HEALTH SCIENCES

Current Researches and New Trends 4

Editor
Assoc. Prof. Dr. Hüseyin KAFADAR

HEALTH SCIENCES Current Researches and New Trends 4

ISBN: 978-9940-46-092-1

2022

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First Edition •© March 2022 /Cetinje-Montenegro

ISBN • 978-9940-46-092-1

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PREFACE

Dear scientists and readers;

Enlightenment has been with the sharing of knowledge from the existence of humanity to the present day. It is clear that valuable researchers and scientists have made the most important contribution to this process. Especially academic researchs are a long process that requires great efforts with care, dedication and patience. Considering that our age is the information age, it is equally important to reach the right information. In this process, the existence of states, nations and countries is only possible with correct information. Our valuable research scientists contribute to this process with their valuable studies. I congratulate our authors who contributed to our book with their chapter authorship.

This book, which deals with current issues in the field of health sciences, includes very valuable studies. For this reason, we believe that this book, which includes current academic and scientific studies, will be an important resource for academicians and readers interested in health sciences and medicine.

We would like to thank all our research writers who contributed to the writing of this book, the valuable staff of our publishing house, and those who worked devotedly in the form, design and printing stages.

Best regards

Assoc. Prof. Dr. Hüseyin KAFADAR

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CHAPTER I

THE MANAGEMENT OF MYASTHENIA GRAVIS

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1. Introduction

"Myasthenia gravis" (MG) was originated from the Greek. The meaning of the words is muscle weakness (myasthenia), heavy (gravis). MG is an autoimmune disease characterized by muscle weakness that increases with action, primarily affecting the oculobulbar muscles, mostly targeting postsynaptic nicotinic acetylcholine receptors (AChR) (Ciafaloni, 2019) . This disease, which has a very high mortality rate due to respiratory failures in its native process, has a particular importance among neuromuscular diseases and even in all neurology practice, as patients can lead a entirely normal life with appropriate treatment. Present of disease in women is bimodal, most prevalent age of between 20-30 years of age and over 50 years. In contrast to over 50 years of age in men. The most prominent property of the disease is muscle weakness, which gains with fatigue and is at least partially relieved by repose. Patients specify that are improve in the morning, and the symptoms increment towards the evening or when tired (Binu, Kumar, Padma, & Madhu, 2022). The presentation of disease advances with remissions and exacerbations. Remissions can keep going from a few days to several years.

2. Evolution of Treatments Principles

Physostigmine, a cholinesterase inhibitor, was used in the treatment of MG in 1934. (Keesey, 1998). In fact, Remen written a report in 1932 that neostigmine was effective for the treatment of MG. However, this important discovery was not noticed in the medical community at that time. (Remen, 1932). In the late 1800s that thymus pathology could be related present in MG patients was considered. (Bell, 1917). Afterward, it was discovered that thymectomy was beneficial in patients, especially whom positive AChR antibody (Gronseth & Barohn, 2000). The treatment of MG improved in the 1970s. Common use of steroids started after azathioprine therapy. Prednisone therapy refuted previous studies and proofed that was influential in the therapy of MG. Plasma exchange was accepted for acute therapy of serious MG in 1976. It was thought that mediators play a role in circulation in MG (Pinching, Peters, & Davis, 1976). The treatments of

intravenous immunoglobulin (IVIg), mycophenolate mofetil and tacrolimus came into use end of the last century.

3. Therapeutic Management of Myasthenia Gravis

3.1. Cholinesterase Inhibitors

The primer treatments for MG are acetylcholinesterase (AChE) inhibitors. These behave by postponing the hydrolysis of Ach at the neuromuscular junction (Binu et al., 2022). The most widely used agent is pyridostigmine bromide in worldwide. The effect of the agent begins in 15-30 minutes, the maximum effect occurs in 1-2 hours, the effectiveness lasts 3-4 hours or longer. Treatment is usually started with 30-60 mg, dose adjustments are made according to drug response or complications. Doses of 180 mg and above are rarely helpful. (Mehndiratta, Pandey, & Kuntzer, 2014). Pyridostigmine for intravenous and intramuscular injection is existent. Rapid-acting intravenous methods can cause serious morbidity due to the risk of bradycardia. The beneficial effect of drug-induced inhibition may decrease over time, so there is a tolerance to the drug. AChE inhibitor management may be decreased when clinical benefit is lost and patients may be restarted if symptoms progress during tapering. AchE inhibitor therapy is usually reliable, however complications may consist. (Binu et al., 2022). The side effects of pyridostigmine are diarrhea, abdominal pain and cramps, nausea, increased salivation, urinary symptoms such as urgency, and increased sweating. Caution should be exercised in obstructive respiratory diseases, bradyrhythmias, renal dysfunction, prostatic hypertrophy and acute myocardial infarction. Cholinergic side effects such as stomach pain and increased salivation can be seen due to Ach that increases in the neuromuscular junction induced by the drug. In case of such a serious side effect, the dose of the drug should be reduced and additional treatments should be added. As a result, we can say that the effect of AchE inhibitors decreases in long-term treatments. These agents provide symptomatic relief.(Mehndiratta et al., 2014).

3.2. Alternative Neuromuscular Conduction Enhancers

Ephedrine was first used for the treatment of MG in the 1930s. It is known that ephedrine has a direct effect on neuromuscular transmission. It has also been shown to be useful in congenital MG. (Lipka et al., 2017). Despite of it does not goals a important therapy choice for autoimmune MG. 3,4-Diaminopyridine, generally used for Lambert-Eaton myasthenic syndrome, could be aforethought for MuSK-related MG, although immense experience hasn’t been published. (Evoli, Alboini, Damato, & Iorio, 2016).

3.3. Immune System Targeted Therapeutics

3.3.1. Corticosteroids

Corticosteroids and other immunosuppressives are the most important treatment step. These agents are the most preferential immunosuppressant for the therapy of mild/severe MG as well as in considered where AchE inhibitor treatment is non-responsive. First-line treatment for MG is prednisolone. If corticosteroids are used in appropriate doses, they provide symptomatic relief within weeks to months (4-8 weeks) in 70-80% of patients (Ciafaloni, 2019). Action of steroids is thanks to suppression of lymphocyte growth and differentiation as well as inhibition of macrophage function and cytokine expression. In ocular MG, it is started at a low dose and increased. Frequently, 20-40 mg/day (0.50-0.75mg/kg/day) is used. A maximum dose of 1mg/kg/day (usually 60mg/day) is recommended for generalized MG. There may be muscle weakness (worsening) that may increase temporarily 1 week-10 days after prednisolone is started, it can be started at low doses and increased with a few days intervals . The disease may exacerbate with complete discontinuation of prednisolone (Binu et al., 2022). In elderly patients, it is preferable to continue treatment at a low dose because of the high morbidity/mortality rates of exacerbations. Discontinuation of prednisolone treatment should be avoided in MuSK (Muscle-specific tyrosine kinase) positive MG and MG with thymoma. MuSK MG responds well to corticosteroids. Corticosteroid requirement may be high in MuSK MG and they may respond in a long time. Corticosteroid side effects; hypertension, hyperglycemia, hypercholesterolemia, cataract and osteoporosis (Bae, Go, & Kim, 2006).

3.4. Other Immunosuppressants

3.4.1. Azathioprine

Azathioprine, which has a safer profile compared to other drugs, is frequently preferred in MG. Its used alone or in combination with corticosteroids. This agent is a purine analog that inhibits the synthesis of nucleic acids. (Maltzman & Koretzky, 2003). Its effect on the immune system is mainly aimed at reducing the count of B and T cells. According to this hypothesis, it was thought to have a direct effect on nucleic acid synthesis.The recommended dose is 2-2.5 mg/kg. It takes 6-12 months for the efficacy to appear. It was observed that the efficacy of the drug on clinical was associated with decrease of white blood cell count and increases of mean red blood cell volume.(Witte, Cornblath, Parry, Lisak, & Schatz, 1984). If either of these are not reported, then the dose may be elevated to its maximum. Side effects; It has toxic effects on liver and leukocytes. An increased risk of malignancy with use under 10 years has not been proven (Ciafaloni, 2019).

3.4.2. Mycophenolate Mofetil

Mycophenolate mofetil was been an gradually popular drug for therapy of MG. Suggested by many neurologists mycophenolate, decreases corticosteroid dose, advances potency, and reduces AChR antibody levels for generalized MG and advanced just ocular myasthenia. (Meriggioli, Rowin, Richman, & Leurgans, 2003). Mycophenolate is hydrolyzed to mycophenolic acid. This inhibits inosine monophosphate dehydrogenase, an important enzyme in the de novo pathway of purine synthesis. (Villarroel, Hidalgo, & Jimeno, 2009). Its cut off T and B lymphocyte proliferation by preventing guanosine synthesis. Mycophenolate is given at a general dose of 1 g twice daily, but there is no data on whether higher doses are more effective. Some substantial side effects are chronic diarrhea, hemolytic anemia and edema, opportunistic infections, teratogenicity.

3.4.3. Methotrexate

There is no clear consensus on the treatment of methotrexate in MG. Benefit of methotrexate was recommended, but found no protective effect from steroid after 1 year of therapy. (Pasnoor et al., 2016). It is similar to azathioprine in terms of taper the steroid dose. Methotrexate is a selective inhibitor of dihydrofolate reductase. Treatment management of this drug is done with a maximum of 20 mg weekly, with folate and leukoverin support. In addition to tolerable side effects such as hepatotoxicity, leukopenia, anemia, infections, vomiting, serious undesirable adverse effects such as renal failure and pulmonary fibrosis can be seen.

3.4.4. Tacrolimus

Tacrolimus, which has been preferred worldwide for many years due to its immunosuppressive effect, is still used frequently in the Far East. Contrary to what was initially thought it has been proven to have no effect on the use of low-dose prednisolone. The suggested dosage of this agent is 0.035 mg/kg twice daily. (Kanai et al., 2017). It is a calcineurin inhibitor which modulates the activity of T cells that support antibody-producing B cells (Azzi, Sayegh, & Mallat, 2013). It could also improve T regulatory cells. Tacrolimus enhances muscle contraction through modulation of intracellular calcium release channels, which will rapidly increase muscle contraction. Common adverse effects are diarrhea, tremor, and paresthesias. The most serious side effect is nephrotoxicity (Binu et al., 2022).

3.4.5. Cyclosporine

The other steroid-sparing immunosuppressant preffered for MG is cyclosporine, a cyclic undecapeptide, but this treatment is not compatible for most individuals due to nephrotoxicity. (Tindall, Phillips, Rollins,

Wells, & Hall, 1993). It is a calcineurin inhibitor that selectively inhibits the transcription of proinflammatory cytokines and Interleukin-2 in T lymphocytes. Efficacy is earlier than azathioprine, at approximately 4-6 weeks. 5 mg/kg/day in two divided doses are suggested. Its use in the therapy of MG is limited due to its dose-related side effects.Nephrotoxicity, opportunistic infections, bone marrow suppression, gingival hyperplasia, hyperkalemia and hypertension are seen.

3.4.6. Cyclophosphamide

Another agent with steroid-sparing properties in the management of MG is cyclophosphamide. There are oral and intravenous forms for treatment-resistant patients. (Hart, Sathasivam, & Sharshar, 2007). Via the liver's cytochrome P450 oxidase system, cyclophosphamide is revised to phosphoramide mustard, which introduces alkyl radicals into DNA and compromises cell replication. This mechanism is probably cytotoxic to lymphocytes. The others complications contain hemorrhagic cystitis, diarrhea, nausea and vomiting which may be serious.

Rituximab

It is a monoclonal antibody that specifically direct binds to the CD20 transmembrane antigen on B lymphocytes. Particularly in MuSK positive MG, which does not respond adequately to the immune treatments used at the initial, it is safe and effective, low severity of the disease and young age are indicators of good response to treatment. Standart dosing of rituxan is once a week period for 4 weeks at a dose of 375 mg/m^2. Repeated doses are given every 6 months. (Stieglbauer, Pichler, & Topakian, 2017). Various infusion-related reactions may occur (eg: fever, headache, nausea). It can prevented with premedication and slowing the infusion rate. The most serious side effect associated with this agent is progressive multifocal leukoencephalopathy.. (Hehir et al., 2017).

3.4.7. Eculizumab

Targeting the complement system has been discussed for many years for the treatment of MG. However, only one agent was considered for treatment. (Kusner & Kaminski, 2012). Positive results of the phase 3 study were observed in those who did not benefit from immunosuppressive therapy. It has been approved by the FDA for use in patients with AchR antibody-positive generalized MG. Eculizumab is among the most expensive agents in use at expense of nearly $400,000 per year (Howard Jr et al., 2017).

4. Non-Therapeutic Management of Myasthenia Gravis

4.1. Plasma Exchange

Plasma exchange application has a fast healing effect in the fatique condition. (Binu et al., 2022). It is used to relieve weakness and improve muscle functions before surgeries, after thymectomy and in myasthenic crisis. The mechanism of action of plasmapheresis; It is in the form of removing pathogenic antibodies and possible supporting protein structures from the circulation.(Ciafaloni, 2019). The treatment process normally encloses five exchanges. The major advantage of this treatment over other options is the rapid effect that occurs within days. Usually, after the second plasma exchange, patients respond to treatment, at least the progression stops. It is known that plasma exchange gives more successful results than IVIg in Musk positive patients. During the infusion patients may complain of paresthesias from citrate-induced hypocalcemia, and hypotension may occur at initiation of the exchange (Shemin, Briggs, & Greenan, 2007). A major disadvantage is its short duration of action. Being an expensive method, coagulation disorders and hemodynamic imbalance are some other negative aspects of this treatment. (central line insertion).

4.2. Intravenous Immunoglobulin

Intravenous immunoglobulin treatment containing Ig antibodies obtained from pooled human plasma is another antibody-mediated medication. The standard treatment is 2 g/kg in 5 days. Studies evaluating the effects of plasmapheresis and IVIg treatment in myasthenic crisis have shown that plasmapheresis has a better clinical effect. Ancak yan etki ve komplikasyonların IVIgde daha az olduğu saptanmıştır. (Binu et al., 2022). Some of the mild side effects of IVIg are dizziness, chills, headache. Infrequently, major complications happen with IVIg. Anaphylactic reactions present in people with immunoglobulin A deficiency, which may be occur in 1/1000 individualsIt indicates the effect of intravenous immunoglobulin on the immune system by various mechanisms. They affect the autoimmune phase by various mechanisms, including competition with autoantibodies, inhibition of cytokines, interaction with the Fc receptor on macrophages or immunoglobulins on B cells, and antigen recognition by sensitized T cells. (Luzi, Bongiorno, & Bruno, 2009).

5. Thymectomy

One of the earliest treatments for individuals with MG is thymectomy.. Thymoma is presented at a rate of 10-15%, it increases with age. Thymectomy should be performed in all MG patients with thymoma. In patients with tumor-associated MG, this operation is performed to remove the thymic tumor and to treat the Mg itself. The basic logic is to eliminate

the thymus tissue, which is the center of antibody production, and to reduce the amount of AChR antibodies in the circulation. As it is known, this surgery option is performed in those younger than 60 years of age and in the early stage. Thymectomy is recommended in generalized AChR positive MG and seronegative MG. It's not suggested in MuSK positive MG (Binu et al., 2022).

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CHAPTER II

ALGORITHMS AND BASIC DIAGNOSTIC CONCEPTS IN EMERGENCY RADIOLOGY

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1. Emergency Radiological Approach in Suspected Acute Cerebrovascular Events (SVOs)

- The first imaging method to be applied is non-contrast cranial computed tomography (CT) (Byrne, Walsh, Sugrue, Nicolaou, & Rohr, 2020).
- Non-contrast cranial CT excludes intracranial hemorrhage and masses to a large extent and at high sensitivity. In the first stage, it distinguishes between hemorrhagic and ischemic events (de Lucas et al., 2008).
- CT findings are normal in most patients with stroke in the early period.
- In the hyperacute period (first three to six hours), an ischemic event may not be asymptomatic in non-contrast CT (Gao et al., 2017).
- Hyperdense middle cerebral artery sign, effacement of cerebral sulci, narrowing of cisterns, loss of gray-white matter separation, and low density in the affected area are significant findings in non-contrast CT (Wardlaw & Mielke, 2005).
- If there is a finding of SVO on CT, CT angiography (CTA) or perfusion CT examination can be performed while the patient is still in the imaging room (Balcı & Onur, 2016; de Lucas et al., 2008).
- Perfusion CT examination contributes to the identification and characterization of the salvageable area (penumbra) that has not progressed into necrosis but shows ischemic changes (Sanelli et al., 2014).
- In the presence of stroke, possible wide vascular stenosis-occlusion, especially the proximal occlusions of the Willis

polygon can be successfully identified using CTA and perfusion CT (Balcı & Onur, 2016).

- Diffusion-weighted imaging (DWI) becomes positive within minutes, apart from exceptional cases (Kloska, Wintermark, Engelhorn, & Fiebach, 2010).
- Signal increase in the affected area in DWI is a positive finding. Signal loss is observed in the same area in apparent diffusion coefficient maps (Karaali, 2021).

2. Emergency Radiological Approach in Suspected Cerebral Traumatic Lesions

- The first choice is cranial CT without contrast enhancement (Doppenberg & Tuttle, 2019).
- Magnetic resonance imaging (MRI) can be performed if CT fails to clarify the clinical situation. MRI should also be used primarily to reveal the cause of new neurological deficit findings that occur in the subacute and chronic stages (Kılıç & Yalçın, 2016).
- MRI should be first undertaken without contrast enhancement.
- If there is a suspicion of a fracture involving the carotid canal, CTA or magnetic resonance angiography (MRA) should be performed (Biffl et al., 2009).
- If venous damage is suspected, CT venography or MRI venography examinations can be undertaken (Biffl et al., 2009; Khandelwal et al., 2006).
- If there is a suspicion of cerebrospinal fluid leak, maxillofacial CT may be useful in rhinorrhea, temporal bone CT in otorrhea, and brain CT cisternography where necessary (Kılıç & Yalçın, 2016).
- The presence of pneumocephalus should suggest that the fracture is related to mastoid cells, paranasal sinuses, or external environment.
- If there is an extension to the carotid canal in skull base fractures, possible vascular damage should be investigated by performing CT or MRA (Kılıç & Yalçın, 2016).

2.1. Basic radiological characteristics

Extra-axial hemorrhages:

- Epidural
- Subdural
- Subarachnoid

Intra-axial lesions:

- Diffuse axonal injury

- Contusion
- Intraventricular hemorrhage
- Brainstem injury

Traumatic ischemia

Brain herniation

2.1.1. Epidural hematoma:

- does not cross sutures,
- may cross the point where the attachment point of the falx cerebri or the midline,
- is frequently accompanied by fractures,
- is frequently on the impacted side,
- mostly has a temporoparietal location, and
- is mostly seen in middle meningeal artery injury (Young & Destian, 2002).

2.1.2. Subdural hematoma:

- is more common in children and the elderly,
- does not cross the midline,
- may cross sutures,
- is more common on the contralateral side,
- presents as a common cause of the traumatic rupture of the bridging veins,
- is not often accompanied by fractures,
- requires surgical intervention if its thickness exceeds 10 mm or causes more than 5 mm subfalcine herniation (Bullock et al., 2006; Kılıç & Yalçın, 2016) and
- is observed in different densities in different processes in CT. As hematoma ages, its density decreases. Since it is isodense with the brain in the subacute process, it may be difficult to detect on CT.

2.1.3. Subarachnoid hemorrhage:

- is more common in high-intensity traumas,
- should be searched between sulci and cisterns.
- is common in the posterior Sylvian fissure and interpeduncular fossa, and
- is detected with higher sensitivity using the fluid attenuated inversion recovery sequence compared to the T1 and T2 sequences in MRI (Noguchi et al., 1995).

2.1.4. Cerebral contusion:

- may have normal findings in initial and early CT,
- can be focal or multiple,
- is more commonly seen in the frontal and temporal lobes,
- appears hyperdense on CT if hemorrhagic, and
- may have increased hemorrhagic contusion dimensions in subsequent examinations and may coalesce and be observed as intraparenchymal hematoma (Alahmadi, Vachhrajani, & Cusimano, 2010; Kılıç & Yalçın, 2016).

2.1.5. Diffuse axonal injury:

- is more common in severe traumas,
- usually has normal findings in initial CT,
- may later present with the development of petechial hemorrhages,
- presents with lesions that are most commonly seen at the gray-white matter border, and
- is also common in the corpus callosum and brainstem (Kılıç & Yalçın, 2016).

2.1.6. Brain Herniations:

- Subfalcine herniation

It is detected as a midline shift on CT and herniates into the cingulate gyrus (Riveros Gilardi et al., 2019). The midline shift being less than 5 mm indicates a good prognosis while a midline shift of more than 15 mm is considered a poor prognostic criterion (Ross, Olsen, Ross, Andrews, & Pitts, 1989). If subfalcine herniation causes the compression of the anterior cerebral artery or pericallosal artery, it may be complicated by ischemia that occurs in the irrigation areas of these arteries (Riveros Gilardi et al., 2019). Contralateral leg weakness is one of the most common complications and is related to anterior cerebral artery ischemia (Kang & Kim, 2008; Laine, Shedden, Dunn, & Ghatak, 1995).

- Transtentorial herniation
  It is complicated by temporoparietal ischemia due to posterior cerebral artery compression (Kirshner, Staller, Webb, & Sachs, 1982).
- Tonsillar herniation

3. Emergency Radiological Approach in Spinal Trauma

- Plain radiography is the first choice (Parizel et al., 2010) due to its wide availability and accessibility.

- Non-displaced small fractures can be overlooked (Munera, Rivas, Nunez, & Quencer, 2012).
- The main examination method is CT.
- CT fails to detect ligament and spinal cord injury (Balcı & Onur, 2016).
- There is no need to administer contrast material in the CT examination if the thorax and abdomen will not be examined by CT.
- MRI is effective in the evaluation of paraspinal soft tissues and the spinal cord (Balcı & Onur, 2016).
- MRI should be performed in patients with progressive neurological dysfunction.

3.1. Basic radiological characteristics

The distribution of spinal traumas by location is as follows: 55% cervical, 15% thoracic, 15% lumbar, and 15% lumbosacral vertebral (Balcı & Onur, 2016). Although fractures are less common in the cervical vertebrae compared to the other segments of the vertebral column, they have greater clinical significance due to the higher risk of spinal cord injury (Heinemann & Freund, 2006).

In compression fractures,

- the anterior column is affected (Parizel et al., 2010),
- a wedge-shaped deformity is formed in the vertebral body,
- the corpus height of the affected vertebra decreases (Patel & Vaccaro, 2010), and
- fractures are stable (Parizel et al., 2010).

In burst fractures,

- the vertebral body is often fragmented,
- the localization is mostly the T5-T8 segment of the vertebrae and the thoracolumbar region (Parizel et al., 2010),
- more than one vertebral column is affected,
- fractures are instable, and
- the extension of fracture fragments into the spinal canal is common; therefore, there is a risk of spinal cord injury (Parizel et al., 2010).

