that there is a significant relationship between CVD and blood lipid levels, and increased high-density lipoproteins (HDL) have a reducing effect on the risk of CVD development. There is a significant relationship between the formation of atheroma plaque seen in CVD and high plasma levels of serum cholesterol, triglycerides and low-density lipoproteins (LDL). Knowing the causes of CVD plays an important role in early diagnosis. Paraoxonase (PON), which is in the HDL structure, prevents LDL oxidation; It is an antioxidant enzyme that reduces oxidative stress in atherosclerotic lesions, and its low activity is a risk factor for CHD (1-3).

PON; It is synthesized in the liver and given to the circulation. PON; it has both arylesterase and paraoxonase (aryldialkyl phosphatase; E.C.3.1.8.1) activity. PON; It is a calcium-dependent ester hydrolase

with a glycoprotein structure capable of hydrolyzing paraoxon, the active metabolite of parathion, an organophosphorus insecticide. Apart from parathion, PON can hydrolyze organophosphorus insecticides such as diisopropyl fluorophosphate. At the same time, it also catalyzes the hydrolysis of nerve gases such as sarin and tabun, which are from the same chemical group as organophosphorus insecticides, various carbamates, and many aromatic carboxylic acid esters (4,5). PON; It is known to take place in the HDL structure, and HDL is located on the outer surface of the cell membrane. PON; It can easily bind to HDL lipids through its hydrophobic N-terminal domain. PON; It is a protein of 354 amino acids with a molecular weight of 43 kDA. PON has two main functions. Participating in the detoxification of organophosphate-containing compounds such as paraoxone, a pesticide. Another function is to protect LDL from oxidation by hydrolyzing lipid peroxides. In addition to lipid peroxides, PON also acts on hydrogen peroxide. Therefore, it is thought to have peroxidase-like activities (6-8).

2. PARAOXONASE and CARDIOVASCULER DISEASE

The main pathology seen in atherosclerosis is formations in the intima called atheroma, which expand into the vascular lumen, weaken the media under the endothelium, prepare the ground for thrombosis. The formation of atherosclerotic plaques in the coronary arteries and narrowing of the vascular lumen and as a result of this narrowing, due to the decrease in blood flow, ischemic events and CVD, coronary heart diseases (CHD) occur in the relevant tissue. Atherosclerosis is

most commonly seen in the coronary arteries, cerebral arteries and aorta (9). Vascular endothelial damage is essential in the formation of atherosclerotic plaque. When the endothelium is damaged, the permeability of the endothelium to LDL cholesterol increases. Meanwhile, with the damage of the vascular endothelium, its antioxidant properties are lost. LDL in the intima is easily oxidized here. In the endothelium, chemotactic adhesion molecules are formed for monocytes and lymphocytes, and these cells are attracted to the intima. Here, with colony stimulating factor (CSF), monocytes proliferate, transform into macrophages and form fatty foam cells by incorporating oxidized LDL cholesterol. Extracellular lipid accumulation also begins in the intima as a result of the fragmentation of the foam cells, which grow too large by incorporating LDL cholesterol in an uncontrolled manner. Meanwhile, the smooth muscle cells in the media migrate to the intima through cytokines and growth factors secreted from the endothelium, platelets, and macrophages, where they proliferate and turn into foam cells by including oxidized LDL cholesterol. Smooth muscle cells also acquire a secretory feature and begin to synthesize and secrete proteoglycans and connective tissue elements such as collagen and chondroitin sulfate. These connective tissue elements form a fibrous sheath over the lipid pool of extracellular lipid and foam cells growing towards the lumen. The higher the blood cholesterol level in the person, the larger the lipid pool and the higher the number of monocytes and lymphocyte cells in the plaque. While monocytes cause weakening of the fibrous sheath with the matrix metalloproteinases (such as collagenase) they secrete,

lymphocytes impair the synthesis of the fibrous sheath with the IFN-y they secrete. Thrombus formed as a result of rupture of the fibrous sheath with the effect of local and systemic factors causes acute coronary events such as sudden death, acute myocardial infarction and unstable angina pectoris (9-11). (Tablo 1).

Table 1. Developmental stages of Atherosclerosis in CVD

- Chronic endothelial injury, increased permeability and adhesion - Response to injury
- Monocyte and platelet adhesion, lipid infiltration
- Accumulation of monocytes and macrophages with lipids in the intima layer
- Increase in intimal smooth muscle with chemotaxis and subsequent stimulation of growth factors
- Phagocytosis of lipids by macrophages and smooth muscle cells
- Oily streaking
- Proliferation of smooth muscle cells
- FIBROUS ATHEROME

It has been proven that there is an inverse relationship between serum PON activity and lipid peroxidation. PON reduces oxidative stress in serum and tissues and thus provides protection against CVD. PON; It

reduces the oxidation of LDL and at the same time causes the destruction of oxidized lipids on oxidized LDL and prevents their uptake by macrophages. PON; It also protects macrophages from oxidative stress. PON; It also reduces cholesterol biosynthesis of macrophages. It also increases the transport of cholesterol in macrophages to HDL via a membrane transporter, that is, the return of excess cholesterol content in macrophages to the liver. PON reduces the lipid peroxide content of macrophages; It prevents the increase of CD36 expression of macrophages and the uptake of oxidized LDL into cells. One of the basic steps of atherosclerosis, macrophages' phagocytosis of oxidized LDL through their scavenger receptors and their transformation into foam cells are prevented by PON, and in this way, its antiatherogenic effect and thus CVD occurs (12, 13). In a clinical study, it was determined that the decrease in PON activity increased carotid atherosclerosis and LDL oxidation (14). In a study on experimental animal models, it was shown that increased PON activity reduces atherosclerosis (15).

3. CONCLUSION

The results of these studies on CVD in the literature are consistent with our findings. Although it is useful to support this study with new studies, the evaluation of the activities of paraoxonase enzymes in routine biochemistry laboratories may provide evidence for the diagnosis and follow-up of CVD.

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CHAPTER 6

TELE-NURSING DURING COVID-19 OUTBREAK

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INTRODUCTION

COVID-19 first appeared on December 31, 2019 in the city of Wuhan, Hubei Province, People's Republic of China. Coronaviruses (CoV) are a large family of viruses that cause diseases ranging from the common cold to more serious diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). COVID-19 has not been previously identified in humans. From the moment it emerged, it has been on the agenda of the world in terms of the consequences it causes and the threats it poses at the global level (Üstün & Özçiftçi, 2020). With the COVID-19 pandemic, there is an unprecedented crisis at the global level. All humanity knows that nothing in the world will ever be the same as before. This process, which deeply shakes all individuals, societies and countries and affects them in multiple dimensions, is also a lesson for humanity. It has brought with it many problems to humanity. Of course, these problems have affected both the functioning of the nursing profession and the working conditions of the members of the profession (National Academies of Sciences, 2020).

1. NURSING

Nursing is a professional job based on theoretical and applied education. The practice dimension of education is called clinical teaching and it constitutes one of the complementary and cornerstones of nursing education. Clinical teaching is a learning process that focuses on working directly with patients and their problems and allows students to learn in real terms, taking into account their individual

learning needs (Lin et al., 2014; 2013; Ünsal et al., 2013; Valiee et al., 2016). The most important dimension of the fight against epidemics is the nurses who treat and care for patients and spend their shifts actively at the patient's bedside. As more data emerge about the risks associated with the outbreak, new standards should be evaluated and implemented. All nurses should be well trained in universal precautions against infection(Leblebicioğlu & Aktaş, 2020).

2. TELE-NURSING

Tele-health technologies enable nurses to serve everyone who needs care, wherever they are. Thanks to telehealth services, follow-up, and consultancy services can be provided by specialists for physical distances, those who have problems in accessing health services, or disadvantaged groups who do not have the financial and moral power to reach health services. (Toffoletto & Tello,2020). Tele-nursing is defined in many ways in the literatüre (AMA,2021; Schlachta-Fairchild et al.,2008). The International Council of Nurses (2008) defined tele-nursing as a service that enables nurses to care for rural or remote populations, communicate effectively with patients with chronic diseases, and intervene effectively in the promotion and education of healthy living (Glinkowski et al.). Tele-nursing is one of the recommended methods to improve health services in the world. By using telenursing, great information transfer can be achieved in a short time and it refers to the representation of nursing services through the application of communication technologies such as telephone, computer, and internet (Hall et al., 2015). Among the technological

devices, the telephone is a traditional device that has been widely used since the past. Since this technology is accessible to almost all patients, families can find answers to their questions with phone calls. (Chien et al., 2006). Tele-nursing is an evolving specialty with strong evidence for the benefits of its use, as demonstrated by the increase in the number of research on tele-nursing and the presence of research developed in different countries and different populations (Souza-Junior et al.,2016).

Tele-nursing increases patients' quality of life, patient care, counseling, and patients' access to treatment by providing necessary information. It reduces the cost due to the decrease in the need to go to health institutions and early detection of complications (Alpay et al., 2009).

Although tele-nursing service is a new service, it has developed rapidly in Europe and the United States and is now actively used in various healthcare services. In the follow-up of patients with post-surgical or chronic diseases who have difficulty in reaching the hospital, home patient care is provided by phone call. (Sevean et al., 2008).

3. TELE-NURSING IN PSYCHIATRY

It is known that psychiatric nurses who take an active role in the field of health use tele-health services. Following technological developments and using information systems are among the roles of nurses. Communication is the basis of tele-nursing applications. Tele-nursing is compatible with the therapeutic communication skills of psychiatric nurses (Özgüç & Tanrıverdi, 2019).

In the study of Uslu and Buldukoğlu, it is stated that tele-nursing services have positive effects on schizophrenia patients. It has been observed that patients with schizophrenia spend more time in social environments after tele-nursing services, reduce the time spent in the hospital, and re-admissions to the hospital after discharge. In the study conducted by Uslu and Buldukoğlu, it was underlined that tele-nursing services gave positive results and was an effective method. (Uslu & Buldukoğlu, 2016). In a study conducted by Özkan et al., it was stated that after the post-discharge tele-nursing services of schizophrenia patients, treatment compliance and returning to social life increased in patients (Özkan et al., 2013). In a similar study by Montes et al. (2011) it was found that tele-nursing services provided to schizophrenia patients after discharge increased the patient's adherence to treatment (Montes et al., 2011).

In recent studies, there was no significant difference between face-to-face psychiatric interviews and tele-psychiatry interviews. It was stated that access to health services became easier with tele-psychiatry, a 25% decrease in hospitalization rates with regular meetings, and a decrease in health expenditures. Positive responses were obtained in psychiatric patients with attention deficit, hyperactivity disorder, panic disorder and agoraphobia in children and adolescents (Hilty et al., 2013; Malhotra et al., 2013).

Tele-psychiatry provides easy access and quality service to patients whose income is low. With tele-psychiatry, it is easier to reach bedridden patients. With tele-psychiatry, it is possible to reach more

patients and increase the number of mentally healthy individuals. With tele-psychiatry, more attention is paid to the privacy of the patients and stigma is prevented. It facilitates access to psychotherapies for individuals with psychiatric illness. It is a useful application in situations where face-to-face therapy is not possible. It provides alleviation of personnel shortage in health services. It offers children and adolescents the opportunity for spiritual development in various environments without harming their social lives. (Deslich et al., 2013; Özgüç & Tanrıverdi, 2019).

4. COVID-19 AND TELE-NURSING CARE

Given the potential capacity of tele-nursing, it is recommended that strong field studies be undertaken in this area. It is stated that the results of such studies can contribute to the rapid and serious use of tele-nursing in the care, education, support, follow-up and counseling of patients. (Kord et al., 2021). The use of tele-care associated with visits that became exceptions during the pandemic is recommended, and tele-care ensures continuity of care in the home care service. These strategies help protect the functional capacity of the elderly, control the stress of caregivers and take social isolation measures (Rodrigues et al., 2021). Tele-health prevents patients with Parkinson's from traveling to an in-person care center during the COVID-19 mitigation phase. During the COVID-19 crisis, a tele-medicine program for patients with Parkinson's has been supported in Milan, Italy (Cilia et al., 2020). Based on the findings, self-care education with the tele-nursing approach was effective on HPBs(Health-Promoting Behaviors) in MS(multiple

sclerosis) patients. Therefore, it is recommended to utilize self-care education with the tele-nursing approach to control effective behaviors in MS patients during the COVID-19 pandemic (Pourfarid et al., 2021).

It is a tele-nursing application that can eliminate meetings and face-to-face meetings so that patients can receive the necessary training electronically and remotely during the COVID-19 epidemic. In the COVID-19 epidemic, a change in the conventional management of patients, particularly those with chronic diseases such as MS, is considered necessary, and tele-medicine is introduced as a valid alternative to face-to-face appointments; recommendations are available for using tele-medicine in the management of MS patients (Cerqueira et al., 2021). Tele-nursing increases immunity and reduces the risk of infection in patients with chronic diseases, particularly MS patients, who have underlying diseases and are at high risk for COVID-19, thereby preventing infection and the spread and transmission of the virus (Kord et al., 2021).

In a study evaluating the effect of tele-nursing education program on nurses' compliance with standard precautions during the COVID-19 pandemic. Application of the tele-nursing education program had a positive effect on improving the CSPS of the studied nurses as the tele-nursing appears to be a new opportunity in the COVID-19 Pandemic disaster to lessen the hazard of infection (Rizk & Siam,2021).

The tele-nursing strategy is an effective caring method to ensure continuity of home care for older adults the following discharge from the hospital during the COVID-19 pandemic. The current study results

concluded that telenursing strategy is an effective caring method to ensure continuity of care for older adults following hospitalization and support the informal caregivers. After receiving the tele-nursing education, the knowledge of elderly patient' caregivers about the diseases and their practice regarding essential care improved among the intervention group than among those in the control group (Mohamed et al., 2022).

The positive effect of tele-nursing has been reported in the treatment of chronic diseases, and this technology has reduced both hospitalizations of patients and nursing visits to the homes of chronically ill patients in recent years. However, a standard method has not yet been developed for tele-nursing (Elgaphar et al., 2017). Zheng et al. (2020) reported that a combination of face-to face education and quarterly telephone follow-up could improve self-efficacy for nutrition, stress dimension, and the total score of HPBs (Zheng et al., 2020)

5.CONCLUSION AND RECOMMENDATIONS

During public health crises, alternative strategies such as tele-nursing or tele-medicine can be crucial for the management of patients with chronic diseases, not only in critical moments such as quarantine but also in ordinary health management (Petrelli et al., 2020). The tele-medicine tool is useful for treating high-risk patients with COVID -19 (Rabuñal et al., 2020). Considering the coronavirus pandemic as the greatest crisis of our time, the need for new technologies to seek and receive reliable medical advice and care through a tele-health system is

widely recognised. The future challenges in the field of tele-medicine could be the technological advancement in healthcare systems and the training of future healthcare providers based on clinical simulations and online courses to improve the way of care, towards a remote but still patient-centered care (Asimakopoulou, 2020). Tele-nursing is an evolving field, and with the advent of new technologies, the scope of practice for nurses is expanding. This is an opportunity to fill the gap created by the current shortage of nurses. In times of pandemic, tele-nursing is a way for patients with mild symptoms COVID -19, the chronically ill, and the elderly to remain at home and receive quality health care (Kilova, 2020). It is recommended to evaluate the effectiveness of tele-care practice in different applications using different communication technologies (video conferencing, email, SMS, social media applications). In addition, it might be advisable to support the spread of tele-care administratively, economically and technologically and make it a routine health policy to support adherence to medication therapy after discharge as well as in outpatients. (Karabulut, 2021). During the COVID -19 pandemic, tele-medicine is considered as an essential tool to protect patients and health care providers by reducing person-to-person contact, thus slowing COVID -19 transmission.

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CHAPTER 7

COVID-19, NURSING CARE AND ETHICS

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INTRODUCTION

COVID-19 first appeared on December 31, 2019 in the city of Wuhan, Hubei Province, People's Republic of China. Coronaviruses (CoV) are a large family of viruses that cause diseases ranging from the common cold to more serious diseases such as Middle East Respiratory Syndrome (MERS-CoV) and Severe Acute Respiratory Syndrome (SARS-CoV). COVID-19 has not been previously identified in humans. From the moment it emerged, it has been on the agenda of the world in terms of the consequences it causes and the threats it poses at the global level (Üstün & Özçiftçi, 2020). With the COVID-19 pandemic, there is an unprecedented crisis at the global level. All humanity knows that nothing in the world will ever be the same as before. This process, which deeply shakes all individuals, societies and countries and affects them in multiple dimensions, is also a lesson for humanity. It has brought with it many problems to humanity. Of course, these problems have affected both the functioning of the professions and the working conditions of the members of the profession. Nurses have faced ethical dilemmas in the fair distribution of resources during the COVID-19 pandemic. In any health crisis or emergency, nurses always prioritize achieving the best goals of care for their patients. However, with COVID-19, nurses were asked to make a patient selection and to determine the groups that would receive care in this direction. In this context, an international standard should be determined on the priority of care, which will actually eliminate the ethical dilemma. An effective approach should be determined for the effective use of bed capacity and

fair distribution of respiratory support devices, especially in intensive care units. The purpose of all these is to ensure consistency in decision-making in emergencies that compete with time to eliminate the burden of individual decision-making and to ensure that nurses adhere to their legal obligations and the basic ethical principles of justice and equality (Institute of Medicine, 2012; National Academies of Sciences, 2020).

1. NURSING

Nursing is a professional job based on theoretical and applied education. The practice dimension of education is called clinical teaching and it constitutes one of the complementary and cornerstones of nursing education. Clinical teaching is a learning process that focuses on working directly with patients and their problems and allows students to learn in real terms, taking into account their individual learning needs (Lin et al., 2014; 2013; Ünsal et al., 2013; Valiee et al., 2016). Nursing students, who will be the health care professionals of the future, gaining a professional ethical stance and behavior during their education will be effective in displaying a humane approach in their professional life and providing individualized care (Korhan et al.,2018). The most important dimension of the fight against epidemics is the nurses who treat and care for patients and spend their shifts actively at the patient's bedside. As more data emerge about the risks associated with the outbreak, new standards should be evaluated and implemented. All nurses should be well trained in universal precautions against infection.

Although nurses still need to discuss their ethical concerns with colleagues and other health professionals (e.g. patient rights), a fully ethical discussion with colleagues/doctors cannot be achieved due to conflicts and interpersonal difficulties. Ensuring that nurses participate more in decisions in practice can contribute positively to reducing the stress caused by ethical problems. It is clear that in-service training and professional ethics consultations should be addressed daily in order to ensure the integrity of nursing practices and the quality of patient care (Leblebicioğlu & Aktaş, 2020).

1.2. ETHICS

The word ethics is derived from the Greek word “ethos” meaning “character”, “habit”, “tradition”, “custom”. The object of ethics is humanbeings and their actions. Social and individual relations are carried out based on some basic values. Ethics is a sub-discipline of philosophy that deals with problems related to values and actions, and strives to reach correct information in this context (Oğuz et al., 2005). Values are the human possibilities that are related to the humans, that belong to the humans, that they realize or can realize. Ethical values, on the other hand, are certain person possibilities and people's having some experience and action opportunities in interpersonal relations (Kuçuradi, 1998). Values are the goals and beliefs that form the basis of a behavior and decision-making process (Chitty & Black, 2007). Values in a profession are professional practice standards that are preferred by professionals and that establish frameworks for evaluating behavior (Weis & Schank, 2009). Understanding the patient/healthy

individual both physically and emotionally is an indicator of the ethical sensitivity of health professionals. Because sensitivity is an integral part of the moral response. "Ethical Sensitivity", which is the ability to identify ethical problems, should be defensible in line with ethical principles. Ethical sensitivity is extremely important in terms of solving ethical problems, clarifying or justifying action, as well as preventing ethical dilemmas. Nursing is based on professional philosophy and a scientific ethical structure (Tosun, 2021). Ethical decision making is important in terms of being aware of ethical problems that arise in the field of health and displaying a professional approach to ethical problems (Burkhardt & Nathaniel, 2013). Ethics education will facilitate the systematic approach by improving the decision-making skills of nurses, providing a facilitating effect in realizing contemporary nursing practices, and improving the analytical mindset (Özlem, 2016). In some cases, although the values of the healthcare professional and the patient overlap, ethical dilemmas may occur if the healthcare professional refuses to provide healthcare to someone of the opposite sex due to religious reasons and/or the patient refuses to receive services from the healthcare professional of the opposite sex (Ancell & Sinnott-Armstrong, 2017). Nurses, who are in constant communication with the patients in the health sector and are the main employees of care and treatment, often face ethical problems that they have difficulty in solving due to their expanding role and responsibilities (Aslan et al., 2003; Ertuğ et al., 2014; Filizöz et al., 2015). When the literature is examined, the ethical problems that nurses frequently encounter; It is stated that there are protection of patient rights, care of the patient in

the terminal period, obtaining informed consent, sharing of limited resources and unethical attitudes of colleagues (Callaghan, 2003).

