CURRENT RESEARCH IN MEDICINE AND HEALTH SCIENCES

Editors
Nizami Duran
Meriç Eraslan

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Editors • Prof. Dr. Nizami Duran • ORCID: 0000-0002-2766-3491
Assoc. Prof. Dr. Meriç Eraslan • ORCID: 0000-0001-7541-7554

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e-mail • livredelyon@gmail.com

PREFACE

Dear Reader,

This book is an essential resource that includes studies on human health, medicine, dentistry, and physiotherapy. It is a valuable reference work for students, academicians, and all healthcare professionals studying in the field of health. Researchers working in this field will also find this book extremely useful and valuable for their research. The book is designed for academics working in the field of medicine and public health and their students studying in this field. It is easy to read and covers basic concepts in healthcare. The book is divided into nine chapters, each dealing with a different topic. The first part covers neurological diseases, and the second part deals with Alzheimer's inflammation. The third section includes the treatment algorithm for pulmonary hypertension. The fourth chapter covers the analysis of abbreviations used in the field of blood physiology. The fifth chapter is about chylothorax, while the sixth chapter covers diabetes and sepsis mortality. The seventh chapter covers a study in the field of physiotherapy, and the eighth and ninth chapters include two studies in the field of dentistry. I believe that this book can be the first reference point for those who want to pursue a career in public health. It will also be a valuable resource for those choosing a career in clinical medicine.

I would like to express my deep gratitude to all the academicians who contributed to the preparation of the book, as well as the publishing house employees and management who contributed to its publication.

Editor
Prof. Dr. Nizami DURAN
Hatay Mustafa Kemal University, Medical Faculty

CONTENTS

CHAPTER I

DUAL TASK IN DIFFERENT NEUROLOGICAL DISORDERS

Gülfem Ezgi ÖZALTIN

(Dr.), Research Asist., Inonu University
E-mail: gulfemezgi.ozaltin@inonu.edu.tr,
ORCID: 0000-0003-1591-4844

1. Introduction

1.1. Dual Task

Dual task is defined as performing two actions (tasks) specific to different purposes at the same time, which can be done separately at different times. As in daily life activities, it allows two activities to be done at the same time, such as talking on the phone while walking or thinking about what to do while walking. All the factors that make up the movement require attention and memory as they affect each other. (1)

The tasks targeted during dual tasking are determined as motor motor, cognitive motor, cognitive cognitive. Targeted tasks influence each other during the activity. However, no clear consensus has been found about the direction of this interaction. Several theories have been proposed about the execution and processing of tasks:

Capacity sharing theory: Plummer et al. defined by. According to this theory, two tasks can proceed in parallel, but the central processing capacity is limited. (2) Total attention and capacity are distributed according to the tasks performed. Selecting and preparing for tasks is done within limited capacity. Ultimately, the system aims to fulfill the requirements of the task by blending the most relevant information with the task. (3) However, since tasks are shared within a limited capacity, less attention and capacity occurs. Capacity distribution may vary depending on the task or upon request. In other words,

if simultaneous tasks do not exceed the current capacity, the tasks do not affect each other, but when a task strains the existing capacity, double task confusion occurs. (4)

Multiple resource capacity model: Instead of a single central processing capacity or a single focus of attention, it is assumed that there are processing resources that can function parallel to each other and simultaneously. If tasks are shared for the same resource, performance loss occurs. (5)

Bottleneck Theory: If two different tasks are performed at the same time and receive stimulation from the same place, central processes concentrate on only one task and postpone the other task. That is, when two stimuli are given at the same time, one is detected while the other is ignored. If both are detected, a bottleneck occurs and a task is delayed. For example, if a cognitive task given during walking conflicts with the same neural networks, either the motor task or the cognitive task is postponed. (6)

Cross-Talk (Task Resource Theory) theory: Contrary to other theories, cross-talk theory suggests that dual task task selection facilitates each other instead of negatively affecting each other when the tasks are in similar areas. (7)

Dual task motor can be motor, motor-cognitive or cognitive-cognitive. In the evaluation of dual task tasks, each task should be evaluated separately and together, and the main focused factor should be evaluated separately. After task performances are evaluated, they can be expressed as numbers or percentages (e.g. dual task-single task). When a homogeneous evaluation is desired, factors that will affect the dual task (environment, age, attention, difficulty level of the task, etc.) should be taken into account. Directives given during evaluation should be fit for purpose. When the aim is to measure attention capacity only, it should be focused on a single task; When the aim is to measure motor capacity only, it is necessary to focus on the motor task; It should be noted that when the aim is to examine the effect of dividing the focal point on tasks, the same importance should be given to the tasks. Frequently used tasks related to dual tasking in the literature are shown in Figure 1. (8-10)

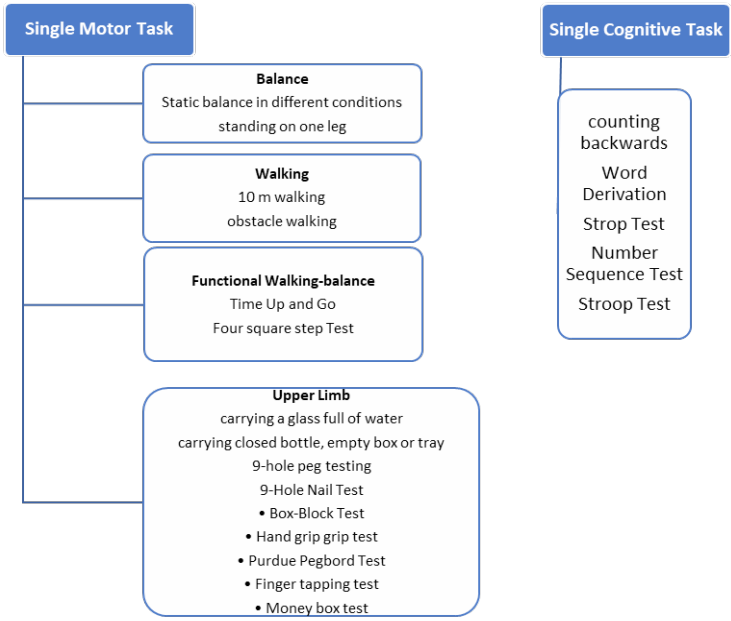

Figure 1: Dual Task Activities

Since dual tasking is a task that we frequently use in daily life activities without realizing it, its place in many different pathologies has been researched in the literature and has been used for its treatment. Previous studies have shown that the inferior frontal gyrus, anterior cingulate cortex and inferior frontal gyrus areas are active during a dual task. While lateral prefrontal cortical structures are more active in tasks requiring goal-oriented attention; The striatal structures of the basal ganglia are more active in more automated, practiced tasks that can be carried out with less attention. (6, 11)

1.2. Dual Task in Parkinson Diseases

In Parkinson's Disease, impairment of dopaminergic activity in the basal ganglia causes the automaticity of movement to deteriorate and increased attention while performing the movement. Freezing of gait (FOG) is defined as a decrease in step length during walking and a short-term decrease or cessation of forward movement. (12) Due to these reasons, functional mobility has been observed to decrease in Parkinson's Disease patients. Decreased functional mobility is associated with increased fall risk and decreased quality of life. It has been suggested that this may be due to decreased automaticity during movement and decreased executive function in the FOG frontal region. (13) It has been found that when a motor task is given along with a cognitive task in

Parkinson's patients, there is more activation in the middle frontal gyrus (MFG), prefrontal cortex, temporal lobe, parietal cortex, and cerebellum compared to healthy controls. (14) It has also been observed that the cerebellum, precuneus and prefrontal cortex have a supervisory role during dual task activities. (14) It has been observed that the structural connectivity of the right pedunculopontine nucleus (PPN) and activation in the prefrontal areas, pre-supplementary motor area (pre-SMA) and posterior parietal cortex are reduced during dual task activities in those with FOG. (15, 16)

O'Shea et al. examined the effects of dual-task interventions on walking in PD and examined the effects of motor and cognitive secondary tasks on walking. It has been recognized that walking performance decreases in both dual-task tasks, but to a negligible extent. (17) Canning et al. examined motor dual task instructions in patients with mild to moderate Parkinson's disease. Parkinson's patients were instructed to walk at a normal pace, hands-free, and to carry a cup while walking. While performing the dual task, the participants first focused on walking while carrying a glass in their hand and completed the task in this way; Then, he was instructed to direct his attention to the tray and glasses and asked to walk. At the end of the study, it was observed that when they directed their attention to walking, they walked faster and with longer steps than those who were instructed to walk without attention guidance. Based on the results of this study, it was seen that using special instructions to direct attention during dual tasks was effective. (18) Spildooren et al. investigated the effect of dual tasking in Parkinson's patients with and without freezing of gait (FOG). Spilhood et al. According to reports, 360-degree rotation and dual-tasking are the most obvious triggers for freezing. It was observed that Parkinson's patients and controls without FOG decreased the tempo during turning, while those with FOG increased it. They think that this may be due to dual task confusion during rotation and may be related to FOG. (19)

Dual task training constitutes an alternative treatment option for cognitive and motor functions affected by the impaired dopaminergic system. When the studies were examined, it was seen that dual task training had positive effects on step length, walking speed and balance in individuals with Parkinson's. (20)

1.3. Dual Task in Hemiplegia

According to WHO, stroke has become one of the most common causes of death in the world. (21) Motor disorders (unilateral paralysis of the body) and cognitive disorders are observed after cerebrovascular accident. Cognitive impairment occurs in approximately 25% of people who experience CVO. Of

those who did not have a stroke after CVO, approximately 50-75% had mild to moderate cognitive impairment. (22) Dual task, in which cognitive and motor tasks are given in a complex manner, has begun to be used frequently as both an evaluation and treatment method in individuals with stroke. Activities of daily living require patients to walk in simple and standard environments as well as in challenging, complex, multitasking environments. For this reason, training in cognitive functions as well as single motor functions is very important in the rehabilitation of individuals who have had a stroke. (22) When studies in the literature are examined, the general opinion is that dual task training increases motor performance such as balance, walking and upper extremity functions. However, there are also studies showing a decrease in cognitive responses to cognitive exercises given during walking.

As a result, we can say that dual task training contributes to walking, balance and upper extremity skills in stroke patients.

1.4. Dual Task in Multiple Sclerosis

Multiple sclerosis is a chronic, demyelinating, progressive, autoimmune disease of the central nervous system. The disease is characterized by clinical symptoms such as loss of balance, gait disturbance, muscle tone disorders, coordination, diplopia, cognitive impairment, and loss of attention. (23) Difficulty in motor and cognitive tasks has been associated with falls in patients with MS because they require simultaneous division of attention. (24, 25) Studies on dual task performance in MS have shown that lower dual task performance occurs as the level of disability and cognitive dysfunction increases. However, cognitive-motor interaction may not depend only on motor skills and cognitive level. For this reason, a more comprehensive evaluation with other clinical findings of MS may be recommended. (26) Dual task training in individuals with Multiple Sclerosis, as in individuals with Parkinson's disease and stroke, remains up-to-date in the literature. In a meta-analysis study, it was observed that dynamic balance and functional mobility increased after dual-task training. (27)

2. Conclusions

As a result, dual tasking is a complex situation. It requires dividing the focus of attention and available capacity. There is a decrease in dual task performance in Parkinson's, stroke and multiple sclerosis. In this case, we can say that the dual task training used has a positive effect on motor performance (walking, balance, falls). However, there seems to be no consensus on which of the theories underlying dual task performance is based on this improvement.

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CHAPTER II

NEUROINFLAMMATION IN ALZHEIMER'S

Disease: A Complex Interplay

Pınar KILIÇASLAN

(Asst. Prof. Dr.), Izmir Democracy University, Faculty of Medicine,
Department of Histology and Embryology
E-mail: klcsln.pnr@gmail.com
ORCID: 0000-0002-9413-1735

1. Introduction

Inflammation is a defensive system in the body that keeps the internal environment of the brain stable by mending, renewing and eliminating damaged tissues and cells as well as infection-causing agents, parasites, and toxins. (1)

The complex process of neuroinflammation involves immune cells in the central nervous system (CNS) being activated. It is described as a neurological or spinal cord inflammatory reaction. Numerous things, such as an infection, an injury or a persistent illness can cause this reaction which can affect brain function in both positive and negative ways. Furthermore, the context, length and progression of the initial stimulus or insult all affect how much neuroinflammation occurs. For example, inflammation can result in edema, tissue damage, immune cell recruitment and possibly even cell death. However, not all definitions of the term "neuroinflammation" are the same. (2)

An important factor contributing to neuroinflammation is the activation of the CNS's resident immune cells, called microglia. These cells can create a wide range of pro-inflammatory chemicals, such as reactive oxygen species (ROS), chemokines and cytokines, and they can respond to a broad range of stimuli. Apart from microglia, neuroinflammation can also be attributed to other immune cells such astrocytes and peripheral immune cells. (3)

Acute neuroinflammation may serve as a defense mechanism in the event of damage or infection, but chronic inflammation has been linked to a number of neurological conditions, such as multiple sclerosis, Parkinson's disease and Alzheimer's disease. Persistent inflammation can cause the generation of harmful chemicals and the activation of cell death pathways which can hasten the degeneration of neurons and other brain cells. (4)

2. Clinical Signs and Symptoms

The most prevalent cause of dementia is Alzheimer's disease (AD), a neurodegenerative condition marked by memory loss and gradual cognitive impairment. Language impairment, visuospatial problems and personality changes are additional clinical symptoms of AD that significantly lower patient quality of life and impose significant societal responsibilities. Alzheimer's Disease International reports that 75% of dementia patients worldwide go undiagnosed, and in certain low- and middle-income nations, this percentage may reach 90%. According to the World Health Organization's most recent estimates, 55 million individuals worldwide suffered from dementia in 2019. By 2050, that figure is predicted to increase to 139 million people. (5)

3. Etiology

The progressive neurodegenerative illness known as Alzheimer's disease (AD) is typified by the build-up of tau protein tangles and beta-amyloid plaques in the brain, along with inflammation and neuronal death. Although the precise origins of AD are still unknown, a number of factors, including as age, heredity, tau protein tangles, beta-amyloid accumulation, inflammation and oxidative stress have been linked to the disease's pathogenesis:

3.1. Genetics: A variety of genetic changes and the ensuing dysregulation of gene activity and function characterize AD, a chronic neurodegenerative illness. Nonetheless, similar to other neurodegenerative illnesses, Alzheimer's disease is not solely a genetic condition. Various biological mechanisms, such as immune system performance, tissue microenvironment and epigenetic processes, all contribute to the disease's progression. (6) Given that early-onset familial AD is known to be caused by mutations in the APP, PSEN1 and PSEN2 genes, genetic factors are likely to contribute to the development of AD. However, according to some studies, these mutations are uncommon and only contribute to a small portion of cases. Following the demonstration of the importance of microglia in the etiology of AD, research has revealed rare coding variations in

genes expressed in microglia, such as TREM2, PLCG2 and ABI3, which are linked to an elevated risk of AD. (7,8)

3.2. Age: As people age, the incidence of AD rises, making age the primary risk factor for the disease. Glial cell alterations brought on by aging result in persistent chronic inflammation. Prolonged inflammation makes the brain more vulnerable to neurodegenerative diseases. An increase in astrogliosis and microglial activation is linked to the neuroinflammation process in AD. However, age-related elevated inflammation is linked to an increase in tau-related neurofibrillary tangles and beta amyloid plaques in the brain's temporal cortex and hippocampal regions. (9)

3.3. Amyloid-beta Accumulation: One of the main theories about the etiology of AD is the build-up of beta-amyloid plaques in the brain. The beta-amyloid protein fragment is produced when the amyloid precursor protein (APP) is broken down by enzymes. Some of the studies showed that beta-amyloid can collect to create plaques that can impair regular neuronal function and cause neurodegeneration. (3,10)

The aggregation of Aβ peptides results in the development of neurotoxic oligomers and insoluble fibrils, which in turn cause plaques to form in the brain parenchyma and surrounding blood vessels, as per the amyloid hypothesis. Research on the particular neurotoxic pathways that underlie Aβ disease is quite comprehensive. According to studies, these Aβ plaques can interfere with synaptic transmission and set off a series of events that lead to neurodegeneration, which can disturb normal neural function. (10) These oligomers have been linked to oxidative stress, calcium homeostasis disruption, and synaptic dysfunction, all of which can lead to neuronal damage and death.

3.4. Tau Protein Tangles: Tau protein helps to maintain microtubules and promote intracellular transport, making it a crucial structural element of neurons. According to a study, tau protein in AD has the potential to become hyperphosphorylated and form neurofibrillary tangles, which can impair neuronal function and hasten neurodegeneration. (11)

3.5. Inflammation: The pathophysiology of AD has been linked to neuroinflammation, which is characterized by the activation of astrocytes and microglia. Inflammation can interfere with normal brain function and cause damage to or death of neurons. (12) Neuroinflammation has been shown to exacerbate Alzheimer's disease, the world's most common cause of progressive

cognitive deterioration. Neuroinflammation is caused by the combined action of innate and adaptive immune cells residing in the brain. (13)

3.6. Oxidative Stress: The pathophysiology of AD has also been linked to oxidative stress, which is the outcome of an unbalanced concentration of reactive oxygen species (ROS) and antioxidants. In addition to impairing regular neuronal function, oxidative stress can cause damage to and death of neurons. (14)

Microglia and astrocyte activation are two aspects of neuroinflammation that have been linked to the pathophysiology of AD. According to studies inflammation can impair normal brain function and cause damage to or death of neurons. (12,15)

4. Neuroinflammation

The neuroimmune axis associated with Alzheimer's disease has been established by studies conducted in the last ten years. Alzheimer's disease development and progression are significantly influenced by the interaction between innate and adaptive immune cells both inside and outside the brain. It has been postulated that the brain's immunological homeostasis is severely disturbed, which considerably contributes to neuroinflammation, even if the adaptive immune system's role in Alzheimer's disease is not entirely understood. Proinflammatory phenotypes and activity of brain-infiltrating T cells directly contribute to neuroinflammation. The pro-inflammatory actions of the adaptive immune system in Alzheimer's disease are indicated by the downregulation of regulatory T cell activities and the augmentation of effector T cell activities in the brain, blood and cerebrospinal fluid. (13)

Pro-inflammatory cytokines, chemokines and reactive oxygen species are released by activated microglia and astrocytes in AD. These substances can worsen neuroinflammation and increase the risk of neuronal damage and death. Furthermore, according to studies, beta-amyloid plaques have the ability to trigger an inflammatory response by activating the innate immune system. (12,15)

4.1. The Role of Microglia

The immune cells that live in the brain, known as microglia, are essential to the etiology of Alzheimer's disease (AD). The accumulation of neurofibrillary tangles (NFTs) and amyloid-beta (Aβ) plaques in AD causes microglia to become activated. (12,16)

The brain's native immune cells are called microglia. They can maintain the homeostasis of the internal environment of the brain in normal physiological states by promoting neurogenesis, immunological surveillance, repairing cellular damage and protecting against inflammation. But in pathological conditions, an overabundance of inflammation occurs in the brain as a result of microglia that are hyperactivated in reaction to disease-related stimuli. Persistent inflammation inhibits brain regeneration and increases the release of inflammatory cytokines, which limits the positive actions of microglia and has neurotoxic effects. (1)

In AD, microglia display a pro-inflammatory phenotype that can worsen neuronal death and damage by producing chemokines, cytokines and reactive oxygen species. Furthermore, by preventing Aβ from being cleared, active microglia can also encourage Aβ accumulation. (4,17,18)

Conventionally, microglia are categorized into two subtypes based on their characteristics and roles in distinct states. The M1 phenotype, which stimulates inflammation, and the M2 phenotype, which suppresses inflammation. The many different states and roles that microglia play in development, plasticity, aging and illness, which have been clarified recently, are incompatible with this classification. While M1 and M2 are still commonly used, we should firmly refrain from using them to classify microglia; instead, we should name them using more sophisticated approaches to investigate their functional condition. According to recent research, microglia can exist in a variety of dynamic, multidimensional states and can transition between active states in response to a range of stimuli and microenvironmental changes. (1)

When Aβ plaques are encountered, microglia can become activated, which causes the release of proinflammatory cytokines and chemokines such MCP-1 (monocyte chemoattractant protein 1), TNF-α and interleukin-1β (IL-1β). (19) Additionally, Aβ plaques can trigger the multi-protein complex known as the NLRP3 inflammasome, which produces IL-1β and further aggravates neuroinflammation. (20) By phagocytosing Aβ peptides, microglia can aid in the clearance of Aβ in addition to inducing inflammation. (21)

Recent research has pinpointed particular biochemical pathways that underlie AD-related microglia activation. For instance, the microglial response to Aβ plaques and NFTs has been linked to the triggering receptor expressed on myeloid cells 2 (TREM2). It has also been demonstrated that additional molecular pathways, such as the NLRP3 inflammasome, contribute to AD pathogenesis and microglial activation. (22,23)

It has been demonstrated that the NLRP3 inflammasome contributes to the pathophysiology of Alzheimer's disease (AD) and microglial activation. The pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18)

are released when the multiprotein complex known as the NLRP3 inflammasome activates caspase-1. (22-26)

It's interesting to note that Aβ assemblies can cause lysosomal disruption, NLRP3 inflammasome, and cathepsin-B release, all of which raise the amount of cytokines in the IL-18 family. Pro-inflammatory mediators including TNF-α and IL-1β may be involved in hypothalamic dysfunction, poor neurogenesis and cognitive impairment in addition to other variables. Nonetheless, data indicates that a major contributing element to the accumulation of Aβ in AD is the LPS-induced release of pro-inflammatory cytokines (IL-6, IL-1β and TNF-α). Furthermore, comprehensive investigations indicate that complement activation, activated microglia accumulation, and regenerative tissue response are characteristics of amyloid plaques. These requirements fit the traditional definition of an inflammatory response. (27)

Apart from Aβ, it has also been demonstrated that tau protein and reactive oxygen species (ROS), which are linked to AD pathogenesis, trigger the NLRP3 inflammasome in microglia. The NLRP3 inflammasome in microglia may be the target of a future therapeutic approach to treat AD. Numerous substances have been found to suppress the NLRP3 inflammasome, and some of them have demonstrated encouraging outcomes in preclinical investigations. (22)

Still, not every AD microglia possesses a pro-inflammatory characteristic. According to recent research, some microglia may have a neuroprotective phenotype in which they release substances that help neurons survive, like insulin-like growth factor 1 (IGF-1). (28) IGF-1 is a peptide growth factor that has been linked to the pathophysiology of Alzheimer and that supports neuronal survival, proliferation and differentiation. IGF-1 is produced in the brain by glial cells, including microglia, as well as neurons. (29,30)

Research has demonstrated that IGF-1 can enhance cognitive performance in animal models of AD and shield neurons from Aβ-induced damage. It has also been demonstrated that IGF-1 produced by microglia stimulates neurite outgrowth and synapse formation. (31)

IGF-1 produced from microglia, however, plays a complicated role in AD since, in some circumstances, it can also encourage neuroinflammation. Furthermore, alterations in IGF-1 signaling, such as a reduction in IGF-1 and its receptor expression, have been noted in the AD patients' brains. (32)

The development of targeted therapeutics focused at regulating microglial activity and lowering neuroinflammation may result from a deeper comprehension of the molecular underpinnings behind microglial activation in AD.