In spondylolysis,

- there is a pars interarticularis defect,
- the frequent localization is at the L4-L5 level, and

- bilateral cases may be accompanied by spondylolisthesis.

In spondylolisthesis,

- the ventral subluxation of the vertebral column is observed due to bilateral pars defect, and
- the most common localization is at the L4-5 and L5-S1 levels.

A CT examination is indicated in traumatic spinal events other than stable compression fractures, isolated spinous or transverse process fractures, and spondylolysis.

4. Emergency Radiological Approach in Maxillofacial Trauma

- Plain roentgenograms have poor accuracy.
- Appropriate positioning for X-ray is difficult in trauma cases.
- The success of direct radiography in demonstrating the severity of the fracture is limited (Mehta, Butala, & Bernstein, 2012).
- CT is the most common evaluation tool (Toprak & Gökaslan, 2016).
- CT images have high resolution.
- CT allows for 3D reconstruction and plays an extremely important role in surgical planning.
- CT also successfully characterizes accompanying soft tissue injury.

In isolated orbital blow-out fractures,

- the orbital floor is mostly fractured (Toprak & Gökaslan, 2016),
- bone structure displacement into the maxillary sinus can be observed,
- maxillary sinus aeration is reduced in direct radiography,
- there may be air inside the orbit, and
- the coronal section is the best plane to demonstrate soft tissue hernias.

In orbital blow-in fractures,

- there is a fracture on the base of the frontal bone and the roof of the orbit due to the frontal impact, and
- frontal lobe contusion may simultaneously accompany these traumas.

In nasal fractures,

- the localization is generally the lower 1/3 of the nasal bone,

- most fractures are displaced,
- the septum is also affected in type 2 and 3 nasal fractures,
- septum fractures may be complicated by perforation in the absence of an appropriate diagnosis and treatment approach, and
- sutures and the nasociliary groove should not be confused with fractures.

In mandibular fractures,

- the most common localizations are the corpus, corner and ramus, and
- care should be taken in the presence of condylar fractures including the capsule. If these cases are not treated, they may be complicated by temporomandibular ankylosis (Murray, 2013).

In Le Fort fractures,

- fractures occur along the weak lines of the face,
- all types present with the fracture of the pterygoid plates of the sphenoid bone,
- type 1 causes a floating palate,
- type 2 causes a floating maxilla, and
- type 3 causes a floating face, where the face is separated from the skull.

5. Emergency Radiological Approach in Suspected Pulmonary Thromboembolia (PTE)

- In cases where myocardial infarction, pneumothorax, and pneumonia have been excluded based on clinical findings and radiography, elevated D-dimer is an imaging indication for PTE.
- First-choice imaging is CTA for the diagnosis of PTE (Sadigh, Kelly, & Cronin, 2011).
- In cases where a definitive decision cannot be made, ventilation-perfusion scintigraphy can be performed.
- Direct radiography may be non-diagnostic even in massive pulmonary embolism, but it is useful in differential diagnosis.
- In approximately 90% of patients with PTE, the origin is deep vein thrombosis (DVT) in the lower and upper extremities (Sadigh et al., 2011). If there are accompanying DVT symptoms in highly suspected cases, DVT can be revealed using venous color Doppler ultrasound. However, since the complete pulmonary embolization of the thrombus in the leg may be the case, this evaluation may give false negative results.
- In CT,

- a filling defect is observed in the pulmonary artery lumen,
- there may be a wedge-shaped consolidated area at the periphery of the parenchyma, and
- pleural effusion may be an accompanying finding.

- Scintigraphy shows ventilation-perfusion mismatch.
- The gold standard is catheter angiography; however, it is often not preferred because it is invasive and has a risk of morbidity and mortality.

6. Emergency Radiological Approach in Thoracic Trauma

- First choice is direct radiography.
- In most of these trauma cases, direct radiography is performed under portable conditions and with the patient in an unfavorable position.
- Significant traumatic lesions, such as rib fractures, tension pneumothorax, hemothorax, and mediastinal hematoma can be detected using portable radiography (Oikonomou & Prassopoulos, 2011).
- It is difficult to recognize pathologies such as pulmonary contusion on direct radiography.
- Following direct radiography, further evaluation is made with CT.
- Contrast-enhanced CT imaging must be performed to exclude vascular injury.

In pneumothorax,

- air in the pleural space is radiolucent (dark) on direct radiography,
- CT is the most sensitive method for detection, and
- the possibility of rib fractures and lung laceration should be considered (Oikonomou & Prassopoulos, 2011).

In pulmonary contusion,

- opacities are observed in the lung areas in direct radiography, and
- CT has high sensitivity after trauma (Schild et al., 1989).

In pulmonary laceration,

- oval or multiloculated air-fluid collections are observed in the area surrounded by opacity due to contusion on CT.

In great vessel injury,

- direct radiography shows mediastinal enlargement and effacement in the aortic arch and proximal section of the descending aorta,

- aortic injury should be suspected if there is effacement in the right paratracheal line in direct radiography, and

- successful characterization can be obtained and complications can be detected using CT

In esophagus traumas,

- the incidence is rare,
- the cause is generally iatrogenic, and
- pneumomediastinum, left pneumothorax, or pneumohemothorax may be observed.

7. Emergency Radiological Approach in Hemoptysis

- The first preferred imaging method is plain radiography. However, the positive diagnostic value in these cases is around 50% (Hirshberg, Biran, Glazer, & Kramer, 1997). The findings can be interpreted as normal even in cases of malignancy (Herth, Ernst, & Becker, 2001).
- If direct radiography findings are normal, hemoptysis is not of recurrent nature, and there is no radiofrequency application for lung cancer, there is no need for further imaging in the emergency department.
- If there are pathological findings in direct radiography and there is a risk factor for malignancy, a CT examination should be performed.
- The evaluation of bronchial arteries and other vascular structures is also important.
- A contrast-enhanced examination must be included in the CT protocol.

8. Emergency Radiological Approach in Pediatric Trauma

- In order to reduce radiation exposure in pediatric trauma cases, the 'as low as reasonably achievable' principle should be observed (Egloff, Kadom, Vezina, & Bulas, 2009).
- Care should be taken to use gonad shields in pediatric cases if the examination is to be performed with imaging devices involving radiation exposure.
- The use of CT should not be avoided if required by clinical findings.

- It is important to re-define imaging protocols in pediatric cases by adjusting the dose (lower dose).
- Major traumatic findings, such as contusion, diaphragmatic rupture, and aortic injury may be overlooked in chest radiography performed as the first examination in thoracic traumas.
- If there is clinical suspicion of an important pathology that will affect the clinical course of the case, CT should be undertaken even if chest radiography findings are normal.
- Ultrasound can be used to investigate free fluid in abdominal trauma.
- Contrast-enhanced abdominal CT is necessary to exclude pathologies in abdominal trauma.

9. Emergency Radiological Approach in Abdominal Trauma

- In a patient with unstable hemodynamics, focused assessment with sonography for trauma (FAST) is performed in the resuscitation room (Ghafouri et al., 2016).
- The presence of diffuse intra-abdominal free fluid is important for surgical decision-making; however, there are also studies reporting that FAST negativity does not exclude the need for laparotomy (Bode, Edwards, Kruit, & van Vugt, 1999).
- A contrast-enhanced abdominal CT examination should be the first preferred imaging modality in abdominal trauma (Ghafouri et al., 2016).
- Abdominal CT scan is often included in multiple CT examinations in the presence of multi-trauma.
- Portal venous phase must be present in the examination.
- If active vascular damage is suspected, arterial phase images should also be obtained.
- If urinary tract injury is suspected, late phase images should also be added to the imaging protocol.

Areas evaluated for the presence of fluid in FAST:

- Subxiphoid (pericardial area)
- Right upper quadrant (Morrison, right subphrenic)
- Left upper quadrant (perisplenic, left subphrenic)
- Pelvic and bilateral paracolic

Types of traumatic injury to the liver, spleen and kidney:

- Subcapsular hematoma
- Parenchymal hematoma

- Laceration
- Fragmentation
- Ureteropelvic junction injury (kidney)

High-density fluid, contour abnormality, parenchymal heterogeneity, and loss of contrast enhancement in the organ lodge or abdomen are the main CT findings indicating traumatic lesions.

10. Suspected Acute Cholecystitis

- Ultrasound is the first-choice and most frequently used diagnostic tool in radiological diagnosis (Katabathina, Zafar, & Suri, 2015).
- Radiological and nuclear medical examinations reveal acute cholecystitis, as well as associated complications at high success rates (Yokoe et al., 2012).
- Sonographic Murphy's sign accompanying cholelithiasis is an extremely sensitive finding.
- Increased sac wall thickness (3 mm) and presence of pericholecystic fluid are important findings.
- Hepatobiliary iminodiacetic acid (HIDA) scintigraphy can be performed in inconclusive cases.
- The gallbladder is not observed in HIDA scintigraphy in acute cholecystitis.
- Bladder stones, distention, and contrast enhancement in the surrounding tissue can be seen on CT.
- CT has less sensitivity than ultrasound in the diagnosis of acute cholecystitis in the emergency department.
- MRI has high sensitivity for acute cholecystitis.

Ultrasonographic findings in acute cholecystitis:

- Gallstones (frequent)
- The gallbladder wall being thicker than 3 mm
- Murphy's sign
- Pericholecystic fluid
- Edema in the wall of the gallbladder and hypoechoic halo around the gallbladder

11. Suspected Acute Pancreatitis

- If paralytic ileus accompanies clinical manifestation, ultrasonography has limited contribution to the diagnosis.
- Direct radiography findings that may serve as warning signs of acute pancreatitis include the sentinel loop sign (secondary to gas distension in duodenojejunal loops), colon cut-off sign (secondary

to distended colon segment in the left upper quadrant), effacement in the left psoas muscle contour, and ascites (O'Connor, McWilliams, & Maher, 2011).

- CT is the most effective radiological diagnosis method for acute pancreatitis.
- A contrast-enhanced CT examination is very effective in demonstrating pancreatic necrosis.
- Ultrasound findings in acute pancreatitis:
  - Diffuse-focal enlargement of the pancreas
  - Hypoechoic and irregularly contoured pancreas
  - Pancreatic duct dilatation
  - Peripancreatic fluid collection, abscess, and pseudocyst (O'Connor et al., 2011)
- CT findings in acute pancreatitis:
  - Focal or diffuse enlargement of the pancreas
  - Heterogeneous contrast enhancement pattern
  - Loss of contrast enhancement in necrotic areas
  - Presence of peripancreatic fluid, abscess, and pseudocyst

The Balthazar scoring system, based on the CT severity index, is used to grade acute pancreatitis.

12. Emergency Radiological Approach in Suspected Intestinal Obstruction

- The contribution of direct radiography to the diagnosis of intestinal obstruction varies widely and is limited.
- Direct radiography has low sensitivity in determining the etiology of intestinal obstruction. Even if intestinal obstruction is identified on direct radiography, a CT examination is often required (Thompson et al., 2007).
- The presence of free air on direct radiography indicates that intestinal obstruction is complicated by perforation.
- Direct radiography alone is often insufficient in the pre-surgical decision.
- In cases of suspected intestinal obstruction, CT should be the first-choice imaging method.
- A CT examination should be performed with intravenous contrast agent injection if there are no contraindications (Ros & Huprich, 2006).
- Oral contrast agent use is not a necessity.
- CT successfully reveals the obstruction pattern, transition zone, and cause of obstruction.

- The presence of dilated loops showing air-fluid level on direct radiography is important in the diagnosis of small bowel obstruction.
- Gas is not observed in small bowel obstruction due to collapse in colonic segments.
- An ultrasonographic examination can offer an idea about the differentiation of mechanical or paralytic ileus at an early stage.
- While peristalsis is not detected in paralytic ileus in ultrasonography, back-and-forth fluid movement can be observed in dilated loops in early mechanical ileus.

13. Emergency Radiological Approach in Suspected Intussusception

- Ileoileal intussusception is the most common form.
- It can be characterized by ultrasound in pediatric cases.
- With early diagnosis, ischemic complications can be prevented (Williams, 2008).
- The typical ultrasound findings are bowel-within-bowel appearance and the ‘target’ or ‘ox eye’ sign.
- The reduction status can also be followed up using ultrasound (Williams, 2008).
- On CT, it can be seen as a target sign in the early period and a sausage-shaped lesion in the late period.

14. Emergency Radiological Approach in Suspected Mesenteric Ischemia

- CT angiography is the first-choice modality (Stone & Wilkins, 2015).
- In addition to very successfully characterizing arterial occlusion and critical stenosis, CTA can also characterize ischemic events caused by superior venous occlusion and detect accompanying secondary findings (Stone & Wilkins, 2015).
- CTA should be performed using multiphasic/biphasic protocols. There is no consensus on the use of oral contrast (Balcı & Onur, 2016).
- As a luminal contrast agent, the patient can be given water to drink before the examination.
- Edema, thickening, and contrast enhancement in the intestinal wall should be evaluated together with the vessels (Balcı & Onur, 2016).
- Plain radiography, ultrasonography, catheter angiography, and CTA/MRA can be used for the diagnosis of mesenteric ischemia.

15. Emergency Radiological Approach in Suspected Acute Appendicitis

- There is no definitive radiological algorithm (Balcı & Onur, 2016).
- Ultrasound of the right lower quadrant is often performed as the first-choice modality (Balcı & Onur, 2016).
- Basic supportive ultrasonography findings of acute appendicitis in the right lower quadrant:
    - Appendix vermiformis diameter being 6 mm or greater
    - Immobilization and unresponsiveness to compression
    - Periappendicular or pericecal free fluid
    - Inflammatory echo changes in the right lower quadrant and/or periappendicular mesentery tissue
- CT reveals acute appendicitis, its accompanying findings, or other intra-abdominal pathologies that may be confused with acute appendicitis.
- CT also reveals pathologies very successfully in acute appendicitis cases complicated by perforation, abscess, and plastronated appendix.
- Although there are different recommendations in the literature, intravenous and oral contrast enhancement should be used in CT performed in the suspicion of acute appendicitis (Balcı & Onur, 2016; Paulson & Coursey, 2009).
- CT findings in acute appendicitis:
    - Dilated appendix (diameter > 6 mm)
    - Abnormally enhancement of the appendiceal wall
    - Periappendicular adipose tissue infiltration
    - Appendicolith
    - Small bowel obstruction and presence of pelvic fluid in the right lower quadrant or perforation in some cases
- In case of negative ultrasound in pregnant patients with the suspicion of acute appendicitis, MRI should also be undertaken.
- In children, the investigation should be started with ultrasound, and CT should be performed in inconclusive cases.

16. Suspicion of Diverticulitis

- CT is the preferred imaging method (Destigter & Keating, 2009).
- CT can successfully differentiate between epiploic appendagitis and omental infarction.
- CT successfully reveals accompanying complications.

- If there is no contraindication, intravenous contrast material should be used (Jang et al., 2000).
- CT findings supporting the diagnosis of diverticulitis:
  - Pericolonic adipose tissue infiltration
  - Increased intestinal wall thickness
  - Abscess
  - Peritoneal fluid or air
  - Intramural sinus tract
  - Colovesical or colovaginal fistula

17. Suspicion of Urolithiasis

- Direct radiography may show radiopaque stones; however, its sensitivity is low, which may result in overlooking small stones.
- An ultrasound examination is important in pediatric patients and pregnant women.
- CT is the primary imaging method for the characterization of urinary stones and hydronephrosis (Andrabi et al., 2015).
- Intravenous or oral contrast material is not used in CT stone protocol.

18. Suspicion of Ovarian Torsion

- Ultrasound is the preferred imaging method, but CT and MRI can also be used for diagnosis.
- The main B-mode finding is an increase in ovarian dimensions (Chang, Bhatt, & Dogra, 2008).
- Doppler ultrasound findings may vary, but the main Doppler finding is the loss of arterial flow (Chang et al., 2008).
- While low or absence of venous flow is common in the color Doppler examination, absence of arterial flow is a rarer finding for a poor prognosis.
- Normal flow due to intermittent torsion or dual blood flow from the ovarian and uterine arteries can be seen and does not exclude torsion.
- MRI can be used as a problem solver in inconclusive cases.

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CHAPTER III

BONE HEALING AND OSSEOINTEGRATION

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Bone healing

A series of physiological events are observed in the healing of bone tissue following injury. Bone growth occurs with the destruction of a part of the previously formed bone tissue and the construction of another part at the same time (Cheung A., 2006). Physiological reactions are aimed at restoring the deteriorated bone integrity. Unlike soft tissue healing, scar tissue is not formed in this type of healing. Factors such as support of the recipient site, adequate blood supply and stability of bone segments are important for bone development (Rosenberg E., 1998). The recovery phases cannot be separated from each other with definite boundaries, and each phase takes place within the preceding or following phase (Kılıçoğlu SS., 2002).

Injuries to bone tissue generally heal in two ways. In primary healing, the broken parts come into contact with each other. This healing is also called direct bone healing or intramembranous ossification (61). In endochondral ossification, which is defined as indirect bone formation or secondary healing, there is a cartilage tissue formation that leaves its place to bone tissue as calcification. If we rank the secondary fracture healing phases as classically accepted (Kılıçoğlu SS., 2002).

- Inflammation phase
- Repair phase
- Remodeling phase

1. Inflammation phase

The site of inflammation begins within a few hours after trauma and continues for several days until it is replaced by developing soft callus. This phase includes vasoconstriction, vasodilation, clot formation (hemostasis), phagocytosis (leukocytosis), revascularization, and granulation tissue synthesis. It is the stage that starts with bleeding caused by vascular injury and subsequent hematoma and covers the first 2 weeks after injury. The resulting hematoma is a hypoxic acidic formation limited to the surrounding soft tissue areas. Platelets rapidly occlude damaged vessels from leaking blood, and fibrin is stored within the hematoma to

form a necrotic clot (Fellah BH., 2007). The first cells to appear at the site of inflammation are precursor cells called mesenchymal stem cells, which have the ability to differentiate into many cells. The clot first fills with cells of acute inflammation and within a few days with cells of chronic infection and macrophages. Collected mesenchymal stem cells organize the clot. The hematoma is surrounded by firm soft tissues. Chemotactic residues direct monocytes and macrophages towards the wound site. Endothelial cells synthesize plasminogen activator and procollagenesis. Growth factors secreted from α-granules of degranulated platelets direct polymorphonuclear leukocytes (PMN), lymphocytes, monocytes and macrophages (Errikson RA., 1983).

During this period, there is a decrease in the oxygen level and pH level, and an environment in which macrophages can function is created. While PMs remove microbial invasion and microdebris, macrophages coalesce to form multinucleated giant cells. At the same time, macrophages cause the release of factors that will increase cellular activity and mitosis (Dörtbudak-Kneissl E., 2000).

Within a few days, hematoma is organized, phagocytes and necrotic tissues are removed by lysosomal mechanism. After the fibroblasts come to the region, the clot is replaced by reparative fibrovascular granulation tissue within 3 or 4 days with capillaries growing inward (Betz RR., 2002).

2. Repair phase

Granulation tissue formation has an important place in the healing process. The first step is the organization of the hematoma. The differentiation of the precursor cells that respond to local stimuli begins to organize the hematoma that has formed (Frost HM., 1989). The osteoblasts supplied by the osteoprogenitor cells in the granulation tissue form the organic matrix of the reticulated bone and initiate mineralization in two phases (Firatli E., 2004).

The first phase is the formation of organic matrix. In this phase, collagen I (procollagen) and amorphous substance is secreted from the entire surface of the osteoblasts and begins in the place called the "calcification front". Macromolecules consisting of collagen fibers, proteoglycans, proteinpeptides and lipids show a special structure within the amorphous structure. They line up with a regular interruption, forming channels or holes to accommodate inorganic crystals. Since some of the proteoglycans and protein peptides are removed with the tissue fluid with the mineral deposition, the volume of the organic matrix does not increase with mineralization (Byrd HS., 1993). In this circuit, the pH of the region is acidic (Frost HM., 1989). It is known that cells that play a role in the repair process are of mesenchymal origin (Oral O., 2000).

The second phase is the calcification period. As in the inflammation phase, the cells that play a role in the repair process are also of mesenchymal origin; it is known that they make collagen, cartilage and bone tissue (Fleet JC., 1996). Core formation is formed by the local deposition of bone minerals, especially calcium and phosphate, and the spread of mineralization from there. Mineralization begins with matrix vesicles and occurs first inside the osteoid tissue collagen fibrils and then parallel to the fibrils between them (Byrd HS., 1993). Matrix vesicles contain lipid, condensed calcium phosphate, alkaline phosphatase, alkaline adenosine triphosphate and prophosphatase enzymes (Frost HM., 1989). Callus is the newly formed and structurally irregular tissue with the differentiation of cells, the secretions of the cells and the maturation of the extracellular matrix at the end of weeks. Callus; It consists of vascular elements, stromal products, cartilage and cells. Cartilage is replaced by woven bone. Woven bone then transforms into lamellar bone consisting of layers such as bone leaves to strengthen the bone segments (Fleisch H., 1997).

The repair phase is characterized by the formation of this callus and begins with vascular growth, osteoid secretion, and preparation of fibrocollagen fibers. A temporary callus made of cartilage is produced at the wound site. Combination begins in the first 4-6 weeks. Mesenchymal cell proliferation was detected in the defect area in the first 16 hours. This proliferation peaks at 32 hours after fracture. The blood vessels that begin to form become visible at the light microscopic level in 2-3 days and become evident in the first week. In parallel with the proliferation process of osteogenic cells, capillary budding begins. In the early stages, periosteal vessels help capillary budding (Oral O., 2000). In the early stages of bone healing, periosteal vessels, and in the late period, feeder vessels help capillary budding. However, since capillary development is not as rapid as osteogenic cell development, cells at the deep level close to the bone, where nutrition is better, turn into osteoblasts. Cells located above the granulation tissue belt not close to the bone are poor in circulation. Cells sometimes differentiate into chondrocytes because the capillary growth rate in this region is not compatible with cell proliferation. Cartilage tissue occurs on the outer surface of the belt (Ham AW., 1971). In the early stages of the repair phase, cartilage formation (cartilage callus) becomes evident. Vascular regeneration occurs by budding in existing blood vessels, and if blood supply is sufficient, osteoblasts provide a matrix suitable for normal bone development in the callus. Osteoblast activity continues and cartilage is replaced by cancellous bone, which acts as a bridge between the fractured fragments. With the continuation of osteoid deposition, cancellous bone can be replaced by cortical bone (Rosenberg E., 1998). Proteoglycans, polypeptides, lipids and amorphous substance secreted from the surface of osteoblasts settle in the osteid tissue as special

molecules. It has a special structure to be suitable for organic matrix mineralization (Robert B., 1983).