1.3. ETHICS IN NURSING CARE

In today's world where social changes are experienced rapidly, certain value principles are needed in every field. The fact that advances in science and technology cause some value problems to arise increases the importance of ethics in the field of health (Aksu & Akyol, 2011). The scope of health care ethics includes the analysis of moral responsibilities and ethical judgments heard by health care providers and the examination of right thinking in patient care practices (Karagöz, 2000). For this reason, it is important to know ethical principles and codes very well and to develop attitudes and behaviors in this direction. The nursing profession, which is a part of the health care system, requires making the right decision for the patient in many areas of practice. With their expanding roles and functions, nurses have to make more complex decisions compared to the past and take responsibility for these decisions (Callaghan, 2003). Nursing, which is based on the philosophy of humanistic and holistic care, undertakes the responsibility of care for individuals who cannot meet their needs on their own. While fulfilling these responsibilities, nurses also make decisions and take action for the well-being of the individual (Dalcalı & Şendir, 2016). During the care process, conflicts may occur between the nurse's own values and the values and expectations of the patients and their relatives who are cared for, and these conflicts cause ethical dilemmas (Aitamaa et al., 2010; Dalcalı & Şendir, 2016).

Nurses should have moral responsibilities in order to give care. According to Paul Ricoeur, ethics is the good life. The purpose of living well as a nurse is to relieve pain. According to Ricoeur, “Suffering strikes at the very root of the goal of the good life, and suffering undermines both self-esteem and autonomy. Because of the passivity of the sufferer, care is ethically asymmetrical.” He emphasizes that the care relationship is an asymmetrical relationship. (Fredriksson & Eriksson, 2003).

According to the existential psychologist Rollo May (1909-1994), care is “the most constitutive phenomenon of human existence”. Expressing that care is what makes people human, May states that care makes love and desire possible, and is also the source of being conscientious (Reich, 2014). Some nurse theorists, who contributed significantly to the theoretical knowledge load of nursing, also expressed their understanding of the concept of care within the framework of nursing care. Madeleine Leininger (1978) stated that care, as a doctrine that forms the basis of nursing practices, is at the center of nursing, which is a profession that includes the value-belief system (McFarland & Madeleine Leininger, 2006).

Nursing care affects the religious and cultural practices of the patients and their socioeconomic status. Cultural and religious beliefs affect the individual's approach to the health care system, personal health practices and nurse-patient communication. If the nurse does not know the cultural and religious beliefs of the individual to whom she is responsible, she has difficulty in understanding the behaviors and

beliefs of the individual and it is not possible to provide effective care (Mete, 2014). Nurses should be able to plan their care according to the religious and cultural beliefs and practices of the patients they care for.

The economic status of individuals is one of the important factors affecting the utilization of the health care system. Increasing costs of health services and increasing individual payments prevent individuals from benefiting from care services (Dinç, 2010). In this case, care is offered not to everyone in need, but to those who have money, the affective and human dimension of care is ignored, and it affects nurse-patient communication negatively.

Nurses believe that they have the right to receive high-level service, as they find the individual they take care of as valuable and unique as a whole with their values, beliefs and attitudes, actions and behaviors. This belief necessitates an ethical approach in care (Babadag, 2010). Nurses have to make an effort to make the right decision for the patient in many areas of practice and take responsibility for these decisions (Burkhardt & Nathaniel, 2013). In order to provide quality care, nurses are expected to constantly improve their professional competence, be sensitive to human and moral care, and provide appropriate care in line with professional values (Dinç, 2009).

In professional nursing practices, it is thought that ethical issues should be given importance in the education of health workers in order to increase ethical sensitivity in patient care. In order for nurses and midwives to recognize ethical problems and make the right decisions, their level of ethical sensitivity must be high. Studies on ethical

sensitivity were mostly conducted on nurses and nursing students (Pekcan, 2007; Elçigil et al., 2011; Tosun, 2005)

In a study conducted with nurses working in the clinic, it is stated that 54.9% of nurses have problems in making the right decision regarding ethical dilemmas (Aksu & Akyol, 2011). In a study conducted by Dikmen with intensive care nurses, it was reported that 62% of nurses had problems in producing solutions in the face of ethical problems (Dikmen, 2013). In a study conducted by Gül et al. with student nurses, it was reported that students could not make decisions in line with ethical principles in the face of dilemmas and problems due to their low clinical experience (Gül et al., 2013).

Ethical principles define the values of the profession and inform how professionals should behave accordingly. Ethical issues are a very difficult issue to solve. Ethical dilemma is defined as the existence of more than one solution alternative to the problem. The basic thing to do in solving ethical dilemmas is to decide what should be done in line with universal ethical principles (Menendez, 2013).

The most important responsibility of health professionals; emerging ethical problems should be resolved by taking the basic ethical principles. Emerging ethical issues should be addressed together with human rights, patient rights, allocation of limited resources, and the effects of life-extending interventions on quality of life. Decision-making processes based on ethical principles should be used in the solution of ethical problems. In this context, ethical principles such as

"benefit", "do no harm", "autonomy" and "social justice" come to the fore (Tel, 2012).

Basic ethical principles in nursing practice; in order to eliminate the harm that may arise as a result of the application and taking the necessary precautions accordingly, not causing harm, as well as obtaining benefit. Autonomy is to involve individuals in the decision-making process and to respect their decisions (Hunt, 2020). Informing the patient about the procedure to be performed and inclusion in the process in this way and leaving the application decision to him is the opportunity to make a decision offered to the patient as a requirement of the principle of autonomy. For this reason, autonomy and informed consent are considered together. Autonomy is also a sign of respect for the patient himself and his decision. The patient has the right to refuse treatment as well as the right to accept it. For this reason, it is necessary to respect the patient's autonomy no matter what decision he takes (Menendez, 2013). In addition, the informed consent obtained before the procedure is the patient's consent for what to do. Here, the prerequisite, the risks and benefits of the procedure/procedure to be applied are explained in a way that the patient can understand, and the procedure should be applied if allowed. Informed consent is the decision-making process between the healthcare professional and the patient (Berman et al., 2016). In practice, it has been determined that acting in accordance with the principle of autonomy is beneficial for the individual. This also ensures quality care and patient safety (AllahBakhshian et al., 2017). While justice is the most violated ethical

principle, it requires an equal and fair distribution of resources. Within the scope of this principle, it is also important for the health professional to accept responsibility for his own actions and results, and to be accountable for his practice/ initiatives when necessary. Integrity and honesty are the real and accurate sharing of patient information. Loyalty is showing the necessary care in sharing information about the patient. Advocacy is to defend the patient's rights as necessary and to encourage them to express their needs (Hunt, 2020).

Ethical problems that midwives and nurses frequently encounter are as follows: Finding different approaches with other members of the team and the institution regarding the care and treatment of patients, protection of patient rights, obtaining informed consent, fetal surgery, abortion practice, allocation of limited resources, patient privacy, patient care that does not comply with treatment, narcotic drug administration, dependent patient care, unethical attitudes of colleagues, etc. (Pekcan, 2007; Elçigil et al., 2011).

CONCLUSION AND RECOMMENDATIONS

The primary ethical value of nurses in caregiving is the well-being of the healthy or sick individual, no matter how different their beliefs are from the value system of the individual they care for and their relatives (İbrahimoğlu, 2017). The development of ethical sensitivity allows nurses to reveal an attitude that provides quality and ethical principles towards patients. In addition, in the ethics education in nursing, discussing the experiences and case studies that can predispose to ethical values can be more instructive in terms of predisposition to

ethical values (Kırca et al., 2020). It is recommended to organize post-graduate and continuing education programs in order to increase the ethical sensitivity of nurses and thus to recognize and solve ethical problems (Kahriman & Çalık, 2017). Nurses, who direct the health system with their expertise, knowledge and skills, have faced many problems and ethical dilemmas due to the pandemic today. In order for nurses to take the most correct ethical decision-making steps for relevant ethical problems, ethical guidelines for the COVID-19 pandemic should be established at the international level (Palandöken, 2020). In cases of epidemic or similar crisis, nurses' ability to perform nursing care in line with ethical principles has a very important place. In addition, it is recommended to conduct studies examining the ethical attitudes and behaviors of actively working nurses and nursing students.

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CHAPTER 8

EFFECTS OF STRESS ON MALE REPRODUCTION

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INTRODUCTION

Although technology makes our lives easier, it causes some negative effects on health. Especially the reproductive system, which is very sensitive to environmental stimuli, suffers from this situation from time to time (Demirci, 2014). It is known that changes in lifestyle, increases in stress and some chemicals that affect the endocrine system adversely affect reproductive health (Awadalla et al., 2011). A suitable micro-environment is necessary for the testicular morphology not to deteriorate and for normal testicular functions to continue in a healthy way. This micro-environment includes suitable temperature, adequate blood supply and a balanced hormonal stimulation (Shalet, 2009). It has been explained that stress causes disorders in the neurological, gastrointestinal, cardiovascular, urinary systems, etc. (Banasr et al., 2017; Li et al., 2019; Nirupama et al., 2013). It has also been reported that in chronic stress, neuron formation in the hippocampus is suppressed and memory impairments occur (Qiao et al., 2016).

Hans Selye (Hinkle, 1974), who introduced this term to the medical literature, defined stress as the body's response to any change (Selye, 1950). Stress appears to be divided into acute and chronic. In scientific studies, it is seen that chronic stress is divided into Unpredictable = indefinite chronic stress (the stressors in the stress protocol are randomly arranged) and mild chronic stress (the stressors in the stress protocol are applied less severely) (Willner, 2017). It was thought that acute stress generally does not cause a pathological condition and keeps the organism on the alert against external threats.

In chronic stress, a number of psychological and traumatic effects occur (Chockalingam et al., 2019; Pandarakalam, 2018).

It has been reported that both psychological and physiological stress can cause sexual dysfunction and infertility (Baldwin, 2001; Kennedy et al., 1999). Stress is thought to have a strong effect on the development of depression (Qiu et al., 2014). Chronic stress can lead to depression by disrupting the functioning of neurotransmitters (serotonin etc.) in the brain (Fahim et al., 2019). As a matter of fact, it is known that adrenal corticosteroid secreted under stress causes depression by disrupting cortical function (McEwen, 2007). Again, a decrease in the amount of serotonin in the brain may cause depression to be experienced again in a patient with depression (Robinson et al., 1989).

Corticotropin-releasing factor and arginine vasopressin, which are released from neurons in the hypothalamus during stress, produce and release adrenocorticotropic hormone (ACTH) from the anterior pituitary. Secreted ACTH induces glucocorticoid synthesis from the adrenal glands (Nicolaides et al., 2015). Cortisol, which regulates circadian rhythm, blood pressure, carbohydrate, fat and protein metabolism and is known as the stress hormone in humans, is corticosterone in rodents. Normally, during stress, cortisol level rises (Stephens and Wand, 2012). This rise in cortisol level damages organs and tissues and disrupts homeostasis (Mariotti, 2015). Again, under stress, there is an increase in the secretion of inflammatory stockins. If there is no increase in the amount of cortisol secreted under stress,

cortisol-induced pressure on the increased inflammatory secretion cannot occur and stockin secretion occurs above the expected, and these over-released products may lead to shock and vascular decompensation (McEvven, 1998). In addition to the ones listed above, oxidative stress is induced as a result of chronic stress and the amount of free oxygen radicals in the cell increases (Belviranlı and Gökbel, 2006). Especially, differentiating environmental factors and changes in lifestyle (smoking, alcohol, obesity, environmental pollution, etc.) cause oxidative stress by causing a decrease in antioxidant activity and harm the male reproductive system (Tremellen 2008).

It has been reported that adrenal corticosteroid released due to stress causes depression by disrupting cortical function (McEwen, 2007), and it can also activate the inflammatory response in the brain, which may cause neurochemical changes and depressive behavior disorders (Miller et al., 2009). In addition, it has been reported that increased serum corticosterone induces Leydig cell apoptosis and impairs Leydig cell steroidogenesis (Gao et al., 2003). Studies have reported that chronic stress causes a significant decrease in serum testosterone levels and testicular expression of steroidogenic acute regulatory protein (StAR), cytochrome P450 side chain cleavage (CYP450scc) enzyme and C-kit. It has also been reported to significantly reduce serum total antioxidant capacity levels (Fahim et al., 2019). Arun et al (2016) determined that the expression of testicular 55 kDa phosphorylated protein (a protein that may be important in sperm head

and acrosome formations) was significantly increased in rats subjected to chronic stress.

Another study found that chronic unpredictable mild stress (CUMS) increased circulating corticosterone concentration and both serum and cavernous inflammatory markers/mediators, including tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), C-reactive protein (CRP), intercellular adhesion molecule (ICAM). In the same study, it was reported that it reduced the expression of endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS) in the corpus cavernosum (Yazir et al., 2018). Juarez-Rojas et al. (2015) reported that the stress created by immersing rats in cold water may cause a decrease in testosterone levels by activating the intrinsic/extrinsic apoptosis pathways in the testicles.

Inactivation begins when the stimulus that creates stress ends. Thus, cortisol and catecholamine secretions return to their initial values. However, if inactivation does not occur at the desired level, exposure to stress hormones may continue (McEvven, 1998). Therefore, the release of cortisol increases and accumulates. As a result of this accumulation, some problems (increase in blood pressure, weakening of the muscles, change in mood, osteoporosis, type 2 diabetes and damaged brain functions) occur in the organism (Stephens and Wand, 2012).

Stress creates its effects on male reproduction especially by affecting SAS (sympathetic-adrenal system) and HPA (hypothalamic-pituitary-

adrenal) axis (Flak et al., 2014). Chronic stress primarily affects the HPA axis and, by activating it, creates an increase in glucocorticoids. Increased glucocorticoids cause suppression of HPG (hypothalamic-pituitary-gonadal) function. As a result, chronic stress suppresses the release of GnRH (gonadotropin-releasing hormone), leading to decreased secretion of LH and FSH (luteinizing and follicle-stimulating hormones) (Gilbeau et al., 1985). It has also been reported that apoptosis occurs in Leydig cells with the increase in serum corticosterone level under stress and steroidogenesis is impaired in Leydig cells (Gao et al., 2003). Stress is among the information reported to cause anxiety about sexual performance in men, occasional erectile dysfunction, and a decrease in the frequency of coitus (Flak et al., 2014). It is useful to remember that testosterone production and sperm structure are impaired in the case of constant exposure to stress (Wingfield and Sapolski, 2003).

The increase in the number of infertile animals and individuals, as well as the increase in the rate of stress today, have caused scientific research on infertility to focus on stress. The relationship between infertility and psychological stress is not clear. While stress causes infertility, it has been reported that being infertile can also cause stress (Sahin et al., 2009). It has been reported that glucocorticoids, which increase in the case of exposure to stress during pregnancy, pass from the mother to the fetus and cause problems on the fetal HPA and HPG axis (Takahashi et al., 1998; Williams et al., 1999). Haron and Mohamed (2016) found that prenatal restraint stress harms reproduction in male rat pups, creates undesirable changes in sperm

parameters, and decreases testosterone levels. It has been reported that chronic stress causes significant changes in testicular parameters of adult rats, but the distress that occurs with the removal of the stress stimulus is almost resolved. However, it has been suggested that if the same stress is applied in the prepubertal period, testicular changes are more permanent and continue even after the end of stress stimulation.

Findings from testicular biopsies of sentenced and awaiting prisoners are the first documented study to clearly demonstrate the effect of stress on spermatogenesis. In these biopsies, it was noted that spermatogenesis was almost stopped and there were no spermatogenic cells in the tubules except Sertoli cells and spermatogonia (Amelar et al., 1977). Sandler (1965), in a long-term study in an infertility clinic, concluded that adoption facilitates conception.

In this chapter; Stress, which is an inevitable factor in our daily life, is discussed. In particular, the relationship between long-term stress, which is described as chronic, and male reproduction, which has a very important place in the continuation of the generation, was mentioned. Again, applied stress protocols are briefly mentioned. Finally, the problems caused by stress on male reproduction are listed under the headings and some explanatory information is presented.

STRESS PROTOCOLS APPLIED IN EXPERIMENTAL STUDIES

*Exposure to heat: at 45°C for 5 minutes (Sakr et al., 2015).

*Deprivation of food and water: for 18 hours or 24 hours (Fahim et al., 2019; Sakr et al., 2015).

*Float in cold water: for 5 minutes in water at 4°C (Fahim et al., 2019; Sakr et al., 2015).

*Applying a reverse light/dark cycle: While the lights are off from 7 am to 7 pm, the lights are on from 7 pm to 7 am (Fahim et al., 2019; Sakr et al., 2015).

*Keeping in a tilted cage: at a 45° angle (Fahim et al., 2019; Sakr et al., 2015).

*Restriction: For 4 hours only in a 12x5.5 cm cage with holes suitable for ventilation (Fahim et al., 2019).

*Squeezing the tail: Squeezing the tail from a distance of 1 cm for 1 minute (Fahim et al., 2019).

*Keeping in a wet cage (20 hours or 21 hours in a bed where 100 g sawdust and 200 ml water are mixed) (Fahim et al., 2019; Sakr et al., 2015).

*Applying a rocking motion: In a cage placed on a rotating device (120 rpm) for 10 minutes (Fahim et al., 2019).

*Exposing to a predator: Keeping a cat in the same cage with the experimental animal, separated only by wire mesh (Ribeiro et al., 2018).

*Keeping in a dirty cage: for 24 hours (Zou et al., 2019).

*Applying physical restraint: for 2 hours (Zou et al., 2019).

*Keeping in a noisy environment: for 4 hours in an environment of 100 decibels (Ribeiro et al., 2018).

*Administering glucocorticoids (Yazawa et al., 2000).

EFFECTS OF STRESS

1) Effects of stress on appetite and body weight

People's reactions to stress and depression can be different. For example, some people avoid eating in case of stress, while others eat unconsciously. This difference varies according to the brain region of that person affected during stress (Simmons et al., 2016). In experimental studies, it was observed that there were significant decreases in body weight of stress group rats (Arun et al., 2016; Fahim et al., 2019; Salami et al., 2020; Yazir et al., 2018; Zou et al., 2019). As a matter of fact, it has been reported that corticosterone, which is excessively secreted under stress in rats, increases protein catabolism and lipolysis, leading to a decrease and depletion of body reserves (Arun et al., 2016). Low sucrose consumption in stressed rats (Fahim et al., 2019; Sakr et al., 2015) is also manifested in anhedonia, a very important symptom of depression (Abo-youssef, 2016). It has been reported that decreases in body weight cause disruption in the hypothalamic-pituitary-gonadal axis in experimental animals (Cameron and Nosbisch, 1991) and humans (Reid and Van Vugt, 1987). Indeed, after weight loss, there were decreases in GnRH, LH and androgen release (Howland, 1975). It is also reported that there are significant decreases in the absolute weights of the testis,

epididymis and vas deferens, as well as the dimensions of the seminal vesicle under stress (Arun et al., 2016).

2) The effect of stress on oxidative stress and biochemical parameters

Some environmental factors (smoking, alcohol, obesity, environmental pollution, etc.) affect the male reproductive system in different ways through oxidative stress by causing a decrease in antioxidant activity and excessive production of free radicals (Tremellen 2008). While low levels of reactive oxygen species (ROS) are required for many physiological processes such as sperm capacitation, acrosome reaction, and penetration of sperm into the zona pellicida, overproduced ROS leads to sperm abnormalities and infertility (Sikka, 2001). Studies have shown that there is a significant increase in testicular malondialdehyde (MDA) in rats exposed to CUMS; A decrease in some biochemical parameters such as glutathione (GSH), superoxide dismutase (SOD) and catalase has been reported (Bagheri et al., 2021; Salami et al., 2020). In line with these findings, it can be said that CUMS causes testicular dysfunction and oxidative stress (Fahim et al., 2019; Sakr et al., 2015). In another study, It has been found to CUMS cause nuclear factor-κB (NF-κB), TNF-α, IL-Iβ and Bcl-2-associated X protein (Bax) cause a significant increase in testicular expression and a decrease in B-cell lymphoma-2 (Bcl-2) expression (Fahim et al., 2019). Yazir et al (2018) found that the levels of TNF-α, IL-1β, IL-6, CRP, and ICAM-1 increased in the stressed group.