4.2. The Role of Astrocyte

According to some studies, astrocytes are the most prevalent glial cells in the central nervous system (CNS) and are crucial for maintaining brain homeostasis and neuronal function. (33) Astrocytes experience major alterations during the pathophysiology of Alzheimer's disease (AD), which aids in the illness's advancement. The accumulation of β-amyloid (Aβ) plaques in the brain, which can set off a chain reaction of neuroinflammatory reactions mediated by astrocytes, is one of the defining characteristics of Alzheimer's disease (AD). Astrocytes in AD brains frequently exhibit a reactive phenotype, which is defined by increased production of intermediate filament proteins such glial fibrillary acidic protein (GFAP) and increased cytokine and chemokine secretion. (34)

According to recent research, astrocytes are essential for the phagocytosis and breakdown of Aβ, which removes it from the body. Numerous Aβ receptors are expressed by astrocytes, including scavenger receptor class B type I (SR-BI), which binds and internalizes Aβ in a way that is lipid-dependent. Additionally, to stop the accumulation of Aβ, astrocytes can release Aβ-degrading enzymes such as neprilysin, insulin-degrading enzyme (IDE), and endothelin-converting enzyme 2 (ECE2). (35)

Through their intimate contacts with neurons, astrocytes not only play a role in Aβ clearance but also influence synaptic function and plasticity. Glutamate, D-serine and ATP are among the substances that are known to be released by astrocytes and which influence synaptic transmission. Cognitive decline and synapse loss in AD may result from dysregulation of astrocyte-mediated synaptic function. (36)

Moreover, neurovascular coupling—the mechanism that connects brain blood flow to neuronal activity—is also mediated by astrocytes. By generating endfeet that come into touch with blood arteries and modifying vascular tone through the production of vasoactive chemicals, astrocytes are able to regulate cerebral blood flow. Impaired neurovascular coupling has been linked to the pathophysiology of AD and can exacerbate cerebral hypoperfusion and neuronal dysfunction. (37)

On the other hand, astrocytes exhibit a variety of intricate roles in the pathophysiology of AD, such as neuroinflammation, synaptic function, Aβ clearance and neurovascular coupling.

When astrocytes come into contact with Aβ plaques, they can become activated and release proinflammatory cytokines including IL-6 and IL-1β. Furthermore, apolipoprotein E (apoE), a protein implicated in Aβ transport

and metabolism, is secreted by astrocytes and can aid in Aβ clearance. (19,38)

There hasn't been much research done on or documentation available regarding the function of T lymphocytes, or adaptive immune cells, in AD pathogenesis. As opposed to astrocytes and microglia, which are innate immune cells activated by the accumulation of proteins in AD and create neurotoxic and inflammatory substances that enhance aberrant cleavage of the amyloid precursor protein (APP), the formation of Aβ and the phosphorylation of tau. A change in lymphocyte function in AD may have a role in the disease's progression. (13)

According to reports, pro-inflammatory mediators secreted by dysfunctional T cells in AD contribute to neuroinflammation and are a crucial modulator in the pathophysiology of this neurodegenerative condition. (39)

T lymphocytes have the ability to activate astrocytes and microglia. T cells encourage neuroinflammation and take role in astrocyte activation. T cell-secreted interferon-γ causes brain-reactive astrogliosis and astrocyte proliferation. (40) Additionally, by controlling a number of astrocyte signaling pathways, the interleukin-17 released by Th-17 cells stimulates astrocytes. The cytokine induces the activation of inducible nitric oxide synthase, boosts the signaling of interleukin-6 and regulates the expression of macrophage inflammatory proteins-1α (MIP-1α) via the PI3K/Akt and NF-κB signaling pathways. (13)

There are two outcomes for T lymphocytes (CD4 + and CD8 + T cells) in the brain. Through the CNS lymphatic system, T lymphocytes return to the periphery if they are unable to identify an antigen and are not activated. As a result of their inability to identify the relevant antigen, the T cells are unable to pass through the blood-brain barrier and finally die. Nevertheless, they start an effector immune response if they are activated by the interaction of a cognate antigen with their receptor. (40) Effector immune response progresses to a neuroinflammatory state that modifies BBB permeability and secretory capacity. (41) The weakened blood-brain barrier modifies cytokine reactions and permits a large-scale influx of immune cells into the brain, exacerbating the continuing neuroinflammation. (40) T cells use a series of secretory chemicals and immunological signals to regulate neurohomeostasis. (42) All subtypes of CD4 + T cells participate in and greatly aid in maintaining neurohomeostasis at the physiological level. But during dementia, the subtypes have different activities that could either promote neurodegeneration or neuroprotection. (9)

In summary, AD can cause neuronal damage and cognitive impairment due to the inflammatory response triggered by the accumulation of Aβ plaques

in the brain, which is mediated by astrocytes and microglia. New therapeutic strategies for the treatment or prevention of AD may be developed as a result of our growing understanding of the processes behind this inflammatory response.

However, there are intricate connections between the brain and the intestines. A growing body of clinical and preclinical information pertaining to the correlation between gut microbiota and brain function indicates that gut microbiota plays a central role in the etiology of neurodegenerative diseases (NDs). More research has also been done recently on the microbiota-gut-brain (MGB) axis, which is an important channel for two-way communication between the gut and the brain. The gut microbiota has the potential to impact the brain through multiple mechanisms, such as immunological stimulation, small molecule metabolites, and the vagus nerve of the colon. For instance, abnormal gut microbiota can activate peripheral immune signals through the vagus nerve, which can then transmit the signals to the central nervous system (CNS). (43) Examples of these signals include increased serum pro-inflammatory cytokines (TNF-α, IL-6, IL-1 and IFN-γ) and decreased anti-inflammatory cytokines (IL-4 and IL-10).

Numerous contemporary treatment modalities for AD neuroinflammation are under investigation. Using nonsteroidal anti-inflammatory medicines (NSAIDs) is one strategy; in preclinical models of AD, NSAIDs have been demonstrated to decrease neuroinflammation and beta-amyloid accumulation. However, the outcomes of NSAID clinical trials have been conflicting; although some have shown a decrease in cognitive deterioration, others have shown no benefit at all. (44)

Known for their anti-inflammatory properties, substances such as minocycline have shown to be able to inhibit microglial activation and have neuroprotective benefits. (45) Subsequent investigations endeavor to enhance our comprehension of microglial dynamics and create focused therapies to proficiently govern their reactions.

5. Therapeutic Approaches

Researchers have developed and are testing a number of potential interventions targeted at different targets in ongoing clinical trials. These include interventions to relieve behavioral psychological symptoms, neurotransmitter modification, anti-inflammation and neuroprotection, anti-tau and anti-amyloid, and cognitive enhancement.

The investigation of neuroprotective drugs provides a new approach for treating Alzheimer's disease. Nerve growth factor (NGF) and brain-derived

neurotrophic factor (BDNF) have demonstrated potential in enhancing the survival and functionality of neurons. (46) These drugs may mitigate the detrimental effects of neuroinflammation on synapse function and cognitive decline by promoting neurotrophic signaling. Future research must focus on understanding the mechanisms by which neuroprotective drugs interact with inflammatory pathways.

Another strategy is to target beta-amyloid particularly with immunotherapy. Aducanumab and solanezumab, two monoclonal antibodies that target beta-amyloid, have demonstrated encouraging outcomes in clinical trials. The FDA approved aducanumab in 2021 for the treatment of early Alzheimer's disease. But there are worries about possible negative effects and the need for more study to find the best treatment schedule and dosage. (47)

Other strategies involve controlling astrocyte activation with medications like ibudilast and using small molecule inhibitors to target the inflammasome and microglial activation. Furthermore, dietary changes and lifestyle therapies including exercise have been suggested as possible treatment approaches for AD neuroinflammation.

Application of mesenchymal stem cells (MSC) is an additional treatment strategy for AD. MSCs have a spindle shape, stick to plastic, go to the site of injury, and have multiple potencies. They can come from the bone marrow, adipose tissue and Wharton's jelly, among other places. Their potential as therapeutic tools has gained significant attention in recent years because to their immunomodulatory properties, neurotrophic activities, and multipotency. (48)

Using MSCs to treat AD causes astrocytes to proliferate, glutamate and gamma-aminobutyrate to be metabolized, neural cell necrosis to be inhibited, and growth factors (such as brain-derived neurotrophic factor [BDNF]) to be released, stimulating neural progenitor cells to enhance neurogenesis through their antiapoptotic and antioxidant properties. MSCs also have modulatory effects on the immune system, preventing further tissue damage caused by chronic neuroinflammation by promoting the activation of anti-inflammatory microglia (M2) and avoiding or reducing proinflammatory microglia (M1) activation. Studies have demonstrated that MSCs can increase autophagy activation, which is probably the cause of Aβ plaque lysosomal clearance. Moreover, MSCs promote Aβ by hastening the development of microglia close to Aβ deposits. (49)

Amyloid β (Aβ) peptides and oxidative stress have been found to be crucially linked; oxidative stress is induced by Aβ peptides, and this leads to mitochondrial malfunction and an increase in the production of reactive oxygen species (ROS). Oxidants and oxidation products generated as a result of oxidative

stress can then raise the production of the protein known as amyloid precursor protein (APP), which causes Aβ to build up and exacerbates the situation further. Antioxidants have been suggested as possible therapeutic agents to prevent oxidative damage, although there has been mixed results about their effectiveness in clinical settings. It has been proposed that the inherent anti-inflammatory and antioxidant properties of hydrogen could be advantageous in the management of AD. (50)

Low-dose radiation therapy (LDRT), which includes low-dose ionizing radiation, has recently been shown to have preliminary preclinical and clinical data that may one day be used to treat AD. Although the field is still in its infancy and more research is needed to fully understand and assess its potential, the function of RT as a potential therapy modality for AD has shown encouraging early results. (51)

N-Methyl-D-aspartate glutamate receptors (NMDARs) have a role in a number of physiopathological processes, such as neural network activity, excitotoxic events, synaptic plasticity and cognitive decline. A series of pathogenic processes, most notably in Alzheimer's disease (AD) and even other neuropsychiatric illnesses, can be set off by abnormalities in NMDARs. Synaptoprotection, which makes up 17% of phase 3 pharmacological development, primarily targets NMDARs. The majority of NMDAR-based medications under trial right now are non-competitive NMDAR antagonists. Furthermore, focusing on non-neuronal NMDAR may offer a hitherto overlooked method of reversing dementia. According to studies, determining the specific molecular pathways may aid in the development of efficient treatments. (52)

The enteric nervous system and central nervous system are impacted by dysregulation of the composition and quantity of gut bacteria. Diverse NDs have been linked to various gut microbiota and product diseases. One interesting avenue to improve NDs would be to target particular commensal bacteria enrichment (or therapy). In the near future, treating NDs may depend heavily on the MGB axis being intervened upon by the gut microbiota. (43)

In 1980, gene therapy was presented to the medical community as a possible cure for genetic problems in lieu of traditional pharmaceuticals. It wasn't in the spotlight, though, until lately, when gene therapy gained prominence in medical studies due to advancements in biotechnology. (53)

Gene therapy can correct the defective genes in one of the following ways:

(1) A normal gene replaces the mutated gene,
(2) A functional gene is added to potentially combat the disease,

(3) The abnormal gene is reverse-mutated,
(4) The disease-causing gene is inactivated.

As our understanding of the etiology and mechanisms underlying AD incidence has grown, so too has the range of technologies available for target identification in gene therapy. The least developed proteins include apolipoprotein E and endothelin-converting enzyme (ECE), which both need more research before they may be employed as therapeutic targets to treat AD. Without a doubt, as medical research and technology develop, gene therapy will become standard procedure for treating AD. (53)

Even though pharmaceutical approaches to treating neuroinflammation in AD have advanced significantly, further study is still required to completely comprehend the intricate mechanisms underlying neuroinflammation in AD and to optimize therapy dose and timing.

6. Conclusion

In summary, there are a variety of dynamic therapy modalities for neuroinflammation and Alzheimer's disease. There is therapeutic potential in tackling tau and amyloid-beta diseases, modifying microglial responses, utilizing neuroprotective medicines and targeting inflammatory mediators. With a deeper comprehension of the complex link between neuroinflammation and Alzheimer's disease, new and more focused therapies are probably on the horizon.

Recognizing the constraints and difficulties in converting preclinical data to clinical efficacy is essential. Because Alzheimer's disease has many facets, treatment must be both comprehensive and individualized. Pharmacological therapies and lifestyle changes may work in concert to provide a more comprehensive and successful approach to controlling neuroinflammation and Alzheimer's disease.

This scientific opinion concludes by highlighting the obstacles and areas of hope for treating neuroinflammation in Alzheimer's disease. A promising future is presented by the convergence of basic research, clinical trials, and creative therapeutic approaches. The scientific community's combined efforts have the potential to revolutionize the field of neuroinflammation therapeutics and offer hope to those impacted by this detrimental disease, even though the path to a permanent cure for Alzheimer's disease may be complex and difficult.

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CHAPTER III

PULMONARY HYPERTENSION TREATMENT ALGORITHM

Ömer KÜMET

(MD), Health Science University Van Training and Research Hospital,
E-mail: omerkumet@hotmail.com,
ORCID: 0000-0001-5369-5414

1. Introduction

Definitions regarding Pulmonary Hypertension (PHT) are based on the hemodynamic evaluation made by right heart catheterization (RHC) and 5 different classifications developed as a result (1). The main purpose of the PHT clinical classification is to categorize PHT-related clinical conditions that share same pathophysiological mechanisms, clinical situations, hemodynamic features, and treatment management. Treatment algorithms were also created based on these classifications. According to current hemodynamic criteria, PHT can be diagnosed in patients with mean pulmonary artery pressure (mPAP)>20 mmHg and pulmonary vascular resistance (PVR)> 2 wood units, but the effectiveness of drugs indicated in the treatment of PHT has been shown only in patients with mPAP> 25 mmHg and PVR> 3 wood units (WU) (2). No clear results were obtained in studies regarding the effectiveness of PHT drugs in patients with intermediate values.

Management of PHT patients is a process that requires a comprehensive treatment strategy and multidisciplinary care. In addition to PHT-specific medications, individualized supportive treatments, and complementary elements should also be included in this process. PHT and right heart failure should be managed appropriately, and processes such as physical activity and rehabilitation, anticoagulation, oxygen support, iron supplementation, vaccination, psychosocial support, and pregnancy should be carefully considered.

2. Group 1 PHT Treatment Algorithm

Group 1 pulmonary hypertension is the most important group in which PHT drugs are effective. Determining the treatment strategy in patients with idiopathic PHT, hereditary PHT, and drug-related PHT depends on the vasoreactivity test. PHT patients who respond positively to the acute vasoreactivity test during hemodynamic examination are considered vasoreactive and respond positively to treatment with calcium channel blockers (CCBs). Vasoreactivity testing helps to identify patients who can be treated with high-dose CCB (2). Vasoreactivity testing is not recommended in other groups of PHT patients. This test should be performed in PHT-specialized centers. Vasoreactivity testing is recommended with inhaled nitric oxide, inhaled iloprost, or intravenous epoprostenol (3). In cases where cardiac output increases or does not change, a decrease of >10 mmHg to the value of mPAP <40 mmHg should be considered as a positive response to the vasoreactivity test. The application route, dose, half-life, and duration of administration information for the compounds recommended for vasoreactivity testing are shown in Table 1.

Table 1. Agents recommended for use in vasoreactivity testing

Agent	Application route	Half-life	Dose	Duration
Nitric oxide	inhalation	15-30 seconds	10-20 p/ min	5-10 min
Iloprost	inhalation	30 minutes	5-10g mg	10-15 min
Epoprostenol	intravenous	3 minutes	2-12 ng /kg/ min	10 min

Nifedipine, diltiazem and amlodipine are the most commonly used calcium channel blockers for the treatment of vasoreactive PHT patients (4). Amlodipine and felodipine started to be used more in clinical practice due to their long half-lives and good tolerance. The daily effective CCB doses for the treatment of PHT are quite high, so target doses should be increased by titration. The starting and target doses of all drugs for the treatment of pulmonary hypertension are summarized in Table 2. Treatment decisions at diagnosis and while follow-up should be made by the PHT team with a multidisciplinary approach, according to the presence of cardiopulmonary comorbidities and the level of the disease determined by the risk category.

Table 2. Starting and target doses of PHT drugs in adults

	Starting dose	Target dose
Calcium Channel Blockers – Oral administration		
Amlodipine	5 mg, 1x1	15-30 mg, 1x1
Diltiazem	60 mg, 2x1	120-360 mg 2x1
Felodipine	5 mg, 1x1	15-30 mg, 1x1
Nifedipine	10 mg, 3x1	20-60 mg, 2 or 3x1
Endothelin Receptor Antagonists (ERA) – Oral administration		
Ambrisentan	5 mg, 1x1	10 mg, 1x1
Bosentan	62.5 mg, 2x1	125 mg, 2x1
Macitentan	10 mg, 1x1	10 mg, 1x1
Phosphodiesterase - 5 inhibitors (PDE- 5i) – Oral administration		
Sildenafil	20 mg, 3x1	20 mg, 3x1
Tadalafil	20 or 40 mg, 1x1	40 mg, 1x1
Prostacyclin analogs – Orally administered		
Beraprost sodium	20 μg, 3x1	40 μg, 3x1
Beraprost extended release	60 μg, 2x1	180 μg, 2x1
Treprocytinil	0.25 mg x2 or 0.125 mg x3	max tolerable dose
Prostacyclin receptor agonist – Oral administration		
Selexipag	200 μg, 2x1	1600 μg, 2x1
Soluble guanylate cyclase stimulator – Oral administration		
Riociguat	1 mg, 3x1	2.5 mg, 3x1
Prostacyclin analogs – Administration by inhalation		
Iloprost	2.5 μg, 6x1-9x1	5.0 μg, 6x1-9x1
Treprostinil	18 μg, 4x1	54-72 μg, 4x1
Prostacyclin analogs – Intravenous or subcutaneous administration		
Epoprostenol IV	2 ng /kg/ min	Dosage range 16-30 ng /kg/ min
Treprostinil Sc or IV	1.25 ng /kg/ min	Dosage range 25-60 ng /kg/ min

The evidence-based PHT treatment algorithm for idiopathic, hereditary, drug-related, and connective tissue disease (CTD)-related pulmonary arterial hypertension patients in Group 1 is summarized in Figure 1. The presence of cardiopulmonary comorbidity noted in the diagram is associated with

conditions at increased risk of left ventricular diastolic dysfunction, including diabetes, chronic coronary syndrome, hypertension, as well as low DLCO (<45% of predicted value), which may include signs of mild parenchymal lung disease. (5).