3. **Remodeling phase**

By reshaping the bone, bone production is obtained that can survive biomechanically and metabolically under environmental conditions. However, bone quality decreases in adult individuals with advancing age. For this reason, the missing bone needs to be replaced or renewed. This process is formed by remodeling of poor quality bone by destruction and new lamellar bone formation, respectively. This phase begins in the middle of the repair phase and normally lasts 4-16 weeks in humans, and continues for years. It is the transformation of strong and irregular hard callus into more regular lamellar bone (El Montaser MA., 1997). Over time, when the units responsible for reshaping the bone invade the healing area, lamellar bone begins to replace the reticulated bone. This mechanism continues until bone of normal size, shape and strength is formed. All these reactions are known as activation-resorption-formation. Osteoblasts are activated by signaling factors and empty a bone area; osteoclasts are stimulated and begin resorption by attaching to the area exposed by osteoblasts (Baron T., 1982). Areas of osteoclastic resorption, called Howship's lacunae, are then filled by osteoblasts. Over time, they secrete osteoid, which will calcify and form new bone (Galletti G., 1991).

This remodeling process can take months or even years. However, the formation of a sufficiently strong bone is usually completed in about 6 months. The self-renewal rate of the cortical bone of an adult is 20 years, and the cancellous bone is known as 1-4 years. The bone renews itself completely within a certain period of time, allowing it to resist forces and to regulate and meet the calcium balance required by the skeletal system in order to eliminate structural damage throughout life (Gautschi OP., 2007).

Osseointegration

The main criteria which determining the success of dental implants is the concept of osseointegration defined by Branemark in 1976. Osseointegration was defined by Branemark as the direct contact between the implant surface and living bone tissue under the light microscope (Branemark PI., 1983, Albrektsson&Wennerberg, 2019). Osseointegration was also defined by Zarb & Zarb in 1985 as the dynamic interaction of a biocompatible implant with living bone without a soft tissue layer between the implant and the bone tissue (Smith&Zarb, 1989).

Osseointegration is the result of molecular and cellular events that occur after preparation of the implant bed and insertion of the dental implant which means that the newly formed bone contacts directly with the implant surface New opinion about osseointegration was but a foreign body

reaction where the tissues aimed at embedding the titanium material in bone as a mode of protection for nearby tissues (Albrektsson&Wennerberg, 2019).

Healing in the primary bone is normally the same as healing around the implant surface. Studies have reported that healing occurs in three phases (osteophilic, osteoconductive, osteoadaptive) during osseointegration on titanium dental implants (Linkhart TA., 1996).

1. Osteophilic phase

There is a space between the implant surface and bone when implant is inserted into the cancellous bone marrow. This space is filled with blood clot and then coagulation process starts. While most of the dental implant surface is in contact with extracellular fluid and cells, very little of it comes into contact with bone. During implant-host interaction, platelets are activated; many cytokines and growth factors (Platelet Derived Growth Factor, TGF-B, Vascular Endothelial Growth Factor) are released, which regulate the production of adhesion molecules, stimulate cellular proliferation to increase collagen synthesis, and regulate bone metabolism. A general inflammatory response begins in the host in response to the surgical procedure. Inflammatory cells respond to foreign antigens introduced into the environment by the surgical procedure at the end of the first week. Neutrophils, monocytes, and macrophages cause the release of proteolytic enzymes. Fibroblast-like cells release growth factors, and increasing cell number and formation in the environment increases the need for nutrients and oxygen. Therefore, vascular growth from the surrounding vital tissues begins on the third day and continues until the third week until the mature vascular network is formed (Zoltos et al., 1995). Bone morphogenetic proteins (BMP) are released with implant placement. Cellular differentiation, proliferation and activation begin. Ossification begins in the first week with osteoblast migration from the endosteal surface of trabecular bone and buccal & lingual cortical bone towards the implant. The osteoid structure is formed by the production of woven bone and collagen matrix by osteoblasts. The osteophilic phase continues up to 1 month.

2. **Osteoconductive phase**

When the bone cells reach the metal implant surface, they begin to spread over the entire implant surface and an osteoid structure is formed. Initially, this tissue contains immature connective tissue matrix and thin layer of woven bone. Within 3-4 weeks, the woven bone covers the entire implant surface and is harder than at the beginning and continues to act as a skeleton during the bone formation stage (osteoconductive). Fibrocartilogenous callus turns into bone callus over time (similar to endochondral ossification). Formation of osteoblasts, osteoid tissue and

osteocytes takes place. Osteocytes form primary osteons. This process continues until the 3rd month, and 4 months after the implant is placed, the surface is filled with maximum bone (Zoltos et al., 1995)

3. Osteoadaptive phase

The osteoadaptive phase begins 4 months after implant placement. There is a balanced remodeling that starts and continues when the implant is opened and the prosthesis is loaded. Primary osteons are replaced by lamellar bone and bone marrow. Bone marrow; It has a trabecular structure containing blood vessels, mesenchymal cells, adipocytes. At the end of 6-12 weeks, the space around the implant is filled with mineralized bone. Recovery continues for up to 6 months. There is usually no gain or loss of bone contact when implants are loaded. However, after loading, thickening of the woven bone around the implant and reorientation of the vascular structure may occur (Quirynen M., 1995).

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CHAPTER IV

IDIOPATHIC GRANULOMATOUS MASTITIS

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Idiopathic granulomatous mastitis (IGM), which can mimic breast cancer clinically and radiologically, was first described by Kessler and Wolloch in 1972. Histologically, non-caseating granulomatous inflammation is an important diagnostic finding (Kessler et al., 1972). It is of unknown etiology yet. However, it may be related to undetectable microorganisms or autoimmune reactions (Yılmaz et al., 2001). Normal endogenous bacterial flora of the breast, dermal flora such as coagulase negative staphylococci, Propionibacterium spp. and Corynebacterium spp. includes. These bacteria can penetrate through the skin into the breast tissue (Pereira et al., 2012). Recently, there are studies focused on Corynebacterium in the etiology of IGM (Taylor et al., 2003; Renshav et al., 2011; D'Alfonso et al., 2015; Tauch et al., 2016; Yu et al., 2016).

Two types of granulomatous mastitis have been identified: idiopathic (granulomatous lobular mastitis) and specific granulomatous mastitis. Idiopathic granulomatous mastitis is usually observed in the young middle ages (3rd to 4th decade) and 1 to 2 years postpartum (Heer et al., 2003). Although oral contraceptives have been shown as etiological factors, their effects have not been clearly demonstrated and are still controversial. Idiopathic granulomatous mastitis has been identified to be associated with some autoimmune diseases such as erythema nodosum, polyarteritis nodosa, Wegener's granulomatosis and lymphocytic alveolitis (Diesing et al., 2004; Bani-Hani et al., 2004). Specific granulomatous mastitis is frequently seen in Asian and African countries. It can also be detected at any age.It may occur during the course of tuberculosis, some Corynebacterium species, various fungal (actinomycosis, histoplasmosis) and parasitic infections (schistosomiasis, filariasis) or as a clinical manifestation of sarcoidosis (Diesing et al., 2004). There is an increased risk in pregnancy, breast feeding, breast trauma, alpha-1-antitrypsin deficiency, and hyperprolactinemia with galactorrhea (Bani-Hani et al., 2004; Goldberg et al., 2000).

Idiopathic granulomatous mastitis is a disease that can mimic breast cancer. Recent studies (Miliauskus et al., 1995) have shown that T lymphocytes are formed by immunohistochemical damage to the ductal epithelium. It is a

painful or painless palpable mass in the breast that is frequently encountered in IGM. Clinical findings include erythema, tenderness, and an increase in temperature, as well as acute inflammation. Sometimes, it can mimic breast cancer with fistula, abscess and ulceration, retraction and nipple discharge in the breast (Bani-Hani et al., 2004; Tavassoli, 1999). It may give the appearance of an infectious disease with localized temperature increase, hyperemia and tenderness findings in some patients. Axillary lymph nodes are very rarely palpable. Ultrasonographic and mammographic findings of granulomatous mastitis have similar characteristics to breast cancer, but preoperative diagnosis and management of the disease involve many difficulties (Heer et al., 2003; Cakır et al., 2002). IGM mostly presents as a unilateral, irregular, painful and firm mass in the breast (Al-Khaffaf et al., 2008; Sakurai et al., 2011; Ozel et al., 2012; Akcan et al., 2006; Vinayagam et al., 2009; Gurleyik et al., 2012; Bakaris et al., 2006; Patel et al., 2009). Granulomatous inflammation of IGM can be confused with breast cancer (Al-Khaffaf et al., 2008; Ozel et al., 2012; Patel et al., 2009; Akbulut et al., 2011). According to Aghajanzadeh et al. found synchronous bilateral breast cancer findings in 1% of cases in their study and in 18% of cases in Gautier et al.'s study (Aghajanzadeh et al., 2015; Gautier et al., 2013). According to Aghajanzadeh et al. (Aghajanzadeh et al., 2015) also found skin erythema and edema (11 to 31% of cases), isolated skin induration (20% of cases), and to a lesser extent a tender and palpable mass. Pinkish skin changes were reported in 40% of patients and asymmetric breast enlargement in approximately 20% (Baslaim et al., 2013). These findings are also observed in inflammatory breast cancer (IBC).

The mammographic finding of IGM shows microcalcification clusters with spiculated calcification (Figure 1), while ultrasonography finds these areas hypoechogenic (Fletcher et al., 1982; Jorgensen et al., 1992; Memis et al., 2002). Although MR demonstrates solitary masses and parenchymal asymmetry, diffuse, heterogeneous or ring-shaped contrast enhancement in lesions are monitored (Asoglu et al., 2005; Han et al., 1999). In cases (Handa et al., 2014) where heterogeneous or extremely dense breasts are present, there are no mammographic findings. Several studies (Hovanessian Larsen et al., 2009; Al-Khawari et al., 2011) have also found a lesser degree of asymmetrically dense breast parenchyma or global asymmetry granulomatous mastitis. Breast deformity is less frequently reported (Dursun et al., 2012). The mammographic finding of IGM (Hovanessian Larsen et al., 2009; Dursun et al., 2012; Oztekin et al., 2016; Yıldız et al., 2015; Fazzio et al., 2016) also shows axillary adenopathy, focal skin thickening or edema.

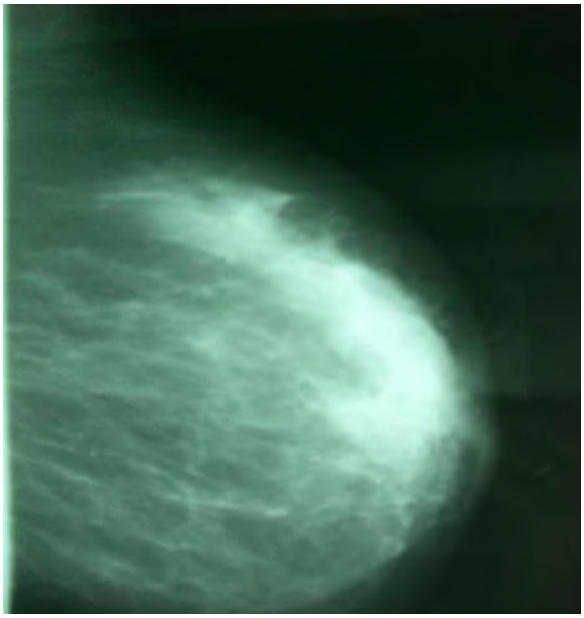

Figure 1. The mammogram showed speculate calcifications in right breast of the patient.

Ultrasonographic findings of IGM are a large and irregular hypoechoic mass with tubular extension (Aghajanzadeh et al., 2015; Al-Khawari et al., 2011; Oztekin et al., 2016; Yıldız et al., 2015; Fazzio et al., 2016; Poyraz et al., 2016; Lee et al., 2006). Confluent lesions or collections with tubular extensions are seen as the more common finding (Gautier et al., 2013; Memis et al., 2002). Tubular extensions indicate (Memis et al., 2002) that the IGM surrounds the mammary lobules.

Doppler US shows that the lesion and surrounding tissues are hypervascular (Handa et al., 2014; Al-Khawari et al., 2011; Fazzio et al., 2016). Advanced disease may have fluid collections or abscesses, ranging from 6.6% to 54.0% (Dursun et al., 2012; Yıldız et al., 2015; Fazzio et al., 2016; Poyraz et al., 2016; Tse et al., 2003). On MR images, a heterogeneously enhancing mass (or masses) are commonly described as rim-enhancing lesions (Figure 2), and may also show associated segmental or regional non-mass enhancement (Al-Khawari et al., 2011; Dursun et al., 2012; Oztekin et al., 2016; Yıldız et al., 2015; Fazzio et al., 2016; Poyraz et al., 2016). Yildiz et al. reported (Yıldız et al., 2015) in their study IGM, a T2-hypointense mass with irregular borders. T2 hyperintense masses were found on MR images in the majority (80%) of patients. In general, the boundaries and shapes of these masses vary greatly (Handa et al., 2014; Dursun et al., 2012; Poyraz et al., 2016). In most cases (Fazzio et al., 2016), restricted diffusion of the affected breast parenchyma and T2 hyperintensity (representing edema) are seen (Figure 3). In imaging methods, it may present with various non-specific signs

(Table 1) that often mimic the signs of malignancy. The reasons for this can mostly be attributed to changing histopathological features such as inflammatory reaction, abscess and fibrosis (Poyraz et al., 2016).

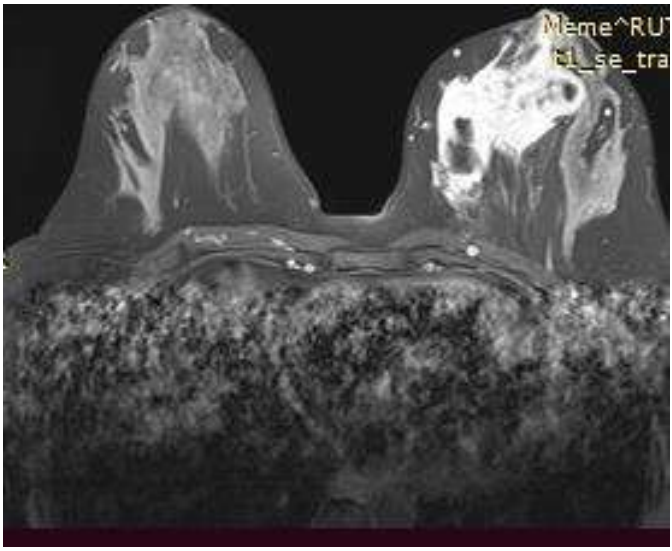

Figure 2. A heterogeneously enhancing mass (or masses) are commonly described as rim-enhancing lesions

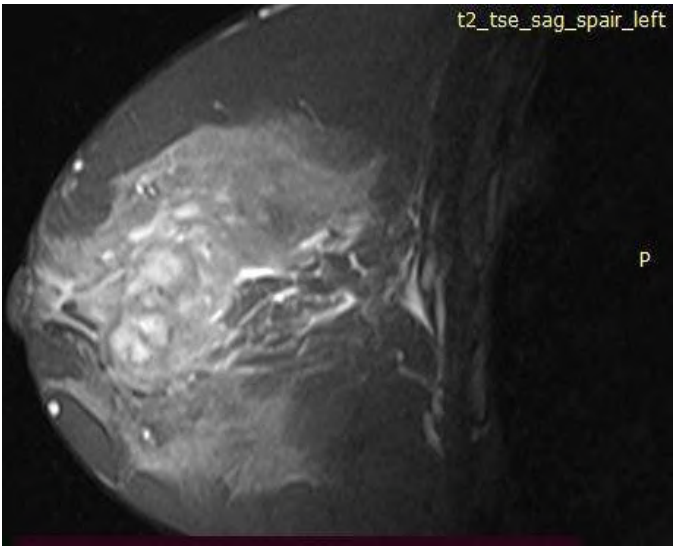

Figure 3. Restricted diffusion of the affected breast parenchyma and T2 hyperintensity

Table 1: IGM Imaging Findings	Finding Prevalence (%)
Mammography	
Focal or global asymmetry	36–75
Irregular focal mass	11–67
Normal findings	8–45
Axillary adenopathy	15–18
Skin thickening with edema or trabecular thickening	5–21
Asymmetrically increased breast density	4.5–17.0
Architectural distortion	9
Circumscribed mass	9
Calcifications	Very rare
US	
Irregular hypoechoic mass with tubular extensions	40–100
Axillary adenopathy	28–60
Circumscribed hypoechoic mass	25–52
Skin thickening and edema	17–60
Abscess and/or sinus tract	6.6–54.0
Heterogeneous hypoechoic mass (or confluent masses) with indistinct, lobulated, or angular margins	6.6–33.0
Parenchymal distortion with or without acoustic shadowing, no discrete mass	4.0–26.7
Normal findings	3.4–20.0
Heterogeneous parenchyma or parenchymal edema	10–13
Multiparametric MR imaging	
T2 hyperintensity (edema) of breast stroma	Majority
Rim-enhancing lesions (microabscesses) or heterogeneously enhancing masses, with or without NME	71–86
Segmental or regional NME	30–80
Contrast enhancement with variable kinetic properties:	
Type I	38.0–82.7
Type II	13.8–40.0
T2-hypointense enhancing mass with irregular margins	20

Note.— MR = magnetic resonance, NME = nonmass enhancement.

Histopathological diagnosis is extremely important for the management of the disease. Fine-needle aspiration biopsy, tru-cut or open surgical biopsy may allow to make diagnosis. Although fine needle aspiration biopsy is an easy and minimally invasive approach, it has limitations due to its lower diagnostic accuracy than tissue biopsies. Studies on the use of fine-needle aspiration biopsy n pathological diagnosis (Tse et al., 2003) are limited, but the diagnostic accuracy rate of aspiration biopsy has been reported to be 50% in a series of 11 patients. There are cases in the literature (Bani-Hani et al., 2004; Imoto et al., 1997) that were evaluated as malignant as a result of fine-needle biopsy and underwent mastectomy. If the diagnosis cannot be made after fine needle biopsy or there is doubt in the diagnosis, it must be confirmed by tissue biopsy. Core needle biopsy has an important role in the diagnosis of IGM with an accuracy rate of 94-100% (Gautier et al., 2013; Oztekin et al., 2016; Oran et al., 2013; Akahane et al., 2013). However, it is unknown whether Core needle biopsy exacerbates inflammatory changes in silent or mildly symptomatic IGM. Histopathological granulomas are typical. Although rare, necrosis may be observed. Langhans giant cells are frequently seen. Lymphocytic infiltration and associated lobulitis are frequently seen (Figure 4). Lymphocytic vasculitis is rare. Necrosis is usually present in mastitis due to tuberculosis, and may be nodular, sclerosing and disseminated. There are usually various lymph node involvement and systemic findings due to tuberculosis (Tse et al., 2003).

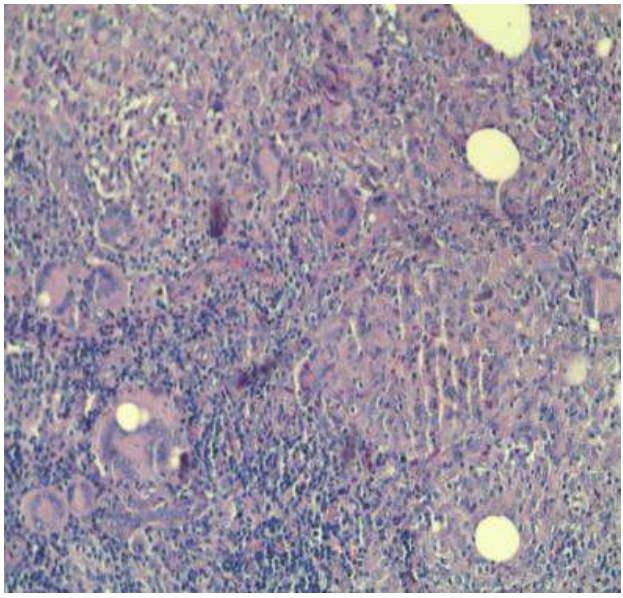

Figure 4. Histopathologically, granulomas are typical. Although rare, necrosis can be seen. Langhans-type giant cells are frequently seen. Lymphocytic infiltration and related lobulitis are frequently seen.

So far, no consensus has been reached on the treatment modality. Surgical intervention should be avoided as the first approach in IGM cases with minimal clinical findings. However, surgery should be considered in patients who do not respond to medical therapy or who have severe clinical findings. Several studies (Gurleyik et al., 2012; Asoglu et al., 2005; Azlina et al., 2003) have preferred stepped care model. Treatment includes antibiotics, then steroids and finally surgical operation. The response to the preferred treatment probably depends on the severity of IGM. A representative algorithm or diagnosis and management of the IGM at the University of Texas Health San Antonio is also presented in Figure 5 (Hovanessian Larsen et al., 2009). Treatment options include drug therapy with corticosteroids or methotrexate, as well as close regular surveillance and conservative measures such as an aggressive wide local surgical excision approach (Lai et al., 2005; Erozgen et al., 2010; Akbulut et al., 2011; Ahmed et al., 2016).