3) Effect of stress on histopathology and immunohistochemical parameters

It has been reported that stress causes disruptions in spermatogenesis. Reported information includes decreased testicular Johnson score, necrosis of Leydig cells, damage to Sertoli cells, degeneration of germ cells, atrophy of seminiferous tubules, decrease in tubule diameters, increase in tubule wall thickness, and decreases in spermatogenic cells in experimental groups administrated with CUMS (Fahim et al., 2019; Sakr. et al., 2015). Zou et al (2019) reported that stress causes reductions in tubular diameter and epithelial height. The same investigators reported that the cell cycle stopped in the G0/G1 phase in spermatogonia. Yazawa et al (2000) found that the apoptotic index in germ cells increased in rats treated with dexamethasone. Fahim et al (2019) found that in CUMS exposure, there was thickening of the seminiferous tubule basement membrane, degeneration and necrosis in spermatogenic cell lines, and some tubules appeared completely empty.

4) The effect of stress on sperm parameters

In experimental studies; Results showed that while sperm count and motility decreased in CUMS groups, abnormal sperm count increased (Arun et al., 2016; Sakr et al., 2015). Zou et al (2019) suggested that there may be two reasons for the decrease in sperm concentration in chronic stress. One of them is that the cell cycle in spermatogonia is stopped in the G0/G1 phase, and the other is increased apoptosis in spermatogenic cells. In another experimental study; It has been

reported that sperm count and motility decreased, and there was no difference in sperm morphology in rats exposed to heat stress at 35°C for 6 hours for 20 days (Yates et al., 2010). Bagheri et al (2021) and Salami et al (2020) found that there were deteriorations in sperm quality in stress group rats in their studies.

5) Effect of stress on reproductive hormones

In studies where different stress protocols were applied, it was determined that there were significant decreases in testosterone hormone levels (Yates et al., 2010; Yazir et al., 2018). It has been reported that chronic stress increases glucocorticoid levels (Ulrich‐Lai and Herman, 2009), suppresses the release of gonadotropins, and inhibits testosterone biosynthesis by acting directly on Leydig cell receptors (Lin et al., 2014). Bagheri et al (2021) reported in their study that there were decreases not only in testosterone but also in FSH and LH levels. In other studies reported on stress; In CUMS groups; In addition to testosterone, it was stated that while serum and hippocampal serotonin decreased, corticosterone increased (Fahim et al., 2019; Sakr et al., 2015). Fahim et al (2019) attributed the decrease in serum testosterone level under stress to the decrease in testicular gene expression levels of StAR and CYP450scc, two key steroidogenic proteins effective in testicular steroidogenesis. Zou et al (2019) have suggested that the increase in the amount of corticosterone in the stress state is due to the increase in the weight of the adrenal gland. As a matter of fact, the HPA axis is activated under stress and this creates an increase in the weight of the adrenal gland.

In another study, it was reported that there was a decrease in testosterone level and significant increases in corticosterone and blood glucose levels (Arun et al., 2016). Zardooz et al (2006) linked the increase in blood glucose level under stress to increased corticosterone. He argued that increased corticosterone under stress stimulates gluconeogenesis by acting on liver and muscle tissues, which in turn causes an increase in blood glucose levels (Zardooz et al., 2006).

CONCLUSION

The incidence of stress, which includes many complications that negatively affect the quality of life of humans and animals, is increasing day by day. Especially the problems it creates on reproduction are worrisome for the future. It is known that some antidepressants are used in the literature and in general life in order to minimize the complications on health. However, the damage these antidepressants cause to the reproductive system is significant. For this reason, taking into account the damage that occurs in addition to antidepressants, some antioxidant, anti-inflammatory, anti-apoptotic etc. The combined use of chemical agents with potent effects may be considered.

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CHAPTER 9

WOMEN WITH EPILEPSY, PREGNANCY, BIRTH AND POSTPARTURE

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INTRODUCTION

Pregnancy should be a matter of concern and discussion for every woman of childbearing age with epilepsy. Patients and neurologists should definitely plan pregnancy in advance (Dupont & Vercueil, 2021). The first aim in women with epilepsy is to give full information to the patient and her partner, even if pregnancy is not considered. There are misconceptions about having a child in a woman with epilepsy and her husband. For this reason, the woman and her partner should know what can be done during pregnancy, what is possible and what should be restricted before getting pregnant. The healthcare professional should pay special attention to the care of women with epilepsy. Health professionals should be able to predict pregnancy, the risk of seizures during pregnancy, fetal risks associated with the use of antiepileptic drugs should be considered, and the risks of insomnia due to delivery, postpartum breastfeeding and infant care should be predicted (Özkan E, 2021).

In this section, current data on the risks of being pregnant with epilepsy and antiepileptic drugs will be reviewed, and the necessity of planning pregnancy before becoming pregnant and being ready for the possibility of becoming pregnant will be emphasized. In addition, the effects and approaches of the burdens of infant care in the postpartum period on women with epilepsy will be reviewed.

1. WOMEN WITH EPILEPSY AND BIRTH CONTROL

The choice of contraception method for women with epilepsy is difficult due to possible interactions between the atepileptics used and hormonal contraception methods. Of the contraceptives, combined estrogens and progesterone contraceptives are not recommended in patients using enzyme-inducing antiepileptics, as subcutaneous progesterone implants may be ineffective (Reimers, Brodtkorb & Sabers, 2015). Vaginal rings with high progestin content are also not recommended.

Some enzyme-inducing antiepileptics change the effect of contraceptives depending on the dose (topiramate above 200 mg/day and perampanel above 12 mg/day) (Rosenfeld, Doose, Walker & Nayak 1997; US Food and Drug 2014). For these and similar reasons, hormonal contraception is not recommended. Containing complex interactions between hormonal contraception and antiseptics, this World Health Organization (WHO) meeting with epilepsy recommends avoiding controlling a combination containing pills and progesterone. Intrauterine device is among the first recommended methods for women who want birth control.

2. WOMEN WITH EPILEPSY AND PREGNANCY

Women of childbearing age with epilepsy should be informed that pregnancy is not a contraindication in epilepsy. There are still women who think that epilepsy prevents marriage and having a baby. The

planning and proper control of pregnancy by epileptic women will depend on the woman's current knowledge. For this reason, it is very important to address this issue in women with epilepsy early in life, for example, during adolescence. The content of preconception counseling includes information on minimizing the teratogenic risk of antiepileptic drugs and optimizing seizure control before conception.

The message to be given when pregnancy is considered should be clear, careful and the patient should not be alarmed. It should be remembered that there is an increased risk of fetal malformations, but it is manageable, especially when pregnancy is planned, and accompanying precautions are taken. Women with epilepsy have more fear of childbirth than other women (Turner et al. 2008). The need for information is clearly felt in women with epilepsy (Henning, Alfstad, Nakken & Lossius, 2019). Women with epilepsy have lower knowledge of pregnancy than women without epilepsy (Saramma, Sarma & Thomas 2011). Informing women with epilepsy about pregnancy is very important because unplanned pregnancies have been shown to be associated with more adverse fetal outcomes than planned pregnancies (Leach, et al. 2017; Zhang, et al. 2020).

If pregnancy is planned, the drug dose is tried to be reduced to the lowest dose that can control the seizure. Single drug administration and treatment at the lowest effective dose have been reported as the most effective method. Women with epilepsy are recommended to use high-dose folic acid (5 mg/day) before pregnancy and for at least the first 3 months after pregnancy (ACOG, 2019).

Although there is no conclusive evidence that congenital malformations are reduced in the children of epileptic women using folic acid, there are new studies in favor of folic acid supplementation before pregnancy in women with epilepsy. According to the results, positive neuropsychological effects of preconception folic acid supplementation were demonstrated in both healthy children and children exposed to fetal antiepileptics (Meador, et al. 2020). In addition, recent studies have reported that the lack of information on the use of folic acid during pregnancy is high (Herzog, et al. 2017).

Women should be informed that there may be an increase in the frequency of seizures during pregnancy and that the baby may be harmed during the seizure.

During pregnancy, monitoring should be done by taking into account the bidirectional interaction between seizures and ongoing pregnancy. In fact, changes in seizure frequency during pregnancy and the effects of seizures on pregnancy and fetal development are legitimate questions. In the case of previously well-controlled epilepsy, the expected disease course is no change. If seizures recur during pregnancy, it is usually due to increased metabolic catabolism of the drug used. In this case, the drug dose may need to be adjusted (Reisinger, et al 2013).

A woman who had seizures before pregnancy was 3-4 times more likely to continue having seizures during pregnancy than a woman whose seizures were completely controlled before pregnancy (Vajda, O'Brien,

Graham, Hitchcock & Lander 2018). An increase in seizures may occur during pregnancy in a quarter of cases. The increase is mostly in the early and late stages of pregnancy. It is important to identify the factors causing the increase. For example, factors such as the increase in vomiting in the first 3 months, sleep disorders, anxiety, the fear of the baby's exposure to drugs should be determined and precautions should be taken. Again, a change in medication or a reduction in the dose administered may trigger this condition (Cagnetti, Lattanzi, Foschi & Provinciali 2014). Absence of the menstrual cycle during pregnancy provides a 50% reduction in the frequency of epileptic seizures.

The first aim of the approach during seizures during pregnancy is to provide stabilization. The aim of the approach is to get the best results for the fetus while providing seizure control for the mother. After stabilization is achieved after the seizure, airway patency is provided and oxygen therapy is given. The patient's vital signs are taken, monitored, blood sugar is measured and intervention is made in the presence of hypoglycemia. Collaboration is sought by asking a neurologist for consultation. If necessary, the patient is referred.

Stabilization of the pregnant woman who has seizures should be provided first. Epilepsy management in pregnancy includes seizure control for the mother and aims to achieve the best results for the fetus (Pack & Benson 2020). After stabilization is achieved in the pregnant woman who has had a seizure, the respiratory tract is opened and oxygen therapy is given. Vascular access is opened and fluid is inserted. If there is hypoglycemia, the blood sugar is checked and intervened.

Consultation from a neurologist is requested. The pregnant woman is monitored during the infusion and evaluated for arrhythmia. If there is arrhythmia, anti-arrhythmic medication is given and consultation from the cardiologist is requested. If necessary, the patient is referred to 112. The first preferred drug in the treatment is intravenous magnesium sulfate (as a 6 mg loading dose and 2 mg/hour maintenance dose). Meanwhile, pregnant; should be evaluated in terms of epilepsy, preeclampsia and status epilepticus (SE) (single seizure that lasts longer than 30 minutes or recurrent seizures that last longer). If necessary, the drug of the pregnant should be changed or polytherapy should be started (Dilek, 2016).

3. WOMEN WITH EPILEPSY AND BIRTH

It is recommended that women with epilepsy give birth in a center where neonatal resuscitation can be performed and maternal and neonatal intensive care conditions are available. Because complications during pregnancy are more common in women with epilepsy, and the need for resuscitation and intensive care is more common (Kahvecioğlu, 2018; Güler & Kahvecioğlu, 2019). There is no obstacle for women with epilepsy to have a vaginal delivery.

If the woman has a seizure at the time of delivery, the use of drugs such as short-acting drugs (phenytoin, benzodiazepines) is recommended.

The risks of benzodiazepines such as apnea and hypotonia to the newborn should not be forgotten. The fetus should be followed up continuously with NST (nonstress test) in seizure status and drug use.

In women with epilepsy, the use of vacuum and forceps may be recommended to shorten the second stage of labor (Başgöl & Oskay, 2012; Bayrak et al. 2014; Reisinger, et al. 2013).

CONCLUCSION

Epilepsy during pregnancy is considered as a high-risk pregnancy. However, it does not prevent pregnancy. If a woman with epilepsy is considering pregnancy, this must be planned. Therefore, nursing care should be provided to epilepsy patients who want to become pregnant, starting from the pre-pregnancy period and during and after the perinatal period.

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CHAPTER 10

OBESITY AND MIDWIFERY CARE DURING PREGNANCY

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1. INTRODUCTION

Obesity, which is a pathological condition, is an excessive and abnormal increase in body fat. Obesity is determined by looking at the body mass index (BMI). BMI is calculated by dividing body weight (kg) by the square of height (m2) (BMİ=kg/m2). Individuals with a BMI equal to or greater than 30 kg/m2 are defined as obese. Individuals with a BMI <18.5 kg/m2 are defined as low, and those with a BMI between 18.5-24.99 kg/m2 are defined as normal weight. More than 4 million people die each year due to obesity. More than 650 million adults in the world are thought to be obese. 40% of adult women are overweight and 15% are obese (WHO, 2020). In Turkey, the obesity rate has been reported as 21.1%. On the other hand, 24.8% of women were obese, 30.4% were preobese; has been reported to be (TUIK, 2020).

Obesity negatively affects women's reproductive abilities. It has been reported that girls diagnosed with obesity enter puberty earlier. In addition, the menstrual cycle patterns of obese women are disrupted. It has also been reported that there is a relationship between obesity and cancer diseases (Chang, 2020).

Factors such as advanced age, marriage, increase in the number of gravida, use of oral contraceptives, low education level, excessive weight gain during pregnancy, limitations in social life due to low socioeconomic status, and limited physical activity are risk factors for obesity (Mangemba, 2020; Chatterjee, 2020).

2. WEIGHT GAIN DURING PREGNANCY

There are many physical and psychological changes during pregnancy. Weight changes during pregnancy are important for maternal and infant health. There are many factors that affect weight gain during pregnancy. These are factors such as the age of the pregnant woman, the number of births, economic status, physical activity, and pre-pregnancy weight status (Demirer & Yardımcı, 2020). It is the duty of midwives and health personnel that the BMI of women is in the normal range before they become pregnant and that the ideal weight limit is not exceeded during pregnancy. Maintaining the ideal weight of the woman during pregnancy can be achieved with a multidisciplinary approach. Women who are considering pregnancy should be informed about the harms of obesity and excessive weight gain, and they should be provided with nutrition education to reach the ideal weight (Turan & Toker, 2020).

It is recommended not to exceed the recommended weight gain values during pregnancy according to BMI in the pre-pregnancy period. A woman with a BMI value of <18.5 kg/m2 in the pre-pregnancy period is expected to gain a maximum of 18 kilograms during pregnancy, while a woman with a BMI value of >30.0 kg/m2 is expected to gain a maximum of 9 kilograms (Inskip, 2021).

For a healthy delivery and a healthy fetus development, women should gain weight at the recommended weight (Melchor et al., 2019). It has been reported that women who were obese during pregnancy, gaining

less than the recommended weight did not cause any fetal and maternal complications (Khaire, 2020).

Weight change during pregnancy is associated with an increase in fetal components, plasma volume, fat storage, and total water volume. The increase in cardiac output in obese pregnants may be more severe than in normal pregnant women. In obese pregnancies, gastric reflux complaints may be exacerbated by the effect of increased intra-abdominal pressure. Disturbances in the gastrointestinal tract and increased risk of aspiration may occur. In maternal obesity, some breathing difficulties may disappear (Sarno, 2020). With weight gain in obese pregnants; pain in the back and legs and varicose develops (Ramlakhan, 2020).

3. OBESITY AND MIDWIFERY CARE IN PRECONCEPTIONAL, PRENATAL AND INTRAPARTUM PERIOD

Obesity affects the reproductive functions of men and women, reducing the possibility of fertility. Polycystic ovary syndrome is one of the most important factors that reduce the chance of pregnancy in obese women (Moxthe, 2020). In addition, disorders such as menstrual irregularities, miscarriage, anovulation can be seen. Prenatal health level of women is an important factor in having a healthy pregnancy period (Amiri, 2020). Pregnancy of women who were obese before pregnancy before reaching the ideal weight can lead to many complications in terms of maternal and fetal health. In studies on the preconceptional period, it has been

reported that anomalies are more common in babies of obese women. In another study, it was reported that diseases such as preeclampsia, gestational hypertension and gestational diabetes were more common in women who became pregnant before reaching the ideal weight (Dieterich, 2020).

Effective and high-quality care should be given to obese women with a multidisciplinary team approach from the pre-pregnancy periodEspecially in this period, it is very important for midwives to provide physical and psychosocial counseling. To obese women who were given counseling support; it should be explained that physical activity, healthy weight loss and lifestyle changes decrease the rate of infertility and increase the chance of conception (Greig, 2021). During this period, midwives should primarily provide weight control of obese women with individual diet and physical activity support.

Obesity in pregnancy; It is known to cause many complications such as GHT, GDM, abortion, preterm labor, sleep problems, venous thromboembolism and asthma (Lewandowska, 2020). Diabetes and obesity are independent risk factors in determining fetal size. Studies have found that the risk of gestational diabetes mellitus is 2-3 times higher in obese pregnant women than in normal-weight pregnant women (Duman & Bayram, 2018). On the other hand, the risk of hypertension and its complications (preeclampsia, eclampsia, hellp syndrome) is increased in obese pregnants (Duman & Bayram, 2018). Obesity accompanying with GDM; GHT causes complications such as cardiovascular diseases and Type 2 diabetes (Bohiltea, 2020). Pregnant

women who are overweight or obese; They are also at risk for glucose intolerance, abortion and sleep apnea (Hajipour, 2021). There are studies in which weight problems during pregnancy negatively affect mental health (Du, 2021). During this period, midwives should evaluate the nutritional habits of obese pregnant women and encourage adequate and balanced nutrition. After the fourth month of the pregnancy period, it is inconvenient for obese women to make a weight loss program with an uncontrolled diet. Complications that may occur can be prevented by monitoring and evaluating the weight of obese pregnants under midwife control (Dieterich, 2020). First of all, the BMI of the obese pregnant should be calculated, and the amount of weight that should be gained during pregnancy should be determined. An obese pregnant woman should be told that an average of 6-8 kg will be sufficient for her and her baby's health. If the obese pregnant woman gains weight outside of the ideal, her eating habits should be reconsidered, physical activities should be regulated, and if necessary, light exercises should be suggested and improvements should be made (Christenson, 2020; Dieterich, 2020). On the other hand, it is recommended that pregnant women do prenatal screening tests during this period. Prenatal ultrasound (USG), glucose tolerance test (GTT) and preeclampsia screening should be done in obese pregnants (Bayram, 2020). In many studies, cesarean section rates were found to be higher in overweight and obese women compared to normal weight women. Obese pregnant women commonly have an increased risk of overterm birth and, accordingly, induction of labor (Degez, 2021). Having a thick fat wall in obese pregnant women may complicate fetal

monitoring during labor. Therefore, monitoring from the mother's abdomen may not yield accurate results (Apay, 2010). Obese pregnancies are in the risk group in terms of macrosomia. It is difficult to accurately predict the fetal birth weight during this period. It is inevitable for healthcare professionals to encounter unwanted vaginal delivery complications due to fetal macrosomia (Gorban de Lapertosa 2020). In addition, the duration of cesarean section is prolonged in obese pregnants, and the risk of thromboembolism, skin infection, endometritis and postpartum hemorrhage increases (Polic, 2020). For this reason, delivery in obese pregnant women should be carefully planned and managed effectively. In cesarean deliveries, epidural anesthesia should be preferred instead of spinal anesthesia if the pregnant woman is in the latent phase (Özcan et al., 2016). In the admission of pregnant women with BMI>40 kg/m2 to the hospital for delivery, vascular access should be established first, vital signs should be followed carefully, and an explanation should be given to her and her family about complications (infection, bleeding, macrosomia, shoulder dystocia) that may occur during delivery. A multidisciplinary team approach should be adopted and uninterrupted communication should be established with the obese pregnant.