Combination therapy with ERA + PDE5i + IV/sc prostacyclin analog should be considered initially in Group 1 PHT patients who do not have cardiopulmonary comorbidities and present with a high risk of mortality (Class IIa). The addition of selexipag should be considered in patients who are evaluated in the low-medium risk group during their follow-up while they are under ERA+PDE5 (Class IIa) (6). If a moderate-high or high risk is detected during follow-up while under ERA+PDE5i treatment, IV/sc prostacyclin analog should be added and referral should be considered for evaluation in terms of lung transplantation. (Class IIa) (7). If the patient is initially in the low or intermediate-risk group, the ERA+PDE5i combination is recommended as initial treatment. In combination therapy, especially Macitentan+tadalafil and Ambrisentan+tadalafil combinations have been proven to provide mortality advantage and are primarily recommended, but other ERA and PDE5i combinations can also be started. It is not recommended to start initial oral treatment with a triple combination along with selexipag treatment (2).

The results of studies based on mortality/morbidity as the primary outcome measure in patients planned for sequential combination therapy prove the effectiveness of some treatments. Adding macitentan to the treatment of patients receiving PDE5i or oral/inhaled prostacyclin analog, and adding selexipag or oral treprostinil to the treatment of patients receiving ERA and/or PDE5i therapy is recommended with a class I recommendation as it provides a mortality advantage (8). Adding bosentan to sildenafil treatment is not recommended. When studies based on the 6-minute walking test for effectiveness were examined, it was proven that the most beneficial combination was obtained by adding sildenafil to epoprostenol. To increase exercise capacity, the addition of inhaled treprostinil to sildenafil or bosentan monotherapy or the addition of riociguat to bosentan should be considered. Riociguat and PDE5i combinations have no place in the treatment of PHT.

Suitable patients who continue to have a high risk of mortality despite medical treatments should be evaluated for lung transplantation. Potentially suitable candidate patients who fail to respond adequately to oral combination therapy as indicated by intermediate-high or high risk or a REVEAL risk score >7 are recommended to be referred for lung transplantation. Additionally, patients with a REVEAL risk score >10

despite optimal medical therapy including Sc or iv prostacyclin analogue should be enrolled in the lung transplantation list. In particular, patients with progressive hypoxemia such as pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis and patients with non-end-stage progressive liver or kidney failure due to PAH or life-threatening hemoptysis should be prioritized for lung transplantation.

There are some specific treatment algorithms for specific PHT subtypes. In patients with PHT associated with drugs or toxins, if there is a medium or high risk at the time of diagnosis, PHT treatment should be started immediately. Additionally, exposure to the responsible substance must be terminated as urgently as possible. If diagnosed in the low-risk group, it should be re-evaluated 3-4 months after discontinuation of the suspected drug/toxin, and if hemodynamics have not returned to normal, PHT treatment should be considered.

The treatment algorithm in PHT associated with connective tissue disease should be as in Figure 1. In addition, the underlying connective tissue disease should be treated according to current guidelines. Since the risk of interaction between antiretroviral drugs and PHT drugs is high in HIV-associated PHT patients, monotherapy should be considered initially, followed by sequential combination therapy if still necessary. In cases of PHT associated with portal hypertension, monotherapy should be considered first, followed by sequential combination therapy if necessary, considering the underlying liver disease and liver transplantation indication. Liver transplantation should be prioritized whenever possible in the treatment of portopulmonary PHT.

Treatment of pulmonary hypertension related to congenital heart disease varies depending on the output of the systemic-pulmonary shunt, the defect size, and pulmonary vascular resistance. A specific clinical classification developed to better define PHT associated with congenital heart diseases is summarized in Table 3.

Figure 1: Evidence-based PHT treatment algorithm for idiopathic, hereditary, drug-related, and connective tissue disease-related pulmonary arterial hypertension patients in Group 1

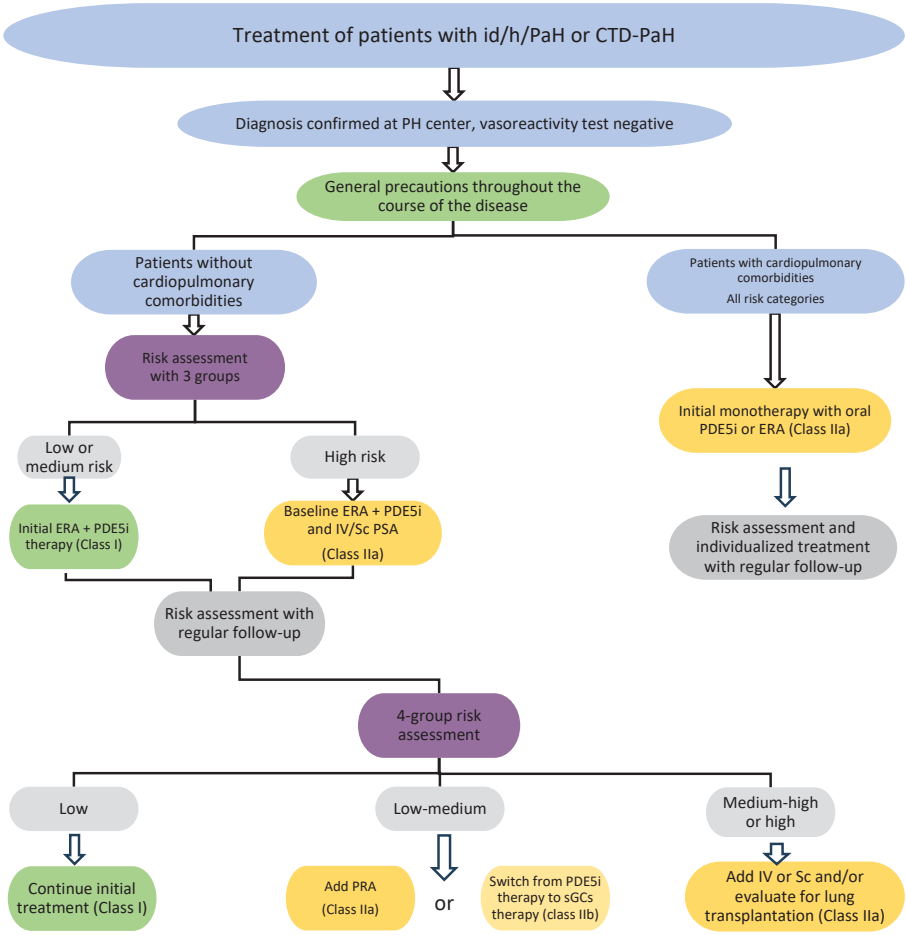

Table 3. Congenital heart disease associated pulmonary arterial hypertension classification

1. Eisenmenger syndrome Major extracardiac and intracardiac defects that begin as a systemic-to-pulmonary shunt and progress to highly increased PVR and bidirectional or reverse shunt. Secondary erythrocytosis, cyanosis, and multiple organ involvement are usually present. Defect closure is contraindicated.
2. PHT associated with dominant systemic-pulmonary shunt • Fixable • Cannot be fixed It covers medium to large defects. Mild to moderately increased PVR and systemic-to-pulmonary shunting continues to predominate, but cyanosis is absent at rest.
3. PHT with small/incidentally detected defects Significantly increased PVR in the presence of a cardiac defect that is not considered hemodynamically significant (usually VSDs <1 cm and ASDs <2 cm on echocardiography) which alone does not explain the increase in PVR. Its clinically very similar to idiopathic PHT. Defect closure is contraindicated.
4. PHT after defect repair CHD is repaired but PHT persists immediately after repair or recurs or develops months or years after repair. There is no significant, postoperative hemodynamic residual lesion.

Shunt closure (surgical or interventional) should only be considered in patients with dominant systemic-pulmonary shunt that is not accompanied by severe PVR increase. Shunt closure is recommended for ASD, VSD, and PDA patients with Qp/Qs>1.5 and PVR below 3 (Class I). If the calculated PVR is between 3-5 in these patients, shunt closure with a class IIa indication should be considered. For VSD and PDA patients with PVR above 5, after a careful examination in specialized centers, patients may be advised to close the shunt. In ASD patients, if PVR falls below 5 after specific PHT treatment, closure may be considered, but if PVR remains above 5, shunt closure is contraindicated.

Bosentan treatment is recommended to increase exercise capacity in symptomatic patients with Eisenmenger syndrome. Other ERAs, PDE5 inhibitors, riociguat, prostacyclin receptor agonists, and prostacyclin analogs should be considered in all adult congenital heart disease patients including Eisenmenger syndrome. Iron deficiency should be investigated and replaced if necessary. Among patients with PHT after shunt closure, combination therapy with oral PHT drugs should be started in low-medium risk patients,

and combination therapy containing iv/sc prostacyclin analogs should be started in high-risk patients. Pregnancy is definitely harmful for the Eisenmenger syndrome patients and counseling should be provided. Routine phlebotomy is not necessary to reduce elevated hematocrit.

Suitable PHT patients associated with pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis should be evaluated for transplantation as soon as the diagnosis is made. It may be considered to start PHT medications cautiously, starting as monotherapy (2,9).

3. Group 2 (Left Heart Disease Related) PHT Treatment Algorithm

Right ventricular dysfunction and pulmonary hypertension are often present in people with left heart disease, and this causes increased mortality (10). The most common PHT subtype is the group associated with left heart disease. There are some criteria to evaluate the possibility of pulmonary hypertension in the presence of left heart disease. The treatment strategy should be planned by obtaining clues as to whether the patient has PHT due to left heart disease as a result of the diagnosis of the underlying left heart disease and whether it is controlled or not, evaluation for PHT, patient phenotyping, and, if indicated, invasive hemodynamic examinations. The main strategy in PHT associated with left heart disease is to optimize the treatment of the underlying heart disease. However, a series of pathophysiological processes ranging from left-sided heart disease provided by pulmonary circulation to chronic right heart failure can be observed in many patients. If it is thought to contribute to treatment decisions in PHT associated with left heart disease or if surgical/interventional treatment is planned for tricuspid regurgitation, right heart catheterization should be performed beforehand. Individualized treatment should be administered in PHT centers for patients with combined pre-post capillary PHT with a severe pre-capillary component (PVR>5 WU). The PHT spesific treatments are not recommended for left heart disease associated PHT.

4. Group 3 (Hypoxia and/or Chronic Lung Diseases Related) PHT Treatment Algorithm

PHT is a frequently observed condition in patients with COPD, interstitial lung disease, emphysema, pulmonary fibrosis, and hypoventilation syndromes (11). Even if pulmonary artery pressure is not very high, it worsens the symptoms of lung disease and survival time. The main treatment strategy for group 3 PHT patients is to optimize the treatment of the main lung disease, including oxygen

support and non-invasive mechanical ventilation. Patients should be taken to pulmonary rehabilitation. It is recommended to apply individualized treatments in PHT centers. Referral to PHT centers may be recommended for lung transplantation. The use of inhaled treprostinil may be considered in patients with PHT associated with interstitial lung disease. Ambrisentan is not useful in patients with PHT associated with idiopathic pulmonary fibrosis. In general, the use of PHT-specific treatments is not accepted in patients with lung disease and non-severe PHT.

5. Group 4 (Chronic Thromboembolic Pulmonary Hypertension) PHT Treatment Algorithm

The CTEPH treatment algorithm includes a versatile combination approach consisting of pulmonary endarterectomy, balloon pulmonary angioplasty, and drug therapies, targeting mixed anatomical lesions such as proximal, distal, and microvasculopathy, respectively (12). All patients with CTEPH should be examined by a CTEPH team to evaluate multimodal treatment. In all cases where surgery (pulmonary endarterectomy) is technically possible, surgical treatment should be planned first. If surgery is not possible and in patients with distal obstructions suitable for balloon pulmonary angioplasty (BPA), BPA should be performed in experienced centers. Riociguat has an important place as medical treatment in patients for whom surgery is not possible or who have persistent, recurrent pulmonary hypertension symptoms after endarterectomy. It is the first oral treatment option indicated for CTEPH. Patients who develop severe pulmonary hypertension and whose functional class is III-IV can be expected to benefit from subcutaneous treprostinil treatment. All patients with CTEPH must take anticoagulants for life. Anti-phospholipid syndrome research is also particularly important and positive patients should take warfarin as an anticoagulant. It is important that patients who receive both interventional treatment and medical follow-up should be followed up long-term in centers specialized for PHT.

Group 5 PHT is a group of pulmonary hypertension with uncertain and/or multifactorial mechanisms and includes some pathologies complicated by complex and sometimes overlapping pulmonary vascular involvement. These patients need careful evaluation and treatment should target the underlying pathology. Since there are no randomized controlled studies investigating the use of specific PHT drugs in the treatment of Group 5 PHT and providing positive results, treatment of the underlying disorder remains the gold standard approach.

6. Conclusion

The most important step of the pulmonary hypertension treatment algorithm is to group the disease and make risk classification. Cardiovascular comorbidities also play an important role in determining treatment options. Identifying underlying diseases and treating them in accordance with current guidelines and a multidisciplinary approach allow patients to be treated and followed up correctly.

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CHAPTER IV

ANALYSIS OF ACRONYMS USED IN THE FIELD OF BLOOD PHYSIOLOGY: HEMOGRAM PARAMETERS IN TURKISH ARTICLE ABSTRACTS

Hasan ÇALIŞKAN[1] & Onur AYDIN[2] & Berke SAĞ[3]

[1] (Assoc. Prof.) Balıkesir University, Medicine Faculty, Physiology Department, Balıkesir, Turkey
E-mail: hasanmonica@hotmail.com
ORCID: 0000-0002-3729-1863

[2](Medical Student) Balıkesir University, Medicine Faculty, Balıkesir, Turkey,
E-mail: onurr.aydin33@gmail.com
ORCID: 0009-0006-8738-8811

[3](Medical Student) Balıkesir University, Medicine Faculty, Balıkesir, Turkey,
E-mail: berkesag33@gmail.com
ORCID: 0009-0000-4463-9584

1. Introduction

Medical terminology is a special field language that is constantly renewed and changing. Therefore, it has a structure that is open to new developments. The terms in medical terminology are formed from many different sources and languages. Medicine science consists of approximately 500,000 terms. Abbreviations play an important role in this terminology (1).

Acronyms are abbreviations of a group of words according to certain rules. Although these abbreviations are made in different ways, the ones using

initials are the most preferred. Medical terminology is one of the fields with the highest number of acronyms. There are frequently used acronyms such as USG, EEG, EMG MRI that have even entered the vernacular. In medicine, acronyms can be used for diseases, hormones, diagnostic methods, and many other terms (1-3).

Table 1. Some frequently used acronyms in medicine (2,3)

Acronyms	Mean
ADH	Antidiuretic hormone
FSH	Thyroid-stimulating hormone
DVT	Deep venous thrombosis
ALL	Acute lymphoblastic leukemia.
BP	Blood pressure
ALS	amyotrophic lateral sclerosis
MR	Magnetic Resonance Imaging
EEG	Electroencephalogram
EMG	Electromyography

There may be a difference between Turkish and English usage of acronyms. “bilisayarlı tomografi” can be abbreviated as BT in Turkish articles. In English, it is used as CT (computerized tomography) as an acronym.

Table 2. Acronyms used differently in Turkish and English languages (2,3)

Turkish acronyms	English acronyms	Mean
TME	TMJ	Temporomandibular joint
SFT	PFT	Pulmonary function test
BT	CT	Computed tomography
KT	CT	Chemotherapy

Some words may have multiple acronyms. For example, electrocardiography is used in English texts as ECG or ECG.

Table 3. Words with multiple acronyms (2,3)

Acronyms	Means
ECG, EKG	Electrocardiography
J, jt.	joint
pot, potass.	potassium
UCD, UCHD	usual childhood diseases
VC, vit. cap.	vital capacity
W/C, wh.ch.	wheelchair

Different words may have the same acronym. For example, the acronym for procalcitonin and platekrite is PCT.

Table 4. Different words with the same acronym (2,3)

Acronyms	Means
RA	1. rheumatoid arthritis, 2. right atrium
CHF	congestive heart failure, chronic heart failure
ROM	range of motion, rupture of membranes, right otitis media
R.	rub, rectal temperature
PN	poorly nourished, practical nurse
PI	present illness, pulmonary insufficiency
PE	physical exam, pulmonary embolism, pressure equalizer (tubes)
L.O.C.	loss of consciousness, level of consciousness, laxative of choice

2. Hemogram and Acronyms

A hemogram is one of the most frequently requested blood tests. It is frequently preferred because it gives results in a short time and has a low cost. It provides information about erythrocytes, leukocytes, platelets, and many features related to these cell groups. It is a test used to diagnose many diseases. It is also frequently used for prognosis (21).

The hemogram test is one of the medical tests with the most acronyms. The parameters it analyzes are usually given as acronyms in the test result.

Some of the parameters examined in the hemogram: Total WBC Count (TLC), Total red blood count (RBC), Hemoglobin (Hb) Haematocrit (HCT), Mean

Cell Volume (MCV), Mean Cell Haemoglobin (MCH), Mean Cell Haemoglobin Concentration (MCHC), platelets count, RDW-SD (RBC Distribution Width-Standard Deviation), Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, PDW (Platelet Distribution Width), MPV (Mean Platelet Volume), P-LCR (Platelet Large Cell Ratio), PCT (Plateletcrit).

Authors conducting scientific research primarily look at abstracts in their literature searches. The general request of journals in abstracts is not to use acronyms. If acronyms are to be used, it is requested that the acronyms be explained.

Acronyms are frequently used in articles written in Turkish or containing abstracts in Turkish. Authors draw different paths when using or creating acronyms. They may use the abbreviation of its Turkish equivalent or the equivalent of its English abbreviation. In this study, hemogram acronyms in abstracts, which are the first part read in an article, are discussed. For this purpose, both English and Turkish abstracts of articles whose full text was written in Turkish were analyzed (See Table 5,6).

The authors used acronyms in both Turkish and English abstracts in the form of English acronyms. Some authors did not use acronyms in the abstracts. Some authors used hemogram parameters without acronyms for the convenience of the reader. However, some authors use only English acronyms in the Turkish abstract. Some authors use acronyms differently in Turkish and English abstracts. Some authors use acronyms but do not use the long form in the abstract (See table 5,6).

Using different acronyms, not giving the long form of the acronym, or giving an acronym that is not used frequently may lead to misunderstanding when reading the article.

Table 5. Acronyms in Turkish Article Part 1

Study	**Using Acronyms in Turkish and English Abstracts**	**Turkish abstract**	**English abstract**	**Turkish-English abstract**
(4)	Yes	(**MCV**), (**RD**W)	(**MCV**), **(RDW)**	they used the same acronyms
(5)	Yes	Eritrosit **(RBC)**, Hemoglobin **(Hb)**, Beyaz Küre Sayısı **(WBC)**, Trombosit sayısı **(PLT)**, Ortalama Trombosit Volümü**(MPV)**, Eritrosit Dağılım Genişliği**(RDW)**	Red Blood Cell **(RBC)**, Hemoglobin **(Hb)**, White blood cell **(RBC),** Platelet **(PLT),** Mean platelet volüme **(MPV),** Red cell distribution width **(RDW)**	they used the same acronyms
(6)	Yes	Hemoglobin **(HGB)**, ortalama eritrosit hacmi **(MCV),** eritrosit dağılım aralığı **(RDW)**, trombosit sayısı **(PLT)**, Ortalama trombosit hacmi(MPV), trombosit dağılım aralığı **(PDW)**	Hemoglobin **(HGB),** mean corpuscular volume **(MCV)**, red cell distribution width **(RDW)**, platelet count **(PLT)**, (Mean platelet volume) **MPV,** platelet distribution width **(PDW)**	They used the same acronyms
(7)	None	-	-	-
(8)	Yes	**(HB), (HCT), (PLT), (MCV), (MPV), (RDW), (MCH), (MCHC), (PCT)**	**(HB), (HCT), (PLT), (MCV), (MPV), (RDW), (MCH), (MCHC), (PCT)**	They used the same acronyms
(9)	Yes	Eritrosit hacmi dağılımı **(RDW)** ve trombosit dağılım hacmi **(MPV)**	Red cell distribution width **(RDW)**, mean platelet volume **(MPV)**	They Used the same acronyms
(10)	Yes	**NLO, WBC, MPV, PLO, Hb, MCV, htc**	**NLO, WBC, MPV, PLO, Hb, MCV, htc**	They used the same acronyms

Table 6. Acronyms in Turkish Article Part 2

(11)	Yes	Hemoglobin **(Hb),** hematokrit **(HCT),** ortalama trombosit hacmi **(MPV),** nötrofil lenfosit oranı **(NLO)** ve trombosit lenfosit oranı **(TLO)**	Hemoglobin **(Hb),** hematocrit **(HCT),** mean platelet volume **(MPV),** neutrophil-lymphocyte ratio **(NLR),** and platelet lymphocyte ratio **(PLR)**	**NLO-NLR, and TLO-PLR** are used different acronyms.
(12)	None	-	-	-
(13)	Yes	Nötrofil/Lenfosit oranı **(NLO),** Kırmızı kan hücresi genişliği **(RDW),** Trombosit kütle indeksi **(TKİ),** Beyaz kan hücresi **(WBC)**	Neutrophil/lymphocyte ratio **(NLR),** Red blood cell width **(RDW),** Platelet mass index **(PMI),** White blood cells **(WBC**)	**NLO-NLR, and TKİ-PMI** are used different acronyms.
(14)	None	-	-	-
(15)	Yes	**Beyaz küre (WBC), RDW, Nötrofil/lenfosit N/L**	**White blood cell(WBC), Neutrophil/ lymphocyte N/L**	**RDW** ingilizce özette kullanılmamış.
(16)	Yes	**WBC**	**WBC**	They used the same acronyms
(17)	None	-	-	-
(18)	None			-
(19)	Yes	Nötrofil/Lenfosit oranı **(NLO),** Monosit/Lenfosit oranı **(MLO),** Platelet/ Lenfosit oranı **(PLO)**	Neutrophil/Lymphocyte ratio **(NLR),** Monocyte/ Lymphocyte ratio **(MLR),** Platelet/ Lymphocyte ratio **(PLR)**	Different
(20)	Yes	Kırmızı kan hücresi dağılım genişliği **(KDG), (‘Red blood cell distribution width’ RDW)**	Red blood cell distribution width **(RDW)**	Different. Turkish abstract : RDW=KDG

3. Conclusion

To prevent misunderstand,
Abstract Turkish/English, Full text: Turkish (Option1)
Abstract Turkish/English, Full text: English (Option2)

1. For this reason, it may be the best option for the reader not to use acronyms in the abstract of bilingual articles.

2. If acronyms are to be given, they should be given in long form. Foreign authors cannot understand an article whose full text is in Turkish. In the English abstract, a statement that is given only in acronym form may confuse. For example, the authors may interpret only PCT in the abstract as procalcitonin. PCT used in hemogram has a completely different meaning.