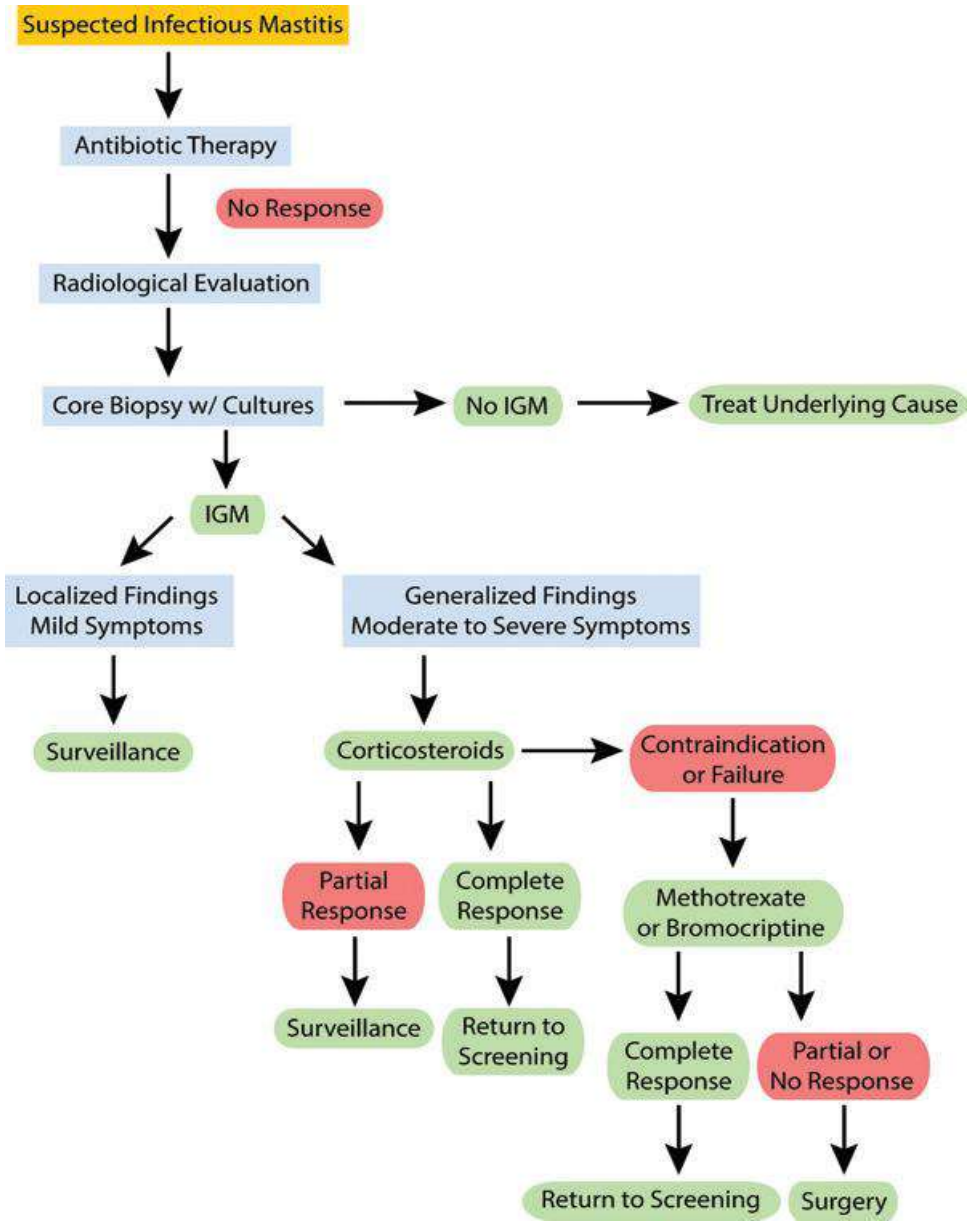

Figure 5.Algorithm for IGM management at University of Texas Health at San Antonio.

Despite the absence of any standard treatment method these days, there are also studies suggesting the excision of the entire tissue that develops granulomatous mastitis (Bani-Hani et al., 2004; Azlina et al., 2003). The ideal treatment of granulomatous mastitis seems to be surgical excision of the entire lesion. For these patients who are usually diagnosed with malignancy or abscess in the preoperative evaluation, limited excisions have restricted benefits and high risk of recurrence. Therefore, wide excision of the lesion is ideal in surgical therapy (Asoglu et al., 2005; Ayeva-Derman et al., 1999). Steroid treatment has been found successful in some recurrent cases and in patients with postoperative pain (Erhan et al., 2000). The recommended dose of prednisolone for steroid treatment in the literature ranges from 0.5 to 2 mg/kg/day (Akcan et al., 2006; Gurleyik et al., 2012; Akbulut et al., 2011; Asoglu et al., 2005; Ayeva-Derman et al., 1999; Erhan et al., 2000; Parlakgumus et al., 2012; Pistolese et al., 2013). Besides, full remission has been also reported in patients diagnosed by fine-needle aspiration biopsy, and after high-dose continuous steroid treatment (Asoglu et al., 2005). Aghajanzadeh et al. (Aghajanzadeh et al., 2015) proposed an IGM treatment strategy of 30 to 60 mg of oral prednisolone per day for 4 weeks, with reduced doses at 3-, 5-, and 6-week periods. In case of failure of the protocol, the addition of methotrexate at a dose of 7.5 to 10.0 mg per week has been recommended. Despite all this, if drug therapy fails, combination therapy with glucocorticoids such as bromocriptine (5 to 10 mg/day), a dopamine agonist and prolactin-lowering drug, can be started. Bromocriptine has been shown to be most effective in cases of concomitant hyperprolactinemia conditions and refractory IGM (Nikolaev et al., 2016).

Anti-inflammatory drugs and colchicine are other medications used in conservative treatment. Appropriate antibiotherapy should be administered in cases with abscess formation.[10] Surgical therapy complications include recurrence, fistula formation and secondary infections. Based on the association of autoimmunity, hyperprolactinemia and microprolactinoma with granulomatous mastitis, it has been reported that remission was achieved with methotrexate (10 to 15 mg per week) in the study in which methotrexate was used in the treatment, but new studies are needed to compare the obtained results (Kim et al., 2003). Kim et al. stated (Kim et al., 2003) that in cases resistant to other treatments, immunosuppressive agents such as methotrexate or azathioprine could be used even if the clinical response was limited, while Asoglu et al reported (Asoglu et al., 2005) that in the presence of clinical findings such as unresponsiveness to medical treatment and recurrent abscess or fistula, wide local excision or even mastectomy (when necessary) could be performed. The surgical therapy of granulomatous mastitis due to tuberculosis is lumpectomy. Cases of mastectomy due to extensive involvement have also been reported. Antituberculous treatment should be added to the surgical therapy in these patients (Diesing et al., 2004).

IGM patients mostly present with a painful or painless palpable mass in the breast. Clinical findings may present as acute inflammation with erythema, tenderness and warmth. Most of the time, it appears as a disease that can mimic chronic breast cancer with fistula, abscess and ulceration, retraction and nipple discharge in the breast (Akbulut et al., 2011). Axillary lymph nodes are very rarely palpable. So far, no consensus has been reached on the treatment modality. Aggressive surgical intervention should be avoided as the first approach in treatment. However, surgical operation should be considered in cases (Ciftcı et al., 2017) that do not respond to medical treatment or have serious clinical findings. In addition, nonoperative approaches and medical treatment with steroids are more preferred in patients with bilateral IGM.

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CHAPTER V

NURSING CARE IN PATIENTS WITH EXTERNAL VENTRICULAR DRAINAGE

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1. Introduction

Health services include prevention, diagnosis, and treatment of many diseases that bring along several risks, one of which is external ventricular drainage (EVD). EVD is a system that allows drainage of blood or cerebrospinal fluid accumulating in the brain tissue due to various causes which results in increased intracranial pressure. It is a method performed for various reasons by neurosurgeons and is also important in terms of nursing care and follow-up (Fışgın, 2008; Öztürk & Özbayır, 2020).

The application, follow-up, and management of external ventricular drainage involves various risks born by factors such as the duration of catheterization, intraventricular and subarachnoid hemorrhage, craniotomy, irrigation of the catheter and the number of replacements (Aydemir et al., 2018). It is especially important where the EVD procedure is performed. Guidelines (American Association of Neuroscience Nurses (AANN) Clinical Practice Guideline Series, 2017 Infectious Diseases Society of America's Clinical Practice Guidelines for Healthcare-Associated Ventriculitis and Meningitis) recommend the procedure to be carried out in sterile environments such as operating rooms (AANN, 2011; Tunkel, 2017). It has been determined that 60% of EVD catheters are inserted in operating rooms, 40% in intensive care units, and 17-20% are replaced (Gündüz, 2006). Although the duration of EVD varies, it was observed that 20% remained for 1-4 days, 33% for 5-9 days, and 47% for more than 10 days. Multiple external ventricular drainage replacement increases the risk of complications. Infection is one of the most common complications with a rate between 8% and 22%

(Aydemir et al., 2018). Complications bring other risks along with the increase in hospital stay, which, accordingly, results in an increase in mortality and morbidity (AANN, 2011; Dasgupta et al., 2018).

2. External Ventricular Drainage System

2.1. External Ventricular Drainage Application

External ventricular drainage is performed to treat increased intracranial pressure (ICP) due to impaired circulation or absorption of cerebrospinal fluid (CSF). CSF drainage is performed to prevent acute brain injury by reducing and managing intracranial pressure (Muralidharan, 2015). It is one of the most common procedures performed by neurosurgeons (Fışgın, 2008). Patient should be followed up in the intensive care unit after the placement of the silicone catheter (Fışgın, 2008; Öztürk & Özbayır, 2020). If EVDs fail to provide a short-term solution to hydrocephalus, and the hydrocephalus does not eventually resolve, it may be necessary to switch to a cerebral shunt (Dasgupta et al., 2018; Muralidharan, 2015).

The cerebral ventricular system is composed of four ventricles filled with CSF: two lateral ventricles, the third ventricle, and the fourth ventricle. They are located deep in the subcortical tissue, each in a separate brain hemisphere. C-shaped lateral ventricles are the largest ventricles and connect the anterior, posterior and diencephalon, and 3rd and 4th ventricles. The fourth ventricle is located in the posterior and consists of the pons and the medulla. CSF flows from the lateral ventricles to the 4th ventricle via the intraventricular foramen and the 4th ventricle by flowing through the Luschka foramen and then the subarachnoid (Dasgupta et al., 2018).

An external ventricular drain is usually inserted to the Kocher point of the skull. It is possible to move the catheter toward the right lateral ventricle or the third ventricle from here (Dasgupta et al., 2018; Gardner et al., 2009; Muralidharan , 2015). External ventricular drainage is a flexible catheter system that is inserted into the lateral ventricle using the Burr Hole method (Dasgupta et al., 2018; Gardner et al., 2009).

Intracranial pressure monitoring (ICP) is used together with EVD in cases of hydrocephalus, CRPS, and neurological dysfunction. Intensive care is necessary for the care of these patients (Dasgupta et al., 2018).

2.2. External Ventricular Drainage Indications

EVD, which is basically applied to reduce the increase in intracranial pressure, is a system that is applied temporarily for follow-up and treatment in various situations. Main indications for external ventricular drainage placement include:

- Increased intracranial pressure
- Subarachnoid hemorrhage
- Intracerebral or intraventricular hemorrhage
- Hydrocephalus (increased CSF or obstruction of the subarachnoid villi)
- Shunt failure
- Tumors

It is especially important to remove blood products from the cerebral tissue as they may lead to various neurological problems and vasospasm. EVD is applied to prevent these complications (Aydemir et al., 2018; Gündüz, 2006).

2.3. External Ventricular Drainage Complications

Various factors play a role in external ventricular drainage complications;

- The area where the EVD catheter is inserted
- Compliance with aseptic techniques and correct skin preparation
- Features of the EVD catheter and attachment system
- Use of prophylactic antibiotics
- Protocol compliance for EVD insertion and management
- Frequency of CSF sampling
- EVD duration and replacement
- Deep vein thrombosis (DVT) prophylaxis
- Type of dressing and change of dressing
- EVD care

Problems associated with these factors increase the risk of complications (Öztürk & Özbayır, 2020).

Complications can be listed as follows:

2.3.1. Bleeding:

Bleeding may occur in the epidural and subdural cavity during the insertion of external ventricular drain. Presence of a coagulation disorder increases the risk of complications (Dasgupta et al., 2018; Muralidharan, 2015).

2.3.2. Mechanical Complications:

These complications occur due to malfunctions in the inserted catheter. Catheter misplacement is among frequent complications. Normally, the EVD should be placed with the tip of the catheter adjacent to the foramen of Monroe of the lateral ventricle (Dasgupta et al., 2018; Muralidharan, 2015). Adjacency is tolerable, but placement in certain critical brain areas such as the internal capsule or brain stem can cause neurological problems.

Migration: Situations such as dislocation or loosening in the catheter fixation, or migration of the catheter away from its intended position may interfere with the drainage of CSF and cause inaccurate intracranial pressure measurement, (Dasgupta et al., 2018; Muralidharan, 2015).

Obstruction: It is a common complication. In particular, blood and blood products may cause an obstruction of the EVD catheter. In such case, drainage cannot be provided and may cause an increase in intracranial pressure. Intermittent catheter flushing may be required (Dasgupta et al., 2018; Gardner et al., 2009; Muralidharan, 2015).

2.3.3. Neurological Complications:

They are usually not common and may be related to poor prognosis of the patient (Dasgupta et al., 2018; Muralidharan, 2015).

2.3.4. Infection:

External ventricular drain creates an opening that extends from the skull to the ventricle which can create a gateway for infections. The rate of EVD-related infection is around 8% to 22%. Significant decreases have been observed in this rate with infection control applications (Aydemir et al., 2018; Muralidharan, 2015; Talibi et al., 2020).

Infections are the most common complications (Gardner et al., 2009; Öztürk & Özbayır, 2020). EVD-related infections are defined as the condition of "a positive CSF culture" (Talibi et al., 2020). Examination of EVD-related infectious agents showed that *Acinetobacter baumannii* was the most frequently isolated microorganism among all reproducing microorganisms (Fışgın et al., 2008).

Development of infection initiates a strong inflammatory response in blood and activates leukocytes. Activated leukocytes are mobilized to phagocytize the blood. The inflammatory response is one of the clinical manifestations of bacterial meningitis. Diagnosis can be made by microbiological CSF analysis, cell count, and clinical examination (AANN, 2011).

External ventricular drain infections cause an increase in morbidity and mortality, as well as reoperations, prolonged hospitalization, workload, and financial costs. In addition, infections contribute to the increase of antibiotic resistance and create doubt towards health services in the society where the legal dimension plays an important role in related problems (Turkish Ministry of Health, 2018).

In Turkey, EVD infections are considered among surgical site infections (SSI) and handled under the title of "ventricular shunt operations". According to the report of the 2020 National Healthcare-Associated Infections Surveillance Network, the weighted mean CAE of ventricular shunt operations has been reported as 4.5 (Turkish Ministry of Health, 2020).

2.4. Follow-up and Care of the Patient with External Ventricular Drainage

EVD procedure is an application that brings along serious complications where close follow-up and care of patients is of great importance. Follow-up, care, and management of complications fall within the responsibility of nurses. Better outcomes are observed in patients with EVD as a result of effective nursing care and follow-up (Çopur et al., 2015; Muralidharan, 2015). Nurses who can make decisions with evidence-based practices can provide the best care for the patient and feel safe with their practices (Çopur et al., 2015). Nurses have a great responsibility in the prevention of EVD-related complications and management of problems. It is important that nurses who care for patients with EVD have sufficient knowledge and perform caring practices based on evidence (Muralidharan , 2015).

While providing nursing care, it is important to monitor the ICP signs and symptoms, to monitor the EVD system and insertion site for CSF leakage. In this regard, it is necessary to monitor, evaluate, and manage patients with EVD by trained and competent nurses who are experts in the field. In addition, deep vein thrombosis (DVT) follow-up and prevention practices are also important since these patients are mostly immobilized (AANN, 2011).

Neurosurgery clinics are units with a high risk of infection due to the patient population and the high number of invasive procedures. It is important to apply patient-based surveillance in detecting infections that may occur during the delivery of health care (Fışgın et al., 2008).

Almost 70% of healthcare-associated infections are considered preventable. Surgical site infection surveillance can reduce SSI rates. When the surgical team surveils the surgical site, they can apply infection control measures more meticulously during the surgery, which

may increase surgeons' compliance with hand hygiene during the procedure and dressing. Therefore, surveillance itself is considered as an infection control measure (Turkish Ministry of Health, 2018).

Postoperative SSI surveillance bears significant importance in these operations. CDC definitions should be used to diagnose surgical site infections (Berríos-Torres et al., 2017). Surgical care practitioners should be trained in this regard and ensure cooperation to make the necessary notifications. The patient and patient relatives should be informed about the associated risks and the procedure. Hand hygiene guidance and hand washing techniques should be conveyed, informing the practitioners that the surgical area should be kept sterilized and untouched (Kalkan & Karadağ, 2017).

Surgical nurses bear important responsibilities in the prevention of infection such as providing preoperative patient preparation, monitoring the application of antimicrobial prophylaxis, ensuring correct ventilation conditions in the operating room, ensuring the sterilization/disinfection of the environment and surfaces, sterilization of surgical instruments, skin preparation of the surgical area, preservation of body temperature, surgical wound care, and providing information to the patient and patient relatives (Kalkan & Karadağ, 2017).

Guidelines for EVD placement, follow-up and care are as follows:

2.5. Guidelines For EVD Placement:

- EVD placement should be performed under operating room conditions with maximum barrier protection.
- Personal protective equipment should be provided (bone cap, mask, sterile cover, sterilized gloves). Sterile equipment should be provided during the insertion process against the risk of contamination.
- Products containing alcohol and chlorhexidine are suitable for skin antisepsis.
- A 3-minute cleaning with chlorhexidine-alcohol-containing products followed by 30 seconds after the application of povidone-iodine.
- Equipment contaminated with patient body fluids should be separated and attention should be paid to personnel exposure.
- Antibiotic-impregnated EVD catheters are recommended for use.
- Irrigation of the EVD site with antibiotic solutions or using antimicrobial ointments on the area does not significantly affect the development of infection, therefore is not recommended.
- A dose of prophylactic antibiotic is recommended before EVD

insertion.

- Administration of intravenous antibiotics during the EVD duration is not necessary and may increase the risk of infection with resistant organisms.

- To reduce the risk of EVD-associated infections, an EVD control protocol of aseptic administration methods, limitation of manipulation, standardization of dressings, and undelayed removal of EVD should be followed (AANN, 2011; Berríos-Torres et al., 2017; Tunkel et al., 2017).

2.6. Guidelines for EVD Follow-up:

- CSF sampling should not be manipulated, except for suspected infection.

- CSF sample should not be taken routinely.

- The drain line should not be changed routinely during the stay of EVD.

- The catheter itself should not be replaced routinely.

- EVD should be removed as soon as clinically possible to minimize EVD-related infections.

- EVD should be removed as early as possible.

- EVD catheters should be removed in case of infection.

- DVT prophylaxis should be applied during the period of immobilization in patients with EVD.

- Routine use of inferior vena cava filters is not recommended for DVT prophylaxis in patients with EVD

- Intermittent pneumatic compression is appropriate for patients in whom pharmacological prophylaxis cannot be administered.

- Pharmacological prophylaxis is recommended after the stabilization of the patient in cases with a high risk of DVT (trauma, malignancy, immobilization, spinal cord injury, etc.) (AANN, 2011; Berríos-Torres et al., 2017; Tunkel et al., 2017).

2.7. Recommendations for Nursing Care During EVD Follow-up:

- Aseptic methods should be followed for dressing the EVD site. Dressing should be done with a mask and sterile gloves after hand hygiene is performed. Care should be taken to ensure that the materials used for dressing are sterilized. If possible, the dressing should not be removed for 48 hours after the surgery (it can be removed if soiled per institutional policy). Hair can be removed during the dressing change, if

present. CSF leakage and signs of infection should be monitored during dressing.

- Follow-up, evaluation, and management of patients with an EVD should be carried out by trained and competent nurses.

- Neurological examination should be performed (every hour or according to clinical necessity) and recorded.

- The entire EVD drainage system should be checked every 4 hours for leakage and fluids.

- Frequent manipulation of the EVD system should be avoided.

- CSF sample should be delivered to the laboratory immediately without delay.

- No difference is observed between proximal versus distal EVD sampling ports and CSF laboratory results.

- If EVD sampling is required; hand hygiene, mask, sterile materials, and sterile gloves should be provided. The EVD incision site should be cleaned with povidone-iodine for 3 minutes and allowed to dry.

- Mask and sterile gloves should be used to change the drainage bag against the risk of bacteria escaping backwards (towards the catheter entry site).

- The drainage bag should only be changed when nearly full (¾) and should not be changed unnecessarily.

- The CSF drainage bag should be kept in an upright position. If it needs to be placed horizontally, collected CSF should be dripped into the drainage bag.

- The EVD tubing access port should be clearly labeled to prevent confusion with intravenous lines.

- Manufacturers are recommended to design different types of access ports to avoid human errors.

- EVD entry site should be dressed with a sterile occlusive dressing.

- Pressure should be monitored with the ICP monitor used for ICP measurement.

- Neurological symptoms should be monitored (AANN, 2011; Tunkel et al., 2017).

While the NCS-IDSA (2017) guidelines (Tunkel et al., 2017) recommend the use of antibiotic-impregnated catheters to prevent infections originating from external ventricular drains, there is no recommendation in this regard in the AANN guidelines (AANN, 2011).

Antibiotic and silver-coated catheters are available to reduce external ventricular drainage-associated infection rates while catheters impregnated with antibiotics are particularly effective against gram-positive bacteria (Gardner et al., 2009).

3. Conclusion

Infections related to external ventricular drainage are mostly caused by skin flora, as are central catheter-related bloodstream infections. The use of protocols for EVD placement and management is very effective in reducing EVD-related infections and other complications. Therefore, it is recommended to follow and expand the use of up-to-date guidelines in EVD follow-up and care.

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CHAPTER VI

EMERGENCY NURSING AND ETHICS DURING THE COVID-19 PANDEMIC

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1. Introduction

COVID-19, which emerged in Wuhan city of China in late 2019, is a deadly form of coronavirus that caused pandemic at a global level, leading to acute respiratory syndrome and pneumonia (Huang et al., 2020). The World Health Organization (WHO) declared this new coronavirus infection a global pandemic on March 11, 2020, after spreading almost all over the world, appearing in many people and causing thousands of lives to be lost (WHO, 2020a).

The world has faced a pandemic not seen since the 1918 Spanish Flu pandemic (Angelos, 2020). The impact of the COVID-19 pandemic, which has become the most important health problem of the 21st century, has not yet been clearly defined. This rapidly spreading pandemic increases the mortality and morbidity rates day by day, and affects all areas, especially our daily life and medical care services (Aslım et al., 2021; WHO, 2020b; Zhou et al., 2020). In addition to threatening global public health, the COVID-19 pandemic is a process that is expected to create different sociological, economic, political, and ecological transformations all over the world (Nicola et al., 2020).

2. COVID-19 Signs and Symptoms

Chills and high fever, cough, shortness of breath, fatigue, muscle or body aches, headache, sore throat, loss of taste and smell, congestion or runny nose, nausea, vomiting, and diarrhea are known as the most common signs and symptoms of the disease. In the COVID-19 pandemic, depending on the incubation period, symptoms may appear 2-14 days

after exposure to the virus. There may be cases with mild or no symptoms, or cases with severe symptoms. The treatment needs of the individuals infected with the disease vary. While the majority of the patients recover without the need for intensive treatment, the need for treatment increases in elderly patients at high risk and patients with chronic diseases (CDC, 2020a; CDC, 2020b; WHO, 2020c).

3. COVID-19 Pandemic and Nursing

Nurses are one of the healthcare professionals who provide continuous and global healthcare services during this pandemic period. They have a critical role in care, in the prevention of diseases, in promoting and improving public health during the pandemic (WHO, 2020d).

Nurses fulfilled their nursing roles and responsibilities at the risk of their own lives by working at the forefront of the pandemic, identifying cases, taking preventive measures, treating patients, and maintaining care during the pandemic (Turale et al., 2020). In our country, especially nurses provided safe and qualified nursing care at the highest level during the COVID-19 pandemic (Çelik et al., 2020).