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CHAPTER 11

NEW VARIANTS OF SARS-CoV-2

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INTRODUCTION

New mutations seen especially in the S protein part of the SARS-CoV-2 virus has resulted in an evolution of the COVID-19 pandemic. There is now an unprecedented global fight and struggle against the new aspects of the pandemic through vaccination campaigns, while numerous studies investigating the effectiveness of several vaccines on the new variants are being continuously published. Unfortunately, scientific evidence in the literature pertaining to the new variants is yet very limited. We will not have better insight in the epidemiology, pathophysiology and neutralization of these variants unless the number of studies reporting outcomes increases. The new variants have been classified by WHO under three titles, including Variants of Interest, Variants of Concern and Variants of High Consequence. Variants of Interest (VOI) such as eta, iota, kappa and lambda variants have genetic phenotypic changes known to affect the virus characteristics, including disease severity, transmissibility, diagnostic and/or therapeutic escape. Variants of Concern (VOC) such as alpha, beta, gamma and delta variants are known to have changes that increase transmissibility of COVID-19, increase virıulance or change the clinical presentation and decrease effectiveness of social measures, diagnostics, and vaccines. The third type, Variants of High Consequence has not been reported so far. This chapter explains the characteristics of new SARS-CoV-2 variants with in the light of the recent literature.

1. SARS-CoV-2 Novel Virus

Coronaviruses are a distinct virus group that can lead to mild-to- severe pulmonary infections in humans. SARS-CoV-2 is a novel Betacoronavirus related to SARS-CoV that causes zoonotic disease, namely coronavirus 2019 disease (COVID-19) (Zhou 2020). The isolation of SARS-CoV from patients' bronchoalveolar fluids and RNA sequencing of the virus have revealed that SARS-CoV-2 is a causative agent of COVID-19 and is a betacoronavirus that had been never seen before (Hu et al. 2021). Human to human transmission of SARS-CoV-2 occurred for the first time in Wuhan city of China and showed a rapid intercontinental spread that resulted in declaration as a pandemic by the World Health Organization (WHO) (Huang 2020). The first entrance of the virus into humans is not clear, although genetic evidence indicates that SARS-CoV-2 is a new coronavirus that possibly originated from animals (Hu et al. 2020). The high infectibility of the virus and abundance of international travels have accelerated global spread of the disease. According to the August 5, 2020 daily report of WHO, there have been 200,174,883 confirmed cases of COVID-19 and 4,255,892 deaths (WHO 1). To find solutions for this lethal pandemic, research efforts are globally ongoing, and new advances are being achieved in clinical research, epidemiology, diagnosis, vaccines, therapy and development of novel drugs (Harrison et al. 2020).

1. Pathophysiology of SARS-CoV-2

In order to activate the endocytic route, SARS-CoV-2 needs proteolytic activation of S protein through proteases, including and transmembrane protease serine protease 2, furin and cathepsin L that have been associated with the cleavage of S protein and to activate the entrance of SARS-CoV-2 virus into the cell (Ou et al. 2020; Shang et al. 2020). TMPRSS2 protease has been shown to be expressed in large amounts in various body regions, including nasal epithelial sites, bronchial branches and lungs with co-expressed ACE-2 receptors (Lukassen et al. 2020). In a study by Hoffmann et al., it was demonstrated that ACE2 and TMPRSS2 are involved in the entrance of the virus host cell (Hoffmann et al. 2020). The positive sense ssRNA of SARS-CoV-2 is released after the virus enters the host cell, and uses ribosomes of the host cell to produce polyproteins. RNA polymerases are also used to duplicate the RNA (Sigrist et al. 2020).

The novel coronavirus also releases specific inflammatory modulators for the stimulation of macrophages (Walls et al. 2020). After the activation of macrophages, chemokines CXCL10 and CCL2 and cytokines IL-1, IL-6, and TNFα are released the circulation. This release causes an increase in the production and recruitment of macrophages and neutrophils, and all these stages lead to dyspnea, hypoxemia and cough later in disease (Wan et al. 2020). On the other hand the released cytokines travel in the blood, affecting the hypothalamus, triggering the release of prostaglandin PGE2, and causing an increase in temperature of the body. Tachycardia can also be

induced by the sympathetics and these abnormal responses may cause septic shock, resulting in multi-organ failure (Vallamkondu et al. 2020).

The pathogenesis of SARS-CoV-2 infection manifests in a wide range from asymptomatic state to mild-to-moderate pneumonia and severe respiratory failure. To enter the human body, SARS-CoV-2 binds to ACE2, which is the host target receptor (Cevik et al. 2020). ACE-2 receptors are abundantly found on the epithelium of several organs, including the intestines, kidneys, brain and blood vessels, which may explain gastrointestinal, cardiovascular and neurovascular involvement (Monteil et al. 2020). In addition, postmortem studies have revealed lymphocytic endotheliitis through pathological examination of the lungs, kidneys, heart and liver as well as myocardial infarction and liver cell necrosis in patients who died from COVID-19 (Varga et al. 2020).

The virus shows active replication in the epithelial cells of the respiratory tract, enters the airways, and pulmonary alveolar cells, causing symptoms such as fever, cough, headache, myalgia and respiratory symptoms. In an animal study by Sia et al., SARS-CoV-2 virus caused transient damage to the olfactory epithelial cells that may explain transient loss of taste and smell in COVID-19 (Sia et al. 2020).

The SARS-CoV-2 is rapidly replicated in humans results in a potent immune response, which is also called cytokine storms that ultimately lead to respiratory failure and acute respiratory syndrome that is accepted as the major cause of death in COVID-19 patients.

2. ADAPTIVE MUTATIONS IN SARS-CoV-2

High mutation rates allow RNA viruses to provide adaptation to hosts. In human CoVs, the rate of mutations is moderate to high when compared with the other single-stranded RNA viruses (Su et al. 2016).

On the other hand, SARS-CoV-2 can exhibit adaptive mutations that can change its pathogenic potential, making the development of novel vaccines and drugs challenging (Giovanetti et al. 2021).

Several mutations, especially in the spike protein that is the binding site of the virus to ACE-2 receptors to gain entrance into cells, have been studied. The most common mutations during summer 2020 include D614G, N439K, and S477N, and these mutations have been reported to increase transmissibility of SARS-CoV-2 (Li Q et al. 2020). It has been shown that Spike D614G boosts the infectivity of the virus by increasing the binding affinity between the ACE-2 receptor and the spike protein (Korber et al. 2020). In a study by Long et al., it was shown that viral load in the upper respiratory tract is higher in patients infected with variant D614G. Mutant strains that carry D614G have been suggested to be less adaptive to the lower respiratory tract (Long et al. 2020).

Multiple mutations related to immune evasion are dramatically increasing. Patterns of the emerging or persisting variants suggests that these mutations reflect non-specific adaptations acquired following zoonosis, but the underlying mechanisms are still unclear (Geoghegan and Holmes 2018). Furthermore, analysis of SARS-CoV-2 genetic

diversity has shown that the most common mutations are highly variable among individuals (Armero et al. 2021).

1. Deletions

Deletions are primarily found in regions that code for proteins which interact with the spike protein and host response. Potential convergent evolution of SARS-CoV-2 has been shown in many countries with deletions in the NSP1 region (Lin et al. 2021). In a study by McCarthy et al., the importance of deletions in the evolutionary trajectory of the virus has been emphasized (McCarthy et al. 2020). In another study by Liu et al., it was argued that isolates containing deletion around the furin polybasic site of the viral spike protein are associated with a mild or asymptomatic disease course (Liu et al. 2020). Recurrent deletion has been found to overcome slow acquisition of substitutions (McCarthy et al. 2020). Apparently, deletions accelerate SARS-CoV-2 antigenic evolution and promote adaptive evolution.

2. The Effects of Novel SARS-CoV-2 Mutations on Vaccination and PCR Tests

SARS-CoV-2 constantly undergoes diversification that lead to problems for both testing and vaccination. For example, substitutions in the E protein have been shown to interfere with PCR testing (Artesi et al. 2020). In general, ORF1ab is conserved more than the S protein, which is in turn conserved more compared to the other ORFs. In a study by Rochman et al., 10 regions from ORF1ab, N and E genes that are commonly used in PCR testing were examined. It was found that the

nucleotide substitutions of ORF1ab were markedly variable compared to those in N. One region in N demonstrated variability in about 1/3 of all isolates (Rochman et al. 2020). Some of the existing vaccines utilize the entire spike protein as the antigen, while others use only RBD (Dong et al. 2020). Most mutations in the RBD have been shown to decrease infectivity, but some have resulted in resistance to antibodies (Oude et al. 2021).

1. NEW SARS-CoV-2 VARIANTS

Mutations are inherent characteristics of all viruses, although the rate of mutation is higher among RNA viruses (Al-mubaid and Al-mubaid 2021). However, coronaviruses lead to lower rates of mutations compared to other RNA viruses. A virus with one or more mutations is referred to as the virus variant. Variants can differentiate in themselves through mutations (WHO 2). New variants are expected as viruses mutate constantly. Many new variants of SARS-C0V-2 virus have been identified globally during the COVID-19 pandemic (Burki 2021).

All variants have one common mutation, D614G that was mentioned above. The D614G is a mutation that causes the replacement of aspartic acid with glycine at position 614 of the spike protein (Volz et al. 2021). This mutation has been associated with higher rates of mortality (Becerra-Flores and Cardozo 2020). In a study by Korber et al., it was found that D614G mutation is associated with higher levels of viral mRNA in the upper respiratory tract of patients with COVID-19.

The SARS-CoV-2 Interagency Group (SIG) has been founded in order to improve coordination among several health authorities, including CDC and FDA. In collaboration with SIG, CDC developed a new classification system for the new variants based on their threat level as variants of concern (VOC), interest (VOI) and variants of high consequence (CDC 1). The WHO and CDC, reported the variants of interest as B.1.526, B.1.525, B.1.427/B.1.429, and P.2. Whereas, variants of concern include Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2), with the Delta variant being the most concerning. To date of this chapter, no variants of high consequence have been identified (WHO 3, CDC 2). On May 30, 2021, Who announced the new naming system for SARS-CoV-2 variants of interest and variants of concern to help public recognition (WHO 4). The list of the variants of interest and variants of concerns is shown in Table 1.

Table 1. SARS-CoV-2 variants of interest and concern

VARIANTS OF INTEREST			
WHO Label	**PANGO Lineage**	**GISAID Clade**	**Country of First Documentation**
Eta (η)	B.1.525	G/484K.V3	Various countries
Iota (ϕ)	B.1.526	GH/253G.V1	USA
Kappa (κ)	B.1.617.1	G/452R.V3	India
Lambda (λ)	C.37	GR/452Q.V1	Peru

VARIANTS OF CONCERN			
WHO Label	**PANGO Lineage**	**GISAID clade**	**Country of First Documentation**
Alpha (α)	B.1.1.7	GRY	United Kingdom
Beta (β)	B1.351 B1.351.2 B1.351.3	GH-501Y.V2	South Africa
Gamma (γ)	P1 P1.1 P1.2	GR-501Y.V3	Brazil
Delta (δ)	B1.617.2 AY.1 AY.2 AY.3	G-478K.V1	India

3.1. SARS-CoV-2 Variants of Interest

Variants of Interest (VOI) have genetic phenotypic changes known to affect the virus characteristics, including disease severity, transmissibility, diagnostic and/or therapeutic escape. VOIs have been found to cause multiple COVID-19 clusters and community transmission (WHO 4).

3.1.1. Eta Variant (B.1.525)

The Eta variant of the virus or B.1.1.7 lineage was first identified in December 2020 in Nigeria and the UK. This variant does not carry the N501Y mutation as in Alpha, Beta and Gamma. However, it has the same E484K mutation with Beta and Gamma variants. This variant has

the same deletions of amino acids valine and histidine. In these deletions, G, U, A and C of the virus's RNA are missing. The Eta has different characteristics from the other variants, including both the E484K-mutation and a new F888L mutation (McNally). Currently, there is no evidence that the Eta variant is more transmissible or that variant increases the severity of the disease. The B.1.525 lineage is more vulnerable to neutralization than most other variants.

3.1.2. Iota Variant (B.1.526)

The Iota variant of SARS-CoV-2 virus arosen in New York City in late December 2020 (West et al. 2021). This variant poses RBD mutations that increase affinity of ACE2 receptors (Khateeb et al. 2021). The B.1.526 lineage of the virus has various mutations in the S protein, including D614G, D253G, E484K, T95I and L5F (Deng et al. 2021). In another study conducted by Duerr et al., vaccine breakthrough infection, which is defined as detection of the virus's RNA in the respiratory smear from a person ≥ 14 days after they completed all CIVD-19 mRNA vaccines approved by the FDA (CDC 2), was not more frequent compared to the other variants (Duerr et al. 2021). Sera collected from vaccinated individuals and convalescent patients retained neutralization against the Iota variant (Zhou et al. 2021).

3.1.3. Kappa Variant (B.1.617.1)

The Kappa variant (B.1.617.1) of the virus was first identified in India in October 2020. Similar to Delta and Delta Plus variants, Kappa variant is also a sub-lineage of the original B.1.617 variant. The Kappa variant

is a double variant due to the L452R and EE484Q mutations. This variant shares these mutations with the Delta variant (Khateeb et al. 2021). The Kappa variant can be detected with positive tests for E484Q. The B.1.617.1 varian is now found worldwide. B.1.617.1 mutations show a modest increase in affinity for ACE2 (Liu et al. 2021). In a study by Edara et al. the Kappa variant was shown to have 6.8-folds higher resistance against neutralization by serum samples collected from the infected and vaccinated persons, although most sera were still able to neutralize the Kappa variant (Edara et al. 2021).

3.1.4. Lambda Variant (C.37)

The Lambda variant of the virus was first identified in Peru and classified as a VOI by the WHO in June 2021 because of its high prevalence in South American countries such as Peru, Argentina, Chile and Ecuador (WHO 4). The spike protein of the C.37 variant has been reported to be more infectious due to the T76I and L452Q mutations. Kimura et al. demonstrated that infectivity of the viruses with Lambda variant is significantly higher than the parenteral D614G (Kimura et al. 2021). In the same study, the Lambda variant showed resistance against antiviral immunity. In several studies, it has been claimed that the Lambda variant may be feasible to cause vaccination breakthrough infection (Hacisuleyman et al. 2021; Jacobson et al. 2021).

3.2. SARS-CoV-2 Variants of Interest (VOIs)

Variants of interest (VOIs) are defined as the variants associated with increased transmissibility, more severe COVID-19 course with higher

rates of hospitalization and mortality, significant decrease in neutralization of antibodies generated by vaccination or previous infection and reduced efficacy of treatment or vaccine (WHO 4). Today, there are four VOCs that have been determined in different regions and at different times and have different mutations and characteristics.

3.2.1. Alpha Variant (B.1.1.7)

The Alpha variant of the SARS-CoV-2 virus was detected first among COVID-19 patients in the United Kingdom in September 2020 (Galloway et al. 2021). This variant involves 17 mutations with 14 being nonsynonymous point mutations and 3 deletions. Eight of the mutations occur in the gene that encode the spike protein, which provides the virus to enter the cells via ACE2 receptor. These three mutations in the S protein are especially concerning, because they are associated with increased transmissibility and infectivity. The HV 69–70 and Y144 deletions have been associated with immune escape in patients with immunodeficiency (Davies et al. 2021). The increased infectivity of the B.1.1.7 lineage has been attributed to the increased interaction between ACE2 receptors and the RBD Y501 mutant residue (Santos et al. 2021). In a study by Graham et al., no relationship was found between B.1.1.7 variant and severity of the COVID-19 (Graham et al. 2021). In addition, the rate of the asymptomatic patients did not significantly change with the increased incidence of the Alpha variant. Studies have reported that the neutralizing activity of vaccine sera

against the Alpha variant continued the B.1.1.7 variant could not escape vaccine mediated protection (Collier et al. 2021).

3.2.2. Beta Variant (B.1.351)

The Beta variant of the SARS-CoV-2 virus was identified first in South Africa in October 2020 and spread quickly (Mwenda et al. 2021). The B.1.351 lineage is determined with multiple mutations. The mutations are accumulated within the NTD and RBD. L18F, D80A, and D215G mutations are observed in the spike protein of the virus (Tegally et al. 2021). N501Y mutation is localized within the receptor binding motif (RBM), which has been proposed to be associated with increased transmissibility (Mwenda et al. 2021). Deletions in recurrent deletion regions (RDRs) potentially defect certain neutralizing antibodies and vaccines (Galloway et al. 2021). In a study by Cele et al., it was reported that B.1.351 may escape the neutralization by antibody response (Cele et al. 2021). This raised concern about the possibility of reduction in protection against reinfection and effectiveness of vaccines that target S protein. Furthermore, the Beta variant is significantly resistant to neutralization by sera and plasma collected from convalescent patients. So far, there is no evidence suggesting an association between the Beta variant and severity of the COVID-19.

3.2.3. Gamma Variant (P.1)

The Gamma variant of the virus was detected first in Brazil in January 2021 (Faria et al. 2021). In January 2021, new Gamma variant cases were seen in Japan through travellers from Brazil (Fujino et al. 2021).

The P.a variant was then spread to many regions of the world including the USA, Germany, France, Italy, and Spain. Phylogenetic studies have shown that the Gamma variant poses 17 mutations with 3 being deletions, 4 synonymous mutations and 4 nucleotide insertions (Faria et al. 2021). Of the 17 mutations, 10 are localized in the S protein, facilitating attachment to ACE2 receptors. E484K mutation of the variant causes resistance to neutralization by antibodies. Vaccine sera and plasma of convalescent patients showed a considerable loss of neutralizing activity against the Gamma variant. The Gamma varian has also caused reinfection as a result of the limited protective immunity produced by primary infection.

3.2.4. Delta Variant (B.1.617.2)

The Delta variant of the SARS-CoV-2 virus was detected for the first time in India in December 2020. The Delta variant was responsible for the second devastating COVID-19 wave in India. This variant harbors 10 mutations, including T478K, P681R, D950N, D614G, T19R, R158G, G142D*, L452R, 156del and 157del, in the spike protein of the SARS-CoV-2. The B.1.617.2 variant is the globally most dominant SARS-CoV-2 strains. As of July 6, the B.1.617.2 variant was responsible for 95% of the COVID-19 cases in England (Burki 2021).

The reproductive number (R0) is aboıut 2.5 in the original SARS-CoV-2 strain. R0 of the Delta variant is 7, indicating a very high transmissibility rate. All currently used vaccines have been reported to be effective against the B.1.617.2 variant, but it is not clear how

efficiently the vaccines protects against long COVID, which is defined as detection of COVID-19 symptoms in a person who had completed all series of the vaccines (Burki 2021). In conclusion, the Delta variant seems to continue its rapid global spread, at least until a more transmissible variant emerges and stops it.

CONCLUSION

The new variants of SARS-CoV-2 virus and especially Delta variant are currently continuing to threaten global health. Efforts and attempts to develop vaccines or modify the existing ones in order to neutralize the effects of the variants continues at a rapid pace. The whole world is in a great fight to eliminate this disaster. Undoubtedly, novel variants will emerge in the near future because of the highly dynamic nature of the virus. On the other hand, the number of studies reporting on the new variants is also increasing. It would be beneficial to update what we know about the new variants constantly in order not to break away from this war.

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CHAPTER 12

PATIENT SAFETY AND THE ROLE OF THE NURSE IN SURGERY

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INTRODUCTION

The “patient safety” concept, which first emerged between 1900 and 1919, evolved with the developments in the field of medicine. Although the patient safety concept only involved ensuring hand hygiene and relieving disease symptoms, it also involved reducing the risk of falls and minimizing drug errors by 1949 (Yardımcı and Başbakkal, 2012; Kowalski and Anthony, 2017).

Patient safety was improved in 2015 by including the attempts to avoid the formation of pressure sores, practices that proved the accuracy of patient data, measures that should be taken to minimize accidents, which might occur during surgery, and measures to avoid the patient from damaging himself/herself (Kowalski and Anthony, 2017). Later, the prevention of infections caused by the hospital, using the correct dose of medicine, patient mobilization, and safe surgery steps were also covered by patient safety (Gökdoğan and Yorgun, 2010; Korkmaz and Argon, 2018; Korkmaz, 2018). In this review, which was prepared based on the literature data, the development of patient safety in surgery, and the role of nurses were discussed.

1. PATIENT SAFETY

Patient safety is defined as the measures applied to prevent or minimize the damage to individuals in the process of benefiting from healthcare services (Yardımcı and Başbakkal, 2012).