3. The use of Turkish acronyms in the English abstract of articles whose full text is in Turkish is also problematic for foreign authors to understand. For example, the neutrophil-to-lymphocyte ratio should be abbreviated as NLR, not NLO.

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CHAPTER V

CHYLOTHORAX

Kadir Baturhan ÇİFLİK

(M.D.), Department of Thoracic Surgery,
Kızıltepe State Hospital, Mardin/Türkiye
E-mail: baturhanciflik@gmail.com
ORCID: 0000-0002-5964-3778

1. Introduction

Chylothorax is the accumulation of chylous fluid in the pleural space as a result of a disruption of the integrity of the lymphatic duct. Chylous fluid forms in the intestines. Small and medium chain triglycerides taken from the diet are broken down into free fatty acids by intestinal enzymes and pass into the portal system. Apart from these fatty acids, which easily enter the portal circulation, complex long-chain triglycerides also combine with phospholipids, cholesterol and cholesterol esters to form chylomicrons in the jejunum. These large molecules then pass into the lymphatic system of the small intestine and form chylous fluid (1-3).

The vessels of the lymphatic system originating from the intestines merge with the cisterna chyli formed by the lymphatic vessels coming from the lower extremity at the level of the second lumbar vertebrae. The cisterna chyli is the origin of the thoracic duct. It enters the thorax through the hiatus aorticus, at the level of the tenth and twelfth thoracic vertebrae, from the right side of the aorta, adjacent to the azygos vein. This canal, which shows many variations after entering the thorax, most often runs close to the vertebral body, runs in the midline at the level of the fifth and sixth thoracic vertebra, and passes from the right hemithorax to the left hemithorax. It goes from the left side of the esophagus to the thoracic outlet posterior part. It forms the arcus at the level of the 6-7 cervical vertebra, on the clavicle. It goes down from the medial aspect of the anterior scalene muscle to the junction of the subclavian vein and jugular vein. It joins the systemic circulation from the right angulus venosus (Fig. 1). The diameter of the ductus thoracicus is initially about 3-4 millimetres (mm).

Its diameter narrows as it extends into the thorax. In adults, its length is about 38-45 centimetres (cm) (2-5).

The lymphatic system begins to form after the 6th week of the embryo. Six primary lymph sacs (two jugulars, two iliac, one retroperitoneal, one cisterna chyli) are formed. These sacs form numerous connections between each other. Two of these connections are the main channel and one is the ductus thoracicus. The ductus thoracicus connects to the venous system. Lymphatic capillaries consist of a single layer of endothelium and the distal part is closed. Lymphatic vessels resemble small veins and their walls consist of connective tissue and smooth muscle. As they contain more valves than veins, the flow from the centre to the periphery is stronger. There are superficial and deep course ones. This entire system is effective in maintaining the fluid balance between tissues and cells and in the formation of the immunological response against bacteria and viruses (Fig. 2) (2,4,8).

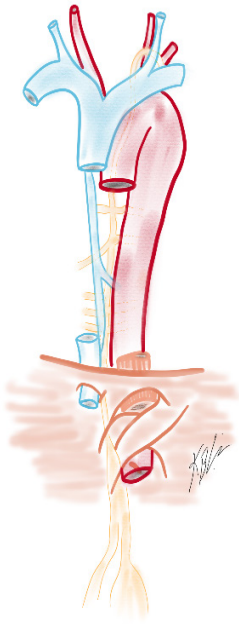

Figure 1. Course of the ductus thoracicus

2. Etiology

Chylothorax can be seen as spontaneous, idiopathic and traumatic. Chylous fluid was described for the first time in history by Bartolet in 1633. In 1948, the first successful ductus thoracicus ligation was performed by Lampson. Over the historical period, the incidence of spontaneous chylothorax has gradually decreased. Increasing traumas, especially due to developing technology, and

surgical operations have become the leading causes of chylothorax in recent years. When the literature is reviewed, it is seen that the majority of reported cases are postoperative (1-4).

If chylothorax is roughly grouped as traumatic and non-traumatic, neoplastic chylothorax is the most common among non-traumatic causes. Postoperative chylothorax is the most common cause of both traumatic chylothorax and all chylothoraxes. Non-traumatic causes include congenital causes, infectious causes and other causes of chylothorax such as rare sarcoidosis and Kaposi sarcoma. Among the traumatic causes, blunt trauma and gunshot wounds are seen. Most idiopathic causes are related to undiagnosed malignancies and constitute 8-10% of all chylothorax cases (4-7).

3. Diagnosis

Symptoms related to chylothorax vary depending on the underlying cause. In general, symptoms such as shortness of breath and cough can be observed, as in pleural effusions. Fever and chest pain are usually not observed. Chylothorax cases, which are small and asymptomatic, can be detected incidentally. It is usually observed in a single hemithorax. Although it varies depending on the anatomical variations of the ductus thoracicus, it is mostly in the right hemithorax. It should not be forgotten that in cases of left-sided and bilateral chylothorax, the possibility of anatomical variation and transmission from the abdomen might occur (1-5).

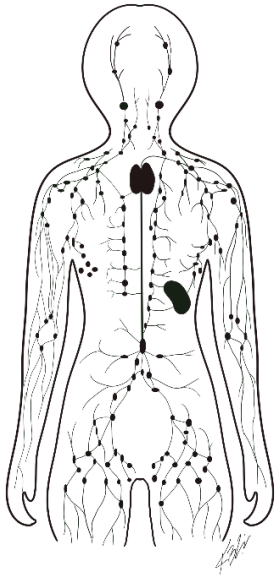

Figure 2. Lymphatic system

Anterior-posterior chest radiography and subsequent thoracentesis are usually sufficient for diagnosis. The “milky” colour of the pleural fluid obtained by thoracentesis strengthens the diagnosis of chylothorax (Figure 3) (2,3). Empyema, malignant effusion, and chronic transudate pleural effusions can sometimes have this appearance macroscopically. Therefore, biochemical analysis must be performed for differential diagnosis. Chylous fluid consists of chylomicrons and low-density lipoproteins. Lymphocyte dominance is observed. Colostrol/triglyceride ratio is less than 1. The pH of the liquid is between 7.4 – 7.8. Thanks to the fatty acids and lecithin in the chylous fluid, it is bacteriostatic and there is no growth in culture. Although high triglyceride levels are a strong indicator for chylothorax, chylothorax can also be diagnosed at lower triglyceride levels of 3-5% (Table 1) (2,4).

In general, in the biochemical examination of the fluid, triglyceride levels above 110 milligrams (mg) / decilitres (dL), cholesterol/triglyceride ratios less than 1, and staining with Sudan III are considered diagnostic (2,4,8-10).

Table 1. The contents of the chylous fluid

pH	7.4 – 7.8
Dansite	1012 -1025
Lymphocyte	400-7000/dL
Oil	0.4 – 0.6 g/dL
Cholesterol	65-220 mg/ dL
Trigiliseride	>110 mmol/dL
Cholesterol / Triglycerides	<1
Total protein	2-6 g/dL
Albumin	1.2 – 4.1 g/dL
Glucose	2.7 – 11 mmol/L
Electrolyte	Low compared to plasma
Lymphocyte	<%80
Erythrocyte	50-600 /mm^3
Chylomicron	Available
Color	Milk-colored
Staining	Staining with red from water
Culture	No reproduction

4. Treatment

The priority in the treatment of chylothorax is to drain the chylous fluid from the pleural space. Thoracenteses can be tried repeatedly, or tube

thoracostomy can also be performed. Following the drainage, the patient's diet must be adjusted to reduce lymphatic drainage. A diet consisting of medium chain fatty acids should be tried. If there is no decrease in drainage despite this dietary change, total parenteral nutrition must be started. After this stage, drainage is expected to decrease below 500 millilitres (mL) per day. Achieving this result shows that conservative treatment can be successful. Success rates with conservative treatment are between 50-60% in the literature (10-12).

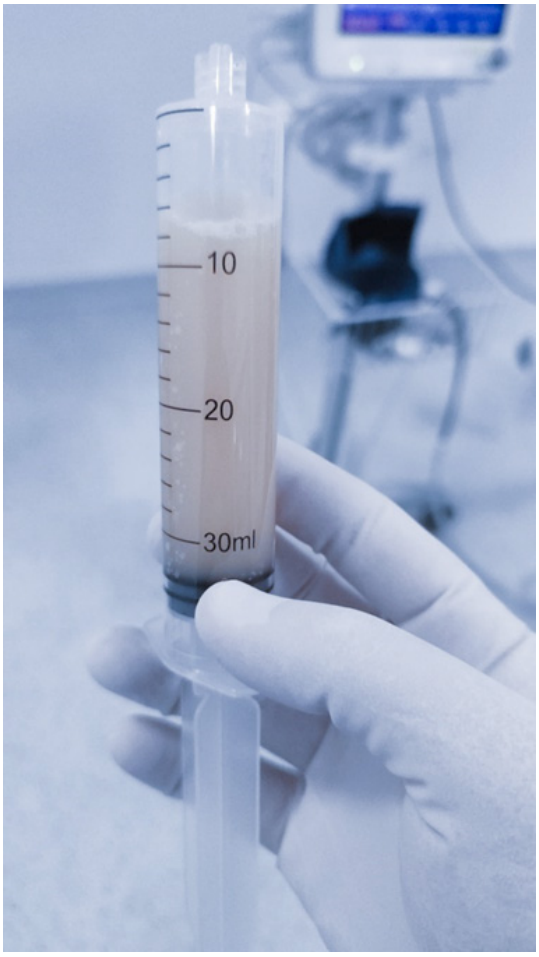

Figure 3. Thoracentesis of chylous fluid

In cases where this first conservative treatment option is not successful, surgical treatment options come to the fore. Nowadays, there is another treatment method that is frequently applied before the surgical treatment. Long-acting synthetic octreotide analogues or somatostatin treatment are tried with the patients in advance to the surgical treatment. These agents would help reduce

the blood flow in the intestines, the intestinal chylomicron production, and fat absorption. However, as it causes malnutrition, constipation and an increase in liver enzymes, it must be carefully applied. Synthetic octreotide analogues are frequently used in our country. It is recommended to apply subcutaneously at a daily dose of 100 micrograms (μg) in 2 or 3 times and it is also recommended that the treatment should be applied for at least seven days (2,3,13-15).

In advance to the surgical treatment, other preferred conservative treatment methods are pleurodesis with sterile TALK powder and povidone-iodine, sclerotherapy with tetracycline and fluoroscopic embolization. If the daily drainage amount does not fall below 500 mL despite the 4 weeks of conservative treatment options, surgery becomes inevitable. As surgical treatment, the ligation of the leaky duct is performed by thoracotomy or video-assisted thoracoscopic surgery (VATS). In order to find the leakage from the ductus thoracicus, which has many different variations, it is recommended to choose the hemithorax where the chylothorax is located for the operation. In cases of bilateral chylothorax, the right hemithorax is preferred (16-19).

It is recommended to increase lymphatic drainage to detect the leak before the operation. For this, olive oil, cream, Evans's blue, methylene blue and sudan black can be used one or two hours before the operation. After detecting the leaky area in the ductus thoracicus, ligation is performed with non-absorbable suture materials. For the leaks of which the location cannot be determined, ligation is performed between the eighth and twelfth thoracic vertebrae, leaving the arch above the hiatus. For this, the esophagus must be released and pulled anteriorly and the boundaries of the aorta and azygos must be clearly defined because the ductus might not be clearly visible. In order to prevent possible complications, boundaries must be established when ligating the tissue between these two vascular structures. Apart from the standard approach with thoracotomy and VATS, there is also a method in which the ductus is ligated by removing the eighth rib in the prone position. In this situation, after periosteating the eighth rib, it is essential to determine the duct that runs in the midline of the azygos posterior to the mediastinum. It is not a widely used method (7,19-22).

5. Conclusion

Chylothorax must be managed in a timely manner and with the right options. It should be kept in mind that it might cause serious malnutrition in the patients. The mortality rates due to chylothorax reported in the literature are considerably high. It is critical to elucidate the etiology and identify the moment when conservative treatment becomes inadequate. It should not be forgotten

that mortality rates have decreased significantly since the surgical description of ductus ligation in 1948. Patients should not hesitate to be referred for surgical treatment.

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CHAPTER VI

THE ASSOCIATION BETWEEN DIABETES AND SEPSIS MORTALITY

Zeynep KARAKÖY[1] & Zekai HALICI[2] & Elif ÇADIRCI[3]

[1]Erzincan Binali Yıldırım University, Department of Pharmacology,
E-mail: zeynep.karakoy@erzincan.edu.tr
ORCID: 0000-0002-4281-0103

[2](Prof. Dr.), Atatürk University Faculty of Medicine,
Department of Pharmacology,
E-mail: hzekai@gmail.com
ORCID: 0000-0001-6854-6059

[3](Prof. Dr.), Atatürk University Faculty of Medicine,
Department of Pharmacology,
E-mail: ecadirci@atauni.edu.tr
ORCID: 0000-0003-0836-7205

1. Introduction

Approximately 49 million people are affected by sepsis each year and 11 million deaths are estimated to be caused by sepsis, accounting for 19.7% of all deaths worldwide (1). Sepsis involves systemic and microcirculatory dysfunction due to intravascular coagulation, increased vascular permeability, altered vascular resistance, endothelial cell damage and compromised oxygen supply. Hypotension and organ dysfunction associated with sepsis is called 'septic shock'. Septic shock has is one of the most common reasons for death in immunocompromised conditions like diabetes (2).

Diabetes mellitus (DM) is a persistent condition characterized by elevated levels of glucose in the blood due to either insufficient insulin production or ineffective insulin utilization. Hyperglycemia triggers many inflammatory responses, including increased oxidative stress, as well as mitochondrial

dysfunction, cell death, tissue damage and organ failure (3). Therefore, the frequency of infection in diabetic patients is more common than in non-diabetic patients. Treatment of infection in diabetes is complicated and morbidity and mortality due to infection is higher in diabetic patients (2).

Insufficient control of blood sugar levels raises the risk of infections affecting the skin, eyes, gastrointestinal tract, urinary tract, and respiratory system. Diabetic wounds that occur in DM patients, affecting approximately 25% of them, are more difficult to heal and have an increased risk of limb amputation. Many uncommon and life-threatening infections are also more common in DM patients. (4).

The aim of this review is to draw attention to the effect of diabetes and its treatment on sepsis mortality in intensive care unit patients.

2. Intensive Care and Sepsis

Sepsis resulting in shock and/or organ failure is the most common indication for intensive care unit admission and one of the leading causes of intensive care unit (ICU) mortality (5).

Due to limited therapeutic options, the prognosis of sepsis is poor. ICU mortality rates range from 36.0% to <55.2%. This makes it the leading cause of death in adult in ICU (6).

Sepsis Intracellular signaling through nuclear factor-κB (NF-κB) leads to upregulation of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukins IL-1β and IL-6. Cytokines activate endothelial cells and neutrophils and increase the expression of adhesion molecules (7).

Severe sepsis causes dysfunction of important organs or tissue hypoperfusion (8). The basis of organ damage caused by sepsis is a disturbance between perfusion and the metabolic requirements of tissues. Cardiac dysfunction caused by inflammation plays an important role in this, and is worsened by disruption of tissue oxygen utilization (9).

2.1. Cardiac Dysfunction

Cardiomyocyte contractility is suppressed by pro-inflammatory cytokines, particularly IL-1β and IL-6. They mediate neutrophil infiltration into the myocardium by inducing the expression of vascular cell adhesion molecule-1 (VCAM-1) on the coronary endothelium. In addition, the chronotropic response is often impaired in sepsis (10). Conversely, sepsis has been demonstrated to correlate with various clinical cardiac events,

encompassing acute heart failure, arrhythmias, myocardial infarction, and non-ischemic myocardial damage (9).

2.2. Respiratory Dysfunction

Studies have indicated that pro-inflammatory cytokines like TNF-α or IL-1β play a role in mediating damage to the alveolar barrier, leading to acute respiratory distress syndrome (ARDS). ARDS is characterized by acute respiratory failure arising from diffuse pulmonary infiltration, which stems from alveolar damage and heightened vascular permeability. Sepsis, a condition occurring in 40% of patients with septic shock, stands as one of the primary causes of ARDS (11).

2.3. Renal Disfonksiyon

The kidneys are another common target for organ dysfunction. Among patients experiencing critical illness, sepsis stands out as the primary cause of acute kidney injury (AKI). The vast majority of patients with sepsis or septic shock develop ABI. In addition, the use of nephrotoxic drugs in the treatment of sepsis also plays a role in the development of AKI. Patients with AKI associated with sepsis have a 62 percent higher mortality risk compared to patients with sepsis without AKI and a 36 percent higher mortality risk compared to patients with AKI not associated with sepsis (12,13).

2.4. Coagulation Disorders

Pro-inflammatory cytokines play a role in elevating the luminal expression of endothelial cells and circulating levels of intercellular adhesion molecule-1 (ICAM-1) and VCAM-1 in serum, which in turn contribute to platelet adhesion and activation of the coagulation cascade. Consequently, thrombocytopenia and/or disseminated intravascular coagulation can develop in patients experiencing sepsis and septic shock (14).

3. Sepsis and Diabetes

It is commonly acknowledged that diabetes negatively impacts the outcome of infections. Increased susceptibility to infection in diabetes has been associated with many factors (2). T2DM (type 2 diabetes mellitus) is a common and devastating disease that complicates the recovery of critically ill patients. T2DM has been shown to worsen the prognosis for infection, with increased morbidity and mortality due to sepsis in these patients compared to

the general population (15). Studies have shown that the risk of pneumonia, tuberculosis, urinary tract infections, fungal infections and postoperative infections are higher in patients with DM compared to patients without diabetes (16). It has been found that diabetic patients have increased blood concentrations of pro-inflammatory cytokines, which may lead to increased insulin resistance and development of vascular diseases (17). Both sepsis and chronic hyperglycemia affect microcirculation and lead to organ damage due to inflammatory mediators (18).

In a study conducted in an intensive care unit, patients whose blood glucose levels exceeded 200 mg/dL (>11.1 mmol/L) demonstrated higher mortality rates compared to those with blood glucose levels below 200 mg/dL (<11.1 mmol/L) (5.0% versus 1.8%, respectively; $p < 0.001$).(19). Similar studies are shown in Table 1.

Table 1. Clinical Trials Investigating The Association Between Diabetes and Sepsis Mortality

Year	Patient	Mortality rate (DM and non-DM)	Study design	Reference
2003	513,749 patients with diabetes	Serious bacterial infections are more common in diabetics. Higher mortality associated with infection in diabetic patients.	Retrospective cohort study	(20)
2009	88 patients aged 65+ with DM 118 controls without DM	People with DM had longer fevers, stayed in hospital longer, and died at a higher rate (12.5% vs. 2.5%) compared to controls.	Retrospective study	(21)
2015	There were a total of 1064 patients diagnosed with severe sepsis or septic shock along with AKI	Of 225 patients with diabetes and AKI, 174 (77.3%) were discharged, while 357 of 446 patients (80%) with AKI and no diabetes were discharged.	Prospective cohort study	(22)
2017	120,000 intensive care patients in the Netherlands between 2009 and 2013	There was no association between diabetes and an increase in 90-day mortality.	Retrospective study	(23)
2018	185,341 diabetic patients	People with DM (especially women and those aged 30-64) have an increased risk of death from infection-related causes.	Retrospective cohort study on a regional electronic archive	(24)
2018	1779 patients with DM+ 11,066 patients without DM	Compared to patients without DM, patients with DM were 21% more likely to develop a new infection.	Cohort study	(25)

4. Effects of Diabetes/Hyperglycaemia on Innate and Acquired Immunity and Other Factors

Hyperglycemia may have a potentially important role in the susceptibility of diabetic patients to infections by impairing the function of neutrophils and macrophages. Strict glycemic control has become mandatory for critically ill patients and especially for ICU patients in the presence of sepsis(26).