A large number of positive COVID-19 cases around the world apply to healthcare institutions for treatment and care. Due to COVID-19, nurses and other healthcare personnel faced ethical and moral problems in providing care for too many patients with limited resources. Nurses had difficulties in accessing adequate and high-quality personal protective equipment during the pandemic. Working on the frontline without sufficient equipment put their life safety at risk (Angelos et al., 2020; Çelik et al., 2020). They experienced problems related to working conditions and the work environment. They struggled with problems such as inadequate rest breaks and break rooms, inadequate and imbalanced nutrition, risk of contamination, accommodation problems, and lack of transportation. In addition to the loss of the patients they provided care for, nurses experienced anxiety and fear for both themselves and their immediate surroundings and felt burned out in terms of psychosocial problems (Çelik et al., 2020; Turale et al., 2020).

4. Emergency Department and Emergency Nursing

Emergency departments are one of the important and high-risk units of hospitals where healthcare services specific to unexpected and urgent health problems such as illness, accident, trauma that occur suddenly are provided. The majority of the patients admitted to the emergency department are at high risk of death, are often unconscious, homeless, and sometimes unidentified (Bayraktar et al., 2018). Since emergencies can

occur at any time, emergency departments provide uninterrupted service 24 hours a day, every day (Morganti et al., 2013).

In order to provide high-quality healthcare in emergency departments, healthcare professionals equipped with the necessary knowledge and skills that meet emergency care needs are required. Nurses working in the emergency department are healthcare professionals who play a critical role in continuous interaction with patients and their relatives (Morganti el al., 2013; Stenson et al., 2020). It is necessary to maintain all kinds of patient confidentiality during the treatment and care in the emergency department (Turkish Ministry of Health, 2018).

While providing treatment and care in emergency departments in line with the attitude and understanding of the healthcare professionals, factors that may pave the way for abuse may arise for the parties. In this regard, emergency departments are units that require quality healthcare service and impose critical ethical responsibilities on healthcare professionals (CENA, 2013; Moskop et al., 2005).

An emergency nurse is a healthcare professional who applies the necessary nursing care to all individuals who have not been diagnosed yet and who need emergency intervention, in the shortest time frame. Nurses working in the emergency department must act according to the ethical principles regulated by the professional standards while performing nursing practices with their professional knowledge and skills. According to the International Council of Nurses, protecting and promoting the health of the individual, preventing illnesses, and alleviating suffering are the four fundamental responsibilities of nurses (ICN, 2012; TNA, 2013).

5. Emergency Nursing and Ethical Problems During COVID-19 Pandemic

Many existing factors such as limited time while providing care in emergency departments, urgent need for patient treatment, unclear and insufficient information obtained from the patients, need for security, and inadequate facilities complicate the duties and responsibilities of nurses and create ethical problems. Ethical problems are also frequently encountered due to unconscious patients, communication problems, lack of proper evidence collection and preservation in forensic cases, triage not performed properly, and large numbers of patients (Denizbaşı, 2021; Jimenaz-Herrera et al., 2015).

Since emergency departments are units with unplanned and sudden admissions and many patients with the need of urgent care within the same period, deciding which individual should be given the priority in treatment and care is very important. The most important and primary

system in managing this process is the triage system (Karaçay et al., 2007; Sabatello et al., 2020; Tanabe et al., 2012). Nurses treat patients fairly in the triage system in terms of ethical considerations. The emergency nurse needs to have the knowledge and skills to make the patient distinction carefully and to provide proper triage as soon as possible. However, today, due to the increase in the number of patients, the applications of non-urgent patients, and the inability to access primary care and treatment centres, nurses face ethical problems in triage (An et al., 2020). Inadequate facilities in the emergency department can lead to incorrect practices, frequent ethical problems, reduced patient/employee satisfaction, and poor quality healthcare services (Schluter et al., 2008).

With the COVID-19 pandemic, the capacities of healthcare systems have increased, however, ethical dilemmas have also emerged (Schreyer et al., 2020). During the pandemic, nurses working in different units against their will faced ethical difficulties due to the exposure to the disease and lack of experience in the clinic. Due to the difficulties, they experienced, nurses suffered from mental health problems such as fear, anxiety, stress, insomnia, and aggressiveness (Liu et al., 2020).

Emergency nurses worked as the forefront heroes during the COVID-19 pandemic. They provided services by creating a successful order in a limited time with their ability to predict the unknown and to come up with new ideas. Nurses with ethical values experienced conflicts many times during the pandemic due to the lack of information about treatment and care. Unclear approaches in the care and treatment of patients admitted to the emergency department reduced the work motivation of nurses. Inadequate access to information and care, violation of the rights of sick individuals caused nurses to face ethical dilemmas and led to low-quality care and decreased patient satisfaction (Bagnasco et al., 2020; Ulrich et al., 2020).

Maintaining nursing care for hours with the same equipment, lack of medical equipment, lack of clean/dirty area separation, and inadequate resting conditions in emergency departments prevented nurses from working efficiently. Wearing protective clothing for a long time raises the body temperature and causes intolerance and loss of concentration while working. Factors such as intense work pace, negative situations encountered and unclear treatment and care approaches, the risk of contamination and the concern of risking the safety of their families, mental fatigue caused nurses to experience moral conflicts while maintaining treatment and care. Workload, increased work shifts and critically ill patients, deaths, and how to overcome these burdens occupy nurses' minds and raise ethical challenges in this area (Jia et al., 2021).

The inability of many critically ill patients to communicate effectively, to participate in the treatment plan, and the lack of adequate safety measures are other factors that compel nurses in terms of ethical issues. Patients' need for emotional support and the burnout of the nurses, the feeling of not being able to spend enough time with their patients significantly reduced the morale and motivation of the nurses. Excessive time spent by some healthcare workers to protect themselves while performing treatment and care led to failures in the fulfilment of ethical obligations. Uncertainties in the management of the process, reducing the frequency of nursing interventions to prevent transmission and infections led to low responsibility awareness, compelling nurses emotionally and morally (Palandöken, 2020).

6. Conclusion

Nurses, who have a crucial role in healthcare services with their knowledge, experience and skills, expertise, and qualified nursing care have faced many problems and ethical dilemmas due to the pandemic. Awareness of ethical sensitivity should be created by organizing in-service training, seminars, etc. in institutions. In order to ensure the standard of treatment and care, it is necessary to have a sufficient number of quality medical equipment, to increase the motivation of nurses, to reduce the excessive workload, to have a sufficient number of well-equipped nurses, to improve working hours and breaks, to support autonomy, and to ensure personal rights. To help nurses gain the ability to make the right decisions on ethical issues during the pandemic, it is necessary to create evidence-based ethical guidelines for the COVID-19 pandemic at the global level.

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CHAPTER VII

SEPSIS, SEVERE SEPSIS AND SEPTIC SHOCK: A SHORT REVIEW

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1. Introduction

Sepsis and septic shock are the second highest cause of death in ICU after cardiovascular disease. About 11% of Intensive Care Unit (ICU) patients in Australia and New Zealand, around 27% of ICU patients in the UK, and approximately 11% of ICU patients in the USA contracted severe sepsis in the last few decades (Angus and Wax, 2001; Padkin et al., 2003; Finfer et al., 2004). The mortality rate among hospitalized patients with sepsis increased over the last several decades in the USA (Angus and Wax, 2001; Martin et al., 2003) and ranged between 26% and 37% in Australia and New Zealand (Finfer et al., 2004).

Sepsis, severe sepsis and septic shock commonly result from infection by bacterial pathogens (Aledo et al., 1998; Kumar et al., 2006b; Lim et al., 2009; Welte and Kohnlein, 2009; Woodhead, 2009). Although inflammatory cytokine storm is thought to be the main cause of septic shock rather than the actual infection, the different frequencies of bacterial pathogens were investigated as the cause of sepsis in several studies (Pinsky and Matuschak, 1990; Rangel-Frausto et al., 1995; Aledo et al., 1998; Cursons et al., 1999; Kumar et al., 2006b). The most common bacteria found in septic shock (83%) are Gram-negative bacteria such as *E. coli* and *K. pneumoniae* (Aledo et al., 1998). However, cases of Gram-negative infections became less common over time (Friedman et al., 1998), and the frequency of Gram-positive pathogens involved in septic shock have increased over the years, Gram-positive bacteria including *S. aureus* and *S. pneumoniae* are implicated in ~ 38% of all septic shock cases in North America (Kumar et al., 2006b). In addition to some therapeutic strategies, an appropriate and adequate dose of antibiotic therapy significantly increases the survival rate of patients with septic shock.

2. Definition and Epidemiology of Septic Shock

Sepsis, severe sepsis and septic shock are systemic inflammatory responses due to an uncontrolled infection (Bone et al., 1992). Patients with severe sepsis constitute approximately 11 % and 11.8 % of all patients

in the Intensive Care Unit (ICU), respectively, in the US and Australia-New Zealand. (Finfer et al., 2004, Martin et al., 2003). It is estimated that an average of $ 16.7 billion is spent annually to care for patients with sepsis (Hodgin and Moss, 2008). Sepsis and septic shock have a high rate of mortality, at around 38% (ARISE; et al., 2007), and are the second highest cause of death in ICU after cardiovascular disease (Brun-Buisson et al., 1995; Martin et al., 2003; Brun-Buisson et al., 2004).

In 1992, Septic shock was defined as sepsis with severe cardiovascular instability, acute organ dysfunction, hypotension and coagulopathy (Bone et al., 1992). In addition to this definition, findings such as hemodynamic instability, arterial hypoxemia, oliguria, and changes in liver function tests also play an essential role in the diagnosis of sepsis according to the definition determined in The 2001 International Sepsis Definitions Conference (Levy et al., 2003). The immune dysfunction resulting from sepsis and septic shock is complex, persistent, and affects the inflammatory and anti-inflammatory systems (Genga and Russell, 2017). Bacteraemia can trigger an inflammatory cytokine storm that induces septic shock, and multiple organ dysfunctions which arise in septic shock are presumed to be the result of this inflammation rather than the actual infection (Pinsky and Matuschak, 1990; Cursons et al., 1999).

3. Bacterial Causes of Septic Shock

The most common types of bacteria found in septic shock are Gram-negative bacteria (47.9% of septic shock cases) such as *Escherichia coli*, *Klebsiella pneumoniae* and *Pseudomonas aeruginosa*, followed by Gram-positive bacteria (38.3%) such as *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Enterococcus faecalis* (Figure 1) (Kumar et al., 2006b). Although the amount of bacteria required to cause septic shock is unknown, the contribution of bacterial load and microbial virulence to septic shock is recognized (van der Poll and Opal, 2008). Moreover, unidentified sepsis may result from translocation of bacteria from the gut and the frequency of polymicrobial bacteremia is not known (Kane et al., 1998; Ammori et al., 2003). The importance of Gram-negative bacteria in septic shock may be related to the influence of LPS from the Gram-negative envelope.

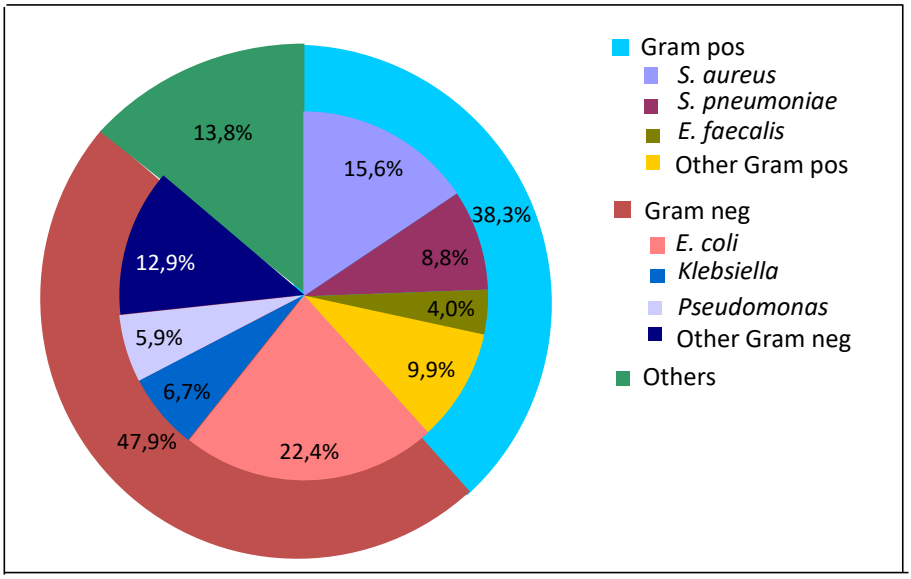

Fig. 1 The percentage distribution of bacterial pathogens that cause septic shock; using data from Kumar et al. (2006b). Other Gram-positive organisms include: Group A *Streptococcus* (3.6%) Other β-hemolytic streptococci (2.2%), *Viridans streptococci* (1.9%), *E. faecium* (1.5%), *Bacillus* species (0.3%), *Corynebacterium jeijkeium* (0.3%), *Staphylococcus lugdunensis* (0.3%). Other Gram-negative organisms include: *Enterobacter* species (4.1%), *Haemophilus influenzae* (2.2%), *Proteus* species (1.2%), *Acinetobacter* species (1.1%), *Serratia* species (1.0%), *Stenotrophomonas maltophilia* (0.8%), *Morganella morganii* (0.7%), *Citrobacter* species (0.7%), *Neisseria meningitidis* (0.3%), *Burkholderia cepacia* (0.2%), *Haemophilus parainfluenzae* (0.2%). Others: yeast/fungi (8.2%), anaerobes (3.6%), *Legionella* species (0.4%), *Mycobacterium tuberculosis* (0.6%)

4. Diagnosis

To be diagnosed with sepsis, an individual must have a probable or confirmed infection and all signs of a slow or sudden change in mental status, a systolic blood pressure reading of 100 mm Hg or less, and a respiratory rate of 22 or higher per minute. Septic shock causes a higher death rate than sepsis. A diagnosis of septic shock requires both a possible or confirmed infection, the need for medication to keep systolic blood pressure higher than 65 mm Hg, and high levels of lactic acid in the blood despite adequate fluids in the serum (Bone, 1993). Having too much lactic acid in an individual's body means that oxygen is not being used properly

by the cells. Doctors often consider it appropriate to perform several tests to detect the underlying infection in diagnosing sepsis. In one of these tests, the blood test, different blood samples taken from two different parts of the body are tested for evidence of infection, abnormal liver or kidney function, impaired oxygen values, electrolyte imbalances, and clotting problems. In addition to the blood test, urine wound secretions or respiratory secretions may also be tested depending on the individual's symptoms (Hotchkiss et al., 2016). If an individual has a wound that appears to be infected, testing a sample of the secretions around that wound can help show which type of antibiotic may work best and most effectively. Sample mucus, especially from individuals who cough with phlegm, can be tested to determine what type of microbe is causing the infection. If the site of infection is not evident, one or more of several imaging tests may be performed for diagnosis. X-rays are an effective method for observing the problems in the individual's lungs. On computed tomography scans, infections in the appendix or pancreas are easier to spot. This technology takes X-rays from various angles and combines these shots to create cross-sectional slices of the internal structures of his body (Acıbadem, 2021; Hotchkiss et al., 2016). The risk factors for septic shock are outlined in Figure 2.

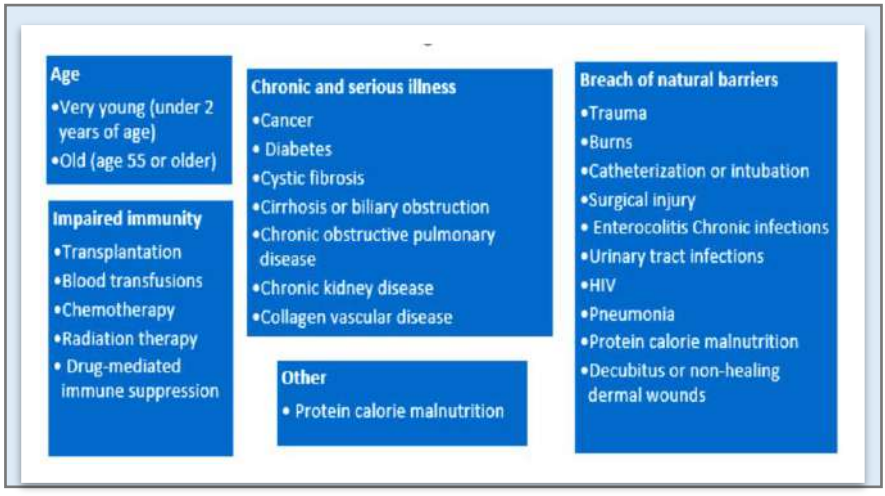

Fig. 2 Risk factors for Septic shock. Adapted from Hotchkiss et al. (2016).

5. Inflammatory Response

Both pro-inflammatory and anti-inflammatory cytokines constitute a part of the immune response mechanism. Although pro-inflammatory cytokines such as tumor necrosis factor (TNF) and Interleukins-1, -6 and -8 (IL-1, IL-6 and IL-8) appear in the early stages of infection, anti-inflammatory cytokines such as TNF receptor 1 (TNFR1), IL-1 receptor antagonist (IL-1ra) are more important in the continuation of the inflammatory process. Several inflammatory cytokines (TNF-α, IL-1β and IL-6) can increase the risk of severe sepsis and death through the inhibition of fibrinolysis and by activating coagulation, with thrombin known to stimulate the inflammatory process (Bevilacqua et al., 1986; Conkling et al., 1988; Esmon et al., 1991; Yan and Grinnell, 1993; Stouthard et al. 1996; Fang et al., 1999; Kellum et al., 2007). Uncontrolled systemic inflammation may lead to multiple organ failure and lethal septic shock (Vervloet et al., 1998; Levi and Ten Cate, 1999).

The three major anticoagulant proteins controlling blood clotting are tissue-factor-pathway inhibitor (TFPI), antithrombin and activated protein C (Figure 3) (Esmon, 1992; Levi and van der Poll, 2005). Reducing the level of activated protein C in patients with septic shock may decrease the mortality rate (Taylor et al., 1987; Kylat and Ohlsson, 2006). Activated protein C inhibits activation of fibrin by inhibiting plasminogen activator inhibitor-1 (PAI-1). The inactivation of thrombin is a significant modulator of coagulation and inflammation in septic shock (Taylor et al., 1987; Fourrier et al., 1992; Kylat and Ohlsson, 2006).

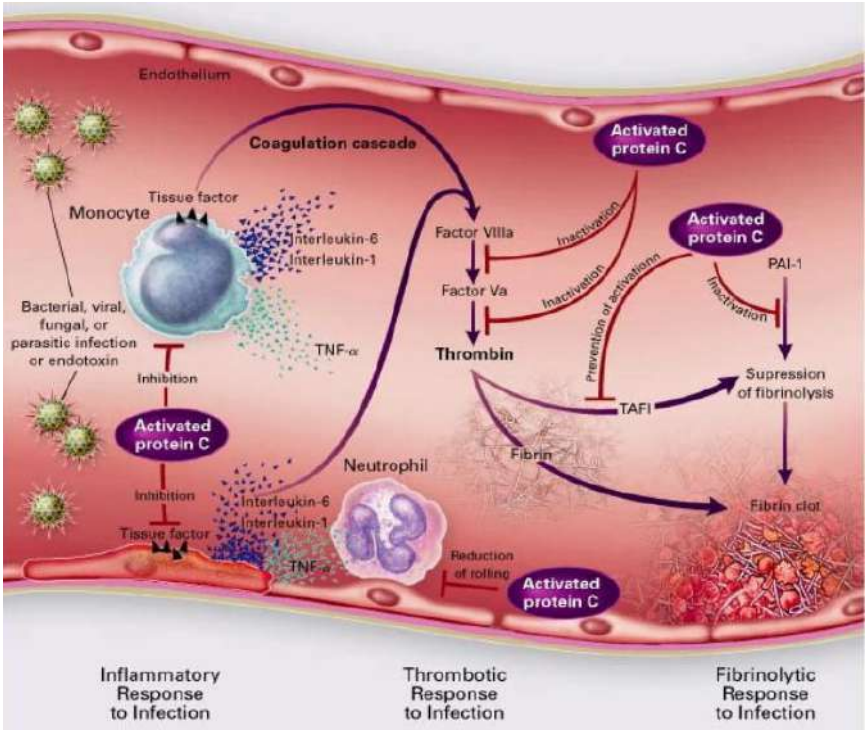

Fig. 3 The role of thrombin and activated protein C in anticoagulation during the inflammatory and procoagulant host responses to infection in severe sepsis (from Bernard et al., 2001)

5.1. The effect of endotoxin on coagulation and cytokine pathways

Lipopolysaccharide (LPS), also known as endotoxin, in the outer membrane of Gram-negative bacteria may drive the pathogenesis of septic shock. Endotoxin (LPS) consists of three main parts: Lipid A, O antigen (a long chain polysaccharide) and the LPS core, where Lipid A is the actual toxic moiety that plays the main role in septic shock (Bone, 1993). LPS, especially Lipid A, activates the coagulation cascade and macrophages through the formation of a LPS-LPS binding protein complex. Activated macrophages produce TNF-α, IL-1, IL-6 and IL-8, which lead to increased body temperature, vasodilation, hypotension and endothelial damage (Figure 4). Even if all pathogens are removed from the bloodstream, TNF and other cytokines continue to drive the process of septic shock (Salyers and Whitt, 1994).

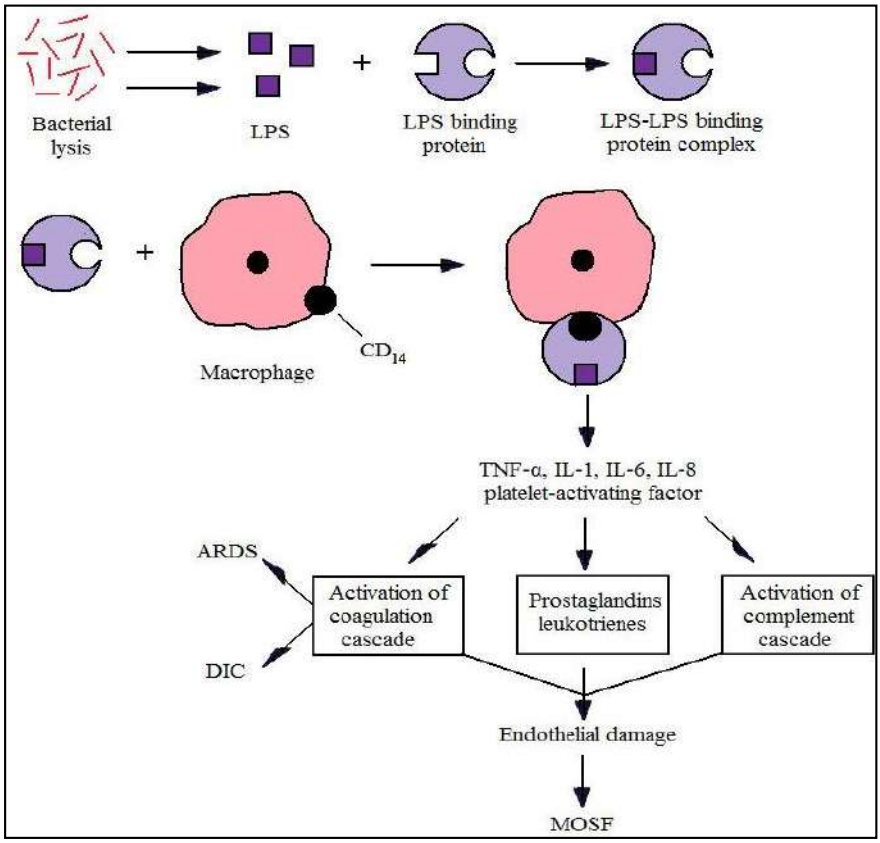

Fig. 4 The role of Gram-negative LPS on the production of cytokines and endothelial damage in Septic Shock. (ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; MOSF, multiple organ system failures) Adapted from Salyers and Whitt (1994)

6. Treatment and Antibiotic Therapy in Septic Shock

Prophylactic antibiotics, maintenance of blood glucose concentrations, selective digestive system decontamination, prevention of iatrogenic infections, and Immune therapies such as vaccines and intravenous immunoglobulin are essential therapies in preventing septic shock (Sharma and Howden, 2001, van den Berghe et al., 2001, de Jonge et al., 2003, Cafiero et al., 1992, Douzinas et al., 2000).