Today, surgery rooms rank the first among the units threatening patient safety. A total of 7.742.707 surgeries were performed in Turkey in 2019 according to annual data (Sağlık Bakanlığı Sağlık İstatistik Yıllığı, 2019). It is seen that almost 50% of medical errors occur in operating rooms in our country (Ertem, Oksel and Akbıyık, 2009; Sağlık Bakanlığı ve Akreditasyon Daire Başkanlığı, 2013). Wrong side surgery is the second most common source of medical errors in surgery rooms. According to the Joint Commission International (JCI), the first cause of wrong side surgeries was the lack of communication between surgical team members in surgery rooms (Haynes et al, 2009; Karayurt et al, 2017; Kesgin, Kurtuluş and Dinç, 2017).

World Health Organization (WHO), in its examination of patient records, found that most of the errors in cases were preventable. WHO invited countries to increase health and safety systems, and provided support to improve patient safety. For this purpose, a Safe Surgery Checklist (SSC) was created on February 9, 2009 with the slogan "Safe Surgery Saves Life" (Sağlık Bakanlığı Güvenli Cerrahi Uygulama Rehberi, 2015; Woodman and Walker, 2018). According to this list, the surgical team must; make sure that the right surgery is performed on the right patient and on the right side, while protecting patients from pain, also protecting them against possible risks of harmful anesthesia, protect patients from the airway and respiratory losses that threaten them, be prepared for the risk of blood loss in patients, avoid applications that may cause allergic conditions in

patients, apply methods that will not cause surgical area infection in patients, prevent that gauze and tools are forgotten in patients, name and label the samples taken from patients, communicate patient information to each other in full form, maintain the capacity and the results of the surgery (Cheek and Jones, 2009; Sağlık Bakanlığı ve Akreditasyon Daire Başkanlığı, 2013;

The target of the Safe Surgery Saves Life Program is to prevent inadequate safety practices and surgical infections related to anesthesia and to eliminate disruptions caused by poor communication between surgical team members (Sağlık Bakanlığı ve Akreditasyon Daire Başkanlığı, 2013; Candaş and Gürsoy, 2015). The purpose of developing a Safe Surgery Checklist is to help to decrease the number of errors in surgical settings, strengthen the acknowledged safety implementations, and to improve interdisciplinary communication and teamwork

The success of the surgical procedure happens with the surgical team working in agreement. Team members should start applying SSC from the time the patient is admitted to the clinic. The Ministry of Health renewed this checklist with the permission of WHO, which said “Each institution can edit SSC according to its needs and procedures”, and published it under the name “Safe Surgery Checklist TR” in 2011. The SSC, which consisted of three stages, of WHO, which was in line with its own requirements, also covers the clinical process and consists of four stages in our country considering the start of the surgical process in the clinic (Pugel et al, 2015; Campionia and Dal Sassob, 2019).

The surgical team member, who fills out the SSC, must also complete the tasks specified in the list at each stage and ensure control. The surgical team member, who fills out the checklist, expresses the list verbally without interfering with the patient (Irmak and Bölükbaş, 2016). The sections in the list are as follows;

1.1. Before Leaving the Clinic

Surgery clinic nurse, surgeon, and anesthesiologist check the patient's identity, side marking, and surgical consent also checking the hunger status, the cleanliness of the surgery area, items such as jewelry and prostheses in the patient, whether there are surgery-specific interventions such as disimpaction, and ensured that patient wears the surgical suit. Diagnosis and examination results are sent to the surgery room with the patient (Sağlık Bakanlığı Güvenli Cerrahi Uygulama Rehberi, 2015; Candaş and Gürsoy, 2015).

1.2. Before Anesthesia Is Administered

The surgery team checks the part that must be filled in the surgery clinic before the patient is admitted along with the procedure to be applied, patient ID, and side marking, and accepts the patient by comparing the wristband and the information in the file. Risk assessment is checked verbally with the entire team (Akalın, Tekin ana Civil, 2012; Pugel et al, 2015).

1.3. Before the Surgical Incision

The surgery team introduces itself to the patient. The family name, surgery side, antibiotic application, blood glucose control, anticoagulant, and thrombosis risk evaluation are performed aloud. The surgeon must also be present in the room at this stage (Grindel, 2004).

1.4. Before Terminating the Surgery

It is the stage where the surgery is completed and final checks are performed. Counting (compress, needle, surgical instrument, etc.), sample (pathology, cytology) are checked and recorded at this stage. Important notes that should be forwarded to the surgery clinic nurse are written down. This stage must be under the control of one person to avoid any deficiencies and problems. The involvement of more than one person in this process may cause that any of these stages are overlooked (Sağlık Bakanlığı Güvenli Cerrahi Uygulama Rehberi. 2015; de Elguea et al, 2019).

2. THE ROLE OF THE NURSE IN SAFE SURGERY CONTROL

Surgical nursing can be defined as a branch in which physiological, psychological, socio-cultural needs of the individual are coordinated and individualized with the nursing care before, during, and after the surgical intervention based on physiological, biological and behavioral sciences in the recovery and improvement of health (Aslan, 2009;

Akyolcu, Kanan and Aksoy, 2012). It is a profession with important effects on improving the education of patients, ensuring their safety, applying scientific principles, and improving and ensuring healthcare in developing societies with rich cultures (Aslan, 2009; Karayurt et al, 2019). The contents of the training of surgical nurses increase the reliability of their applications in addition to their clinical experience. Also, it was emphasized in previous reports that applications must be performed especially by surgical nurses to avoid medical errors with the standard measures taken. After such practices, it was reported that the training of individuals for care should also be given by surgical nurses (Kesgin, Kurtuluş and Dinç, 2017; It was also emphasized that anatomy, pharmacology, physiology, nutrition, microbiology, care, immunology, effective communication and training of the patient, which play roles in wound healing, are important in the nursing education curricula (Akalın, Tekin ana Civil, 2012). It was also emphasized that nursing initiatives are important in terms of the drugs used by patients who undergo surgical procedures, presence of an allergy, use of special materials during the procedure, and management and control of such situations. In this respect, nurses provide patient training, apply scientific principles, ensure patient safety, the right care approach, and improve health in surgical applications in a multifaceted way (Sağlık Bakanlığı Güvenli Cerrahi Uygulama Rehberi, 2015;).

The responsibility of the surgical nurse is for the patient primarily being legally responsible for the quality of care given to patients before, during, and after surgical interventions, in diagnosing and solving the problems of patients, providing communication with other surgical team members, and training the patient. Also, surgical nurses have caring, educational, therapeutic, managing, patient rights protection, researcher, and counseling roles. Effective application of these roles depends on the ability of surgical nurses in using their knowledge and skills to cover the needs of the patient (https://dosyaism.saglik.gov.tr/ Eklenti/27595). For the surgical nurse to provide quality care, s/he must have adequate knowledge on the changes in anatomy and physiology, the consequences for the patient, risk factors in the order of surgery, preventing possible accidents, providing psychosocial support for the patient. Surgical nurses must be skilled in determining the needs of the patient in advance and in implementing appropriate interventions.

Perioperative nursing practices are explained as a process defining the care provided in the surgery room. The purpose of perioperative nursing care, which necessitates that the scope of the surgical intervention and its effects on the patient are known, is to help establish the level of well-being or better conditions for the patient (Sağlık Bakanlığı Güvenli Cerrahi Uygulama Rehberi, 2015; https://dosyaism.saglik.gov.tr/ Eklenti/27595). In line with this purpose, the important elements of perioperative nursing are implementing care as based on scientific grounds, understanding the necessity of different care methods, knowing when and how to start

these, being creative to maintain a technique when the need for flexibility emerges, ensuring trust, and evaluating care targets and the related costs (Kesgin, Kurtuluş and Dinç, 2017). The most important factor that causes problems during the surgical process for the patient negatively affecting the recovery is the effects of the surgical procedure on the patient. When surgical intervention is required, the co-operation of the patient with the surgical nurse has a very important share in the care of the patient as they are together over a longer period of time than the other surgical team members. The surgery room setting, which is unfamiliar for the patient who undergoes the surgical intervention, is lonely and the patient is vulnerable, the surgery room is crowded, and is the application area that requires nursing care (Sağlık Bakanlığı Güvenli Cerrahi Uygulama Rehberi, 2015). The sensitivity of surgical nurses to the patient and the patient's care during the surgical process maximizes the recovery of the patient in the postoperative period (Akalın, Tekin ana Civil, 2012; Pugel et al, 2015).

CONCLUSION

Patients who will undergo surgical intervention try to cope with their concerns before, during, and after their surgery. Surgical nurses, who cover the needs of surgical patients 24 hours a day, care for them, coordinating teammates have great roles in ensuring patient safety. Surgical nurses require safety measures to provide standards as well as professional knowledge and skills in performing these roles. It may be expected with SSC that the number of errors can be reduced in surgical settings, safety practices that are widely acknowledged are

strengthened, and interdisciplinary communication and teamwork improve.

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CHAPTER 13

NON-PHARMACOLOGICAL METHODS USED FOR NIPPLE TRAUMA IN LACTATING WOMEN

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INTRODUCTION

Breast milk is the most ideal method of feeding the baby for the first six months after birth. Breast milk is very important for maintaining community mental health, physical, emotional and mental development in children, and preventing lifelong diseases (Niazi et al., 2019; Morrison, Gentry & Anderson, 2019). American Academy of Pediatrics (APA), breast milk intake in infants; reported that it is associated with a decrease in hospitalizations due to respiratory tract infections, a decrease in the risk of sudden infant death syndrome, positive neurodevelopmental outcomes, and high intelligence scores. Benefits to the mother include a reduced risk of postpartum blood loss, depression, type 2 diabetes, cardiovascular disease, breast and ovarian cancer. It also has economic benefits such as preventing childhood diseases, protecting women's health and indirectly reducing health care costs (Morrison et al., 2019; Gupta et al., 2017). The World Health Organization (WHO), the United Nations International Childhood Emergency Fund (UNICEF) and APA have recommended exclusive breastfeeding for the first 4-6 months and continued breastfeeding until at least 2 years of age with additional food. One of the goals of WHO is to increase the rate of exclusive breastfeeding of infants younger than 6 months to 50% by 2025 (Gupta et al., 2017). Although breastfeeding is very important for babies, breastfeeding rates are much lower than the recommended level (Gianni et al., 2019). While 98% of women all over the world can breastfeed physically, only 35% of children are reported to be exclusively

breastfed in the first 4 months (Niazi et al., 2019; Morrison et al., 2019). Breastfeeding rate is a phenomenon that varies according to geography and time. Although it has been reported that the average rate of breastfeeding in the whole world is 40%; there are quite different rates between countries. While the rate of non-breastfed babies is around 20% in high-income countries, this rate drops to 4% in low- and middle-income countries (Morrison et al., 2019). To investigate the reason for these changes, the breastfeeding processes of women around the world have been examined. For this reason, the reasons why women continue to breastfeed or stop breastfeeding have been the subject of many studies. In general, the underlying factors of breastfeeding discontinuation behavior are; difficulties in breastfeeding, nipple trauma, insufficient milk perception and fatigue (Gianni et al., 2019). Nipple trauma precludes breastfeeding goals, especially in the first 8 weeks of the postpartum period (Laageide et al., 2021). The highest prevalence is 3-7 days after birth. between days (Firouzabadi, Pourramezani & Balvardi, 2020). More than 80% of women suffer from this condition (Gianni et al, 2019). Nipple trauma, which causes the mother to experience negative feelings such as pain, burning and tingling due to breastfeeding, is an important issue that needs to be treated. Especially the ineffectiveness of the drugs used today and/or their possible negative effects on the baby are discussed. Every day, women and physicians are turning to non-pharmacological methods that have been used for hundreds of years, with no reported side effects and proven effectiveness.

1. THE EFFECT OF NIPPLE TRAUMA ON BREASTFEEDING

In order to achieve breastfeeding goals, it is very important to know the reasons for breastfeeding initiation, continuation and discontinuation. Health professionals should know the underlying reasons for the behavior of stopping breastfeeding and should support the action to continue. It has been reported that breastfeeding difficulties encountered in the first month after birth cause early withdrawal from breastfeeding (Gianni et al., 2019). Nipple trauma; It has been defined as a feeling of friction, irritation and pain during sucking. Nipple trauma extends to severe pain due to swelling, painful, cracked, erythematous, edematous, swollen, bleeding nipples in the breast (Abobakar et al., 2020). Nipple trauma is the main reason for stopping breastfeeding early. Nipple sores are seen in 80-90% of breastfeeding women (Niazi et al., 2019; Nayeri, Kheirkhah & Janani, 2019). In studies, the rates of discontinuation of breastfeeding due to nipple trauma vary between 15-76% (Morrison et al., 2019; Shanazi et al., 2015). In addition, nipple trauma can have a reducing effect on milk production as a result of pain inhibiting oxytocin. A traumatic nipple is not a natural part of breastfeeding and needs treatment (Firouzabadi et al., 2020; Niazi et al., 2019). Treatment, on the other hand, is a difficult process as the baby continues to suckle and continues to be exposed to oral flora (Shanazi et al., 2015). As a result of not treating nipple trauma, premature breastfeeding cessation, breast abscess and nipple abscess, insufficient milk release, severe

pain, stress, interruption of mother-baby bonding, bleeding may ocur (Niazi et al., 2019; Abdoli et al., 2020).

Among the causes of nipple trauma, Staphylococcus aureus and Candida albicans infection as a result of the development of settlement agents such as wrong feeding technique of the nipple, the baby is too strong or too weak suck, pull the nipple before sucking the short bridle little language structure, the nozzle washing with soap, saw the Sunshine of the breast, vitamin deficiency, breast pump use, the use of pacifiers and formula can be considered (Niazi et al., 2019; As'adi et al., 2017a).

2. NON-PHARMACOLOGICAL METHODS OF TREATMENT OF NIPPLE TRAUMA

It is reported that the majority of nursing mothers experience nipple trauma due to lack of information about breastfeeding and incorrect use of breastfeeding techniques (Niazi et al., 2019). Breastfeeding education given to women (visual-tactile technology sets, etc.) is known to be preventive. However, in addition to these trainings, supportive and pain-relieving treatment should also be applied (Souza, Pina-Oliveira & Shimo, 2020).

Today, it is widely used among the public due to the use of non-pharmacological agents in the treatment of many diseases, their low cost and easy accessibility. The use of therapeutically effective plants has a long history (Niazi et al., 2019). Herbal agents have been used for a long time in many countries, especially in countries such as Iran

and China. These are reported to have fewer side effects (Niazi et al., 2019; Niazi et al., 2018). Complementary medicine plays an important role in improving the quality of postpartum care. Currently, 40% of commonly used drugs are derived from plants and natural sources (Shanazi et al., 2015). It forms the basis of topical wound care due to its plant extracts, flavonoid and phenolic contents (As'adi et al., 2017a).

Finally, non-pharmacological measures are recommended to the lactating woman to relieve and treat the traumatic nipple, relieve pain, shorten the recovery time for successful breastfeeding, continue exclusive breastfeeding, and prevent infection (Shahrahmani et al., 2018; Abobakar et al., 2020). The different methods that can be used are given under subheadings below.

2.1. Calendula (Calendula officinalis)

Kazemirad et al. in her 2014 study, which included 82 breastfeeding women, women were divided into two groups. Correct breastfeeding technique was explained to both groups. Calendula cream was used in one group and breast milk was used in the other group and they were followed for a week. It has been shown that calendula cream is more effective than breast milk in the treatment of nipple cracks (Kazemirad et al., 2014).

2.2. Honey

It has been proven for many years that honey has healing properties. It has a positive contribution to the wound healing process due to its

acidity level, sugar and other nutrients. It contributes to the development of new tissues by increasing the free oxygen in the wound environment. It has been shown to significantly increase efficacy and epithelization in chronic foot wounds, bedsores and tissue injuries. In the study, it was revealed that honey is effective in nipple trauma and therefore its use can be recommended (Firouzabadi et al., 2020)

2.3. Aloevera

Eshgizade et al. in 2016, a study was conducted to compare the effects of olive oil, aloe vera, and breast milk on pain severity and nipple cracks in lactating women. 90 lactating women with nipple cracks were divided into three groups. The first group applied olive oil, the second group applied aloe vera and breast milk, and the third group applied only breast milk to the nipple and areola. As a result of the applications, the pain intensity and nipple cracking were found the least in the aloe vera group. It was found that the breast milk and olive oil groups equally reduced pain severity and nipple cracking. As a result of this study, it was revealed that olive oil, aloe vera extract and breast milk reduce the severity of pain and nipple cracking in lactating women (Eshgizade et al., 2016).

2.4. Mint (Mentha)

Mint contains menthol and phenol compounds and therefore inhibits bacterial and fungal activity (Abobakar et al., 2020). Topical use of peppermint essential oil or cream prevents infection by inhibiting

inflammatory processes and contributes to the healing process (Gharakhani Bahar et al., 2018). Mint; It is widely used in the treatment of numbness, burns, scars, itching and infection on the skin (Shanazi et al., 2015). The use of peppermint in the treatment of traumatic nipples contributes to the healing of pain and nipple cracks; no side effects have been reported for the mother and baby (Shanazi et al., 2015; Gharakhani Bahar et al., 2018). Mint increases tissue flexibility and prevents cracks (Shanazi et al., 2015).

Gharakhani Bahar et al. conducted a study considering the increasing trend towards traditional medicine and the success of peppermint in nipple cracks. In the study, the effects of peppermint tea, peppermint cream and breast milk on the treatment of breast cracks during breastfeeding were investigated. In the study conducted with 216 people, the applications continued for 14 days. A reduction in nipple crack pain was reported in the mint cream, mint tea, and breast milk groups at 0-14 days after the interventionThis decrease was higher in the breast milk group (Gharakhani Bahar et al., 2018).

Shanazi et al. in his study; It was aimed to compare the effects of lanolin, peppermint and dexpanthenol creams on traumatic nipple treatment. The study was conducted with 126 breastfeeding mothers. As a result of the study; It has been reported that lanolin, peppermint and dexpanthenol creams have similar therapeutic effects on the traumatic nipple (Shanazi et al., 2015).

Tsai et al. in his study, 110 primiparous women were treated with peppermint juice after each breastfeeding for 2 weeks postpartum. It

has been shown to be effective in preventing and relieving nipple pain and cracks (Tsaı, Wang & Chou, 2020).

2.5. Jujube (Zizyphus Jujuba Miller)

Jujube fruit is one of the plants that has been used for a long time with its antimicrobial and anti-inflammatory properties and healing properties of wounds and burns. In traditional Chinese medicine, the unique medicinal properties of this fruit were discovered thousands of years ago. The jujube fruit, scientifically known as Zizyphus Jujuba Miller, belongs to the Rhanmaceae family. Jujube fruit contains fatty acids, beta-Carotene, Alpha-Tocopherol, 7 phenolic compounds, caffeic acid, ferulic acid, p-hydroxybenzoic acid, chlorogenic acid, vitamins A, C, E, ferulic acid, flavonoids, cyclopeptide. It has a positive effect on tissues with its anti-inflammatory, anti-allergic, antiseptic, antiviral, antioxidant, antifungal and bactericidal properties. Shahrahmani et al., in their study, aimed to determine the effect of jujube lotion on the healing of nipple cracks. 100 lactating women were included in the study. As a result of the study; It has been reported that jujube fruit lotion heals nipple cracks faster and better than breast milk (Shahrahmani et al., 2018).

2.6. Purslane (Portulaca oleracea)

Purslane, which has many medicinal uses as a traditional medicine, belongs to the family of Portulaceae. With its antiseptic and antifungal effects, it heals wounds and reduces pain. However, the active components of purslane extract such as flavonoids, tannins,

terpenoids, coumarins and saponins have been shown to have antiseptic, bactericidal and antifungal effects. Studies have shown that it does not show any side effects (Niazi et al., 2019; Niazi et al., 2019).

In a study of 80 people comparing purslane cream and lanolin application; it was revealed that the group in which purslane cream was applied showed a significant decrease in nipple cracking compared to the lanolin group (Niazi et al., 2019). In another study; the effect of nipple trauma treatment with lanolin and purslane cream on the frequency and duration of breastfeeding was investigated. 86 breastfeeding women with nipple trauma were included in the study. Correct breastfeeding technique was explained to both groups. Pain intensity in the purslane cream group was found to be significantly lower than in the lanolin group. The frequency of breastfeeding after the fourth day in the purslane group was found to be significantly higher than in the lanolin group, and there was no significant difference between the two groups in terms of breastfeeding duration (Niazi et al., 2019)

2.7. Olive oil

Olive oil contains flavonoids, antioxidants, antibacterial and antifungal compounds. It is also used for skin health due to its positive effects in the treatment of wounds (Saglık & Kısacık, 2021).