4.1. Dentritic Cells

Dendritic cells (DCs) are an active population of antigen-presenting cells (APCs). They are a critical link between the innate immune response and the adaptive immune response (27). Studies have shown that there is a reduction in the number of DHs in both type 1 diabetes (T1DM) and T2DM. (28,29). T2DM patients had reduced numbers of both myeloid and plasmacytoid DCs compared to healthy controls in a study by Seifarth et al. This may make people with Type 2 T2DM more susceptible to opportunistic infections. (29). Montani et al. demonstrated in vitro that hyperglycaemic serum from T2DM patients prevented monocyte maturation and activation into effective DCs (30).

4.2. Macrophages

Macrophages play an important role in the regeneration and repair of tissues. They act as anti-inflammatories to remove pathogens in the early stages of wound healing. At a later stage, they resolve inflammation and promote tissue repair. In case of pathological conditions, chronic inflammation can occur in the affected tissue if the transition from the pro-inflammatory to the anti-inflammatory proliferative phase is not achieved. (27).

Dysfunctional phagocytosis by macrophages in diabetic mice increased apoptotic cell burden, caused chronic inflammation and prolonged wound healing, reported Khanna et al. (31).

4.3. Neutrophils

Neutrophils are recognised as key elements in the fight against infection. The recruitment of neutrophils to sites of infection is by chemotaxis with complement activation. Activated neutrophils bind to induced ligands on the surface of inflamed endothelial cells via surface receptors. They then migrate into the tissue (27). Sepsis has been shown to downregulate CXCR2, a chemokine receptor expressed on neutrophils. This impairs neutrophil

recruitment. CXCR2 is also a regulator of ICAM-1 expression on endothelial cells (ECs). Neutrophil recruitment to the site of inflammation is further reduced by decreased CXCR2 expression. Decreased expression of ICAM-1 on endothelial cells hinders the recruitment of cytotoxic CD8+ T lymphocytes to infection sites(4).

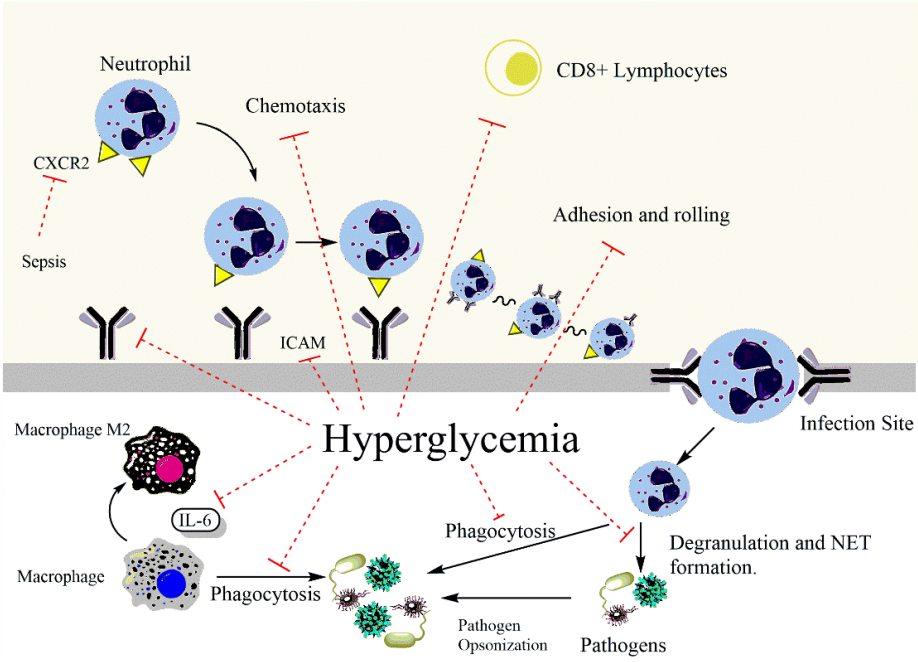

Figure 1. Effect of Hyperglycemia on Immune Factors (4)

5. The Effect of Insulin and Other Anti-Diabetic Drugs on Sepsis Incidence and Mortality

The established effects of insulin and oral antidiabetic medications on modulating the immune system are widely recognized.Their beneficial effects have been demonstrated in diabetic patients with sepsis (4).

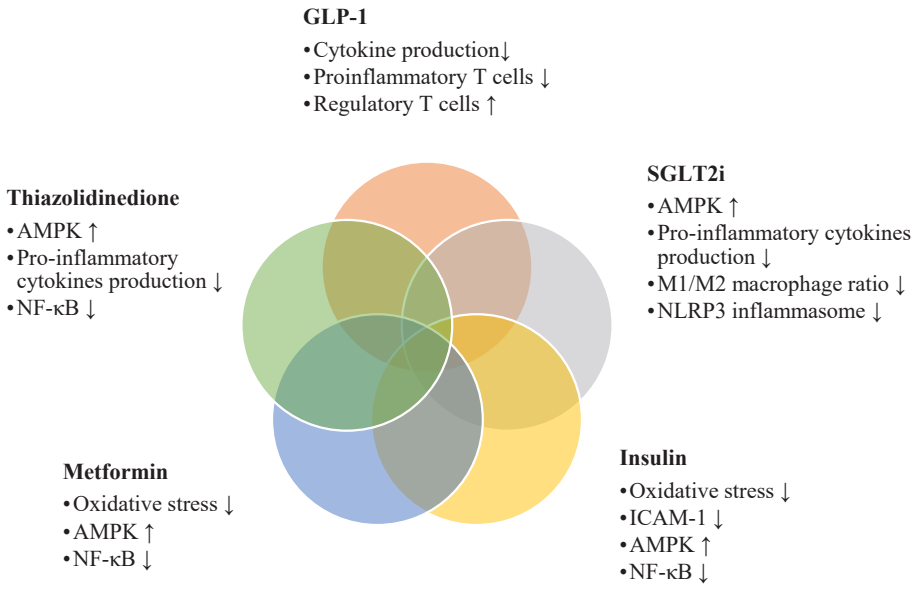

Figure 2. Anti-inflammatory Effects of Insulin and Other Oral Antidiabetic Drugs

5.1. Insulin

Insulin is still the first choice to reduce blood sugar to safe levels. Insulin exerts direct or indirect anti-inflammatory effects, preventing the negative effects of high blood sugar on immune function (32). Studies have shown that insulin has anti-inflammatory properties and suppresses the production of some early pro-inflammatory substances, including TNF-α, superoxide anions, NF-κB (33,34).

5.2. Metformin

Metforminin enfeksiyonlarla mücadelede güvenli ve güvenilir bir antidiyabetik ilaç olarak ünü, otofajinin modülasyonu, mitokondriyal fonksiyon ve immünomodülasyon dahil olmak üzere çok yönlü etkilerinden kaynaklanmaktadır. (35). Gomez et al. reported that metformin reduced the incidence of acute kidney injury from sepsis (36). Furthermore, when the therapeutic effect of metformin in combination with antimicrobial agents against MRS and multidrug-resistant (MDR) *Pseudomonas aeruginosa* was investigated, metformin was shown to synergize with most of the tested agents. (37).

5.3. Thiazolidinedione

Studies on thiazolidinediones (TZD) in diabetic patients have shown that TZD suppress NF-κB. Rosiglitazone reduced kidney damage and improved

other markers of end-organ damage in mouse models of sepsis, while ciglitazone reduced bacterial loads and local inflammation in a mouse model of pneumococcal pneumonia (38–40). Another study has shown that TZDs not only inhibit the response to TNF-α, but also to IL-1β and IL-4 (41).

5.4. Dipeptidyl Peptidase-4 Inhibitor (Dpp4i) And Glucagon-Like Peptid-1 (Glp-1) Receptor Agonists

Recent studies have revealed that glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 inhibitor drugs (DPP4i) exert a direct impact on endotoxemia, irrespective of their abilities to lower glucose levels (42–44).

Yang et al. demonstrated that activation of GLP-1 receptors contributes to impaired inflammatory response by increasing B and T cell proliferation in sepsis patients (45). A number of studies have shown that GLP-1RAs can inhibit inflammatory responses and modulate the immune response in vitro (46,47). In addition, DPP-4i has been shown to decrease ROS formation and increase superoxide dismutase (SOD) activity (48).

5.5. SGLT2- Inhibitors (SGLT2i)

AMPK acts as an energy sensor required for the management of inflammation in macrophages. Empagliflozin, an SGLT2i, decreases the expression of monocyte chemoattractant protein-1 (MCP-1), IL-1β, IL-6 and TNF-α in macrophages. It causes an increase in p-AMPK levels and a decrease in NF-κB levels in macrophages (49).

Due to their cardioprotective and renoprotective properties, SGLT2 inhibitors have garnered significant interest as a class of anti-diabetic medications. A comprehensive meta-analysis conducted by Li et al. revealed a noteworthy decrease in the risk of pneumonia and septic shock among diabetic patients treated with SGLT2 inhibitors (50).

6. Conclusion

Sepsis is the most common cause of death in intensive care units around the world. Diabetes is a prevalent and increasing co-morbidity in patients with sepsis. Although studies have shown a higher risk of infection in diabetic patients, the impact of diabetes on sepsis and the mechanisms underlying their interactions are still debated. Early diagnosis of infection, appropriate antibiotic selection, control of glycemic status and supportive treatment may reduce the morbidity and mortality rate due to sepsis in patients with diabetes. Different

therapeutic options are under investigation, including immune modulatory approaches targeting pathways activated in diabetes and sepsis.

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CHAPTER VII

TUMMY TIME: FROM THE PERSPECTIVE OF A PHYSIOTHERAPIST

Gülfem Ezgi ÖZALTIN[1] & Aymen BALIKÇI[2]

(Dr. Research Asist)., Inonu University
E-mail: gulfemezgi.ozaltin@inonu.edu.tr,
ORCID: 0000-0003-1591-4844

(Dr. Physiotherapist), Fenerbahce University
E-mail: aymenbalikci@gmail.com
ORCID: 0000-0002-7552-8235

1. Introduction

In the early 90s, the American Academy of Pediatrics recommended that babies sleep in a supine position due to sudden infant death syndrome. However, it was observed that SIDS cases decreased by 40%. However, in babies lying on their backs, findings such as head shape abnormalities (plagiocephaly) and motor development delay occur. Tummy time is a form of activity used to prevent head shape abnormalities and support motor development in babies under 6 months of age. For this reason, tummy time has been included as a component in the action guidelines of Australia, South Africa, Canada, the United Kingdom, the National Academy of Medicine, and the American Academy of Pediatrics. It has also been included in the World Health Organization's action guide for children under 5 years of age. (1)

2. How Much And When is Tummy Time?

Tummy time activities have been recommended for babies to be performed in 30-minute periods during the day. (1) Prone positions are recommended after 6 weeks and up to 6 months. When the studies are examined, it is suggested that the best efficiency from tummy time activities is when babies are approximately 4-6 months old. Because it is thought that babies over this age can easily change

the position they are placed in instead of maintaining it. Studies show that only 30% of parents comply with tummy time activities. Hewitt et al. In a pilot study conducted for the adaptation and inclusion of mothers in tummy time, healthy babies and their mothers were included in the study. Participants in the study were divided into 5 groups and the study was carried out for 4 weeks. In the study, GENEActiv was used to measure the physical activity of babies. In the study, a group was established on a social media platform and the responsible researcher shared informative and encouraging posts about the benefits of tummy time and conducted a tummy time study with the mothers. The control group received standard care (such as breastfeeding, tummy time, and development information) from the local health service. There was no difference between the groups in the time the baby spent on the tummy. At the end of the study, while there was no difference in terms of motor development, a medium effect size was observed in favor of the intervention group in terms of the baby's prone and sitting ability. (2) Factors that negatively affect tummy time include the older age of the parents, the time spent awake in the supine position, and the level of education. (3) At the same time, the effect of not having an idea about tummy time and not being guided by experts can be taken into consideration, even if it is minimal.

2.1. Gross Motor Skills

Another study showed that babies who spent more than 15 minutes of tummy time at 2 months of age gained head control earlier. Kuo et al. examined the effect of an early awake prone position on motor development parameters in their cohort study. As a result of this study, it was argued that babies whose tummy time was up to 6 months scored higher in motor milestones, but this was not the case at 24 months. It is also said that babies who are exposed to the prone position reach certain motor development stages more quickly than those who are not. Especially sitting, rolling, crawling-on-abdomen, crawling-on-all-fours). (4) Shiber et al. It evaluated the time four-month-old babies spent in different positions for 24 hours, babies who reached a certain level with the Alberta Infant Motor Scale (AIMS), the effect of time spent awake in the prone position on motor milestones, and the tummy time of babies who could achieve motor milestones. It was observed that the majority of babies spent more than 5 hours in the supine position; It was determined that the time spent face down while awake was 30 minutes or less. Additionally, it was observed that the time spent in the supine position while awake was greater than in the prone position. This study also proved that babies who were able to achieve certain motor

milestones spent more time in the prone position while awake. (5) Davis et al. It evaluated babies 2 months and younger until they were 6 months old. Parents were asked to record their babies' tummy time awake and sleeping positions. As a result of the study, it was observed that babies who slept on their stomachs reached eight motor milestones, except walking, earlier than those who slept on their backs. (6) Carmeli et al. In a longitudinal study in which they examined the relationship between the preferred sleeping position and gross motor development, the Alberta Infant Motor Scale was used to evaluate gross motor development. According to the results of the study, there was no relationship between the baby's preferred sleeping position and gross motor development until the 6th month. It has been observed that babies who sleep on their backs and prefer the prone position when awake do not differ from others in terms of gross motor development. (7)

The relationship between prone position and motor skills may be based on multiple factors. First of all, the awake prone position helps reduce the physiological flexion pattern, improving head and upper body control and shoulder girdle stabilization. (8, 9) By providing a safe posture against gravity, vestibular activity increases, thus allowing the development of the sensory system and increasing postural control. Vestibular function is the sensory system that is vital for the baby's motor milestones. The vestibular system matures in the 4th month of pregnancy and becomes functional after birth. (9) Since the vestibular-ocular reflex provides gaze stabilization, the development of the baby's vestibular system within 1 year after birth will enable the development of postural control, balance, and fine motor skills. (10) This situation can also be explained according to dynamic systems theory. Along with the development of the musculoskeletal system and the development of the central nervous system, the environment and task also have an impact on motor functions. The baby positioned face down is advantageous in terms of motor functions as it is more advantageous in perceiving the environment as well as in the development of the musculoskeletal system. (5, 9)

When the studies are examined, a consensus has been reached that the time spent face down while awake and babies who prefer tummy activities achieve gross motor development in the stages of turning, rolling, crawling, crawling, and sitting earlier than those who do not (except for walking). However, we cannot say that there is a consensus on whether the sleeping position affects the baby's gross motor development. It has been observed that examining the effect of tummy time over an average period of up to 6 months can yield more effective results. Tummy time activities appear to be generally based on parental records.

It has been observed that the Alberta Infant Motor Scale, Denver Developmental Screening test, and Peabody Developmental Motor Scale are generally used for gross motor evaluation results. We recommend that future studies not only evaluate parental views but also measure them by another researcher. In addition, babies who do not prefer the prone position can be encouraged with activities such as spending time with the parent in the prone position, choosing appropriate activities for the child, increasing exploration skills with toys, having the mother position the baby between her legs and spending time, and providing support in the sitting position. (11)

2.2. Fine Motor Skills

Kuo et al. showed that time spent on the tummy and tummy activities did not affect fine motor skills (4). Rosshery et al. He emphasized the importance of the prone position in helping babies explore their surroundings and expand their space. Senju et al. It has been shown that the communication, fine motor, and problem-solving skills of babies who spend time in prone positions up to 6 months of age have significant differences compared to those who do not prefer prone positions (11). Soska et al. examined the effect of postural position (sitting, prone, and supine) on object discovery. They classified exploration skills as verbal manual exploration, oral manual exploration, and visual manual exploration. As a result of the study, it was shown that general grasping skills were highest in the sitting position and that the prone position was more suitable for developing grasping skills than the supine position. Oral manual exploration skills were observed to be in the supine position. It has been shown that grasping objects without bringing them to the mouth is best done in the prone position. It has been observed that visual manual exploration skills are highest in sitting and prone positions. (12)

The supine position allows babies to recognize objects by bringing them to the mouth along with grasping, but since constant movement against gravity is performed, their exploration skills are limited. Although the prone position may seem a little more challenging for fine motor skills as it requires head and body control against gravity, the increase in the visual field is advantageous for fine motor skills.

2.3. Communication, Social, and Interoceptive System

In a study, the communication, personal social skills, and problem-solving abilities of 6-month-old babies who preferred and did not prefer tummy time were evaluated. As a result of the study, it was observed that while there was a

significant difference in communication, personal social, and problem-solving abilities at 6 months, this difference decreased with increasing age (1.5 -2.5 years). (11)

It has been shown that the prone sleeping position of newborn babies reduces the baby's stress level, reduces the time it takes to fall asleep, and increases the duration of uninterrupted sleep. (13, 14) This situation can be explained by Synactive Development Theory. According to the Theory of Synactive Development, the baby can achieve, maintain, and regain self-regulation in all systems. If the baby cannot exhibit self-regulation behaviors, the baby may become stressed and show withdrawal behaviors (cough, hiccup, finger-pointing, etc.). (15) Some studies have shown that babies are more flexible in the prone position, can relax more easily, and have better self-regulation skills. (16)

There are studies in the literature showing the positive effect of the prone position on the interoceptive system, and personal and social skills. However, the number of studies in this field is limited. In this sense, our suggestion is to eliminate the prejudice against the prone position by providing parents with more comprehensive information about the prone position. However, increasing randomized controlled studies will enrich the literature.

3. Conclusion

Until now, it was not recommended to position babies face down due to sudden infant death syndrome. However, as a result of the studies, prone positioning is recommended for at least 30 minutes a day under parental supervision. It has been observed that an awake-prone position has a positive effect on babies' gross motor skills, communication, and social interaction, while prone positioning while sleeping supports babies' self-regulation.

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CHAPTER VIII

PLATELET RICH FIBRIN IN DENTISTRY

Melike BAYGIN[1] & Banu GÜRKAN KÖSEOĞLU[2]

[1](Research Assistant), Istanbul University Institute of Health Sciences, Oral and Maxillofacial Surgery PhD Program,
E-mail: melikebaygin.mb@gmail.com
ORCID: 0000-0002-7994-8229

[2](Prof. Dr.), Istanbul University Faculty of Dentistry, Department of Oral and Maxillofacial Surgery,
E-mail: banugr@istanbul.edu.tr
ORCID: 0000-0003-1442-7032

1. Introduction

Using growth factors, stem cells, bioactive molecules and synthetic tissue materials for tissue regeneration and tissue function repair constitutes the concept of tissue engineering. Three basic elements are important in the regeneration approach in tissue engineering: progenitor cells, scaffold and signaling molecules. (1)

The main disadvantage of synthetic biomaterials is that they are avascular. Vascular support is very important for successful regeneration. If vascular support is not provided, regeneration may fail. (2-3)

Blood is an autogenous source used by the body during the wound healing process. Blood cells are erythrocytes, leukocytes and platelets. Platelet is the smallest cell found in blood. A healthy human blood contains 150,000-4000,000 units per mm3. They are formed when megakaryocytes break into pieces and enter the circulation. They do not contain nuclei when they enter circulation. (4) Platelets are disc-shaped. Their circulation period is approximately ten days. After the period expires, they are broken down by the spleen and reticuloendothelial system. (5) They help the proliferation and activation of cells

due to the growth factors, angiogenic factors, some chemokines and cytokines they contain. It plays an active role in the early phase of wound healing. In addition, platelets secrete many coagulation factors and adhesion molecules. (6) Platelet concentrates were obtained with the idea that using the growth factors secreted by platelets in a more concentrated form than physiological could support wound healing during and after surgery.

Wound healing basically consists of three phases: inflammation-proliferation- remodeling. Inflammation occurs within minutes to hours while proliferation occurs within days to weeks after the injury. Remodeling can take weeks, months, or years after the injury. (6) When a wound occurs, the first response of the organism is vasoconstriction of blood vessels and activation of platelets. Platelets are activated and initiate the coagulation mechanism. Platelets activate thromboplastin and, with the help of calcium, transform prothrombin into thrombin. Thrombin transform fibrinogen into fibrin. Healing begins with the activation of the coagulation mechanism. Fibrin stops blood flow and creates a scaffold for incoming inflammatory cells. (6) The fibrin network activates angiogenesis at the wound site, as well as serving as a scaffold for neutrophils and macrophages, which are necessary to eliminate cellular debris and dead tissues and prevent infection. (7) The number of neutrophils and monocytes increases in the first 2-3 days of the injury. With this inflammatory response, immune system activation is initiated. The initiation of the immune response is preventive in terms of infection. Removal of cellular debris and dead tissues also occurs with this system. (6)

In addition to their essential role in hemostasis, platelets also contribute significantly to other processes that maintain hemostasis. They take part in wound healing, tissue maturation, angiogenesis and inflammation. Platelets secrete growth factors. They also help repair, regenerate tissues and protect healthy tissues by secreting many substances such as fibronectin, sphingosine 1 phosphate and vitronectin. (4) Although platelets do not contain a nucleus, they show intense metabolic activity and contain different types of granules. (8)

Alpha granules: Alpha granules have a heterogeneous structure. They are considered the main granules of platelets. They contain many proteins that are critical for platelet function. It contains platelet factor-4, insulin-like growth factor (IGF-1), platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor beta (TGF-β), fibrinogen, von Willebrand factor (vWF), thrombospondin, fibronectin, factors V and VII, albumin and immunoglobulins can be sorted. Growth factors found in platelet alpha granules are important for wound healing.