Identification of the infective pathogen and relevant resistance can be crucial to the correct and adequate selection of antimicrobial therapy. The use of combination antibiotic therapy (especially broad-spectrum β-

lactams) is preferred in the case of septic shock due to the high prevalence of polymicrobial sepsis (Kumar et al., 2010). Delays in antimicrobial therapy, incorrect or inadequate antibiotic choice, failure to control the source of sepsis in the early stage of septic shock, and resistance to "last line" ICU antibiotics increase the mortality rate of patients with septic shock (Bochud et al., 2004; Kumar et al., 2006b). There is a linear correlation between early antibiotic therapy and mortality rate in septic shock (Figure 5 and 6). The survival of patients treated for septic shock decreases by 7% for every hour the patient is not treated with antibiotics; and if the treatment is delayed 12 hours, the patient‟s survival rate has reduced to 25% (Figure 5) (Kumar et al., 2006b). In cohort studies, inadequate initial antibiotic therapy resulted in a 4–8-fold increase in mortality (Garnacho-Montero et al., 2003, MacArthur et al., 2004). Quick removal of infected tissues or devices is vital, along with antibiotic therapy, to increase the survival rate. After patients are discharged, proper rehabilitation programs and long-term follow-up are crucial (Annane et al., 2005).

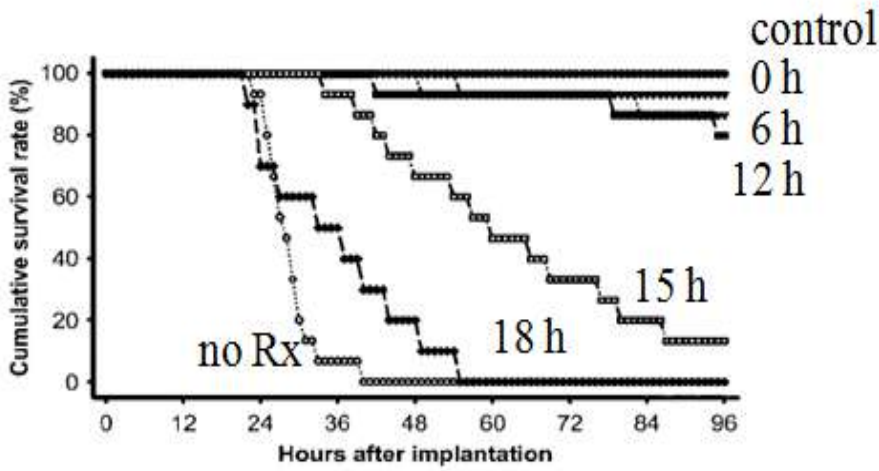

Fig. 5 Survival rate in mice inoculated with 1000 cfu *E. coli*, with antibiotic treatment at 0, 6, 12, 15 and 18 hours after inoculation. No Rx = no antibiotic-treatment. Adapted from Kumar et al. (2006a)

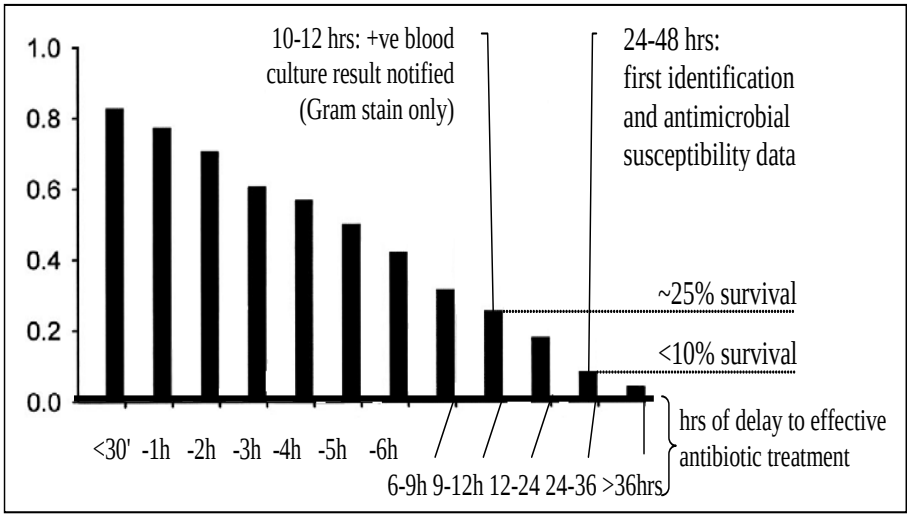

Fig. 6 Likelihood of in-hospital survival from resuscitated septic shock (0.0-1.0), as a function of delay in commencement of effective antibiotics. Adapted from Kumar et al. (2006b)

Septic shock continues to be a significant source of morbidity and mortality and poses a significant burden on the healthcare system. In recent years, the identification of molecules that perceive microbial markers in patients with sepsis has been an essential step in understanding sepsis's molecular and cellular basis. Understanding the links between inflammation, coagulation, and the immune and neuroendocrine systems is essential in the early treatment of septic shock.

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CHPATER VIII

PSYCHOLOGICAL PERSPECTIVE IN CARDIAC TRANSPLANTATION

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1. Introduction

The cardiac transplantation, is a surgical procedure performed on patients with end-stage heart failure when other medical or surgical treatments have failed (1,2). Heart transplantation is, by its nature, a single surgical procedure involving two separate operations for two different people, the donor and the recipient. Replacing the dysfunctional organs of sick people with severe health losses through transplantation and saving their lives is the most promising solution possible to restore healthy life and even body integrity. Transplantation perception and attitude are in close relationship with all elements of culture, science, philosophy and religion. The concept of survival includes overlapping and complementary approaches within the fields of expression of sciences such as philosophy, anthropology, psychology, sociology, as well as medicine (3). Human is a biopsychosocial-cultural being with its most basic elements. Therefore, it seems timely to focus attention on the psychological well-being of cardiac transplant recipients.

2. Heart Failure

The patients who suffered from severe heart failure, the systolic left ventricular function was severely depressed and the left ventricular cavity was markedly dilated. Left ventricular ejection fraction, pulmonary capillary wedge pressure and transpulmonary gradient are reliable predictors of the course of the end-stage heart failure patients (2). Heart failure is not a disease, but a clinical syndrome that can occur due to many different causes. Heart failure is a combination of cardiac structural or functional disorders, symptoms and physical findings that prevent the heart from providing blood and circulatory support to meet the metabolic needs of the tissues (4). Heart failure is a disease that is increasing in frequency, has a high risk of irreversibility, has a poor prognosis and prognosis, is difficult to treat, and is costly in every respect. Heart muscle diseases

(cardiomyopathies), hypertension, coronary artery disease, heart valve diseases, congenital heart diseases, chronic lung diseases etc. conditions that cause or predispose to heart failure.

Most of the patients with advanced heart failure require hospital treatment due to the worsening of their clinical conditions, and they have to be hospitalized in clinics or intensive care units and treated with high-cost methods. There is no treatment alternative other than surgical treatment for patients who are completely incapacitated due to the loss of the heart's ability to contract and/or relax and its unique geometry, and who have no medical treatment option (5,6,7). For patients who do not definitively respond to maximum drug therapy, structures and systems are needed to replace the impaired and nonfunctioning heart muscle. In heart failure that does not respond to treatment, heart transplantation is still the gold standard for the replacement of completely deficient heart muscle (1).

3. Cardiac Transplantation

In the light of advances in basic sciences, medicine, pharmacology and engineering in the field of cardiac surgery and cardiac transplantation, fast progress has been made with sophisticated methods and scientific approaches developed by the pioneers of cardiovascular surgery, especially in the last 30 years (8). The transplantation method, which is a breakthrough in the treatment of heart failure and is identified with the landing of the human being on the moon, has become widespread rapidly.

The use of cyclosporinA (cyclosporine A), a calcineurin inhibitor found in antibiotic research in 1971, for immunosuppression in 1977, started a new era in organ transplantation (5). The survival has improved from 20% of patients who survived at one year after transplantation in the 1960s to the present figures of 80%-85% of patients who are alive at one year, and 50%-70% of patients who are alive at five years after transplantation (1,3).

The most important parameter in the selection of recipient (recipient) and donor (donor) is tissue group (HLA, humanleukocyteantigen). The suitability of the blood group is the main selection criterion (5). Another important parameter is body weight. The body surface area or body mass index of the donor should be within +/- 20% of the recipient. Gender doesn't matter between donor/receiver.

The number of suitable donors for patients waiting for a heart transplant is extremely insufficient, and the waiting times in the "Emergency Heart Transplant List" are getting longer. With the revival of the heart transplant program, the problem of keeping the heart transplant candidates alive

without end-organ damage under appropriate conditions until appropriate donor procurement has come to the fore (9,10,11). While on the waiting list of patients who are candidates for transplantation as a result of terminal heart failure, mortality rates are around 20-40%. The use of mechanical heart assist devices for the purpose of keeping patients alive until heart transplantation or for permanent treatment in patients who are unsuitable for heart transplantation for any reason has significantly reduced the loss of patients on the waiting list (6,12,13,14). Although there is a significant increase in the quality of life of patients with mechanical support devices compared to previous years, there are still important problems that need to be resolved in terms of thromboembolism, bleeding, infection and technical problems related to the device. Another important point is the burden of mechanical support devices on health economy with high costs.

4. Neuropsychological Function of Patients with Severe Heart Failure Disease

Patients with an increased risk of clinical deterioration needed strict medical supervision after the decision to transplantation. Findings developed as a result of heart failure lead to limitation of physical and social activity and deterioration of quality of life. The effort to maintain the quality of life of patients who have to live with a chronic, progressive disease is of interest not only to themselves, but also to their immediate environment and the national health economy. It is accepted that the burden of disease and high mortality risk due to chronic heart failure in the society is a social health priority (2). The most commonly used questionnaires specific to cardiovascular diseases include the following: the Minnesota Living with Heart Failure Questionnaire (15), Kansas City Cardiomyopathy Questionnaire (16), MacNew Heart Disease Health-Related Quality of Life Questionnaire (17), Medical Outcomes Survey Short-Form 36 (18).

Patients who are candidates for heart transplantation should be evaluated before and after consultation-liaison psychiatry (19). Psychiatric examination and neuropsychiatric tests should be done for the patient who is a heart transplant candidate. It is necessary to determine whether the patient who is eligible for a heart transplant has an additional psychiatric disease and to treat it. Consultation-liaison psychiatry technique aims to evaluate the patient's ability to cope with the severe heart failure disease and to gain the ability to cope with those who do not have effective coping skills. The main outcome can be measured anxiety, depression and well-being. These measures could be assessed by means of the Spielberger State Trait Anxiety Scale (20). The medium- and long-term follow-up the Nottingham Health Profile could also be used (21).

Psychiatric problems such as major depressive disorder, anxiety disorder, and adjustment disorder may be seen in patients with end-stage heart failure (22). In patients with end-stage heart failure there would be a high prevalence of impaired cognitive function which is related to the degree of cardiovascular efficiency. Because of this reason, it is imperative to performed to examine cognitive function in patients with end-stage heart failure, to identify and to evaluate changes in cognitive function in the patients who accapted for cardiac transplantation. Patients would be able to develop some adaptation mechanisms to cope with anxiety and fear of death (23). However, as the time on the waiting list increases, the depressive mood and anxiety levels of patients who are hospitalized in the heart failure clinic or intensive care units and treated in isolation from the outside world increase (24). The association of neuropsychiatric disorders with the progression of heart failure includes depression, anxiety disorder, pessimism, apathy, fatigue, sleeping disorders, appetite disorders, future uncertaint, hopelessness about the future, loss of control over own life and anosognosia. Depression is among the most frequent emotional disorders. Its prevalence has been estimated to be around between 30% and 35%, ranging from 20% to 60% in all groups of cardiac transplantation candidate patients (22,25,26).

Estimation of depression in evaluating cardiac transplantation candidate patients, depression rating scales are necessary for the quantification and monitoring of depressive symptoms. A patient with a diagnosis of depression must have depressed mood or loss of interest or pleasure along with symptoms of depression lasting two or more weeks. Depression rating scales as Hamilton Depression Scale (27), Beck Depression Inventory self-assessment psychometric test (28), Minnesota Multiphasic Personality Inventory (29) are suitable to determine the depression severity. Although, there have been no generally accepted guidelines for psychiatric evaluation in organ transplantation.

Patients who are candidates for heart transplantation should also be evaluated in terms of personality disorder. The presence of antisocial and borderline personality disorder should be investigated (29). In case of personality disorders affecting mood and impulse control, appropriate measures should be taken. The patient's anxieties and panic attacks, if any, should be treated with cognitive behavioral approaches before transplantation. In addition, it is necessary to organize social support for patients who are candidates for heart transplantation and to involve the family in the process (30).

5. Psychological Adjustment Before Cardiac Transplantation

Patients registered on the waiting list for heart transplantation experience anxiety and psychological problems arising from the uncertainty about whether the donor heart that will save their lives will be found on time, and they also face a series of procedures, including surgery, after the donor heart is found (24). Anxiety about uncertainty in the process of heart transplantation is a cognitive state that is aggravated by the degree of heart failure, resulting from the feeling of inadequacy due to the inability to control the situation or the helplessness to explain the meaning of the process (31).

In fact, the decision of the patient with end-stage heart failure to have a heart transplant is an indication that she/he has accepted her/his disease and has taken action to fight. In the process of finding the donor heart, due to the symbolic meaning of the heart, in contrast to the efforts of not thinking about the outcome about the possibility of survival and trying to tolerate uncertainty, anger and loss of hope may develop due to the fear of death and uncertainty in parallel with the loss of health (32). The psychosocial situation of the patients who were taken into the heart transplant program, "Why me?". It is expressed in the form of victim psychology, and the fact that they do not reduce their heart failure even though they fully comply with drug treatments and diets leads to a feeling of burnout.

Depression deepens when they realize that nothing can reduce or stop the progression of heart failure, and that the loss of health continues. In heart transplant patients who have to come face to face with the reality of death, loss of authority due to the inability to fulfill their functions and roles, and anxiety about being dependent lead to a feeling of inadequacy. As the donor waiting period increases, their ability to cope with emotions such as anger, dissatisfaction and loss of confidence gradually depletes (33). At the stage of accepting their diseases and conditions, it is important to keep the hope of finding a donor organ with a fatalistic approach. As heart failure progresses, the perception of being a phenomenological “prisoner of the disease” becomes established.

6. Psychological Adjustment After Cardiac Transplantation

In general, psychological adjustment, mood improvement and a high level of well-being are determined in cardiac transplant recipients after transplantation. Scores for anxiety, depression and well-being can be improved significantly after transplantation. On the other hand, the entire biopsychosocioal integrity of a transplant patient could be affected, and the individual could experience a complex and challenging process in the face

of a clear threat of death (24). In addition, after a successful heart transplantation, the individual may not be fully compatible in terms of biopsychosocioal structure; A life with and dependent on another organ may carry anxiety, difficulty in adaptation, and anxieties of encountering a problem at any time.

Depression is a common neuropsychiatric consequence of organ transplantation. The interaction between depression and transplantation is very complex (34). The cardiac recipients' anxiety, depression image quality of life by way of standardized self-assessment questionnaires should be assessed after transplantation, then followed-up at discharge from hospital and at three, siix and 12 months after transplantation regularly (35). High-dose corticosteroid treatment for immunosupressive therapy post transplantation period can lead to the emergence of symptoms steroid depression; even delirium can be seen in these patients. After the transplantation, reassessment of the recipients' anxiety, depression and quality of life levels are necessary (36). Sixty per cent of transplant patients reported an increase in anxiety and thirty-five per cent of 35% of patients recorded scores that indicated mild-to-moderate levels of depression. In patients with an increased risk of clinical deterioration, who needed strict medical supervision after the transplantation progressive heart failure may develop due to rejection after heart transplantation and patients could died after heart transplantation (37).

7. Conclusion

Heart transplantation is performed in order to increase the quality of life as well as giving the patients with advanced heart failure a chance to use their right to life. In patients with end-stage heart failure, neuropsychological dysfunction that may develop before and after heart transplantation can be ameliorated by heart transplantation. Hereby, the medical literature on the psychiatric and psychosocial impact of heart transplantation on recipients is scant and systematic and prospective studies on the psychosocial adaptation of recipients are needed.

It has been tried to develop alternative methods to heart transplantation in order to increase the survival rates and quality of life of patients who do not have a chance for heart transplantation; Apart from the biomechanical engineering studies carried out for the production of mechanical circulation systems, an effective solution method could not be developed.

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CHAPTER IX

BIOPSYHOSOCIAL PROBLEM-BASED GUIDELINES FOR A 15-YEARS -OLD ADOLESCENT GIRL WHO RECENTLY DIAGNOSED WITH TYPE 1 DIABETES

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1. Introduction

The report pursues two aims: to identify the most relevant health-related problems and develop care-plan like recommendations or guidelines for fourteen-year old patient who has recently developed Type 1 diabetes. Both problem identification and suggested interventions are based on a holistic biopsychosocial approach and draw on health psychology theories and research evidence. Furthermore a developmental orientation accounts for future impacts and assesses likely health-related problems and corresponding recommendations. Although the approach is patient centered, focusing on girl, it encompasses the wider social context, specifically her family and school.

Tailored interventions focus on enhanced comprehension of her's condition, effective psychological skills and social 'tools' to long-term adjustment to her chronic condition, which is not curable but can be managed successfully. She was newly diagnosed with Type 1 diabetes. The diabetic specialist nurse has made referral to our health psychology service. We have been provided with her medical records and have seen her parents and her 9 years old brother.

Our overall assessment of the most relevant health related problems are:

-Lack of understanding the condition

-Psychological consequences of diabetes (e.g. possible hypoglycemic attacks)

-Long term commitment to disease management.

-Adherence to Treatment

In this case analysis we tried to identify possible problem and intervention for 15 year old patients who newly diagnosed with type 1 diabetes. Our recommendations can improve her health, quality of life adjustment to her diagnosis and productivity.

2. Lack of Understanding The Condition

The Parent's Perspective

The parents addressed the problem of their limited understanding of the causes and implications of her diabetes. Specifically, the relationship between stress and anxiety appeared to be very significant when parents with a limited understanding of the causes and implications of diabetes (Hoff et al 2005), and this cause Parent's self-blame and overprotective behaviours which can have negative effects on adolescents, and affect the relationships between parents and adolescents Stallwood, 2005; Streisand 2005.

Type 1 diabetes is not contracted as a consequence of life style; it is a genetically inherited disease. Patient's parents, however, believe that their lifestyle and eating habits have caused her to develop her illness. They feel that they are more to blame themselves for her situation. Besides the patient condition they are afraid that her brother may develop Diabetes.

Insufficient understanding of her condition implies the risk of underestimating the potential of diabetes for both physical and psychosocial maladjustment. A clear understanding of diabetes will ensure the best practical and emotional support for her Her parents may also consider her attitude change in the coming years, as she grows in both maturity and diabetes experience. They should therefore understand her current and future changing with perceptions and conceptualization of her illness, to give her tailored support**.**

3. Patient's Perspective

It is very important for patients to understand her illness and why she require treatment in order to seek care and participate in self care activities. According to Lawson et al. (2004) knowledge of the diabetes condition has a significant effect on care activities and patients not seeking regular care held more negative views of the control, course and consequences of diabetes than those who received regular care.

In assessment her developmental stage, Piaget's cognitive theory of development shows that she is in the formal operational stage and that she can think in abstract terms, follow logical propositions, and reason by hypothesis. She becomes concerned with the hypothetical, the future, and ideological problems. She can easily understand the symptoms of her illness and participate in herself care activities. According to Erikson's theory however, she is now in one of the most difficult stage of life as an adolescent. According to the 'problem behaviours' theory (Jessor & Jessor, 1977) she is at her one of the risky stage with problem behaviours amongst teenagers such as drug abuse, drinking, smoke, delinquency. Related to those theories diabetes can be very tough to manage and rapid

growth physically, mentally, and emotionally adds even more challenges to diabetes management. Therefore, she may refuse to adhere to her eating plan, skip insulin injections, or stop checking her blood glucose and tried to act like everyone else (Barlow, 2002).

It appears that she has found it very hard to deal with her illness predominantly through the interactions with her friends and peers, by not going out after school with her friends and not taking part in PE. She is more concerned with being different from others, than with the possible attacks and adherence to her illness in front of her classmates. She has recently had two hypoglycemic attacks after taking part in PE.

4.The perspective of patient's peers and her brother

The necessity of understanding also applies to She brothers, peers and friends. She has told some of her closest friends about her condition. They, however, do not really know what diabetes means or its effects for her. Also her younger brother does not understand her condition and this has caused a lack of support for her. It has become especially difficult for she not to be able to eat whatever her brother eats and do not get enough support from brother and friends. Berlin et al (2006) found adolescent reported problems were predominantly related to unsupportive social and peer groups.

Adherence

Diabetes is unique both in degree to which the patients must assume responsibility for their treatment (Milton, 1989), and the degree to which it imposes a pattern on the lives of those affected, which in turn, governs their use of time and also limits spontaneity in social life (Wysocki et al., 1992). Diabetes treatment consists of interrelated self management behavior that needs to regulate against each other. Adherence may adviser outcomes in the short run (e.g. potential life-threatening hypo attacks) and also serious long term complications e.g. development of long term diabetes related complication such as diabetic renal disease, vascular disease etc. Therefore it is very important to target early adherence. She also has to attend to hospital for biomedical checks and see the doctor and specialist nurse every three months. Overall she has only recently been diagnosed as a Diabetic and has found it difficult to both adjust to her condition and adhere to her new lifestyle regime.