One study compared the effects of olive oil and breast milk in the prevention of nipple trauma. 120 primiparous breastfeeding mothers were included in the study. As a result; Compared to the breast milk

group, olive oil has been shown to be more effective in reducing the severity of pain and preventing the formation of nipple cracks. (Saglık & Kısacık, 2021). In another study; 120 women were included for the comparison of extra virgin olive oil and breast milk. It was revealed that the recovery from nipple trauma was better in the extra virgin olive oil group compared to the breast milk group (Ahmed et al., 2020).

2.8. Gum tree (Pistacia atlantica-Saqez)

The first study to evaluate the effectiveness of gum tree cream against breast milk; It was carried out with 100 women and the groups were followed for 7 days. As a result, it has been revealed that gum tree cream is more effective than breast milk in the treatment of nipple cracks and pain (As'adi et al., 2017a). In another study to investigate the effect of gum tree cream on the healing of nipple cracks in lactating women, 100 women were included and followed for 1 month. As a result of the research, it has been shown that gum tree cream is more effective than breast milk in healing nipple cracks. No side effects were reported in the study (As'adi et al., 2017b).

2.9. Yarrow (Achillea millefolium)

It is a plant belonging to the Asteraceae family. It is one of the widely used plants for the treatment of diseases in traditional medicine. Yarrow, beta-pinene, 1,8-cineole, artemisia ketone, linalool, alpha-thujone, betathujone, camphor, borneol, phenyl acetate, bornyl

acetate, (E)-beta-caryophyllene, germacrene D, caryophyllene oxide, beta-bisabolol, delta-cadinol, chamazulen, flavonoids and alkaloids. The most important properties of yarrow are its antibacterial and anti-inflammatory properties (Abdoli et al., 2020). Yarrow herb is used in traditional medicine for bleeding, menstrual disorders, hemorrhoids, blood in the urine, inflammation, etc. used in treatments. This herb has antipyretic properties. It is also widely used against inflammatory disorders and for the healing of tissue wounds. It can be used in women's nipple trauma (Firouzabadi et al., 2020).

A study by Abdoli et al. to investigate the effect of the topical form of yarrow on nipple fissure included 80 women. Yarrow tea was administered in one group and breast milk was administered in the other group. As a result of the research; it has been shown that the topical form of yarrow is more effective than breast milk in the treatment of nipple pain and cracks (Abdoli et al., 2020).

Firouzabadi et al. conducted a study to evaluate the effects of yarrow, honey, and breast milk on the treatment of nipple fissures and included 150 women. As a result of the research; it has been found that yarrow, honey and breast milk are beneficial in the treatment of nipple cracks and provide equal treatment (Firouzabadi et al., 2020).

2.10. Chamomile

Chamomile is an annual, aromatic herb belonging to the Asteraceae family. It is one of the oldest plants known to date. Its use dates back to Ancient Greece. As components of the chamomile plant; It contains

flavonoids such as Alpha bisabolol, Bisabolol oxide, Chamazulene-Apigenin-Luteolin. Bisabolol and flavonoid are reported to have anti-inflammatory, analgesic and calming effects. Chamomile; it can be used internally or externally for wounds, eczema, burns, skin irritation and rheumatic pains. Naveri et al. included 106 women in their study to investigate the effect of chamomile cream on healing of nipple cracks in nursing mothers. Two groups were formed for chamomile cream and lanolin application and treatment was continued for one week. As a result of the research; it has been shown that chamomile cream is more effective than lanolin in healing nipple cracks and does not cause any side effects (Nayeri, Kheirkhah & Janani, 2019).

2.11. Cabbage Leaf (Brassica oleracea var. Capitata)

Cabbage is reported to contain sulfurheterocytes, sinigrin rapin, magnesium and oxalate. Cabbage has both anti-irritant and anti-inflammatory properties. Abobakar et al. conducted a study to evaluate the effect of non-pharmacological approaches using breast milk, peppermint and cabbage leaves on nipple trauma. The study was conducted with 150 lactating women in 3 groups. As a result; It has been found that breast milk, peppermint and cabbage leaf are equally effective in the treatment of traumatic nipples (Abobakar et al., 2020).

2.12. Breast Milk

Breast milk has antibacterial properties, anti-inflammatory agents and immune factors such as oligosaccharides, lactoferrin, fatty acids, lysozyme, immunoglobulin, lactoperoxidase. Breast milk is used in

the treatment of traumatic nipples. In many studies, it has been revealed that pain is reduced and healing is accelerated by applying breast milk to the nipple after each breastfeeding (Abobakar et al., 2020; Gharakhani Bahar et al., 2018). Since breast milk has both antiseptic and softening properties, it has been reported that some milk remains on the nipple and it dries out on its own (Firouzabadi et al., 2020).

Another factor discussed in the literature in terms of its effectiveness in preventing the development of problems related to nipple damage is breast milk. A simple, accessible and reliable source, breast milk has anti-inflammatory and antibacterial properties and is recommended for use to relieve breast pain. When a few drops of breast milk are applied around the nipple and areola, it acts as a barrier that prevents the deep layer of skin from losing its natural moisture (Saglık & Kısacık, 2021).

2.13. Lanolin

Lanolin is an organic ester obtained from sheepskin, containing 25-30% water (As'adi & Kariman, 2018). Lanolin prevents cracks by creating a moist environment on the skin surface. It contributes to the healing of nipple cracks by accelerating the formation of new epithelial cells. It is the most widely used method in the treatment of nipple cracks. Different results have been reported in cases treated with lanolin. One study showed that the use of lanolin in the treatment of cracked nipples was more effective than breast milk. In another

study, it was shown that the use of lanolin compared to breast milk was not effective in the pain and repair of nipple cracks (Niazi et al., 2019). At the same time, it has been reported in many studies that some women do not want to use it because they are allergic or because they do not see the results of lanolin as effective (Firouzabadi et al., 2020).

CONCLUCSION

As a result; different non-pharmacological methods that can be used in the prevention and treatment of nipple trauma, which has many effects on mother and baby, are discussed. The use and dissemination of these methods is very important in terms of increasing the quality of care and maternal satisfaction.

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CHAPTER 14

EVALUATION OF STROKE

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INTRODUCTION

The World Health Organization (WHO) defines ischemic stroke as neurological dysfunction, which occurs due to focal cerebral spinal or retinal infarction, and this is the definition of ischemic stroke proposed in the 20th century. Stroke is divided into two groups in the form of "ischemic stroke or intracerebral hemorrhage" and "hemorrhagic stroke due to subarachnoid hemorrhage." Before the ischemic stroke, transient ischemic attacks (TIA) may be observed, and a temporary ischemic attack is defined as temporary neurological dysfunction that emerged due to cerebral spinal or retinal ischemia without acute infarction. It has the same pathogenesis as ischemic stroke, with an early risk of recurrence similar to ischemic stroke. In some cases, this risk is higher depending on etiology. Some recent studies have reported brain damage using diffusion-weighted magnetic resonance imaging in about 30-50% of cases defined as TIA, with treatable causes identified in its pathology (1, 2).

Stroke ranks second among causes of death following coronary artery diseases worldwide. It is the primary cause of disability and labor loss in adults. Incidence, prevalence, and mortality rates differ between countries, with the most important reason changing due to risk factors. In some societies, for example, hypertension is more common. In our country, stroke-related deaths are second with 15% (3).

Following age standardization, the incidence of total stroke in patients aged 55 and older is reported to be 4.2-6.5/1000 annually, 3.4-

5.2/1000 of which is also reported to be an ischemic stroke, 0-3-1.2/1000 is primary intracerebral hemorrhage, and 0.03-0.2/1000 is subarachnoid hemorrhage (4).

The average age of onset of stroke is 69.8 in men, while 74.8 in women. The risk factor is lower in women in younger and middle age, and the risk is higher in older age than in men (5, 6). Women aged 55-75 have a higher lifetime risk of stroke (20-21%) than men (14-17%) (7, 8). In research conducted based on age groups, the annual incidence was reported as 12-20/1000 in those under the age of 45 and 0.1-0.3/1000 in those aged 75-84 (4). Again studies have reported a higher incidence of stroke in the black race in all age groups than in the white race (8, 9).

According to the BASIC project, the incidence of ischemic stroke in the over-60s decreased between 2000 and 2010, while no change was reported in the population between the ages of 45 and 59, and the decline in the over-60s was observed in the white race and advanced age (4, 10). In studies where age, gender, and ethnicity were standardized, intracerebral hemorrhage incidence was reported to decline between 2000 and 2010 (11). The risk of intracerebral hemorrhage in the REGARDS study increased with age in whites, while there was no age-related risk in blacks (12).

In gender-based studies, the prevalence of stroke was reported to be 58.8-92.6/1000 in men and 32.2-61.2/1000 in women (4). It was reported that 6.6 million Americans over the age of 20 had a history of

stroke in the period 2009-2012, and the prevalence of stroke was also 2.6% for the indicated period. According to BRFSS data for 2013, the rate of stroke history over the age of 18 was 2.7% (13). Prevalence shows the difference between geographical regions. The far east countries are more affected than western countries. This has been attributed to a high rate of hypertension and a low blood lipid level in easterners. Japanese have a predisposition to intracerebral hemorrhage and intracranial atherosclerosis.

CLASSIFICATION OF STROKE

In the first classifications of stroke etiology, all strokes are divided into two main groups, ischemic and hemorrhagic, based on the pathology of the lesion. Five main groups were then identified, taking into account the pathology of the lesion as well as its localization and mechanism of occurrence. Accordingly, stroke groups are classified as follows (14):

By Mechanism:

1) Thrombotic stroke

2) Embolic stroke

3) Hemodynamic stroke

By Clinical Course:

1) Completed stroke

2) Progressing stroke

By Artery Area:

1) Total anterior circulation infarcts (TACI)

2) Partial anterior circulation infarcts (PACI)

3) Lacunar infarcts (LACI)

4) Posterior circulation infarcts (POCI)

By Clinical Categories:

1) Large artery atherosclerosis (Thrombosis or embolism)

2) Cardioembolism

3) Small-artery occlusion (SAO) (Lacuna)

4) Other determined etiology

5) Undetermined etiology

By Stroke Type:

1) Ischemic stroke

2) Hemorrhagic stroke

Ischemic Stroke

It is characterized by cell damage that occurs when cerebral blood flow or the oxygen and glucose levels required for neuronal structures are below a certain value and this continues for more than a certain period of time (Figure 1). Neuronal damage starts to occur if the blood flow in the brain is at 22 milliliters/100 grams/minute levels, while neuronal death occurs if the blood flow drops below 12

milliliters/100gram/minute (15). Ischemic stroke occurs as a result of blocking cerebral blood flow of any region in the brain (16). Blood cannot be transported to the brain due to occlusion in blood vessels. Ischemic stroke can be focal or global. Neuron death occurs where blood circulation is cut off in the focal ischemia blockage area. In global ischemia, neuron deaths occur in areas of the brain that are more susceptible to ischemia. Occlusions in the focal ischemia occur for embolic or thrombolytic reasons (17). Ischemic stroke accounts for 80% of all strokes in American and Western communities and 72% in our country (15).

Detailed understanding of the toxic mechanisms intertwined with each other at the molecular and cellular level, which result from sudden interruption of blood flow and cause the irreversible death of brain cells, is important for improving diagnosis and treatment approaches. The degree of ischemic tissue damage that starts with focal hypoperfusion depends on the severity and duration of ischemia. Many pathological processes are triggered by cerebral ischemia. These processes include disruption of protein synthesis at the cellular level, depolarization, and cytotoxic edema as a result of sodium and water entry into the cell, increased intracellular calcium, mitochondrial damage, and energy deficiency, DNA damage, overload of the endoplasmic reticulum with unfolded proteins, excitotoxicity, oxidative/nitrative stress, activation of necrosis and apoptosis pathways, as well as, at the tissue level, they are summarized as blood-brain barrier disorder, microvascular damage, vasogenic edema,

and inflammatory reaction. Then it ultimately causes the death of neurons, glia, and endothelial cells (19).

In cerebral ischemia, cells in the brain region where blood flow is severely impaired are rapidly and irreversibly damaged, which is called the nucleus region of ischemia (20). The cells in this region lose their ion homeostasis and structural integrity and swell within minutes. The region between the nucleus and oligemic brain tissue, which maintains its structural integrity but has lost function, is called the "ischemic penumbra." Due to residual blood flow provided by collateral vessels in this region, energy metabolism is partially preserved (21). Pathological processes triggered by ischemia in inverse proportion to the amount and sustainability of residual blood flow lead to permanent damage of tissue in this region within minutes or hours. If regional cerebral blood flow falls below 25%, there is a 95% chance of developing infarct, but if the value is above 50%, the probability is less than 5% (22). Improving blood flow with thrombolysis early in occlusion or suppressing ischemic pathological processes may save the penumbra region, and saving this area provides neurological healing, so this region is the main target in acute ischemic stroke treatments (23).

Oxygen and glucose use of brain tissue is high. Energy generation is almost entirely dependent on oxidative phosphorylation. Focal hypoperfusion reduces the provision of essential molecules such as oxygen and glucose, and as a result of this, the cells' ATP production, which is required as an energy source, is disrupted. The inability of

energy-dependent ion pumps to operate leads to the degradation of ion gradients between the two sides of the cell membrane, resulting in the depolarization of neurons and glia (24). Also, the lack of oxygen triggers anaerobic glycolysis, which causes the accumulation of lactate in the tissue. Increased lactate level contributes to the growth of the infarct and clinical worsening. Excitatory amino acids such as glutamate are well known to be toxic to neurons at high concentrations, leading to neurodegeneration. The extracellular level of glutamate and aspartate in cerebral ischemia has been found to increase. During the acute period of ischemia, non-NMDA receptors are overactivated with excitatory amino acids and cause excess amounts of Na^+, Cl^- and water to enter into the cell, contributing to swelling, particularly in dendrites. Excessive stimulation of NMDA receptors, on the other hand, causes increased calcium in areas where these receptors are dense, and activation of some enzymes that depend on localized calcium (25). These enzymes include phospholipase A2, calpain, cyclooxygenase, and nitric oxide synthase. Activation of these leads to damage to the cytoskeleton and the formation of toxic free oxygen and nitrogen radicals.

In the aftermath of ischemia, intracellular free Ca^{++} increases rapidly in neurons. Calcium input into the cell is thought to be via the ion channel of the NMDA receptor and voltage-gated Ca^{++} channels because both channels are activated as a result of depolarization triggered by ischemia. Furthermore, due to the lack of energy, Na-K ATPase cannot work and Na^+ accumulates inside the cell. Na^+/Ca^{++}

modifiers carry Ca^{++} in while trying to get rid of the Na^{+} that gets in. But the main factor that drives the increase of Ca^{++} inside the cell is the release of cellular storage. These increases in the Ca^{++} level activate destructive enzymes such as lipase, protease, and endonucleases, which can also increase free radical formation in various ways, triggering cell death (25).

Reactive oxygen species (ROS) such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radical (OH^-) can form in many different states. Under normal circumstances, there is a balance between the ability of a metabolic function to continue appropriately and the formation of ROS for antimicrobial activity and their inactivation. But due to the provision of oxygen back into the tissue at ischemia onset and especially in reperfusion after ischemia, more amounts of ROS emerge than the antioxidants' scavenging capacity, which in turn creates oxidative stress for the cell (26).

Increased ROB proteins directly or indirectly damage lipids, nucleic acids, and carbohydrates, disrupting the blood-brain barrier (BBB), leading to vasogenic edema, disrupting blood flow, and causing leukocytes to pass into ischemic tissue (27).

The concentration of nitric oxide (NO) formed in physiological states is non-toxic but, due to increased calcium inside the cell during ischemia, NO synthesis increases excessively and reaches toxic levels. NO reacts with superoxide simultaneously, forming a stronger oxidant, peroxynitrite. Peroxynitrite causes cell damage through many

mechanisms such as lipid peroxidation, tyrosine nitration, sulfhydryl oxidation, nitrosylation, and DNA damage (23).

Calcium accumulation and oxidative stress in mitochondria in ischemia cause the opening of the mitochondrial permeability transition pore (MPTP) which shows high permeability in the inner membrane of the mitochondria. This, in turn, destroys the proton-driven effect and mitochondria membrane potential needed for ATP formation and causes excessive oxygen radical formation. As a result, mitochondria swell and crack and cell death becomes inevitable (28). Meanwhile, proteolytic enzymes scattered from lysosomes to the cytoplasm as a result of membrane changes due to free radicals and energy reduction can also trigger necrotic processes.

The aforementioned toxic mechanisms cause death with necrosis and/or apoptosis in ischemic cells. Some cells, especially those located in the core area of the ischemia die quickly with excitotoxic swelling, osmotic disintegration, and necrosis, while some die more slowly with apoptotic mechanisms, and some exhibit a mixture of apoptosis and necrosis (29). It has now been shown that apoptotic and necrotic pathways of death are not independent of each other.

Consequently, the intertwined toxic pathways outlined above interact with each other at various levels, leading to cell death. In ischemic stroke, edema occurs in two stages: Rapidly developing cytotoxic edema, followed by vasogenic edema, which becomes apparent after 4-6 hours and reaches the maximum in 24-72 hours (20). Cytotoxic

edema is the swelling of neurons mainly due to the loss of function of the Na-K ATPase pump, which occurs when blood flow values drop below 30%. Cytotoxic edema does not produce a mass effect, but a heavy loss of function can occur. In vasogenic edema, there is a net increase in the volume of water and therefore tissue in the brain. If the infarct volume is large, vasogenic edema can cause transtentorial herniation (23).

With ischemia, microvessels are damaged, endothelial permeability increases, basal lamina, and intercellular matrix are destroyed, impairment occurs in the selective permeability and cerebral autoregulation of BBB. When cerebral perfusion pressure decreases, vasodilation occurs in arterioles to provide cerebral blood flow, and vascular resistance decreases. Activating the plasminogen with endogenous plasminogen activators, MMP release, and granular enzymes released from polymorphonuclear leukocytes in ischemia/reperfusion causes the basal lamina to degrade and therefore the BBB to degrade (23).

In cerebral ischemia, tissue damage is associated with the duration of the ischemia and blood flow to the tissue, but by restoring blood flow and oxygen to the tissue, there may also be additional damage to the tissue, which is called "reperfusion damage." Experimental studies have shown that reperfusion damage to the brain after short-term ischemia is low, while reperfusion damage and therefore infarct volume increase when the ischemia duration extends beyond 2 hours (31). The re-occurrence of excitotoxicity by reperfusion, excessive

free radical formation, increased levels of leukotriene and prostaglandin, and the adhesion of leukocytes to the veins by increasing the expression of endothelial adhesion molecules are the mechanisms that create parenchyma and vascular damage through reperfusion. Inflammation, another pathophysiological mechanism after cerebral ischemia, is necessary for cleaning damaged tissue, re-vascularization and structuring, although it has been suggested in most experimental studies that it further increases brain damage and causes stasis and BBB damage in the microvascular bed, resulting in poor prognosis. (32).

Etiology and Classification in Ischemic Stroke

Various classifications were suggested for the ischemic stroke, based on clinical course, presentation, formation mechanism, and vascular irrigation area, one of which was classified based on clinical findings in 1991 by Bamford et al. (*Oxford Community Stroke Project Classification* (OCSP)) (33):

- TACI (Total anterior circulation infarcts)
- PACI (Partial anterior circulation infarcts)
- POCI (Posterior circulation infarcts)
- LACI (Lacunar infarcts)

TACI (Total anterior circulation infarcts)

Acute hemiparesis (with or without sensory defect) is a syndrome characterized by the coexistence of all developing symptoms of cortical deficits and homonymous hemianopia, such as aphasia for the left hemisphere or neglect for the right hemisphere. When a finding (usually hemianopia) is not sufficiently tested for reasons such as disorder of consciousness, the existence of this finding is accepted. Such an infarct is expected to develop as a result of proximal occlusion of the middle cerebral artery (MCA) or internal carotid artery (ICA) occlusion (33).