Delta granules: Another name is dense granules due to their appearance in the electron microscope. Its content consists of calcium, ADP, ATP, pyrophosphate, histamine, serotonin and epinephrine.

Lambda granules: They are also called lysosomal granules because their content consists only of lysosomal enzymes. They have bactericidal effects and are effective at the fibronilysis stage. (8- 9)

Regenerative dentistry is a highly sought-after and developing branch of science. Regenerative dentistry uses biological mechanisms for tissue regeneration. Stem cell technology is used for these biological mechanisms. Regenerative dentistry encompasses tissue engineering and dentistry. (10) Based on the question 'What does our body use to heal?', platelet contrasts were discovered and have been used in many different areas of medical and dental practice for over 30 years.

The main function of platelets is to initiate the hemostasis mechanism and secrete growth factors and cytokines necessary for wound healing. Platelets play a very important role in regeneration by secreting substances such as many growth factors and cytokines. The use of platelet concentrates has been examined in many studies and it has been observed that these products contribute positively to the healing process. Very positive results were obtained when used with various biomaterials. The use of platelet contrasts is a cheap and reliable method. The product obtained is autologous. Therefore, it does not show any immunological reaction and does not carry the risk of infection.

Platelet concentrates are divided into classes to facilitate understanding and interpretation of clinical studies. Cellular content and the presence of fibrin clot were taken into account in classification. (11-12-13) In addition to this classification, Tunalı et al. introduced titanium-prepared platelet-rich fibrin (T-PRF) in 2012. (14)

1) Pure Platelet Rich Plasma (P-PRP).
2) Leukocyte and Platelet Rich Plasma (L-PRP)
3) Pure Platelet Rich Fibrin (P-PRF)
4) Leukocyte and Platelet Rich Fibrin (L-PRF)
5) Titanium-prepared Platelet Rich Fibrin (T-PRF)

2. Platelet Rich Plasma

Platelet Rich Plasma (PRP) is plasma with high platelet concentration, obtained by centrifuging blood in a certain procedure. (15) Ferrari et al. first

reported the use of platelet-rich plasma during open heart surgery in 1987. (16) Since the 1990s, it has been used in regeneration, ulcer treatment, burn treatment, aiding pregnancy by supporting endometrial and follicular growth, muscle repair, bone diseases, skeletal injuries, accelerating post-operative recovery, and especially in the treatment of tendon tears in orthopedics. (6) Since PRP has an osteoinductive effect, it is used in standard treatments of tendon and ligament ruptures in orthopedics. (17- 18)

Platelet-rich plasma is used as a scaffold in regenerative therapy. It contains growth factors that can provide tissue repair and accelerate wound healing. It has been used in endodontics, periodontics, oral-dental-maxillofacial surgery, especially in regenerative applications. Positive postoperative results were obtained. It has been reported that it has effects such as accelerating healing, reducing pain, supporting soft tissue healing and accelerating bone healing. PRP achieves these effects with high concentrations of growth factors and proteins. The quality and functionality of platelets largely depends on the PRP preparation protocol. There are many protocols recommended for PRP preparation. (10)

To prepare PRP, first autologous blood is taken from the patient. The PRP tubes contain anticoagulant. The blood is centrifuged in two stages. The first centrifugation is short and has a light cycle, while the second centrifugation is faster and has a long cycle. (18) On the contrary, some authors suggested performing the first centrifuge fast and the second centrifuge slowly. (19) In the first centrifuge, the blood is divided into three layers. There are erythrocytes in the bottom layer, platelet concentrate (buffy coat) containing leukocytes in the middle layer. In the upper layer, platelet-poor plasma is formed. Generally, the red blood cell layer is discarded and a second centrifugation is performed to obtain a more concentrated platelet layer (20). If inappropriate centrifuge speed is used to prepare PRP, platelets may be damaged. (19) The amount of PRP is generally 10% of the blood volume taken. To give an example, 2 ml of PRP can be obtained by centrifuging 20 ml of blood at 3500 rpm for 15 minutes. (20)

While preparing PRP, it is necessary to use an anticoagulant substance such as calcium chloride and bovine thrombin. It is known that these substances can inhibit wound healing. Also, the preparation technique is difficult. Growth factor release begins 10 minutes after PRP is prepared and 95% is released within the first hour. These limitations have led to the need to find new methods for better tissue regeneration. (19)

3. Platelet Rich Fibrin

Pure platelet-rich fibrin is rarely preferred due to its laborious preparation and high cost. Leukocyte and platelet rich fibrin (L-PRF) was introduced by Choukroun in 2001. L-PRF, the second generation platelet concentrate, is rich in platelets, growth factors and leukocytes. It is autologous, easy to prepare and very inexpensive. It does not contain anticoagulants. 10 ml of venous blood taken into a silica tube is centrifuged at 3000 rpm or 2700 rpm. The centrifuge time for 300 rpm is ten minutes, while the centrifuge time for 2700 rpm is twelve minutes. Since it does not contain anticoagulant, coagulation begins right after the blood comes into touch with the tube. For this reason, blood must be taken very quickly and placed in the centrifuge device. Otherwise, the blood will clot and a small amount of PRF will be obtained. While fibrin initially forms in the upper part of the tube, it comes to the middle part with the centrifugation. Platelets are densely found in this fibrin. At the end of centrifugation, erythrocytes are formed in the bottom layer of the tube, L-PRF is formed in the middle layer, and cell-poor plasma is formed in the upper layer. (21)

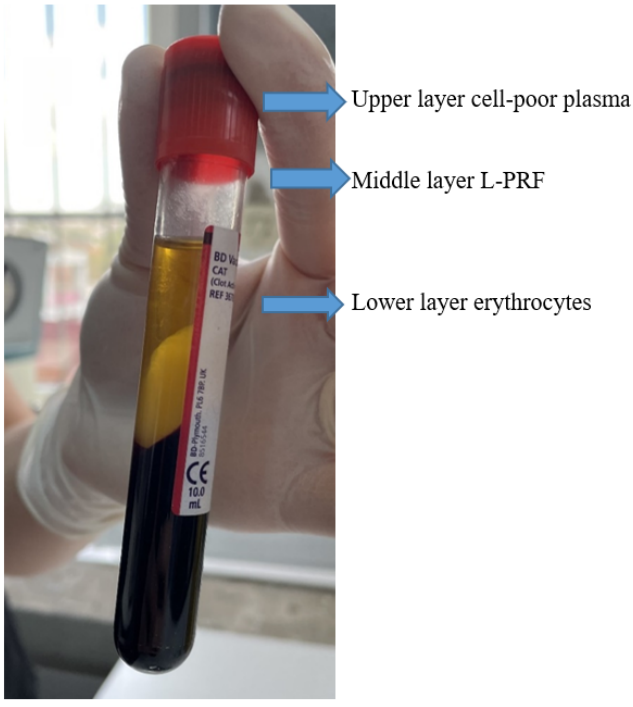

Figure 1. L-PRF image formed after centrifugation.

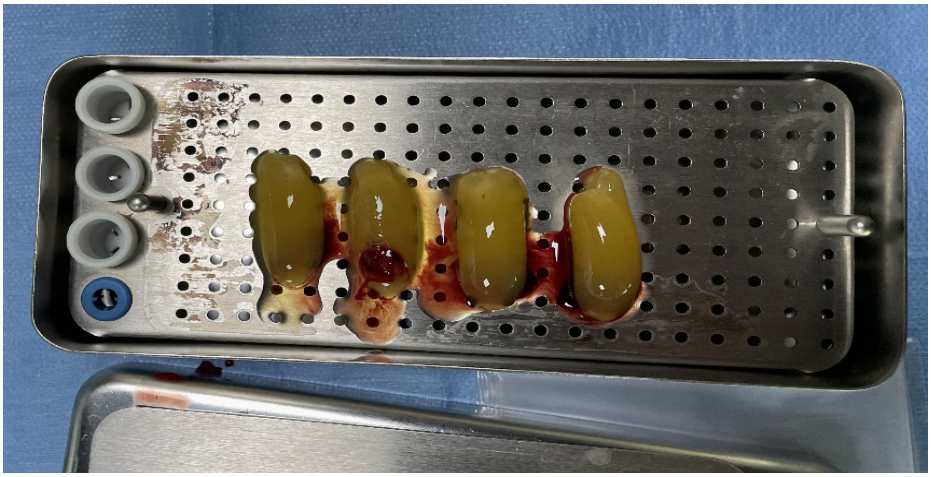

Figure 2. L-PRF fibrins at PRF box

Figure 3. L-PRF can use as a membrane when compressed in the PRF box

Titanium-prepared platelet-rich fibrin (T-PRF) was prepared by Tunalı et al. (14) The success of L-PRF in soft tissue and bone healing has been proven, but no significant effect on guided bone regeneration has been determined. (22) O'Connel argued that during centrifugation to obtain PRF, silica particles migrate to the fibrin layer and this may cause cytotoxicity. (23) In their study

in 2009, Gürbüzer et al. detected abundant crystalline particles in the external layer of PRF in electron microscopy examination. These crystal-like structures have not been seen in the internal layer of PRF. (22) To eliminate these disadvantages, Tunalı et al. obtained PRF by using titanium material, which is highly biocompatible. The titanium tube is obtained from grade IV titanium. To obtain T-PRF, they centrifuged 9 ml of venous blood taken from the patient in a titanium tube at 2800 rpm for 15 minutes. (24)

Titanium is highly biocompatible. The most important reason for biocompatibility is its high corrosion resistance. It also has one of the highest strength-to-weight ratios among metals. It is highly biocompatible due to its resistance to corrosion. Due to its biocompatibility, the polymerization of the fibrin structure formed after centrifugation is strong. It was observed that it formed a tighter and thicker fibrin layer compared to L-PRF. In this way, it has been stated that it can remain in the tissue for a longer time. Remaining in the tissue for a longer period of time creates an advantage in bone healing and bone formation with guided bone regeneration. (24)

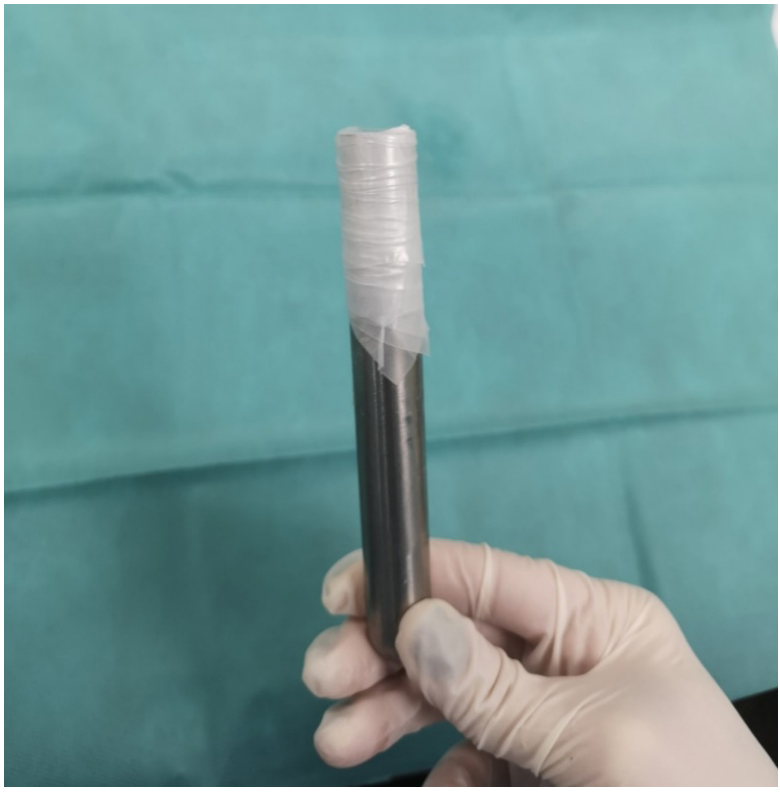

Figure 4. Titanium tube for T-PRF

In many studies, it has been determined that PRF prepared in silica tubes contains silica particles. (22-25-26-27-28) From a clinical perspective, it is estimated that silica particles are minimally absorbed into the circulatory system. Because no complications have been reported due to the use of any type of PRF. However, it should not be ignored that even minimal contamination can cause possible systemic damage. For this reason, the use of tubes made of titanium material, which is highly biocompatible, seems more clinically appropriate.

PRF is used in many treatments in dentistry and oral and maxillofacial surgery. PRF can be used for socket preservation. PRF can be used alone for socket preservation, mixed with bone graft or as a barrier membrane. When used alone for socket preservation, exposure into the mouth does not pose a risk of infection. The flap does not have to be closed primarily, it is sufficient to fix it to the socket with a simple X suture. PRF accelerates healing without creating an immune response and foreign body reaction. (29-30)

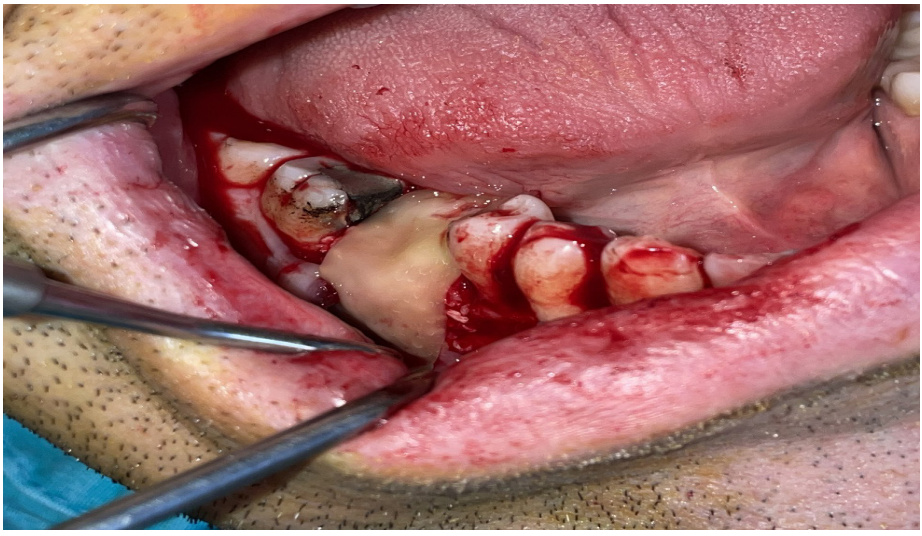

Figure 5. Using L-PRF as a membran at socket preservation surgery

It has been reported that PRF gives successful results when used instead of graft material in sinus lifting operations. It can be used instead of graft material in the sinus lifting procedure, and it can also be used safely instead of membrane. It can also be used in the repair of perforations that occur during Schneiderian membrane elevation. It can be used together with PRP graft materials. It gives very successful results and reduces the healing time. (2-31)

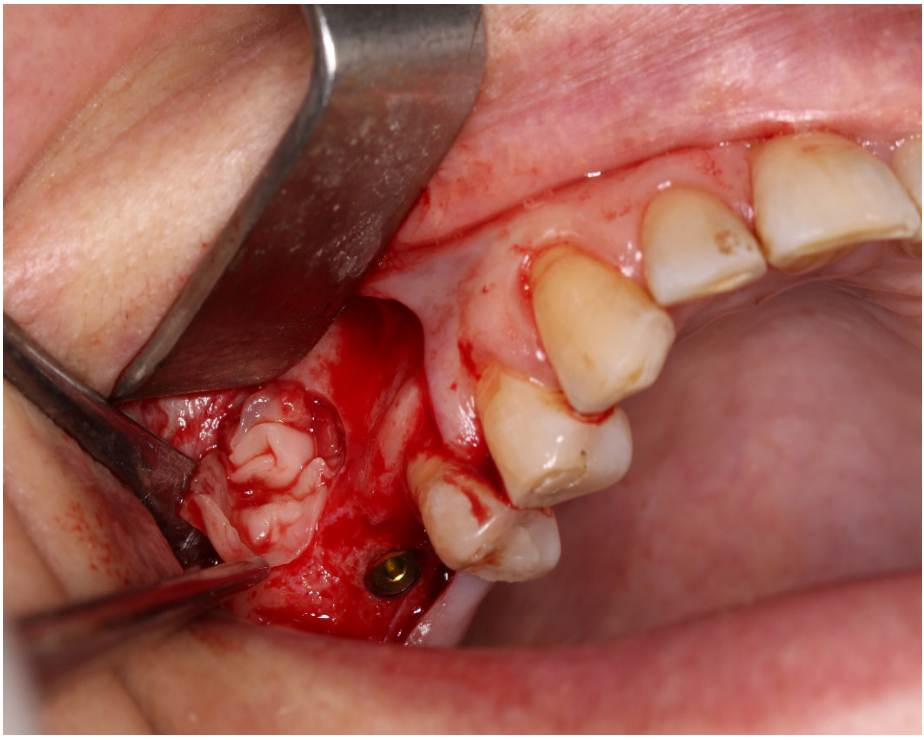

Figure 6. Use of PRF in sinus lifting operation.

The use of PRF in periodontal surgery provides very promising results. Since PRF has a direct effect on soft tissue regeneration, it can be used instead of connective tissue in the treatment of gingival recession, especially in Miller Class I and II recessions. The use of PRF in these operations accelerates wound healing, increases vascularization and reduces patient morbidity. With appropriate patient, PRF can be as effective as the use of connective tissue graft or collagen-derived xenograft materials in Miller Class I and II recession defects. Connective tissue graft surgery has the disadvantage of creating a second surgical area. This disadvantage is eliminated when PRF is used instead of connective tissue graft. There is no risk of foreign body reaction that may occur with the use of xenograft. The cost of surgery is significantly reduced. It has been reported that the combined use of PRF with a coronally advanced flap or connective tissue graft gives more effective results in patients with thin biotypes. (32-33)

Defects in periodontal tissues occur due to destructive products created by bacteria. The use of PRF, which is rich in leukocytes and macrophages that have the ability to eliminate pathogens, gives very promising results in the treatment

of bone defects that occur in periodontal diseases (34). PRF matrix secretes intense growth factor over a certain period of time and helps the regeneration process, tissue repair and blood clot formation. PRF helps hard and soft tissue repair by affecting the migration, proliferation and differentiation of different cell types such as gingival fibroblasts, chondrocytes, osteoblasts and endothelial cells. (35- 36)

Guided tissue regeneration and guided bone regeneration are treatment methods that provide very successful and predictable results. PRF can be used in these treatments by mixing it with graft material. It can also be used instead of collagen membrane by turning it into a membrane. It has many advantages over traditional collagen membranes because it contains autologous growth factors and live immune leukocytes.

Guided tissue regeneration and guided bone regeneration are treatment methods that provide very successful and predictable results. PRF can be used in these treatments by mixing it with graft material. It can also be used as membrane. It has many advantages over traditional collagen membranes because it contains autologous growth factors and live immune leukocytes. These cells fight against pathogens, greatly reducing the chance of infection. For this reason, PRF membranes can be left exposed without risk of contamination, and primary closure of the flap is not mandatory. When mixed with the graft material, it makes bone grafts “sticky”, making them easier to manipulate, while also providing proteins and growth factors responsible for facilitating angiogenesis. Additionally, using PRF instead of collagen membrane significantly reduces the cost of surgery. (2-37)

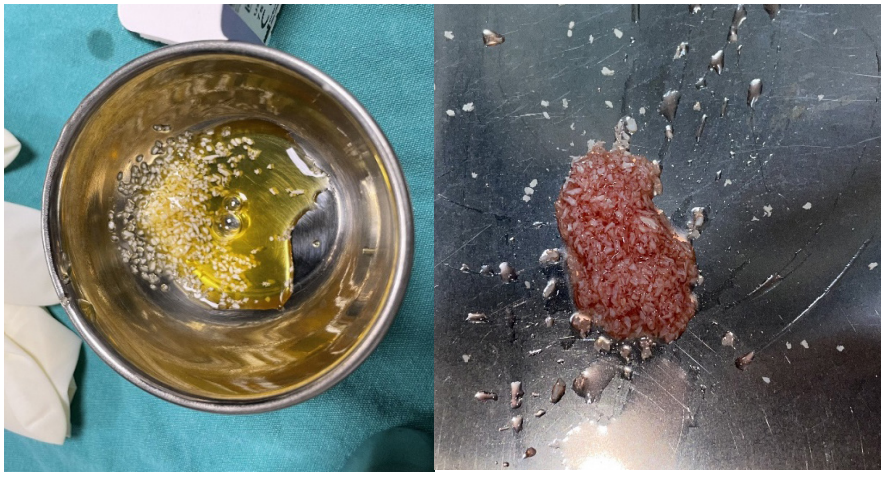

Figure 7. Mixing PRF with the bone graft material. It makes bone grafts ‘sticky’.