5.Psychological Consequences of Diagnosed by Diabetes

Being diagnosed with diabetes can be very distressful for both she and her parents. Since this diagnosis, she and her parents may experience the following reactions (Hampson et al. 2000): denial, anger depression, fear and anxiety, guilt and shame. According to Connel et at (1994) diabetes can cause anger and she may think, "Why am I the one with diabetes?" she

might become angry with her parents, her friends, or her siblings more often than she used to and that can affect she in a negative way towards her relationships with others, her family which can cause isolation.

Depression is three times more common among people with diabetes than amongst the general population (Peyrot & Rubin, 1997). She may feel that she is to blame for burdening the rest of her family with diabetes. She is also terrified of having a hypoglycemic reaction following her two recent attacks that occurred after taking part in PE. She now no longer wants to take part in PE. Even though these attacks were not serious she felt embarrassed and afraid of any more possible attacks. That may have an impact on social activities like going on school trips e.g. because she is very worried about having an attack that, If she falls into this situation how will she be able to tell her friends. It is very difficult for patient to explain her condition to her friends and it has caused anxiety and fear Smyth (1998).

Long term commitment to disease management

According to Taylor (2003) it is the challenging nature of chronic diseases that often they require intermittent adjustment in both physical and social activities

Apart from the physical implications, patients' condition potentially causes future psychological and social problems such as losing control of her disease and difficulties in creating and maintaining social networks. Whereas her condition requires high peer/friends support as well as parental support, there is an inherent risk of her parents becoming overprotective and so endangering the necessity of her increasing autonomy and independence. Especially as a teenager she may expect her friends to be understandable and supportive otherwise she may tend to isolate herself from others.

The life span of adolescence has to be evaluated as the riskiest one for her. This is the period when most people are highly vulnerable in terms of participating in health risk behaviours. Siegel & Scovill (2000) examined problem behaviour theory and they argued that adolescent problem behaviours such as alcohol use, cigarette smoking, widely occur in adolescent. In this case she has to acknowledge about the effects of all these behaviours on her condition. Besides this teenagers deal with a lot of changes in their bodies as they mature, having big physical and hormonal changes. Those same hormones that cause puberty can make good diabetes care tough. Blood glucose may go up and down a lot more, giving her unexplained highs and lows. For adolescents it may seem like diabetes treatment is being adjusted every other week.

As She's body changes, sometimes she will gain weight whilst at others she will lose, so that she may be moody or irritable more often (Siegel et al., 1999; Bornholt et al.(2005)). At this point she needs to learn how diabetes can affect her emotions.

6.Recommendations For Suggested İnterventions

The identified problems provide the framework for the following suggested tailored interventions.

6.1. Increasing understanding of the condition

6.1.1.The Parents Perspective

We could clearly identify the parents' need for a better understanding of patients' condition with having seen the family within our counseling services. We suggest providing assistance two give more information to family within two follow-up sessions.

The explanation of the medical component of patients' diabetic will focus on the fact that no precise physical causes can be identified in her case. Parents who are confronted with a chronic illness of their child are risk of self-blame, for eliminate self-blame it was recommended them to seek more information about diabetes that it is inherited disease. Also family was recommended them to solve this issue which may have effect on relationships between parents and her by diabetic education.

The interviews also revealed that the parents and younger brother understanding of the disorders. Here health psychologist inform biological, psychological, social and behavioural issues regarding diabetes type 1 with consideration of simplified information for younger brother. In the interviews it was identified that her brothers become jealous and fell left out because She suddenly begins get more attention. Even though he does not know her condition clearly, he is fear that he will get diabetes and like she he will not be able to eat whatever he likes. It is very difficult for she to accept the fact that he still able to eat what he wants, when he wants. In this case in interview we let them express their feelings, and acknowledge parents about their attitude to siblings.

Also we identified that having less knowledge about her disease, cause less attention on meals. Families admitted not know alternative cooking techniques for diabetic person. Therefore family was given option of dietary education and alternative cooking methods which is very important for her. It was arranged appointment by dietician and Diabetes. In this case firstly she will be preparing a list of food which she likes to eat. With that it is given option and control to She over her condition

Ethnicity and culture can have effect on Diabetes patients and their treatment, like following appropriate diet, weight control. Povlsen (2005)

suggest that ethnic minorities may constitute vulnerable groups within Western health care systems as their ability to master severe chronic diseases could be affected by barriers such as different culture and health/illness beliefs, communication problems and limited educational background and it was possible to improve health outcome with increasing the knowledge of diabetes among immigrant families children with diabetes

Support group suggested to She's parent to reduce their stress level. Reducing the level of stress experienced by those parents can increase the level of hope and supportive behaviours towards adolescent with diabetes (Hoff, et al 2005). Mullins (2005) also found that the intervention can design to decrease parental uncertainty and distress as well as child behavioural problems by teaching parents' skills to manage uncertainty in support group.

Our evaluation in terms of stable family environment and secure attachment will be stressed in order to positively reinforce the parent's motivation to provide the crucial support to ensure emotional support it will be tried to increase the parents sensations in terms of She's current age specific perceptions of being different and the distress inducing possible attack. This implies that her parents have to take She''s own perceptions, feelings questions into account which are addressed in the next part.

6.1.2 Patient's perspective

Diabetes education is significantly important for her, because it allows patient to understand her disease, and ultimately provides her with the incentive to change. If She does not recovery Diabetes education, this may increase risk of developing complication in future. On the other side having good education can maintain her adjustment to her diabetes, and she can able to manage her diabetes. She definitely needs to understand diabetes is a series medical condition; however lifestyle modification plays a crucial part of the management of Diabetes. Therefore we suggest She to attend Diabetes Education in hospital. It may increase in positive way She's perception to her illness. She's current perceptions of her illness are predominantly of an emotional nature, characterized by feelings of being 'wrong', an outsider.

We found utilization of a high emotional bond between she and her parents would be beneficial. The emotional commitment implies all effort to give her the permanent feelings of being loved and cared for and to increase her awareness of having a supportive brother and friends. More difficult thoughts which She might have include such as potential self-blame, feelings of being punished, or even fear of death. Finding ways to increase her understanding is crucial, since it will reduce her fears. It can be very challenging with a 15-year adolescent girl to accept the reality of

her illness. We would suggest to her attend our support group meetings once a week

There is some evidence that teens with diabetes may be more prone to eating disorders such as anorexia, bulimia possibly because diabetes demands pay closer attention to food. Eating disorders can take a variety of forms Teens with diabetes and eating disorders may learn to manipulate their diabetes treatment in their quest to lose weight. Therefore it is very important to acknowledged She about eating disorders and giving her all necessary information.

Overall even her and her parents complete understanding of diabetes, causes and consequences, treatment would not automatically lead to good self management. To illustrate the importance of that we draw some links with Leventhal self- regulatory framework (1992) that postulates that patients to understand illness from their own beliefs and these beliefs guide coping responses and behaviours (inc adherence), which in turn influence other outcomes such as adjustment, well being (Urguhat et al 2002). It is hence important to identify misconceptions and target them /modify them in order to improve other outcomes. There is also intervention work (Urguhat et al 2002) that shows that changing illness perceptions leads to favorable outcomes

6.2. Adherence to Treatment

Here the most important things to acknowledge to her about the pros and cons to her treatment. She may need some equipment to support her until she adjusts her condition like an alarm to remind her of medication times. Also recording a diary could be very useful when she takes medication. There can be some alternative recommendations like support group to increase support network which Aolto and Uutela (1997) found that good social support increased adherence. Also Gilibrand &Stevenson, (2006) support this with their findings that adherence to self –care was predicted largely by high levels of family support. Some aspects of the health belief model (HBM) have been applied to the understanding of the adherence in diabetes. Brownlee-Duffeck et al. (1987) found that the cost of adherence had only a significant influence on patient's self-reported adherence with this age group and patients' susceptibility on patients' severity scores had only significant influence on HBM. However we can not say the cost of mediation affect on adherence for She, but it may have effect her adherence in early and late adult life span (Somerville,1992)

Also for weight balance, recommend that she attends dietitian education, and health psychologist and She together discussed the psychological and social impact of her weight and how she feels about food. Weight control mostly related to adherence and exercise. Exercise is

very important for her (attending PE class), however she needs to be aware of her blood sugar level while she is doing exercise.

Additionally it is very important to consider that culture can influence adherence (Olsen et al, 2005). In this situation intervention for decreases negative cultural or ethnicity effect on Diabetes can play significant role. Patino et al (2005) assessed TPB among a sample of ethnic minority adolescents with type 1 diabetes that subjective norms and received risk of short term complications was important and addressed intervention by TPB theory can improve adherence among ethnic minority adolescent.

It would be very valuable teaching to her self-management skills such as problem solving and goal setting that may improve adherence, for example Steed (2002) suggested that practical skills training, problem solving and behavioural skills such as goal setting were important components to include in diabetes self-management interventions. The importance of evaluating quality of life, and process variables and improve her self-efficacy should be taken into consideration in intervention development and trial design.

7. Suggestion for Psychological consequences of Diabetes

A diagnosis of type 1 diabetes can be difficult to deal with at any age, but it can be particularly hard for a teenager. She can face special emotional and physical challenges in dealing with her disease. For instance, it may be useful for She to talk to supportive family members and friends about diabetes for decrease her denial depression, fear or anxiety. Learning as much about diabetes as she can may be helpful for dealing with denial. Sharing time with friends or family, also can reduce the level of depression, fear or anxiety for her and her parents however have become very protective and do not allow her to go out with her friends after school. This has increased her distress with her condition. She needs to be sociable and spend time with her peer group.

There is also potential social implication of diagnosis (e.g. restriction in social life; relationships etc.) that she was worried about how to tell her friends about her diabetes. She may have felt that diabetes is something to be ashamed of or she may have been afraid of appearing different from her friends and classmates.

Due to she having been newly diagnosed, it may just take time and encouragement for her to accept her diabetes. We thought disclosure (talking about Diabetes at School) could be very effective especially before going on a school trip. This could be in the context of a school assignment, such as a science project or a speech class. Sharing her feelings and difficulties with friends, family or classmates could help to make her cope

more effectively with her condition, and this can effect positively psychological and physical well being (Henderson, 2002).

We can also suggest Ley's (1982) Cognitive Theory of Compliance for the improvement of She's satisfaction with health professionals correlated with their compliance with medical advice when she attended to hospital. At the same time this can improve adherence and patients understanding.

7.1. Effective Long Term Adjustment

Due to her predisposition she will have to regard the outlined precautions over her entire lifespan. The predicted physical improvements due to adherence and extended parental and peer support, based upon a better understanding, should provide a framework for She's adaptive coping with her condition.

Adolescence must be evaluated as one of the most critical lifespan. In addition to the mentioned inherent risk for her, adolescence is generally critical in terms of developing health promoting and preventive behaviour. According to problem behaviour theory negative effect of peer pressure can cause poor health related behaviour. Despite She's predisposition, the ability to put a rigorous health regimen and stress management techniques into practice should predict a satisfactory lifespan perspective with a relatively high quality of life for her (Cheing et al., 2006). Related to that, regular exercise, balanced diet and adherence to treatment can minimize changer in her body weight over life span (Toobert et al 2000) and She can have a long and healthy life if she adheres her treatment. On the other hand, Diabetes care will become an important part of her life, but it doesn't have to take over her life.

Adulthood and elder age for she are periods that can lead to many different health problems such as heart disease, stroke, and blindness. Over a life span the effect on health and life expectancy of a person in poor metabolic control is dramatic and costly for the health service (Gilibrand & Stevenson, 2006).

Diabetic education is a fundamental part of managing diabetic for her and is a key to preventing the long-term complications of diabetes. The necessity is for permanent control, adherence, and health promoting adjustment and maintaining a supportive social network has been addressed within the case analysis.

Principles of psychological interventions found very successful with adolescents such TPB or HBM (Drator, 2006). A further discussion of the self regulatory theory and other relevant health psychology concepts such as locus of control or self efficacy can be applied to her case but are beyond the scope of this report.

Overall, In this case analysis we tried to identified possible problem and intervention for 15 year old she who newly diagnosed with type 1 diabetes. Our recommendations can improve her health, quality of life adjustment to her diagnosis and productivity.

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CHAPTER X

UTD CLASSIFICATION IN CONGENITAL URINARY SYSTEM DILATATION

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1. Introduction

It is reported that about 25% of congenital anomalies are urinary system anomalies (Isaksen, CV., Eik-Nes, SH., Blaas, HG. and Torp, SH., 2000:179). Congenital anomalies of the urinary system account for 40% of the causes of advanced renal failure in children (Seikaly, MG., Ho, PL., Emmett, L., Fine, RN., and Tejani, A., 2003:796). Dilatation in the urinary system is the most commonly detected urinary system anomaly by the ultrasonography (USG) in the antenatal period. Antenatal and postnatal surveillance of urinary tract dilatation (UTD) is important for the diagnosis and treatment of congenital anomalies of kidneys and urinary tract (CAKUT), which are one of the most common causes of renal failure in children.

There are two causes of antenatal UTD. They are transient dilatation, which is physiologic but has no clinical significance, and CAKUT(Harding, LJ., Malone, PS. and Wellesley, DG. 1999:703; Sairam, S., Al-Habib, A., Sasson S., and Thilaganathan, B., 2001:191). Congenital anomalies of the kidneys and urinary tract include abnormalities of the urinary system such as obstructive uropathy, vesicoureteral reflux (VUR), multicystic dysplastic kidney, congenital megaureter. Physiologic transient dilatation is the most common cause of UTD, with a rate of 41-88%. Other causes include ureteropelvic junction (UP) stenosis (10-30%), VUR (10-20%), ureterovesical junction stenosis (5-10%). Rare causes include multicystic dysplastic kidney, posterior urethral valve (PUV), urethral atresia, ureterocele, double ureter with ectopic ureter (Nguyen et al., 2010:217).

The most important determinant for diagnosing UTD and determining and following the ideal treatment method is the severity of the dilatation. There are several classification systems for evaluating the severity of dilatation in children. The most commonly used classifications are the anteroposterior renal pelvic diameter (APD) measurement, the Society of

Fetal Urology (SFU) classification, and the Onen and Urinary Tract Dilatation (UTD) classification (Grignon, A., Filion, R., Filiatrault D., Robitaille, P., Homsy, Y., and Boutin, H., 1986:645; Fernbach, SK., Maizels, M., Conway, JJ., 1993:478; Onen, A., 2007:200; Nguyen et al., 2014:982).

Although there is still no consensus on what classification should be made for fetal UTD, the UTD classification system is a new and multidisciplinary consensus in classifying prenatal and postnatal UTD. It was determined by the joint decision of 8 societies, including the American Society of Pediatric Nephrology (ASPN), Society for Pediatric Radiology (SPR), American Institute of Ultrasound in Medicine (AIUM), Society for Fetal Urology (SFU), Society of Radiologists in Ultrasound (SRU), Society for Maternal-Fetal Medicine (SMFM), Society for Pediatric Urology (SPU) and American College of Radiology (ACR) (Nguyen et al., 2014:982).

2. UTD classification system

This is a classification system created in 2014 by the joint decision of 8 societies from the fields of urology, radiology, pediatric nephrology, pediatric surgery, and gynecology. In this classification, seven ultrasound findings are used to define antenatal and postnatal urinary tract enlargement. These findings are APD, calyx dilatation, kidney parenchymal thickness, kidney parenchymal appearance, bladder abnormalities, ureteral abnormalities, and fetal amniotic fluid volume.

There are many nonspecific names for urinary tract enlargement: hydronephrosis, pyelectasis, pelviectasis, pelvic fullness, and pelvic enlargement. To avoid confusion, it is recommended to use only the term 'UTD' in the definition.

The AP diameter of the renal pelvis should be measured in the intrarenal region where the pelvis is widest and in the transverse plane. Pelvis measurement in the extrarenal region should not be used. The UTD Classification Committee has decided not to use the terms major and minor when defining calyx dilatation to avoid confusion. Instead, the terms central calyx instead of major calyx and peripheral calyx instead of minor calyx are used, considering their anatomical location.

The UTD classification system promotes standard descriptions of the urinary tract to avoid redundant imaging, follow-up, and anxiety. Nonetheless, a normal appearance of the urinary tract does not completely rule out urologic abnormalities. For example, renal and bladder ultrasound may be normal in VUR (Nelson, CP., Johnson, EK., Logvinenko, T. ve Chow, JS., 2014:397).

Antenatal UTD classification can be applied after the 16th week of gestation, and the classification is made especially after measuring the APD and calyx dilation. Findings are classified according to detection in early (16-27 weeks) or late (> 28 weeks) pregnancy. In the antenatal period, the normal APD should be less than 4 mm before 28 weeks and less than 7 mm after 28 weeks. Cases with antenatal UTD are classified as A1 (low risk) and A2-3 (high risk) (Table 1).

Table 1: Antenatal UTD Classification (Chow, JS., Koning, JL., Back, SJ., Nguyen, HT., Phelps, A. ve Darge, K., 2017:1110)

	NORMAL	UTD A 1	UTD A 2-3
Kidney Pelvic AP Diameter			
16-27 weeks	<4 mm	4-7 mm	≥ 7 mm
>28 weeks	<7 mm	7-10 mm	≥ 10 mm
Calyx	Normal	Normal or Central calyceal dilatation	Peripheral calyceal dilatation
Kidney Parenchymal Thickness	Normal	Normal	Decreased
Kidney Parenchymal Appearance	Normal	Normal	Not normal
Ureter	Normal	Normal	Not normal
Bladder	Normal	Normal	Not normal
Amniotic Fluid Volume	Normal	Normal	Oligohydramnios (Unidentified)

Cases classified as UTD A 1 (low-risk group) are those with an APD of 4 mm or more and less than 7 mm on ultrasonography between 16 and 27 weeks and those with an APD of 7 mm or more and less than 10 mm and with normal renal calyces or renal calyceal dilatation only in the central region from week 28 onward.

Cases classified as UTD A 2-3 (high risk) are those with an APD of 7 mm or more between 16-27 weeks and those with an APD of 10 mm or

more at 28 weeks and later, or those with at least one of the following ultrasound findings: peripheral calyceal dilatation, thinning of renal parenchyma, abnormal appearance of renal parenchyma, ureteral anomaly, bladder anomaly, unexplained oligohydramnios.

In cases with urinary dilatation in the antenatal period, USG control should be performed no earlier than 48 hours postpartum unless severe antenatal findings are present. Before 48 hours, urinary dilatation may be underestimated because of normal physiologic oliguria (Dejter, Jr SW., Gibbons, MD.,1989;667).

In a normal urinary system, where dilation is not defined in the postnatal period, the APD is less than 10 mm and there should be no pelvicalyceal or ureteral dilatation. Postnatal UTD classification is performed irrespective of the age of children. Cases with postnatal UTD are classified into three groups: UTD P1 (low risk), UTD P2 (mid risk), and UTD P3 (high risk) (Table 2).

Table 2: Postnatal UTD Classification (Chow, JS., Koning, JL., Back, SJ., Nguyen, HT., Phelps, A. ve Darge, K., 2017:1110)

	NORMAL	**UTD P1**	**UTD P2**	**UTD P3**
Kidney Pelvic AP Diameter	<10 mm	≥10-15mm	≥15mm	≥15mm
Calyx	Normal	Only central calyceal dilatation	Peripheral calyceal dilatation	Peripheral calyceal dilatation
Kidney Parenchymal Thickness	Normal	Normal	Normal	Decreased
Kidney Parenchymal Appearance	Normal	Normal	Normal	Not normal
Ureter	Normal	Normal	Not normal	Not normal
Bladder	Normal	Normal	Normal	Not normal

Cases classified as low-risk UTD P1 have an APD of 10 mm or more and less than 15 mm on the postnatal USG or only central calyx dilation. Mid-risk cases, classified as UTD P2, have an APD greater than 15 mm, dilatation of the peripheral calyces, or abnormal ureters. High-risk group cases, classified as UTD P3, are those with or without peripheral calyceal dilatation or ureteral anomaly, with or without renal parenchymal thinning, parenchymal change, or bladder change.

3. Surveillance algorithm according to UTD classification

3.1. Algorithm for antenatal surveillance

Antenatal UTD is classified into two groups with definitions of low and high risk in the UTD surveillance guide (Table 3). USG surveillance is recommended for the low-risk group at 32 weeks' gestation. If the degree of hydronephrosis on the USG does not increase, postpartum monitoring is recommended. If an increase in UTD is detected, it is recommended that pediatric nephrology and urology be consulted and close monitoring be performed at 4-6 week intervals.

Table 3: Guideline for antenatal surveillance of UTD classification system (Chow, JS., Koning, JL., Back, SJ., Nguyen, HT., Phelps, A. ve Darge, K., 2017:1114)

	UTD A1(low risk)	**UTD A2-3 (high risk)**
Antenatal Period	1 control USG at ≥ 32 weeks of gestation	Control USG at 4-6 week intervals
Postnatal Period	1. USG: between 48 hours and 1 month 2. USG: 1-6 months later	1 USG per month after the initial USG between 48 hours and 1 month *
Additional Suggestions	If there is any indication, the risk of aneuploidy should be investigated.	Consultation to departments such as pediatric nephrology, urology

*: Particular conditions, e.g. PUV or severe hydronephrosis, may require appropriate treatment.

3.2. Algorithm for postnatal monitoring

In neonates with urinary dilatation in the antenatal period, USG monitoring should be performed after the first 48 hours after birth because urinary dilatation may be underestimated due to physiologic oliguria. In case of severe antenatal findings such as suspected PUV, severe history of oligohydramnios, bilateral severe UTD, USG examination should be performed between 24 and 48 hours postnatally. Apart from these findings, the initial postnatal USG inspection should be performed between 48 hours and 1 month (Nguyen et al., 2014:991). Due to the possibility of patients not being followed up, it is suggested that the USG check can be made within 3-7 days after delivery without discharge (Aksu N et al., 2005:1258).

Table 4: Guide for postnatal monitoring of UTD classification system (Chow, JS., Koning, JL., Back, SJ., Nguyen, HT., Phelps, A. ve Darge, K., 2017:1114)

	UTD P1 (low risk)	**UTD P2 (mid risk)**	**UTD P3 (high risk)**
USG Monitoring	At 1-6 month intervals	At 1-3 month intervals	At 1-month intervals
Voiding Cystourethrography (VCUG)	Physician judgment	Physician judgment	Recommended
Antibiotic	Physician judgment	Physician judgment	Recommended
Functional Imaging	Not recommended	Physician judgment	Physician judgment

If low risk, USG monitoring is recommended at 1-6 month intervals until findings are normal. Antibiotic prophylaxis with VCUG depends on physician judgment, and functional scintigraphic imaging is not recommended. USG monitoring at 1-3 month intervals is recommended for mid risk. VCUG, antibiotic therapy, and functional scintigraphic imaging depend on physician judgment. USG monitoring, VCUG, and prophylactic antibiotic treatment are advocated at 1-month intervals in the high-risk group. Functional scintigraphic imaging is at the discretion of the physician.