PACI (Partial anterior circulation infarcts)

Motor/sensory, cortical symptoms, which make up TACI and are more limited clinical syndrome than TACI, are known for having only two of the hemianopia components or limited motor/sensory symptoms in a particular body part or newly detected isolated cortical deterioration symptoms. It reliably indicates infarction due to occlusion of one of the MCA branches or, rarely, the MCA itself (33).

POCI (Posterior circulation infarcts)

POCI syndrome shows brain stem and cerebellum involvement with occipital lobes fed by the vertebrobasilar system. The brain stem is characterized by the observation of any combination of hemianopia and cerebellum symptoms, indicating proximal or distal occlusion of the arteries forming the vertebrobasilar system (33).

LACI (Lacunar infarcts)

It is known for the presence of motor and/or sensory findings in all or at least two of the organs such as the face, arms, and legs without cortical findings and hemianopia. It usually points to small, deep infarcts due to occlusion in only one of the penetrating arteries that irrigate areas where the fibers that carry motor and sensory messages such as interna, basis pontis to the capsule are congested (33).

In *the Trial of Org 10172 in Acute Stroke Treatment (TOAST)* study published in 1993, which included etiology in addition to clinical findings, ischemic strokes were divided into 5 groups as follows. (34):

a) Large Artery Atherosclerosis (LAA)
b) Cardioembolism (CE)
c) Small-vessel occlusion (SVO)
d) Other Determined (OD) Etiologies
e) Undetermined Causes (UC)

In general, cardioembolism is responsible for 20% of ischemic stroke, large artery atherosclerosis for 50%, and small-vessel occlusion for 25%. There is no precise reason in 25-39% of patients (35).

a) Large Artery Atherosclerosis (LAA)

In addition to clinical findings in these cases, there are findings of significant atherosclerosis-related stenosis (50% and above) or occlusion of the neck or brain vessels in imaging methods.

Intermittent claudication, GIA in the same vascular part, carotid bruit, or low pulse history are findings that support clinical diagnosis. The presence of infarcts over 15 mm in computed tomography (CT) or magnetic resonance imaging (MRI) is potentially associated with large artery atherosclerosis. A 50% or greater stenosis of the appropriate intracranial or extracranial artery is required, proven by Doppler ultrasonography or arteriography (CT or MR angiography or Digital Subtraction Angiography (DSA)). Also, potential cardiac embolism causes should be excluded (34).

b) Cardioembolism (CE)

This group contains arterial occlusion cases thought to be due to a cardiac embolism. For a diagnosis of cardioembolism, at least one source of cardiac embolism must have been determined (Table 1). Clinical and imaging findings similar to those monitored in broad artery atherosclerosis are also found in this type of etiology. A history of systemic embolism or symptoms of GIA or stroke in multiple vessel areas supports the diagnosis of cardiogenic stroke. Causes of thrombosis or embolism due to large artery atherosclerosis should be excluded (34).

Table 1. Causes of cardiac embolism

High Risk	Moderate Risk
Mechanical prosthetic valve	Mitral valve prolapse
Atrial fibrillation (AF)	Mitral ring calcification
AF with mitral stenosis	Mitral stenosis without AF
Left atrial or atrial appendage trombus	Left atrial turbulence
Sick sinus syndrome	Atrial septal aneurysm
Recent myocardial infarction	Patent foramen ovale
(less than 4 weeks ago)	Atrial flutter
Left ventricular thrombus	Bioprosthetic heart valve
Dilated cardiomyopathy	Nonbacterial thrombotic endocarditis
Akinetic left ventricular segment	Congestive heart failure
Atrial myxoma	Hypokinetic left ventricular segment
Infective endocarditis	Myocardial infarction (4 weeks to 6 months)

c) Small-vessel occlusion (SVO)

It's also called a lacunar stroke. In these cases, diabetes mellitus (DM) or hypertension (HT) is frequently present, and this association supports the diagnosis. Localizations, where infarcts occur, are brain stem, basal ganglions, thalamus, corona radiata, internal capsule. Classic lacunar stroke syndromes are known as pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, and dysarthria-clumsy hand syndrome. With radiological methods, the lesion is either not seen at all, or the infarct diameter detected in CT/MR must be less than 15 mm in line with the clinic. There are no cortical signs in the clinic. In these cases, a heart disease that can cause embolism or large vessel diseases that cause 50% or more than 50% stenosis in the ipsilateral artery should not be detected (34).

d) Other Determined (OD) Etiologies

Large artery atherosclerosis, or vascular problems observed without cardioembolic causes, is a type of stroke caused by other rare causes, such as hypercoagulopathy processes or hematological diseases (34) (Table 2). Furthermore, 2-5% of all initial stroke cases are in this group (36), and the diagnosis of these diseases is done by angiography, leptomeningeal biopsy, and detailed hematologic, biochemical, and microbiological examinations (37).

Table 2. Other causes of ischemic stroke

Antiphospholipid antibody syndrome
CADASIL
Disseminated intravascular coagulation
Fabry's disease
Fibromuscular dysplasia
Disorders of thrombosis and hemostasis
Hypoperfusion syndromes
Migraine-associated stroke
Mitochondrial diseases
Moyomoya disease
Vascular wall diseases (dolicoectasia, aneurysm)
Arterial dissection
Sickle cell anemia
Primary or secondary central nervous system Vasculitides
Sneddon syndrome
Vasoconstriction/vasospasm
Thrombatic thrombocytopenic purpura/hemolytic uremic syndromes
Hyperviscosity syndromes
Heparin-associated thrombocytopenia
Medication-related strokes
Iatrogenic causes
Meningitis, vessel wall infections

e) Undetermined Causes (UC)

Patients with stroke whose examinations towards stroke etiology cannot be completed, or whose findings from the examinations do not fully meet the criteria for other etiological reasons or can be explained by multiple etiological factors, are in this group (34).

RISK FACTORS

Seventy-seven percent of strokes are first-time strokes. That's why recognizing and controlling stroke risk factors (primary protection) is so important (38). Conditions that pose a risk for stroke in healthy individuals are addressed in three sections; Unchangeable, changeable, and potential risk factors (Table 3).

Table 3. Risk factors of ischemic stroke

1. Unchangeable risk factors	
Age	
Gender	
Race	
Genetic	
2. Changeable risk factors	
a) Confirmed risk factors Hypertension	b) Undetermined risk factors
Diabetes mellitus	Alcohol consumption
Atrial fibrilation	Metabolic syndrome
Dyslipidemia	Hyperhomocysteinemia
Cigarette	Drug use and addiction
Asymptomatic carotid stenosis	Hypercoagulability
Obesity	Oral contraceptive use
Physical inactivity	Inflammation
	Infection
	Migraine

Sleeping breathing disorders
3. Potential risk factors
Migraine Metabolic syndrome Alcohol consumption (sleep breathing disorders) Sleep apnea Hyperhomocysteinemia Hypercoagulability Infection and inflammation

Unchangeable Risk Factors

The patients with these risk factors are high-risk patients but can benefit from these risk factors by avoiding or treating them. Unchanged risk factors are briefly explained below.

Age: It is highly significant among unchangeable risk factors, with an increased risk of stroke due to an increase in age. The risk doubles every 10 years after age 55 (39).

Gender: While the risk of stroke is higher in men, research has shown a higher incidence of stroke in women between 35 and 44 years of age and over 85 years of age. However, conditions such as pregnancy and oral contraceptive use lead to an increased risk of stroke in young women. It is cited as one of the causes of death at an earlier age due to cardiovascular disease at older ages in men, and the stroke mortality rate is higher in women than in men (40).

Race: Research has reported a higher incidence of stroke in the black and yellow race compared to the white race (41).

Genetics: Having a history of stroke in a mother or father increases the risk of stroke. Research has shown that the risk of stroke is higher in monozygotic twins compared to fraternal twins, while the risk is about 5 times greater in monozygotic twins (42). The majority of coagulopathy states show autosomal dominant transitions, and the antibodies of lupus anticoagulant and anticardiolipin show familial inheritance in about 10% of cases. Factor V Leiden mutation, protein C, S, and other factor deficiencies are thought to lead to an increased risk of venous thrombosis. In addition, stroke can occur in various rare genetic diseases.

CADASIL: (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) is a rare stroke syndrome that makes autosomal dominant inheritance and develops as a result of a mutation in the NOTCH3 gene (43).

Given the above information, it can be said that the stroke has a genetics-based feature, but not a single stroke gene is responsible for stroke, and the association with environmental factors is effective in stroke etiology. Genetic factors are currently considered to be one of the unchangeable risk factors as there is no treatment (44, 45).

Changeable Risk Factors

Stroke risk factors and risk factors related to cardiovascular diseases appear to overlap, and controlling common risk factors for both disease groups is important for the reduction of vascular diseases.

Confirmed Risk Factors

Hypertension: It is one of the major risk factors of both ischemic stroke and hemorrhagic stroke. The risk of stroke also increases due to an increase in blood pressure (46, 47). Controlling blood pressure is therefore important for reducing stroke risk as well as preventing conditions such as congestive heart failure and kidney failure (48). Studies have shown a 35-44% decrease in stroke incidence due to antihypertensive treatments. (49).

Smoking: It acts with different mechanisms in the formation of ischemic stroke. It increases coagulability and blood viscosity, raises the level of fibrinogen, accelerates platelet aggregation, and raises blood pressure (47). Smoking is an independent risk factor in the risk of experiencing a stroke (50). Smoking has been found to be a strong risk factor that increases the risk of ischemic stroke by about 2 times (51). In addition, smoking may also increase the impact of other stroke risk factors. The risk of ischemic stroke increases to 7.2 if smoking and oral contraceptives are used together (52). Passive smoking also increases atherosclerosis. When investigating whether the partners of women who smoked were at risk of ischemic stroke, an increased relative risk of 4.8 times was found in women whose spouse smokes. It had been shown in the Framingham study that with smoking cessation, the risk of stroke decreased each year and was the same as non-smokers after 5 years (45).

Diabetes Mellitus (DM): Plasma insulin levels are high due to having insulin resistance in patients with diabetes. There is sensitivity to atherosclerosis in these patients, and atherosclerosis risk factors (such as HT and hyperlipidemia) are more common (47, 51). DM is reported to independently increase the risk of ischemic stroke by 1.8 to 6 times (53). It has been shown that the risk of ischemic stroke increases 2 times in patients with impaired glucose tolerance (AKS: 110-126 mg/dl) and 3 times in patients with DM compared to patients with normal blood glucose levels (54). In a study of 11140 patients who were under oral antidiabetic treatment, it was shown that effective glycemic control reduced microvascular complications, but there was no change in macrovascular complications such as stroke (55). However, when risk factors such as HT and dyslipidemia are found in conjunction with DM, the risk of ischemic stroke due to these factors is more reduced if glycemic control is ensured (56).

Dyslipidemia: Hyperlipidemia is known to be a major risk factor for coronary artery disease. However, some prospective studies have found an association between serum total cholesterol levels and stroke, there are also studies available that show no significant association between hyperlipidemia and stroke (57). With increased levels of HDL cholesterol, the risk of ischemic stroke is reduced but the risk of hemorrhagic stroke is increased. High levels of triglycerides were found to be associated with an increased risk of ischemic stroke in both men and women (58). In the Rotterdam study, however, serum triglyceride levels were found to be inversely

correlated with hemorrhagic stroke risk. Recommendations for dyslipidemia treatment include statin initiation limit LDL-C > 190 mg/dL and at least a 50% reduction in target LDL-C level (59,60).

Cardiovascular Diseases: There is a strong association between symptomatic and asymptomatic cardiac diseases and cerebrovascular diseases. Dilated cardiomyopathy, heart valve diseases, intracardiac congenital defects increase the risk (61). Myocardial infarction increases the risk of developing AF and can be a source of cardiogenic embolism. The acute coronary syndrome is rarely associated with stroke (62).

Asymptomatic Carotid Stenosis: On the asymptomatic side, the carotid stenosis frequency of more than 50% is 7-10% in men over 65 aged and 5-7% in women (63). In studies, patients with 50-99% asymptomatic carotid stenosis had a 1-3.4% annual risk of having the same-side stroke. As the degree of stenosis increases, so does the risk of stroke (64). A subgroup analysis of another study showed that stroke risk was annually 3% in the presence of asymptomatic 60-74% stenosis, 3,7% in 75-94% stenosis, 2,9% in 95-99% stenosis, and 1,9% at total occlusion (65).

Atrial Fibrillation (AF): There is a 3-4-fold increase in stroke risk following the elimination of other risk factors mentioned above in patients with only AF. The risk of stroke is 20 times higher in patients with AF if age-related vascular diseases are evaluated together (66). The presence of mitral stenosis and accompanying paroxysmal or

persistent AF have the highest risk for embolic strokes, and these patients need to be anticoagulated (67).

Sickle Cell Anemia: Although the prevalence of sickle cell anemia is low, the risk of relativity is 200-400. The risk of stroke is high especially in homozygous patients, and the prevalence of stroke is the lowest (11%) at about age 20. The highest risk of stroke is in childhood, with an annual rate of 1% (63).

Dyslipidemia: Hyperlipidemia is known to be a major risk factor for coronary artery disease. However, some prospective studies have found an association between serum total cholesterol levels and stroke; There are also studies that show no significant association between hyperlipidemia and stroke (68). With increased levels of HDL cholesterol, the risk of ischemic stroke is reduced, but the risk of hemorrhagic stroke is increased. High levels of triglycerides were found to be associated with an increased risk of ischemic stroke in both men and women (69). In the Rotterdam study, however, serum triglyceride levels were found to be inversely correlated with hemorrhagic stroke risk. Recommendations for dyslipidemia treatment include statin initiation limit LDL-C > 190 mg/dL and at least a 50% reduction in target LDL-C level (70, 71).

Obesity: The classification of weight status has traditionally been defined by body mass index (BMI), but the concept of abdominal obesity has become important in recent years, and measurement of either waist-to-hip ratio or waist circumference has become widely

used. It is considered abdominal obesity that the waist circumference is more than 102 cm in men and 88 cm in women. In broad-scale prospective research, increased weight and abdominal adipose tissue were reported to be from risk factors in stroke (72).

Diet and Nutrition: Increased consumption of fruits and vegetables and decreased oil have been reported to be inversely associated with stroke (60). It has been reported in some prospective research that a high intake of Na causes an increased risk of stroke, while a high intake of K causes a reduction (73).

Physical Inactivity: Those who did regular physical activity appeared to have a reduced risk of cardiovascular and cerebrovascular disease. This protective effect of physical activity is based on lowering blood pressure and controlling other risk factors of cardiovascular disease (47).

Postmenopausal Hormone Therapy: It has been reported that hormone therapy with estradiol does not ensure a reduction in the risk of stroke and death in secondary protection, especially in the first six months the risk is high (47).

Unconfirmed Risk Factors

Alcohol: Alcohol increases HDL cholesterol in case of less use, reduces fibrinogen and platelet aggregation, enables tissue plasminogen activation, but causes vasodilation and cardiac arrhythmia in case of high dosage. Many studies have reported a "J"

relationship between alcohol consumption and ischemic stroke. The protective effect has been shown in light and moderate alcohol drinkers, and increased risk in heavy alcohol drinkers. High-dose alcohol intake has also been reported to cause an increased risk of stroke recurrence. There is a linear association between alcohol consumption and hemorrhagic stroke. The AHA 2011 is recommending alcohol cessation and those who will consume alcohol should not use more than 2 glasses for men and 1 glass for non-pregnant women per day (47).

Hyperhomocysteinemia: Hyperhomocysteinemia is one of the common and independent risk factors for venous thrombosis, atherosclerotic and thromboembolic diseases. High hyperhomocysteinemia was reported as a cause of atherosclerosis and cerebral thromboembolism, while moderate hyperhomocysteinemia was also reported as a vascular risk factor (74).

Hypercoagulability: Thrombophilia such as protein C and S deficiency, APC resistance, ATIII deficiency, and prothrombin 20210 mutation are included in this group. While these are known to primarily lead to venous thromboses, few and poor data are available that they may be a risk factor for stroke if other risk factors are eliminated. On the other hand, many studies are available on antiphospholipid antibody syndrome (AFAS) and lupus anticoagulants (LA), another cause of hypercoagulability (75). When looking at retrospective data, there was an association between AFAS and stroke, but this association was found to be weak in prospective studies (76).

However, studies that reported a strong association between ischemic stroke and AFAS in youngs (< 50 years) found a higher risk, especially in young women (77). It has also been reported that positive LA in women who use oral contraceptives is a major risk factor for ischemic stroke and myocardial infarction (78).

Drug Use and Addiction: Drugs that lead to addiction such as heroin, cocaine, and amphetamine are among the risk factors in both ischemic and hemorrhagic stroke. These specified drugs cause changes in blood pressure, lead to increased risk of infective endocarditis, cause embolisms, and lead to blood viscosity and platelet aggregation by causing hematologic abnormalities (47).

Inflammation and Infection: Inflammatory processes are effective in stroke pathophysiology. It has been reported that there is an association between the level of C-Reactive Protein (CRP), an acute phase reactor, and stroke, also an increase in CRP level leads to an approximately 2-3 fold increase in the risk of stroke (47). It has been reported that because the matrix proteins released by the inflammatory cells in the plaque cause rupture in the fibrous sheath, they are found at a higher rate in symptomatic plaques than in asymptomatic plaques (79). Another inflammatory cytokine that increases in symptomatic plaque is IL-18 which has a proatherogenic feature. The presence of many pathogen microorganisms has been shown in coronary and carotid plaques. Microorganisms such as *C.pneumoniae*, *H.influenza*, *H.pylori*, *M.pneumoniae*, EBV, CMV, HSV Type 1-2 are microorganisms that have so far been found to be associated with

atherosclerotic plaque progression. Despite these findings, there is no evidence that antibiotic treatment lowers the risk of stroke (80).

Migraine: Apart from rare diseases such as CADASIL and AFAS, where strokes are co-occurring with migraine, studies have been conducted into whether migraine itself is also a risk factor for stroke. In these studies, migraine with aura has been shown to have an increased risk of stroke, especially in young women. The risk increases 9-fold with migraines with aura in women using oral contraceptives and smoking. Migraine is thought to show this effect with reduced cerebral blood flow and an increase in platelet activation, particularly in the posterior circulation (81,82).

Sleep-related breathing disorders: It has been reported that the frequency of obstructive sleep apnea syndrome (OSAS) after stroke increases (83). The results of the meta-analysis found a significant association between obstructive sleep apnea syndrome (OSAS) and stroke incidence (84,85). The obstructive apnea-hypopnea index increased the risk of stroke with the increase of AHI index (86). But no study on whether there is a decrease in stroke risk with OSAS treatment is available.

DIAGNOSTIC METHODS

The initial clinical evaluation of the patient with stroke is highly important for the detection of the type of stroke and the clinical condition of the patient. The stroke should be distinguished from other conditions such as brain tumors and subdural hematoma, which can

lead to impaired brain function symptoms and signs. The first question to be asked in stroke cases is whether the stroke is an ischemic stroke or a hemorrhagic stroke. After making this differentiation, it is necessary to determine the subtype of stroke. Clinical neurological care is important in determining the severity of the stroke and can often determine the nature of the stroke. Coagulation disorders that can lead to stroke also need to be investigated (87).

Clinical Evaluation

History: The first stage in the clinical evaluation of patients is to take the anamnesis. The physician should be sure if start time, duration, initial symptoms, progression, or recovery of the stroke are known. If the patient is unresponsive to stimuli or is unable to speak due to aphasia, the anamnesis must be obtained from a family member or the person observing the incident. Through the story, the physician can determine whether there is weakness in one side of the patient's body, difficulty in speaking, whether the patient has a change in consciousness, impaired eyesight on one side of the eye, whether there is cross-eye or double vision, loss of balance, change of sensation, headache or dizziness, whether there is a synchronization disorder in the extremities.

Motor examination: Motor examination is done by evaluating strength and mobility in the flexion and extraction of muscle groups responsible for the movement of each joint in the shoulder, elbow, finger, knee, ankle, wrist, finger, hip, and toe. Muscle tonus needs to

be tested for stiffness or looseness. As well as these, temperature, needle prick, vibration, and joint position sensation should be assessed. Deep tendon reflexes should be evaluated with a reflex hammer. The Babinski reflex should also be investigated (87).