PRF can prevent MRONJ formation due to its mechanical, inflammatory and bioactive properties. Fibrin structure acts as a barrier and prevents the toxic effect of released bisphosphonates on soft tissue, thus supporting soft tissue healing. Platelets stored in these fibrins are responsible for growth factor secretion, regulation of osteoprotegrin and alkaline phosphotase, and proliferation of osteoblasts (38- 39- 40). Application of PRF to extraction sockets after tooth extraction in patients using antiresorptive and antiangiogenic drugs significantly reduces the incidence of MRONJ (41). PRF can be used prophylactically to prevent the development of MRONJ. In addition, patients who have developed MRONJ can be treated with use of PRF following surgical resection of necrotic bone (42).

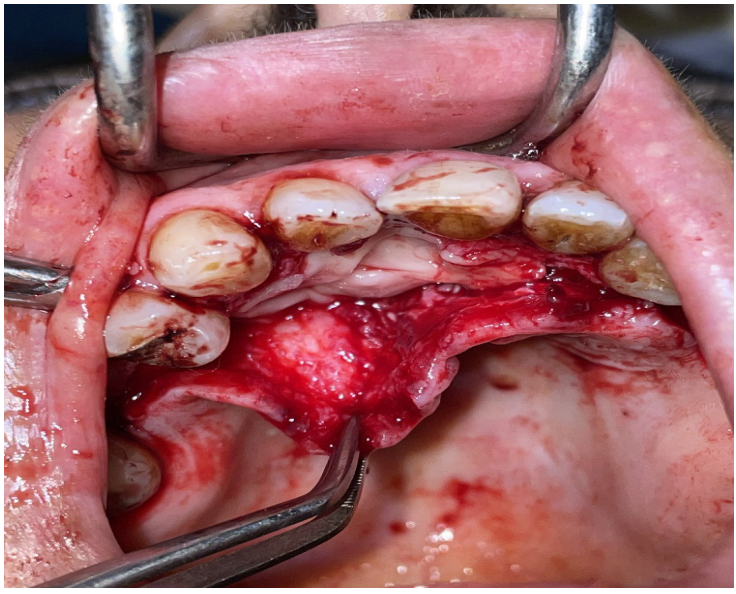

Figure 8. The Use of L-PRF to prevent MRONJ.

4. Result

Platelet-rich plasma is produced from the patient's own blood. Since it is autologous, it is highly biocompatible. It is easy to prepare, cheap and safe. It is used in many areas in oral surgery. It has been proven to have a positive effect on soft tissue and bone healing. Therefore, it can be used safely in regenerative treatments. It can also be used as preventive treatment after surgery in patients at risk of necrosis. It is possible to predict that this autologous, growth factor-rich material will be used more frequently in clinical practice in the future.

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CHAPTER IX

THE USE OF SPATIAL EPIDEMIOLOGY IN DENTAL HEALTH

Bülent BOSTANCI

(Assoc. Prof. Dr.), Erciyes University, Faculty of Engineering,
Department of Geomatics Engineering,
E mail: bbostanci@erciyes.edu.tr
ORCID: 0000-0003-2255-2503

1. Introduction

Studies on dental health and treatments began around 7000 B.C. However, the emergence of dentistry as an independent profession dates back to the 18th century. In the 20th century, parallel to advancements in basic medical sciences, dentistry has also undergone distinctive developments and changes in its practices. It is known that general medicine and dentistry have gone through a common historical development process. Initially, general medicine was followed by surgery and dentistry as they each branched into their respective fields (1). Especially since the beginning of the 20th century, specialization training in dentistry, similar to other fields in general medicine, has continued to increase. Dentistry is a medical discipline that focuses on examining, diagnosing, preventing, and treating diseases, disorders, and conditions related to the oral cavity and the jaw-facial region. Therefore, it encompasses a wide range of fields and specializations.

Orthodontics is the branch of dentistry that deals with diagnosing, preventing, and treating misaligned teeth and jaws that do not fit properly within the mouth and facial structure. *Endodontics* involves the study and treatment of the dental pulp and tissues surrounding the roots of the teeth. *Periodontology* focuses on preventing, diagnosing, and treating diseases affecting the gums and supporting structures of the teeth. *Prosthetic Dentistry* is the specialty area that deals with the design, production, and placement of prostheses for missing teeth and other oral structures. *Restorative Dentistry* is the specialized field that

encompasses the diagnosis, treatment, and follow-up of all conditions affecting the hard tissues of the teeth, whether bacterial or non-bacterial in origin, as well as addressing aesthetic concerns. *Pediatric Dentistry* specializes in the dental care and treatment of children from infancy through adolescence, focusing on oral health maintenance and management of dental diseases. *Oral and Maxillofacial Surgery* is the branch of dentistry that deals with surgical procedures involving the face, mouth, and jaws. *Oral and Maxillofacial Radiology* is where oral and maxillofacial tissues and organs are systematically examined, all physiological and pathological changes related to these structures are evaluated clinically and radiographically, and treatment plans are made (2,3).

Oral and dental diseases are prevalent chronic health issues globally. These diseases include dental caries, diseases affecting the tissues surrounding the teeth, tooth loss, oral and neck cancers, oral mucosal diseases, and jaw and facial traumas (4). The widespread prevalence of oral and dental diseases, their significant impact on individuals and society, and the prohibitive costs of treatment make these diseases an essential public health issue. Regarding spatial analysis and developing solutions for such health problems, researchers increasingly prefer Geographic Information Systems (GIS) today. GIS is an effective tool for analyzing oral and dental health issues, identifying local-scale risk factors, and developing health policies. This makes it possible to take preventive measures related to oral and dental diseases and to manage resources more effectively.

2. Geographical Information System (GIS)

GIS has become one of the most widely used applications in the information and communication age. Especially with the development of satellite-based positioning systems, easy access to location data, and the ability to produce digital maps due to advances in computer technology, geographical information systems have become an indispensable part of our daily lives, even if we are unaware of it. GIS is used in various fields, including navigation systems used in our vehicles or smartphones, urban information systems used by municipalities, weather forecasts, environmental predictions, determining the most suitable transportation networks using vehicle tracking systems, identifying regions where diseases such as COVID-19 are prevalent and determining disease intensity, and many other areas (5,6).

It is possible to define GIS as a computer system that allows operations such as collecting, storing, updating, checking, analyzing, and viewing earth information for a specific purpose. It integrates location-dependent and non-

location-dependent data and displays the results on vector or raster-based maps. A GIS is an information system that creates, manages, analyzes, and maps all data types. GIS integrates location data with descriptive information to link data to a map. This provides a foundation for mapping and analysis in science and nearly every industry. Since Earth-related data typically reference geographic coordinates, GIS is also perceived as a mapping system. In Geographic Information Systems, information includes spatially expressed and attribute information, which explains the spatial data or symbologies (5,6).

The definition of modern GIS, covering its current applications, was provided by Burrough and McDonnell (1998). According to this definition, GIS encompasses all tools that collect, store, query, analyze, transfer, and visualize real-world data for a specific purpose on digital maps (7). All definitions describing GIS meet the following common points (5-10):

Computer-Based System: All definitions emphasize that GIS is a computer-based system or technology. This highlights the role of computers in processing and managing geographical information (9).

Spatial Data: They all mention the significance of geographical or geographically referenced information. GIS deals with data associated with specific locations on the Earth's surface (8).

Data Management: GIS involves storing and managing data containing location-based information. GIS is not limited to displaying maps; it encompasses the spatial identification, management, and analysis of data related to entities (6,7).

Integration of Data and Maps: These definitions emphasize the integration of location data (maps) and descriptive information. GIS integrates spatial data (the location of entities) with attribute data (the characteristics of entities). This integration forms the foundation of GIS functionality (5-7).

Analysis: "Analysis" and "spatial representation of results" demonstrate that GIS goes beyond mere visualization of data on maps, encompassing analytical functionalities. Analytical assessments are used to analyze spatial data and derive meaningful results from them (5,7).

2.1. Important Concepts In GIS

Location: The spatial information related to health studies typically refers to point, line, or area data or specific locations such as neighborhoods, streets, buildings, or even the places where individuals involved in the health-related study reside or work.

Spatial Data: Any data containing coordinates, addresses, or other location information linked to a spatial point or area on a map can be defined as spatial data. Spatial data can be analyzed on digital maps by associating it with attribute or non-spatial data.

Spatial Data Types: In GIS technology, there are two main types of spatial data (Figure 1). Vector data consists of data containing numerical coordinate information. Points, lines, and polygons are the three types of vector data (8). Point data represents a single geographic location, such as the location of a specific address or a well's coordinates. Linear data represents linear features such as roads, rivers, or borders, and spatial data represents areas or specific regions (protected areas, forestation zones, military zones, quarantined areas, etc.), such as the boundaries of countries, states, or land parcels.

Raster data represents spatial data as a grid of cells (6,8,10). Raster data represents a natural geographic area on the Earth's surface using cells of equal size arranged in rows and columns (raster cells). Each cell takes on different color values depending on its geographical area. The size of raster cells expresses the resolution of the dataset and the level of detail of the specified area. Satellite images, scanned maps, orthophotos, and location-based data operate in raster image format. Raster data represent continuous phenomena such as elevation, temperature, or land cover.

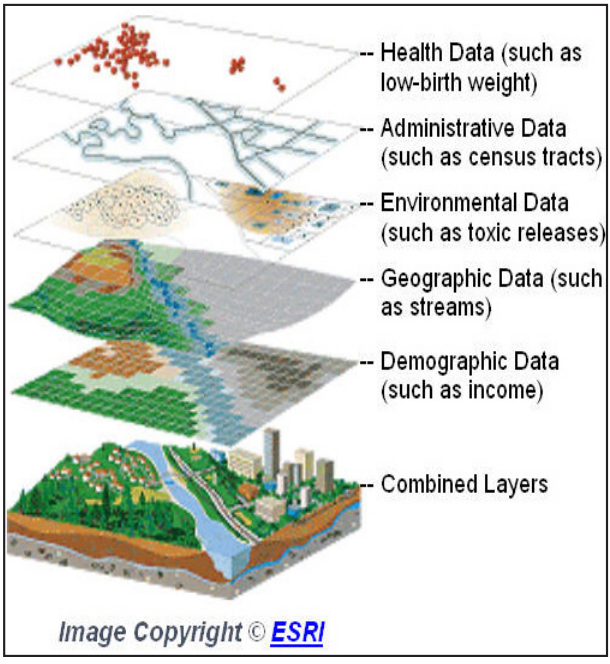


Figure 1. Working principle of GIS based on spatial data

Data Connection: Data from various databases can be linked to location-based units such as points, lines, and polygons using geographical codes (7). In spatial studies, data obtained from patient records can be linked with socioeconomic data using geographic codes between regions, allowing for the investigation of connections between patients' socioeconomic statuses and their diseases.

3. Health and Spatial Epidemiology

In *Airs, Waters, and Places*, Hippocrates explained the importance of the environment for health by stating, "A person's health is influenced by the air they breathe, the water they drink, and the environment in which they live." Since then, policymakers and professionals in the field of health have repeatedly used geographic maps to indicate and analyze the relationships between the environment and diseases. Modern-era evidence of maps being first used for public health analysis dates back to Dr. John Snow, who mapped cholera cases in London in 1854. These maps are referred to as cartograms or topographic maps. However, these maps could only provide limited location information (11,12).

GIS is utilized in two distinct sub-disciplines within the health field for location-based analyses. One of these can be termed spatial epidemiology, a discipline where the spatial distribution, transmission rate, occurrence frequency of patients/diseases, and their connections with the environment are examined. The second can be referred to as spatial health services, a discipline focusing on health planning and managing health services with a spatial perspective. In epidemiological studies aiming at public health, GIS and spatial analyses are preferred for determining the geographical distribution of diseases, identifying temporal-spatial clusters of diseases, locating areas where diseases occur, pinpointing areas of disease intensity, mapping populations at risk for diseases, and investigating risk factors contributing to diseases. These studies have been made possible mainly due to the increase in advanced technical equipment and the availability of online base map series where statistical data can be plotted (13,14). Primarily, GIS can match health-related information of individuals that is not expressed as location information, such as age, gender, smoking habits, and genetic diseases, with locations. As a result, it becomes feasible to easily map any data matched with location information and perform various queries on these maps. GIS can store information about individuals related to the exact location in different data layers. For instance, maps depicting the distributions of various cancer cases in a province are stored under different data layer names in

the database. These layers can be combined to examine various disease-related relationships (15).

Spatial Epidemiology is "the scientific discipline concerned with identifying, measuring, and explaining geographical variations in disease, particularly concerning changes in environmental exposures at small-area scales"(16,17). It helps answer seemingly simple geographical questions like: What is the distribution of the disease? Is the disease a particular situation in a specific geographical area? Is there any model or trend in the frequency of disease occurrence that could help predict future occurrence frequency? What is the accessibility to the nearest healthcare center in a specific region? Thus, the science needed to answer these geographical questions forms Spatial Epidemiology, and GIS is the technology required to address these questions.

In the field of health, GIS-based epidemiology applications can generally be evaluated in four main areas (19):

- *Measurement:* Measuring the distribution of infectious and non-infectious diseases in a region and assessing the impact of the environment on them. It includes not only medical but also demographic and political data.
- *Mapping:* Developing maps that illustrate and characterize the spatial understanding of a population's health. It also measures the access to healthcare services and spatial distribution of healthcare providers.
- *Monitoring:* It allows tracking changes in health and diseases associated with space and time. It can conduct environmental public health surveillance for disease types and exposure conditions. Thus, public health actions can be planned, implemented, and monitored to prevent and control environmentally related diseases.
- *Modeling:* Modeling alternative actions and process operations based on disease risk prediction.

4. Use of Spatial Epidemiology in Dental Health

The role of the environment and location in various aspects of public dental health is now confirmed by researchers conducting GIS-based epidemiological studies (19). Different environmental factors such as access to public and private dental health centers, school dental clinics, shortages of dentists, areas requiring dental hospitals and dental clinics, as well as the effects of interventions on oral health, are being investigated and analyzed concerning dental caries, oral cancers, oral, jaw, and facial injuries, and periodontal diseases, aiming to

explore individual and contextual pathways to oral health outcomes. GIS-based epidemiology can be utilized in dentistry to map and analyze oral health data, such as the prevalence of dental diseases, access to dental care, and the distribution of oral health resources, by studying, visualizing, and interpreting spatial data (19). This information will assist in planning public health interventions and optimizing resource allocation.

Spatial epidemiology is valuable for conducting epidemiological studies on oral diseases (19). Researchers can identify patterns, trends, and potential risk factors in specific geographic areas by mapping the distribution of dental diseases. It can assist in evaluating the accessibility of dental care services in different regions. Planners can identify areas with limited access to dental services by mapping the locations of dental clinics, hospitals, and mobile dental units and work to improve infrastructure.

GIS analyses help in selecting suitable locations for dental clinics. Dentists and healthcare service managers can use spatial analysis to identify areas with high demand for dental services by considering population density, demographic characteristics, and competition.

Spatial epidemiology can be applied in orthodontics to analyze spatial relationships within the scope of craniofacial anomalies. This information can assist orthodontists in treatment planning, especially when spatial considerations are critical. It aids in mapping the incidence and prevalence of oral cancer. Researchers can integrate geographic data with demographic and health information to identify areas with higher oral cancer rates and investigate potential environmental factors.

GIS-based epidemiology plays a role in emergency preparedness for dental health. During infectious disease outbreaks or natural disasters, GIS can assist in assessing the impact on dental health services and planning emergency response strategies. It is utilized for analyzing and designing community water fluoridation programs. Public health officials can determine the effect of fluoridation on dental health by mapping the fluoridation status of water sources and comparing it with oral health data.

GIS can be utilized to analyze the geographic patterns of dental tourism. This involves mapping the movement of individuals seeking dental care across regions and countries, aiding policymakers and businesses in understanding the dynamics of this industry. GIS is used to enhance learning experiences in dental education. It can be applied to create interactive maps when teaching dental anatomy, pathology, and treatment planning in a spatial context to enhance learning experiences for individuals.

Through GIS and spatial epidemiology analyses, the dynamics of dental and oral health in any region can be depicted on maps, and spatial outcomes can be demonstrated. The integration of spatial epidemiology into dentistry aids in the formulation of accurate dental health policies for the country enhances decision-making processes, and improves resource allocation.

4.1. General Overview Of GIS-Based Analyses that can be used in Spatial Epidemiology

4.1.1. Buffer Analysis

Buffer analysis creates buffer zones around input features containing closed areas such as points, lines, or polygons to the desired distance (20) (Figure 2). This analysis allows visualizing all dental clinics within a 1-kilometer distance from the city center.

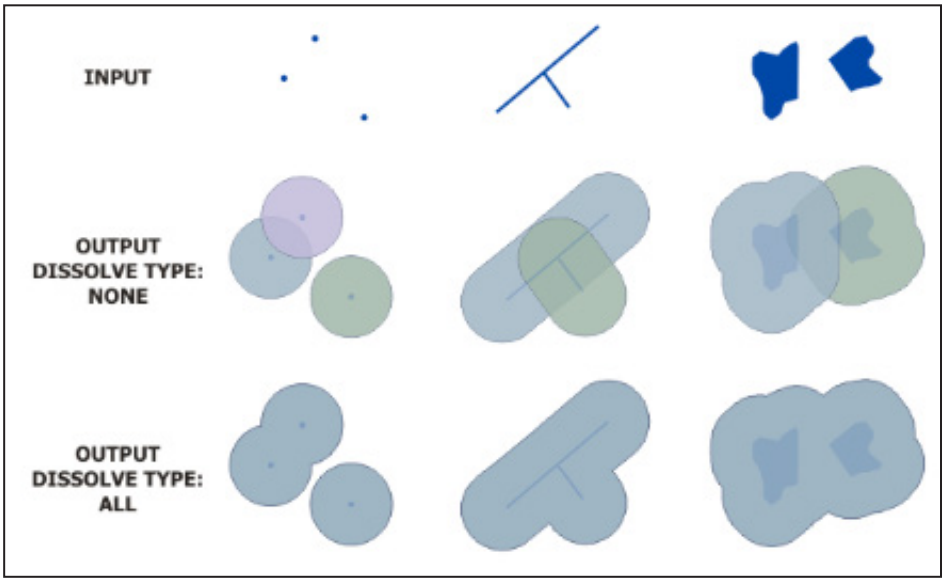


Figure 2. Buffer Analysis (20)

4.1.2. Euclidean Distance Analysis

Distance analysis aids in answering questions such as who will be affected by a particular event, what is closest to a selected center, which structures are adjacent to roads at certain distances, and which route is most efficient (21) (Figure 3). With this analysis, a patient experiencing toothache can quickly determine the shortest path to the dental hospital, facilitating prompt arrival.

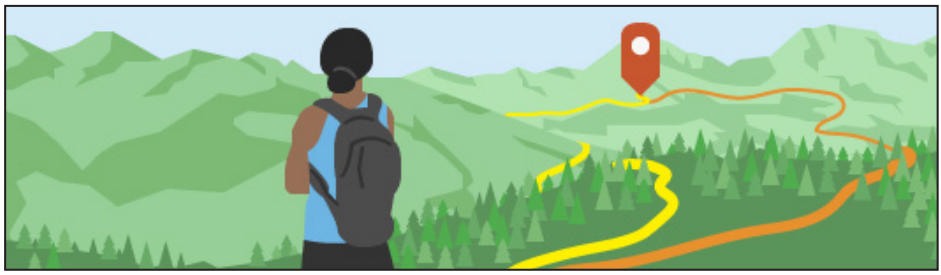


Figure 3. Distance Analysis (21)

4.1.3. Cluster Analysis

Cluster analysis is used to determine statistically significant hotspots or cold spots from data located in a specific area, to examine where data with similar characteristics are concentrated, and to evaluate regions based on attribute data in a location-based manner (22) (Figure 4). Cluster analysis can provide clues as to where outbreaks of infectious diseases or certain dental-related conditions occur, often indicating what might be causing them.

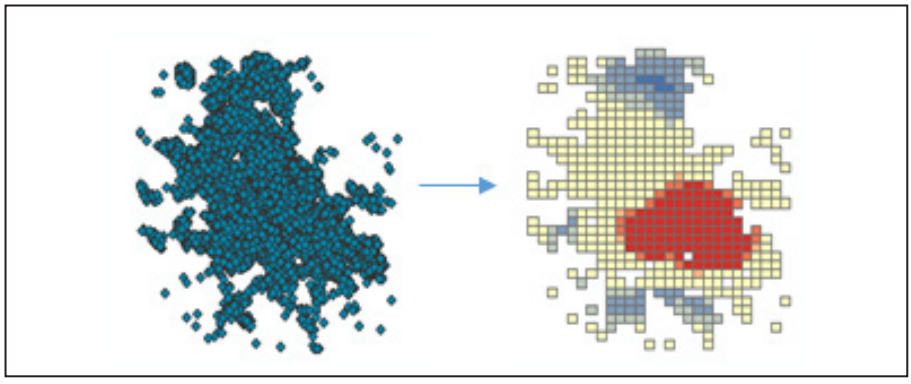


Figure 4. Cluster analysis can identify areas with a high probability (hotspot - red) or low probability (cold spot - blue) of an event or disease occurrence (22).