Cerebellar system examination: It is done by asking the patient to touch his own nose and the finger of the caregiver physician again and again and by asking the patients to move their heels up and down on the shin bone from the knee to the foot. If the patient is able to walk, the gait must be tested. Broad-based walking is one of the indicators of spastic and cerebellar disorders. Neurological history and examination should be synthesized for the detection of anatomical localization and detection of probable causes of stroke. Speech difficulties and a right hemiparesis indicate a left cerebral lesion that mostly begins in the frontal lobe or temporal lobes. In the stroke beginning from the brain root, a cross-syndrome occurs, often accompanied by the same-side cranial nerve inadequacies such as lower motor neuron facial weakness and eye-gaze weakness, and opposite-side hemiparesis of the extremities (87).

Clinical examination: Determining the vascular area of stroke often happens with clinical examination. Patients with paralysis, which involves the face and arm rather than the legs, often have a lesion in the middle cerebral artery area. However, patients with weakness that involves the leg rather than the arm often have a disorder of the senses in the anterior cerebral artery area, as well as, patients with ipsilateral hemianopsia often have a basilar or related lesion in the posterior

cerebral artery area. In the patient with vertigo, nystagmus, hoarseness, dysphagia, ipsilateral horner's syndrome, decreased sensation of a pinprick on the same side of the face and on the opposite side of the body, and sometimes with ipsilateral ataxia, there is usually a lesion in the area of the vertebral artery or posterior inferior cerebellar artery on that side (87).

Determination of etiology and severity: This stage is very important in deciding the appropriate course of treatment. The Glasgow Coma Scale (GKS) and NIHSS (National Institutes of Health Stroke Scale) are used to determine the severity of stroke and level of brain injury. In this way, the severity of the stroke and the level of brain damage are determined as numerical, resulting in important data on treatment and prognosis. These scales are used in the majority of clinical trials with therapeutic methods and substances for stroke, and treatment indications are especially used to decide whether to start thrombolytic therapy (88).

Laboratory Analyses

In order for the appropriate treatment to be determined, hematologic and serum biochemistry tests must be performed (Table 4). Conditions such as anemia, polycythemia, sickle cell anemia, or consumption coagulopathy, which can lead to cerebral tissue hypoxia, can be detected with a CBC. In addition, the platelet count is required to detect hypercoagulability or thrombotic thrombocytopenic purpura or

idiopathic thrombotic purpura, which can cause an ischemic and hemorrhagic stroke (89).

Table 4. Recommended laboratory tests in patients suspected of ischemic stroke

Diagnostic Tests
1. Complete Blood Count
2. Sedimentation
3. Blood Glucose Level
4. Serum Electrolytes (must contain in Mg and Ca)
5. Serum Creatinine Level
6. Prothrombin, Partial Thromboplastin Time
7. Electrocardiography
8. Lung X-ray
9. Urine Examination
10. CT or MRI
11. Carotid Doppler Ultrasonography
12. Holter Monitor
14. CT or MRI Angiography
15. Lumbar Puncture

A white blood cell (WBC) count contributes to the identification of infectious factors (such as endocarditis) or secondary infections (such as pneumonia) and is also important to exclude stroke associated with hematological cancer types such as leukemia. In the case of high white blood cells, prothrombin time and partial thromboplastin time should be measured to exclude the source of hemorrhage and obtain a basic value for anticoagulation or thrombolytic treatment. More detailed coagulation examinations, which include an anticardiolipin antibody, protein S46, and C45, as well as fibrinogen, which can cause an increase in blood density, are specifically investigated for hypercoagulability in young-age stroke patients (89).

Chemical analyses are conducted for the purpose of identifying metabolic syndromes such as hyperglycemia and hypoglycemia, which lead to increased stroke severity. In diabetic patients with focal neurological disorders, measuring capillary blood sugar would be fairly appropriate. Because both hypoglycemia and non-ketotic hyperosmolar state can manifest themselves with focal neurological disorders. These disorders are recovered with the adjustment of glucose (90).

Hypernatremia can lead to an increase in cerebral edema, negatively affecting the termination of stroke. Abnormalities in calcium and potassium levels can cause heart rhythm impairments that lead to malnutrition in brain areas. Conditions such as liver dysfunction and kidney abnormalities can cause impaired consciousness in patients with stroke, causing further complications. High levels of creatine phosphokinase can simultaneously trigger myocardial infarction. However, patients who lie still for a long time may also have an increase in the level of serum creatine phosphokinase, or this may be directly related to ischemia. Electrocardiography (ECG) is important for recognizing heart rhythm disorders that can lead to stroke or maybe a stroke-induced and life-threatening condition. The most important risk factors of cerebral ischemia include atrial fibrillation. Therefore, cases of stroke must be hospitalized and followed up by cardiac monitoring (91).

Imaging methods

The first examination required to exclude intracranial hemorrhage in patients with stroke is non-contrast computed tomography. Computerized brain tomography (CBT) is a widely used, easily accessible, and cheaper technique. Another method used in the early diagnosis of ischemic stroke is magnetic resonance imaging (MRI). This imaging method is used in the diagnosis of ischemic stroke from early periods and has high sensitivity. In studies comparing MRI and CBT, the sensitivity of CBT was reported as 16%, specificity was 98%; Also, the sensitivity of MRI was 83% and the specificity was 96% (92).

In stroke cases, research of etiology and treatment planning may sometimes require studies such as transcranial doppler ultrasound, digital subtraction angiography, CBT angiography, or MRI angiography. Transcranial doppler ultrasonography is especially used in carotid occlusion, but non-invasive and invasive angiographical methods can be useful in various situations where false positivity can be seen (93, 94).

Computed Brain Tomography

When assessing an acute stroke with a CBT technique, an answer is first sought to the question of whether the neurological problem is seen. The appearance of structural lesions that may cause hypertensive hemorrhage, subdural hematoma, and symptoms that may cause similar clinical picture other than ischemia in the early period ensure

the differential diagnosis of stroke from conditions such as trauma, tumors, and abscess. The CBT findings are normal in the early hours of ischemic stroke, and the purpose of CBT during this period in emergency conditions is to exclude the possibility of intracerebral hemorrhage. More than half of brain hemorrhage infarctions were not displayed with CBT taken in the first 12 hours of stroke, a study has found (95). Early symptoms such as cerebral edema or mass impact may occur in CBT in the early period of large infarcts. Other early infarct findings can be ranked as hyperdense appearance in the arteries, parenchymal hypodensity, deletion in the sulcus, loss of gray and white matter separation. CBT is not a very successful method of displaying lacunar and vertebrobasilar system infarcts. In healthcare facilities where thrombolytic treatment is given in ideal conditions, CBT of the patient being brought into the emergency room should be taken within the first 30 minutes (96).

Magnetic Resonance and Magnetic Resonance Diffusion Imaging

Magnetic resonance imaging (MRI) is a superior technique compared to CBT for diagnosing acute ischemic stroke (97). Normal findings can be found in MRI taken during the early hours of a stroke. New MRI techniques, such as diffusion and perfusion, have been developed from the first minutes, allowing for the imaging of stroke, and these techniques can provide detailed information on the hemorrhage and metabolic state of brain regions. These techniques can also detect the dimensions and localization of the ischemic region. In addition, ischemic lesions in the brain stem, posterior pit areas, and lacunar

infarcts can be easily viewed (98). The diffusion imaging technique is an MRI technique sensitive to microscopic movements of water molecules. This technique is based on the velocities of water diffusion (99).

Differential Diagnosis

Although there are positive outcomes due to thrombolytic therapy in the early hours in patients with stroke, the delivery of thrombolytics in cases that may be confused with stroke is not beneficial for the patient and may be one of the major causes of morbidity and mortality (100). In the differential diagnosis of ischemic stroke, metabolic disorders such as demyelination diseases (such as multiple sclerosis), tumors, abscess, encephalitis or other infections, hyperglycemia, hypoglycemia, hypercalcemia, hypocalcemia, hypernatremia, hyponatremia, as well as, trauma types such as the postictal deficit, subdural hematoma and contusion, and diagnoses that may lead to ischemic stroke-like symptoms such as migraine should be excluded. Due to the sudden loss of neurological function, it is considered that there is no difficulty in the differential diagnosis of cerebrovascular disease. The primary diagnosis of stroke is based on neurological examination. Difficulty getting anamnesis from the patient and/or patient's family may occur (101). Points in the anamnesis, which suggests that the symptoms are of nontraumatic vascular origin, are sudden onset of focal or global neurologic loss, symptoms lasting longer than 24 hours, or death before 24 hours (102). Differential diagnosis needs to be done quickly. The approach to a sudden

neurological disorder begins with a careful anamnesis taken from the patient or observer. The clinical picture at the time of admission to the hospital shows the patient's condition and the first step of diagnosis (103).

SCORES IN ISCHEMIA

Determining the etiology and severity of stroke is vital in deciding the appropriate course of treatment for patients. Determining the severity of the stroke and the extent of brain injury using the Glasgow Coma Scale (GKS), NIHSS (National Institutes of Health Stroke Scale) (Table 1.5), and Modified Rankin Scale (mRS) supplies data for both treatment and prognosis. These scales are used in the majority of clinical trials with therapeutic substances and methods for stroke, and the treatment indications are based partly on these scales, especially when deciding whether thrombolytic therapy can be initiated (88).

NIHSS (National Institutes of Health Stroke Scale)

The National Institute of Health Stroke Scale (NIHSS) defined by the American National Institute of Health is widely used in quantifying clinical findings (104). Because the window of opportunity required to make the thrombolytic treatment decision in acute stroke patients is extremely narrow, NIHSS that is completed in 5-8 minutes has been designed to contribute to diagnostic unity among physicians (105). In NIHSS, the total score is between 0-42, assessing 5 key parameters including "level of consciousness," "visual evaluation," "motor functions," "sense and neglect," and "cerebellar functions" (Table 5).

NIHSS identifies neurological loss in patients with stroke and gives prognostic value to the likelihood of developing complications (106).

Table 5. NIHSS (National Institute of Health Stroke Scale)

	Level of Consciousness **1.a Level of Consciousness Responsiveness**
0	Alert; Responsive
1	Not alert; Verbally arousable or aroused by minor stimulation to obey, answer, or respond.
2	Not alert; Verbally arousable or aroused by minor stimulation to obey, answer, or respond.
3	Totally unresponsive; Responds only with reflexes or is areflexic
	1.b Level of Consciousness Questions
0	Correctly answers both questions
1	Correctly answers one question
2	Does not correctly answer either question
	1. c Level of Consciousness Commands
0	Correctly performs both tasks
1	Correctly performs 1 task
2	Does not correctly perform either task
	2. Speech
0	Normal; clear and smooth speech
1	Mild-to-moderate dysarthria; some slurring of speech, however the patient can be understood
2	Severe dysarthria; speech is so slurred that he or she cannot be understood, or patients that cannot produce any speech
	3. Visual field test
0	No vision loss
1	Partial hemianopia or complete quadrantanopia; patient recognizes no visual stimulus in one specific quadrant
2	Complete hemianopia; patient recognizes no visual stimulus in one half of the visual field
3	Bilateral Blindness, including blindness from any cause
	4. Horizontal Eye Movement
0	Normal; Able to follow pen or finger to both sides
1	Partial gaze palsy; gaze is abnormal in one or both eyes, but gaze is not totally paralyzed. Patient can gaze towards hemisphere of infarct, but can't go past midline
2	Total gaze paresis; gaze is fixed to one side
	5. Language

0	Normal; no obvious speech deficit
1	Mild-to-moderate aphasia; detectable loss in fluency, however, the examiner should still be able to extract information from patient's speech
2	Severe aphasia; all speech is fragmented, and examiner is unable to extract the figure's content from the patients speech.
3	Unable to speak or understand speech
	6. Motor Arm
0	No arm drift; the arm remains in the initial position for the full 10 seconds
1	Drift; the arm drifts to an intermediate position prior to the end of the full 10 seconds, but not at any point relies on a support
2	Limited effort against gravity; the arm is able to obtain the starting position, but drifts down from the initial position to a physical support prior to the end of the 10 seconds
3	No effort against gravity; the arm falls immediately after being helped to the initial position, however the patient is able to move the arm in some form (e.g. shoulder shrug)
4	No movement; patient has no ability to enact voluntary movement in this arm
	7. Motor Leg
0	No leg drift; the leg remains in the initial position for the full 5 seconds
1	Drift; the leg drifts to an intermediate position prior to the end of the full 5 seconds, but at no point touches the bed for support
2	Limited effort against gravity; the leg is able to obtain the starting position, but drifts down from the initial position to physical support prior to the end of the 5 seconds
3	No effort against gravity; the leg falls immediately after being helped to the initial position, however, the patient is able to move the leg in some form (e.g. hip flex)
4	No movement; patient has no ability to enact voluntary movement in this leg
	8. Limb Ataxia
0	Normal coordination; smooth and accurate movement
1	Ataxia present in 1 limb; rigid and inaccurate movement in one limb
2	Ataxia present in 2 or more limbs: rigid and inaccurate movement in both limbs on one side
	9. Facial Palsy
0	Normal and symmetrical movement
1	Minor paralysis; function is less than clearly normal, such as flattened nasolabial fold or minor asymmetry in smile
2	Partial paralysis; particularly paralysis in lower face
3	Complete facial Hemiparesis, total paralysis in upper and lower portions of one face side
	10. Sensory

0	No evidence of sensory loss
1	Mild-to-Moderate sensory loss; patient feels the pinprick, however he or she feels as if it is duller on one side
2	Severe to total sensory loss on one side; patient is not aware he or she is being touched in all unilateral extremities
	11. **Extinction and Inattention**
0	Normal; patient correctly answers all questions
1	Inattention on one side in one modality; visual, tactile, auditory, or spatial
2	Hemi-inattention; does not recognize stimuli in more than one modality on the same side

Modified Rankin Scale

The modified Rankin Scale (MRS) is a scale developed for assessing independence rather than performing specific tasks. Thus, developing physical and mental fits against neurological deficits are also evaluated. Before the stroke, the patient's ability to perform all activities is evaluated (107,108). The stages of MRS are as in Table 6 (109).

Table 6. Modified Rankin Scale

	Modified Rankin Scale
0	No symptoms
1	No significant disability, despite symptoms, the patient is able to perform daily activities and tasks
2	Slight injury; unable to carry out all the usual tasks and activities that he did in the past, but able to do his own work without assistance
3	Moderate disability; needs some help to do his own business, but can walk on his own unaided
4	Severe disability; unable to walk unaided and meet unaided bodily needs
5	Very severe injury; bedridden, incontinent and in need of constant care and attention
6	Death

TREATMENT FOR ISCHEMIC STROKE

Intravenous Thrombolytic Treatment

Dissolving the fibrin in the blocked vein with the plasmin in the acute ischemic stroke is the basis for thrombolytic therapy, where the goal is to re-opening the affected vessel and recover penumbra tissue. Fibrinolysis, a key part of the normal hemostatic cascade, is an event that enables fibrin to be solved, circulation in the veins to be improved, and facilitates the process of repair that occurs following tissue damage. In order for the fibrinolytic system to become active, plasminogen must be converted to plasmin, which is ensured by the activation of the plasminogen with tPA or urokinase released from the endothelium (110). The primary target for treating acute ischemic stroke is the restoration of perfusion, thereby reducing neurological impairment, prolonged incapacity, and stroke-related mortality (111). After the NINDS rtPA Stroke Trial study, approval was given by the FDA to tPA treatment for ischemic stroke cases in 1996. In the placebo-controlled study published in 1995, which included 624 patients, 0.9 mg/kg intravenous rtPA was applied to stroke patients within the first 3 hours. After implementation, the overall incapacity rate decreased from 40% to 28%, overall results from 43% to 32%, daily life activities from 53% to 38%, and neurological deficits from 34% to 20%, and this treatment continued to yield beneficial results after 1 year (101). The most significant risk in intravenous rtPA application is symptomatic intracranial hemorrhage. In the NINDS rtPA Stroke study, intracranial hemorrhage rates were 6.4% and 0.6%

in patients who received rtPA and placebo, respectively, while mortality rates at 3 months and 1 year were similar. Subsequent studies reported an increased risk of hemorrhage with a lack of compliance with the treatment protocol. It was reported in the SITS-MOST study (*Safe Implementation of Thrombolysis in Stroke-Monitoring Study*) that the symptomatic intracranial hemorrhage rate continued by neurological worsening was 7.3% (113).

The Multicenter Acute Stroke Trial of Europe (MAST-E), *The Multicenter Acute Stroke of Italy* (MAST-I), and *The Australian Streptokinase Trial* (ASK) are studies that were discontinued due to high rates of intracerebral hemorrhage after streptokinase use, and considering these studies, treatment with streptokinase is not recommended.

Endovascular Interventional Treatment

Options for endovascular treatment that can be applied in the treatment of ischemic stroke include treatment options such as intraarterial thrombolysis, mechanical recanalization applications, and placing stents with acute angioplasty (115).

Intraarterial Thrombolytic Treatment

Intraarterial thrombolysis is applied in the form of local infusion of a low dose of the thrombolytic agent into or near thrombus for the purpose of safely increasing recanalization rates (116).

Furlan et al. (116) reported that in patients with occlusion in the medial cerebral artery detected by angiography, intra-arterial prourokinase was administered via a microcatheter and compared with the control, providing an advantage of 66% vs 18% in recanalization rates; Although it caused an increase in the risk of early symptomatic intracranial hemorrhage, it was reported that there was a significant increase compared to the placebo group when the 90-day prognosis rates were examined.

Intra-arterial administration together with intravenous thrombolysis is intended to provide faster recanalization in major arterial occlusions; It is reported that the patient group in which this method is most beneficial is the patients with proximal intracranial artery occlusion, such as the distal internal carotid artery, medial cerebral artery or basilar artery, where the risk of failure of intravenous rtPA alone is high.

Mechanical Embolism Treatment

The mechanical thrombectomy can be applied alone or together with pharmacological thrombolysis. Mechanical embolism treatment can be applied in different ways, such as breaking down the thrombus, removing it, and increasing thrombolytic penetration. Methods such as removal or aspiration of the thrombus with different devices or removal after compressing it between the stent and the vessel are employed (111).

Acute Intracranial Angioplasty and Stent Placement

The implementation of extracranial angioplasty and stent placement is generally applied prophylactically, but can also be done as an emergency treatment when the stroke is due to extracranial carotid or vertebral artery occlusion, or when the extracranial congestion must be exceeded to reach intracranial congestion (111).

Antiaggregant Medicines

The secondary goal of acute stroke treatment is to prevent cerebrovascular events from recurring early. Antiaggregant medication is also used for this (111). The most investigated antiaggregant drug is acetylsalicylic acid (ASA). In studies, ASA treatment has been reported to produce significant reductions in death and incapacity, resulting in a slight increase in hemorrhage (117).

Anticoagulant Drugs

As in antiaggregant drug therapy, it is aimed to prevent recurrence of early-stage cerebrovascular events in anticoagulant drug therapy. Intravenous (IV) anticoagulant drugs have been widely used to stop neurological impairment, prevent early recurrent embolism, and improve neurological outcomes in emergency stroke treatment. On the other hand, it is underutilized less and less because the results are not positive and the complications are greater than the benefit (111). In a review study comparing parenteral anticoagulant to ASA application, ASA was reported to do better, providing a lower rate of major

extracranial hemorrhage and mortality (111). In the IST study, 5000 or 25000 U subcutaneous standard heparin was administered within 48 hours after stroke, and although the risk of early recurrent stroke decreased, the increase in hemorrhage complications resulted in an adverse assessment of the benefit/risk ratio, which also applies to patients with atrial fibrillation (111). Treatment with low molecular weight heparin (LMWH) in ischemic stroke has been reported to have no significant benefit compared to placebo in 3-month follow-up (106).

CONCLUSION

Stroke, which is one of the cerebrovascular diseases, is a clinical picture that occurs due to the deterioration in cerebral blood flow, which can result in death, and which occurs with cerebral dysfunction. The conditions associated with stroke, which is one of the important causes of mortality and morbidity in the community, have constituted an important part of many studies. There are many risk factors thought to be related to stroke. Identification and prevention of these factors will reduce the mortality and morbidity of patients.

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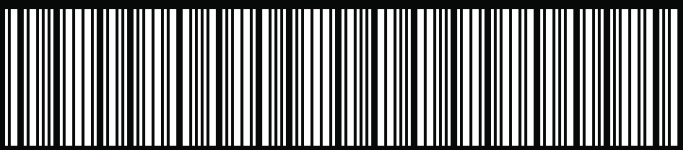

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