4.1.4. Reclassification Analysis

Reclassification tools reclassify cell values using various methods (23) or transform them into alternative values (Figure 5). Reclassification is functional when values in the input layer are replaced with new ones. It can be evaluated that the value of a cell on a raster map should be a different value over time. For example, reclassification may arise due to changes in land use over time in an

area, or reclassification may be necessary based on the type and intensity of a disease after an outbreak. Reclassification analysis helps in reinterpreting dental health data, aiding in overlay analysis.

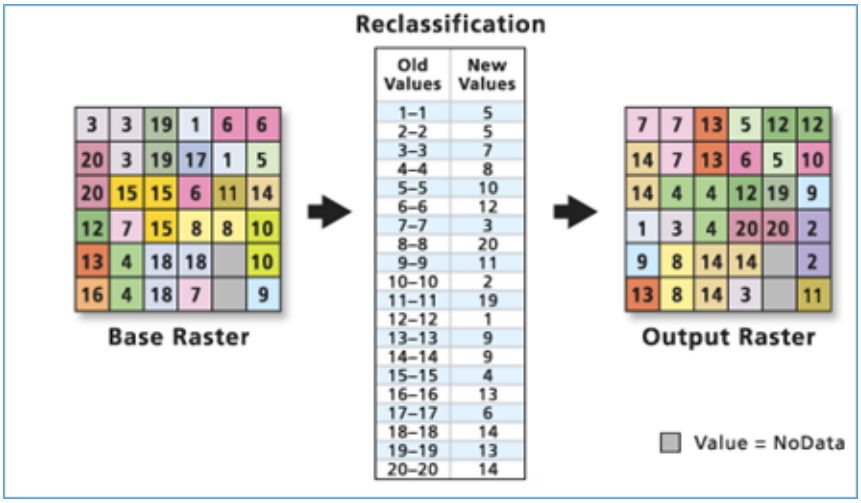


Figure 5. Reclassification Analysis (23)

4.1.5. Average Nearest Neighbor Analysis

The Average Nearest Neighbor tool measures the distance between each feature's centroid and its nearest neighbor's centroid. Then, it takes the average of all these nearest neighbor distances (24). If the average distance is less than the average for a hypothetical random distribution, the distribution of the analyzed features is assumed to be clustered. The features are considered homogeneously distributed if the average distance is greater than the average for a hypothetical random distribution. It can be used to examine whether distributions of patients/diseases in dental health are clustered or homogeneously distributed (Figure 6).

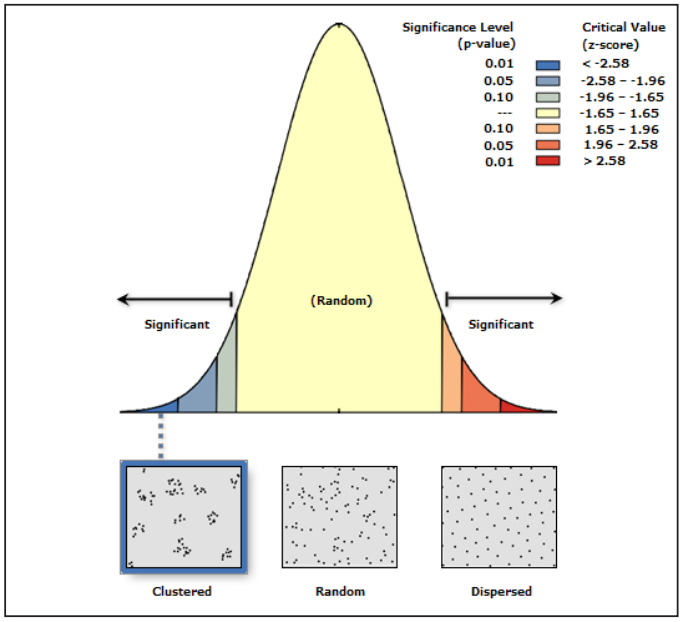


Figure 6. The average nearest neighbor analysis spatial distribution of data

4.1.6. Density Analysis

The Density tool allows the measured quantity of an input point layer to be distributed along the selected area to create a continuous surface (Figure 7). Analyzing the location data of patients visiting the dental hospital will allow us to understand from which city neighborhoods they predominantly receive treatment services (25).

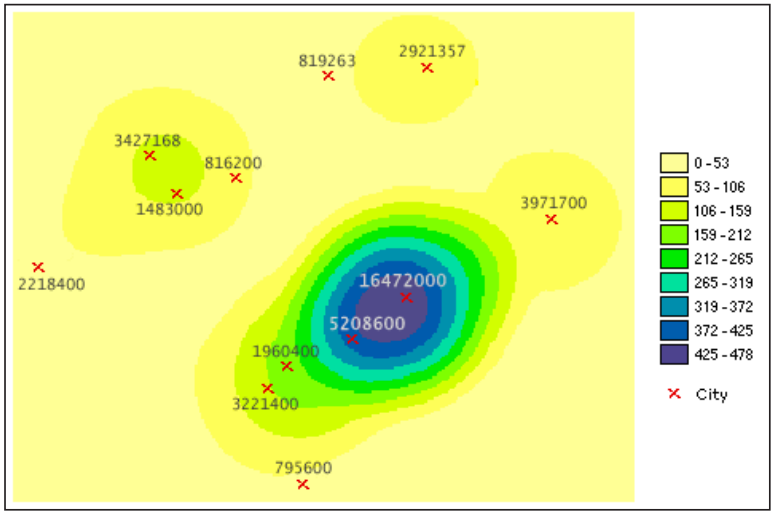


Figure 7. Mapping the density of cities according to population values (25)

4.1.7. Network Analyses

A network comprises interconnected elements, such as edges (lines) representing possible routes from one location to another and nodes (points) representing connection junctions. People, resources, and goods tend to travel along networks: cars and trucks travel on roads, planes fly along predetermined flight routes, and oil flows through pipelines. Modeling potential travel routes with a network allows for analyzing the movement of substances such as oil, trucks, or other materials along the network. The most common network analysis is finding the shortest path between two points. With network analysis, a company selling dental supplies can organize couriers to deliver materials to dental clinics.

ArcGIS software divides networks into utility networks and network datasets (26).

Utility networks (utility and river networks

Service networks such as river networks and utility lines like electricity, gas, sewer, and water lines simultaneously allow movement in only one direction at the edges. An entity on the network (for example, oil flowing in a pipeline) cannot choose which direction to go; its path is determined by external forces such as gravity, electromagnetism, water pressure, etc. An engineer can control the flow of matter by manipulating how external forces affect it.

Network datasets (transportation networks

Transportation networks like roads, pedestrians, and railways allow travel at the edges in both directions. An entity on the network (such as a truck driver traveling on roads) typically has the freedom to decide the destination and the direction of travel (Figure 8).

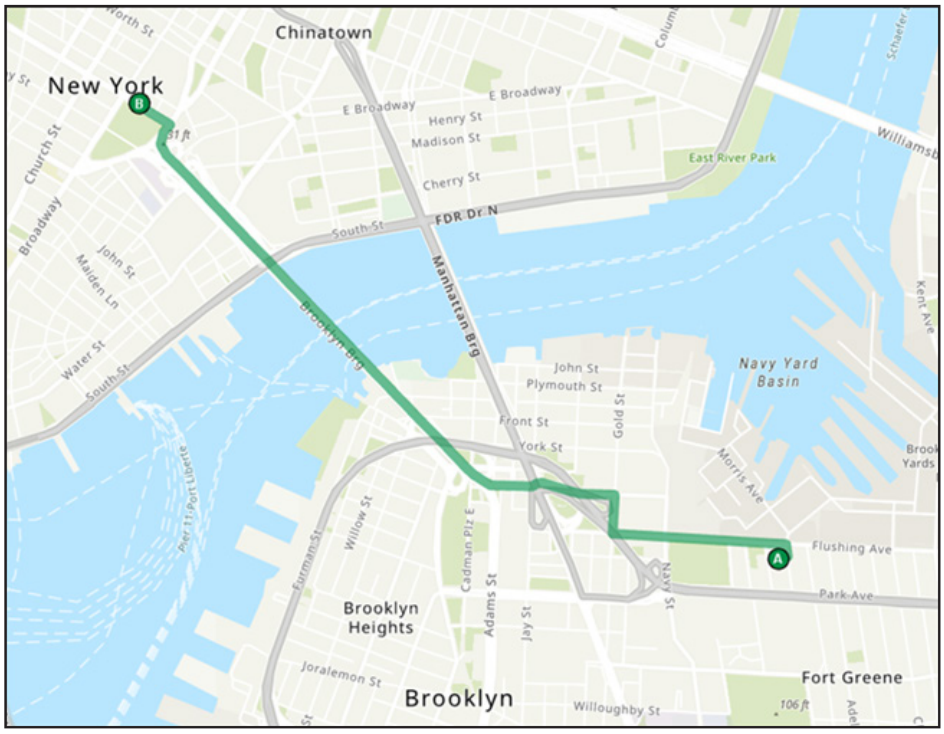
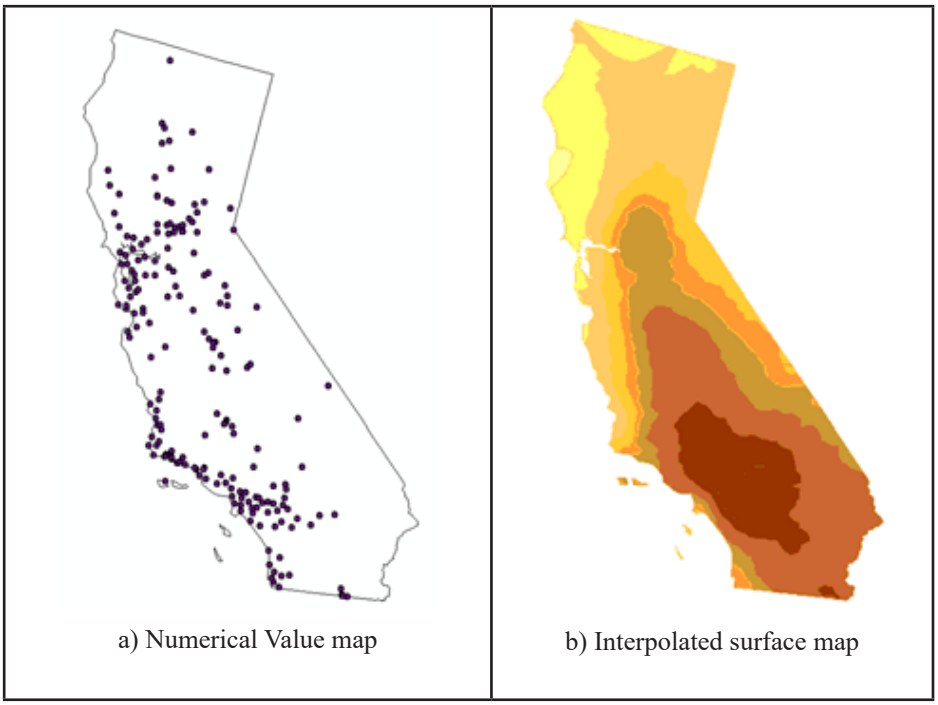


Figure 8. Determination of the most appropriate and shortest route (26)

4.1.8. Interpolation Analysis

Interpolation estimates values for other cells within a defined surface area based on a limited number of sample data points (27). It can estimate unknown values for any geographical point data, such as elevation, precipitation, chemical concentrations, and noise levels (Figure 9). Income of patients admitted to a hospital with interpolation analysis



a) Numerical Value map

b) Interpolated surface map

Figure 9. Intermediate value determination analysis (27)

4.1.9. Overlay Analysis

Overlay analysis is a group of methodologies used in selecting the most suitable location or in suitability modeling (28, 29). This technique applies a standard value scale to different and dissimilar inputs to create an integrated analysis (Figure 10).

Suitability models determine the best or most preferred locations for a specific phenomenon. An example could be determining suitable areas for a health facility.

The general steps for performing layer overlay analysis are listed below:

- Identify the problem.
- Break the problem down into submodels.
- Identify the critical layers.
- Reclassify or transform data in a layer.
- Weight the input layers.
- Add or merge layers.
- Choose the best places.
- Analyze.

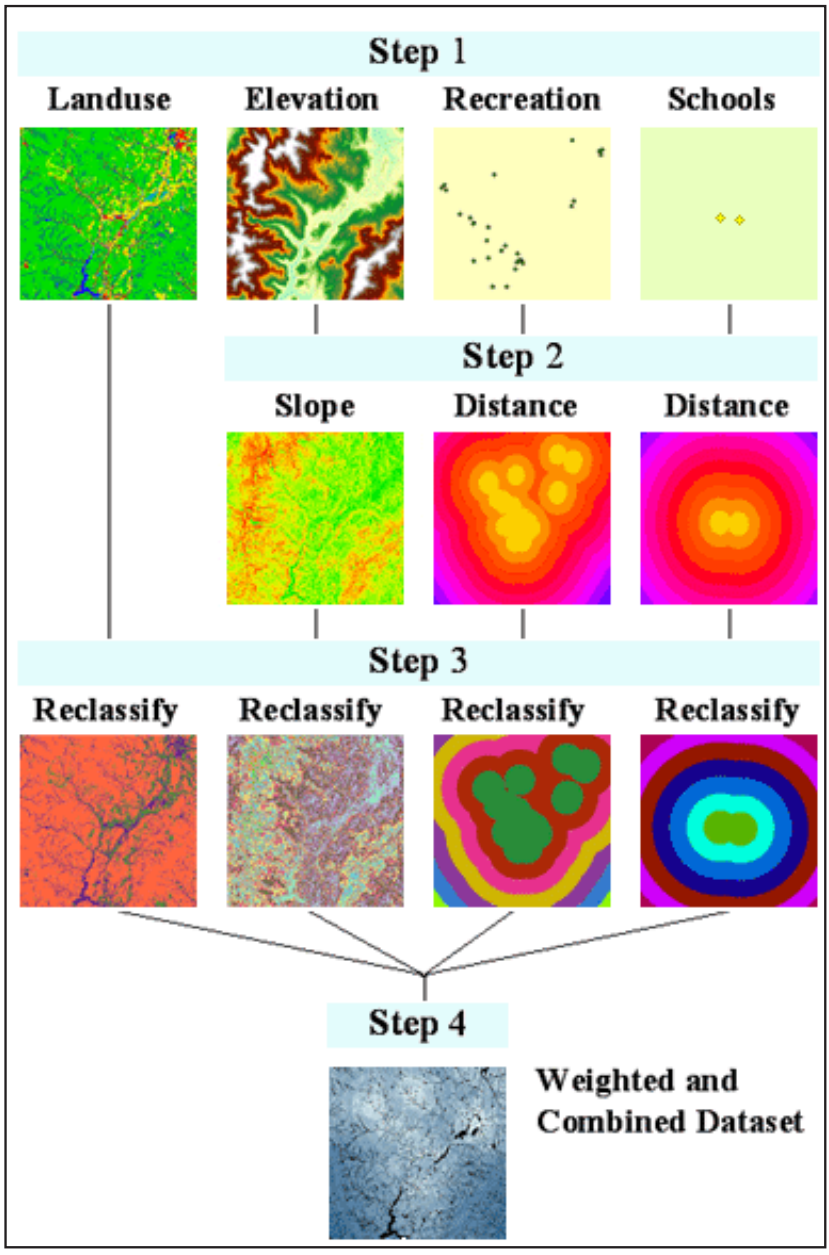


Figure 10. Weighted overlay analysis (29)

4.1.10. Site Selection Analyses

Site selection is one of the fundamental and critical decisions in establishing, expanding, or relocating any business. The construction of a new healthcare facility is a long-term and significant investment, and in this regard,

determining the location is a critical factor that can influence the success or failure of the healthcare facility. One of the primary objectives in selecting a site for a healthcare facility is to find the most suitable location that meets the defined selection criteria and desired conditions. GIS are potent tools for spatial analysis, providing functionality for capturing, storing, querying, analyzing, visualizing, and outputting geographic information. Geographic Information Systems are used with decision support systems (DSS) and multi-criteria decision-making methods (MCDM), among other systems and procedures. The synergistic effect created by combining these tools contributes to the efficiency and quality of spatial analysis for healthcare facility site selection. During the site selection process, the analyst identifies the most suitable location that meets the selection criteria (Figure 11). The selection process aims to optimize a desired set of objectives for a specific facility. Such optimization often involves numerous decision factors that may conflict with each other, and the process typically entails a range of potential sites, each with its advantages and limitations.

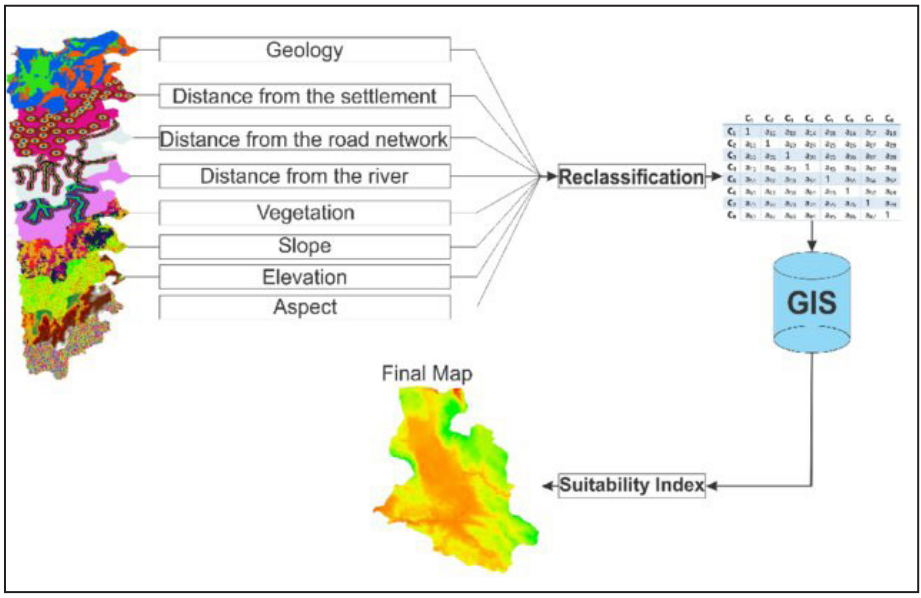


Figure 11. Site selection analyses (30)

5. The Future of Spatial Epidemiology in Dental Health

Like in all other fields, GIS and spatial epidemiology are technologies that can collect, store, analyze, and visualize various geographic data, providing an innovative application area in dentistry. The areas expected to see intensive use

of thematic maps and spatial epidemiology analyses in dentistry in the future can be listed as follows:

Disease spread analysis: GIS-based epidemiological studies can map dental health data geographically and analyze how diseases spread in specific areas. This will assist in the planning of dental health policies and preventive measures.

Accessibility analysis: The geographic locations of dental clinics and health service facilities can be used for accessibility analyses. This way, areas with complex access to dental services can be identified, contributing to a more equitable distribution of healthcare services.

Healthcare Planning: Spatial analysis can be used in planning dental clinics, hospitals, and other healthcare facilities. Thus, the locations of facilities that will provide adequate dental health services in the areas where they are needed can be determined more effectively.

Resource Management: Distributing dentists, equipment, and other resources within the country or specific regions can also be tracked and managed geographically. This situation can help with more effective utilization and management of resources.

Patient Population and Distribution: GIS-based epidemiological analyses can analyze the dental health profile of the population in a specific region. This enables directing dental health policies and campaigns to particular communities.

Natural Disaster and Emergency Management: GIS-based analyses can help direct dental health services quickly and effectively to areas affected by natural disasters or emergencies.

Effective Conduct of Public Health Campaigns: GIS-based analyses can target dental health education and awareness campaigns. It can serve as an effective tool for identifying needs in specific geographic areas and informing communities in those areas.

Infection Control and Outbreak Monitoring: Spatial epidemiology can focus on controlling infectious diseases that arise in dental clinics and healthcare facilities and need to be monitored. Additionally, it can monitor and control contagious patients/diseases during epidemic situations.

6. Results

GIS-based analyses are increasingly used to evaluate spatial data of patients who visit dental health institutions. Spatial epidemiology allows researchers to examine spatial relationships between health outcomes and environmental,

demographic, or socioeconomic factors. These examinations will help identify potential disease risk factors. Spatial epidemiology provides the following important benefits in the field of dental health:

- Identifying oral health problems caused by environmental factors.
- Ensuring equal regional distribution of dental health services.
- Selecting the most suitable dental hospital location based on factors such as population, density, transportation, and land situation.
- Determining the density of patients or types of diseases applying to the dental hospital on a neighbourhood basis.

In addition, with the increasing use of artificial intelligence-supported spatial epidemiology in dental health areas, more accurate results can be produced by evaluating the factors causing diseases and their location-based outcomes. Integrating GIS and spatial epidemiology into dentistry will contribute to more effective planning of dental health services, better resource management, and improved dental health access for societies. However, it is crucial to consider critical issues such as patient data security and privacy when utilizing GIS and spatial epidemiology in dentistry.

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