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CHAPTER XI

VITAMIN B_6 PYRIDOXAL PHOSPHATE (PLP)

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1. Introduction

PLP is one of the most ancient cofactors, and it can catalyze chemical transformation, such as a transamination even without an enzyme. All animals are auxotrophic for PLP, meaning they need to supplement their diet with vitamin B6 in order to survive. PLP is actually involved in a staggering number of biochemical transformations. PLP is the cofactor derived from vitamin B6. This cofactor is very important for a number of reactions. Transamination reaction is a crucial reaction fort he metabolism of all amino acids, malate-aspartate shuttle that transfers redox equivalents, reducing equivalents between mitochondria and cytosol [Eliot and Kirsch, 2004].

Vitamin B6 known as pyridoxine. This is the molecule that we ingest when we get our Daily vitamin supplement in the body, this gets oxidized to form intermediate called pyridoxal. The active co-factor, PLP is actually the phosphorylated version of pyridoxal.This requires one molecule of ATP and the enzyme pyridoxal kinase. These enzymes are only active when the PLP cofactor is covalently bonded to a lysine residue in the active site [Sheldon and Brady, 2018].

When substrate is available, the transimination reaction occurs, in which the PLP becomes covalently bonded to the substrate, forming what is commonly known as external aldimine [Cerqueira et al.,2011]. Vitamin B6 is a necessary component in the synthesis of many different products such as Cysta thiamine, heme, niacin, histamine,serotonin epinephrine, norepinephrin, dopamine, GABA. [Dunathan,1966].

PLP-dependent enzymes in the catalysis of a wide variety of chemical reactions, with high regio- and stereoselectivity Vitamin B6 gets converted to PLP and is used as a cofactor in decarboxylation, transaminase and glycogen phosphorylase. Viatmin B6 can be found in many animal products and especially in pork, turkey, beef, bananas, potatoes, and pistachios. Deficiency in vitamin B6 can lead to a few pathologies such as sideroblastik anemi, peripheral neuropathy, convulsions, hyperirritability.

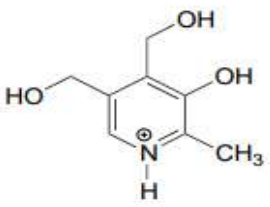
A deficiency in vitamin B6 can lead to a few pathologies such as sideroblastik anemi, peripheral neuropathy, convulsions, hyperirritability [Fernandes, 2017].

Transaminases (EC 2.6.1.X), also known as aminotransferases, are PLP-dependent enzymes responsible for the transference of an amino group from an amino donor to an acceptor (Figure 2). PLP, the cofactor, acts as the transient keeper of the amino group, being bound as a Schiff-base to a lysine residue in the active site(the internal aldimine) [Oliveira,2011].

The transamination reaction can be considered as two different half-reactions (Scheme 2). In the first half-reaction, the amine group of amine donor (either an amino acid or another amine) replaces the lysine residue in the internal aldimine, originating the external aldimine. Then, the first half of the reaction culminatesin the generation of pyridoxamine 5'-phosphate (PMP) and the corresponding ketone. In the second half-reaction, the amine group now present in PMP is transferred to the amine acceptor (ketone, keto acid or aldehyde) with the regeneration of the internal aldimine and formation of the corresponding amine, completing the catalytic cycle [Cerqueira et al., 2011].

2. Vitamin B6 Structure

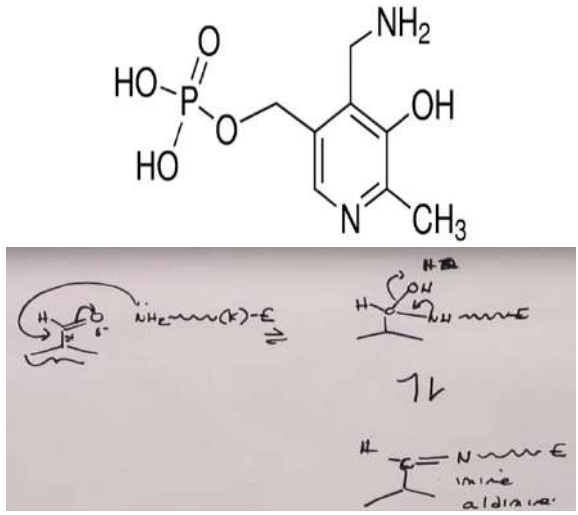
Vitamin B_6 is the cofactor. As in the case of all vitamins, inside the cell it has to be converted into the active form of the cofactor. The active form is Pyridoxal phosphate (PLP). Pyridoxal phosphate has this structure. The pyridine ring is 6; so it may or may not be protonated. So pyridoxal means that this is an aldehyde.



pyridoxine (vitamin B_6)

pyridoxal phosphate (PLP)

The second form of the cofactor is pyridoxamine. This is called PMP. It is always bound in the active site of the enzyme and it binds in the active site of the enzyme through ε amino group of a lysine. An amino group attached to a lysine, in the active site of enzyme. This ketone converted into an imine. The carbonyl is polarized, delta δ^+, delta δ^- [Ghislieri and Turner, 2014].



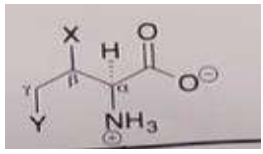
Pyridoxamine 5'phosphate (PMP)

If it count the number of protons they move around a lot in the active site. And the fact is, that it want to protonate something to make it into a better leaving group, it want to deprotonate something to make it function more like a nucleophile, or as a base, and nature has figured out how to orchestrate all the residues in the active site to do this.

It is going to have a proton transfer. This gives it a tetrahedral intermediate, or transition stage. And now what will happen is that it wants to lose a molecule of water. So again, it needs to pronate that, and what it form then is a new carbon doubly bonded to a nitrogen, rather than doubly bonded to the oxygen, that's covalently bound to the enzyme. And so, this is called an imine. And because it's an imine of an aldehyde, it's called an aldimine. So whenever it isolates the enzyme, whenever it isolate the enzyme, the pyridoxal is always covalently bound. This bond is chemically easy to hydrolyze, but it's always covalently bound. The way nature figures out how to do this is by orchestrating the active site, with acid based catalyst sitting around in the right place, to allow them to do the chemical transformation that this protein has evolved to do.

Generalizations;

a) PLP is able to mediate chemistry at the α, β and γ positions of the amino acid.



i. At α position; transamination, epimerization, decarboxylation and aldol reactions.
ii. At β position; eliminations and replacement
iii. At γ position; elimination and replacements

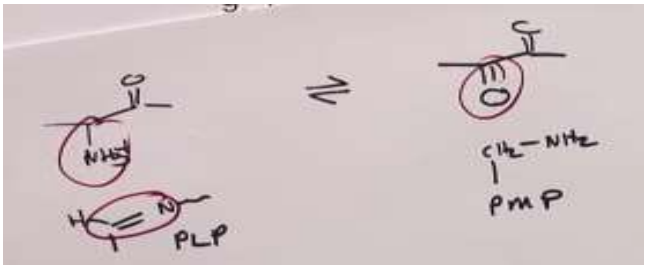
b) PLP is always covalently bound to the enzyme as a Schiffs base (imine) with an active site lysine (lys).

c) The first step is a transamination reaction with the amino acid, liberating the lys which then functions as a general acid catalyst (gac) or general base catalyst (gbc) in further steps in substrate transformation.

d) The second step in all PLP reactions is generation of a carbonion at the α carbon of the amino acid. This can be done by the removal of the proton from the α position or by decarboxylation of the aminoacid. This intermediate is the precursor that both β and γ elimination reactions and that both β and γ replacement reactions.

e) The final step in all PLP reactions is transamination to reform the schiffs base with the lysine at the active site.

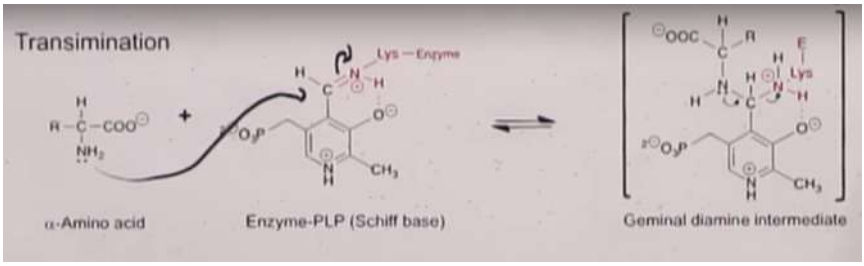
You get cleavage of the C-C bound that is loss of CO_2, that is a decarboxylation reaction. You are going to cleave the C-H bond. Amino acid are in the S configuration but for example in cell wall, in bacteria, they can be either the S or the R configuration. You can cleave this C-C bond between α and β position. This is the reverse aldol reaction.Is what happens to this C-N bond. Amino acid is going to get converted into a ketone group [Hne and Bornscheuer,2009].



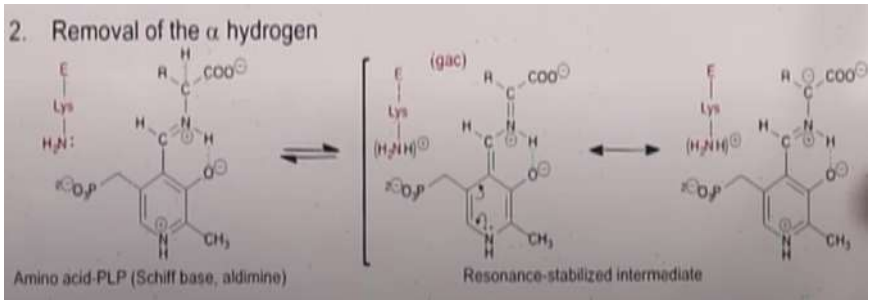
We are going to use the imine of pyrodoxial phosphate that we have in the active site of the enzyme. So this is sort of like a carbonyl and that's going to get converted into the amine, the pyridoxamine. So these are the two forms of the cofactor. So what are we going to be focusing on, is how this reaction, actually, happens, and this is the most complicated of all the pyridoxal phosphate dependent reactions.

If you look at the TCA cycle, you'll see alpha ketoglutarate. That going to interconvert with the amino acid. Pyridoxial is going to be converted into pyridoxamine. So we're going to have PLP converted into PMP. The

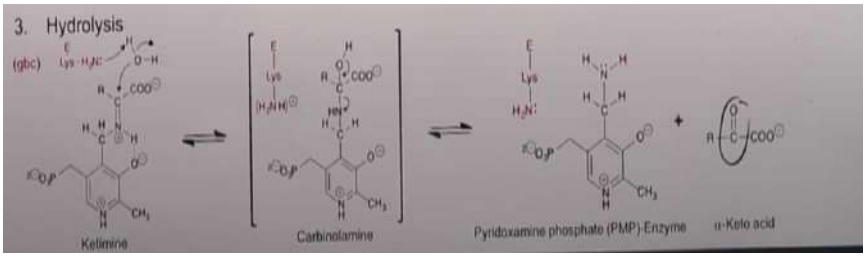
transformation; the cofactor changes its structure from an imine into an amino group. How do we think about the mechanism of these PLP enzymes? The first step; you're going to start out with an imine bound to the active site of the pyridoxal phosphate and an amino acid. So that's called a transamination reaction. So this lysine-- nature has figured out how to minimize the numbers of acid and base groups constrained in the region, the active site, where all the chemistry happens. Every pyridoxal enzyme is distinct and has additional groups in the active site.



The second step in all of these reactions is-- all amino acids have an hydrogen, that alpha hydrogen has a very high pKa. It's very hard for a normal amino acid side chain, in the active site, to remove proton, because it's not acidic enough.



3. The last step is hydrolysis ; pyridoxal is always in the imine, covalently bound. And so that's why it's that transimination, rather than a transamination. All pyridoxal enzymes go through these three, general steps.



The first step, in all these reactions is transimination. Schiff-base is pyridoxal. It's covalently bound to the lysine in the active site. There is the protonation state of this imine. Depending on what's in the active site, it could be protonated, or not protonated, if it's protonated, it enhances reactivity for nucleophilic attack. The active site is going to manipulate itself to put in the protonated state.

There is an amino acid, it has a protonated imine, and so this is the nucleophile, and it can attack the carbon of the imine to form a tetrahedral adduct. That's what transimination is, one imine to another imine. The imine that's covalently bound to the protein through pyridoxal, to an amino acid imine. That's the first step.

The second step is that ultimately, in almost all pyridoxal reactions. That α hydrogen, again, is extremely non-acidic but by complexing the amino acid to pyridoxal. This is what the function of the cofactor. It easier for a group in the active site, a general base catalyst, like lysine, can now pull off this proton to generate this intermediate. Now why is this hydrogen more acidic? Well, if you look at the structure, you can draw all kinds of resonance structures which shows that this carbanion is more stabilized, because it's attached to the pyridoxal cofactor. The key here is you can remove the alpha hydrogen, because you're able to delocalize these unpaired electrons on this carbon over the entire system. Here's the carboxylate, a pi cloud that delocalizes where these electrons are completely delocalized over the aromatic ring. This pyridine ring is planar. This is already set up so that it can delocalize over this whole system. If you look at this structure, this molecule is an imine of an alpha keto acid (exp. Oxaloacetic acid, alfa-ketoglutarate, pyruvate)

The last step in all PLP dependent transaminations is hydrolysis. The only pyridoxal phosphate requiring enzyme that goes from the aldehyde, or imine, to the pyridoxamine are these transamination reactions [Daidone et al., 2012].

3. Conclusion

The consequence of their widespread occurrence and crucial importance is that a number of them are current drug targets. For example, inhibitors of -aminobutyric acid aminotransferase are used in the treatment

of epilepsy, serine hydroxymethyltransferase has been identified as a target for cancer therapy [Oppici et al., 2013], and inhibitors of L-DOPA decarboxylase are used in the treatment of Parkinson's disease [Oppici et al., 2013]. Genetic defects affecting PLP enzymes have been also implicated in a number of diseases, including Primary hyperoxaluria type 1, which is caused by mutations in alanine-glyoxylate aminotransferase [Fenalti, 2013]. Finally, several PLP enzymes are autoantigens in autoimmune disease, for example, glutamate decarboxylase in type I diabetes and SLA/LP in autoimmune hepatitis [Paiardini, 2013].

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CHAPTER XII

EXAMINATION OF RELATIONSHIP BETWEEN INDIVIDUALS' EATING ATTITUDE BEHAVIOURS AND BODY IMAGE PERCEPTION

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1. Introduction

Eating disorders point to serious problems with eating behaviours. Behaviour is found to be abnormal because it is different than regular eating behaviours, and above all it has negative effects on the physical and mental health of the individual. It affects more women than men and it starts generally at puberty or adulthood. It is observed that behind the eating disorder there are psychological problems. Eating disorders also includes subjects such as fear from being fat, obsessions about being thin, self-esteem, depression, power, controlling himself, body image perception and obsessions about that. This points out that there is a relationship between body image perception and eating disorder. Body image perception has a relation with how one perceives his body and body parts, his idea about what is ideal and what he has and how he evaluates the distance between the two, identity and personality concepts(Zhang et al., 2021).

The physical properties of a person affects body image perception because it is an effective factor for one's self-evaluation as well as his social evaluation about himself. Body image is defined as physical appearance of one. Body image has an important role on how one perceives himself. Even though one does not have an abnormality with his appearance, if his body image is damaged then he will have his body image and self-evaluation damaged as well (Orsel et al., 2004). When one's body image perception is found to be related with being fat and passion for getting thinner, we will see eating behaviour goes in parallel this is the starting point of our research.

This research is planned for the purpose of defining eating behaviour score by the EAT-26 test comparing this score with BCS(Body-Cathexis

Scale), as well as finding how these two parameters are related with each other.

2. Material and Method

The universe of the study consists of 366 volunteer participants who do not have any psychological health problems and who meet the inclusion criteria between ages 18-56 who are members of a Private Yoga Center in Istanbul.

2.1.Research Questions

The study consists of 4 different parts: Demographic Information, EAT-26 (Eating AttitudeTest), BCS (Body Cathexis Scale) and FFQ (Food Frequency Questionnaire).Demographic Information consists of 7 questions, EAT-26 26 questions, BCS 31 questions and FFQ 34 questions. The total of the questions is 98. In the Demographic Information section, general descriptive statistics such as age, height, weight, educational status, gender is asked to participants. Exercise status is also asked in this section as it can be associated with many other data of the survey. The EAT-26, BCS and FFQ scales are internationally used valid scales. The EAT-26 scale was developed in 1982 to determine the risk of eating disorders. EAT-40, the previous version of the EAT-26 scale, was composed by Garner & Garfinkel in 1979 for the detection of Anorexia Nervosa, and then EAT-26 was developed for the detection of all kinds of eating disorders risk. The BCS Body Cathexis Scale was composed by Secard & Jourard in 1953 and adapted to Turkish society by Hovardaoğlu in 1986.

The FFQ Food Frequency Questionnaire of the National Health and Nutrition Examination Survey (NHANES) is applied to the participants which is a reliable questionnaire organized by the National Center for Health Statistics (NCHS) to evaluate the nutritional status of individuals. EAT-26 Eating Attitude Test consists of 26 questions and each item of EAT-26 is consisted of 5-point likert scale from “Always” to “Never”. The evaluation of the scoring is the total score obtained: > 20 There is a risk (there is a risk of eating attitude behavior disorder <20 No risk. Min. score is 0 points. Max. score is 78 points.

BCS Body Image Scale consists of 31 questions and each item of BCS is consisted of 5-point likert scale from “Don’t like at all” to “Like very much”. The evaluation of the scoring is the total score obtained. The BCS score for each participant is reached by dividing the total score obtained into 31. 1 point expresses strongly negative and 5 points means strongly positive body image perception. Min. score is 31 points. Max. score is 155 points.

2.2. Statistical Analysis

	Min-Max	Avg±sd
Age	18-56 years	37,40±9,16 years
Height	150-185 cm	166,12±7,74 cm
Weight	45-130 kg	68,04±14,34 kg
BMI	16,30-42,61 kg/m^2	24,58±4,48 kg/m^2
	n	**%**
Gender		
Female	313	85,5
Male	53	14,5
Marital Status		
Married	281	76,8
Single	61	16,7
Divorced	24	6,6
Educational Status		
Primary School	4	1,1
Secondary School	3	0,8
High School	48	13,1
Undergraduate	226	61,7
Graduate	85	23,2
Exercise Status		
Always	49	13,4
Usually	152	41,5
Hardly Ever	118	32,2
Never	47	12,8

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analysis. Descriptive statistical

methods (mean, standard deviation, frequency, percentage, minimum, maximum) were used while evaluating the study data. The suitability of quantitative data to normal distribution was tested by Shapiro-Wilk test and graphical analysis. Independent groups t test was used to compare normally distributed quantitative variables between two groups. One-way analysis of variance and Bonferroni corrected binary evaluations were used for comparing more than two groups of quantitative variables with normal distribution. Pearson correlation analysis was used to evaluate the relationships between quantitative variables. Statistical significance was accepted as $p < 0.05$ (Kalaycı,2010).

3. Finding

This study was conducted on a total of 366 participants with age range between 18-56 on February - March 2021 term.

Table 1. Descriptive Statistics

	Min-Max	**Avg±sd**
Age	18-56 years	37,40±9,16 years
Height	150-185 cm	166,12±7,74 cm
Weight	45-130 kg	68,04±14,34 kg
BMI	16,30-42,61 kg/m^2	24,58±4,48 kg/m^2
	n	**%**
Gender		
Female	313	85,5
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Marital Status		
Married	281	76,8
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Primary School	4	1,1
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High School	48	13,1
Undergraduate	226	61,7
Graduate	85	23,2
Exercise Status		
Always	49	13,4
Usually	152	41,5
Hardly Ever	118	32,2
Never	47	12,8

The height of participants ranges between 150-185 cm and the average is 166,12±7,74 cm. The weight range is between 45-130 kg and the average is 68,04±14,34 kg.The BMI range is between 16,30-42,61 kg/m^2 and the average is 24,58±4,48 kg/m^2.The %85,5 of participants are female (n=313), the %14,5 are male (n=53). The %76,8' (n=281) of the participants are married, %16,7 (n=61) are single, %6,6 (n=24) are divorced. The %1,1(n=4) of the participants has primary school, %0,8 (n=3) has secondary school, %13,1 (n=48) has high school, %61,7 (n=226) has undergraduate, %23 (n=85) has graduate educational status. The %12,8 (n=47) of the participants has stated "never" for their execise status, the %32,2 (n=118) "hardly ever", the %41,5 (n=152) "usually", the %13,4 (n=49) "always" (Table 1).

Table 2. Distribution of Responds for EAT-26

	Always	Usually	Often	Sometimes	Rarely	Never
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Am terrified about being overweight.	63 (17,2)	37 (10,1)	73 (19,9)	108 (29,5)	50 (13,7)	35 (9,6)
Avoid eating when I am hungry	13 (3,6)	12 (3,3)	37 (10,1)	101 (27,6)	92 (25,1)	111 (30,3)
Find myself preoccupied with food	16 (4,4)	37 (10,1)	74 (20,2)	143 (39,1)	67 (18,3)	29 (7,9)
Have gone on eating binges where I feel that I may not be able to stop.	4 (1,1)	34 (9,3)	39 (10,7)	144 (39,3)	99 (27)	46 (12,6)
Cut my food into small pieces	28 (7,7)	18 (4,9)	56 (15,3)	100 (27,3)	99 (27)	65 (17,8)
Aware of the calorie content of foods that I eat.	17 (4,6)	17 (4,6)	44 (12)	89 (24,3)	79 (21,6)	120 (32,8)
Particularly avoid food with a high carbohydrate content (i.e. bread, rice, potatoes,etc.)	17 (4,6)	26 (7,1)	53 (14,5)	102 (27,9)	99 (27)	69 (18,9)
Feel that others would prefer if I ate more	20 (5,5)	11 (3)	41 (11,2)	60 (16,4)	72 (19,7)	162 (44,3)
Vomit after I have eaten	0 (0)	1 (0,3)	1 (0,3)	5 (1,4)	18 (4,9)	341 (93,2)
Feel extremely guilty after eating	13 (3,6)	14 (3,8)	27 (7,4)	115 (31,4)	103 (28,1)	94 (25,7)
Am preoccupied with a desire to be thinner	29 (7,9)	35 (9,6)	60 (16,4)	72 (19,7)	77 (21)	93 (25,4)

Think about burning up calories when I exercise	1 (0,3)	7 (1,9)	14 (3,8)	56 (15,3)	92 (25,1)	196 (53,6)
Other people think that I am too thin	13 (3,6)	19 (5,2)	42 (11,5)	60 (16,4)	72 (19,7)	160 (43,7)
Am preoccupied with the thought of having fat on my body	20 (5,5)	27 (7,4)	60 (16,4)	91 (24,9)	89 (24,3)	79 (21,6)
Take longer than others to eat my meals.	25 (6,8)	24 (6,6)	29 (7,9)	91 (24,9)	100 (27,3)	97 (26,5)
Avoid foods with sugar in them	15 (4,1)	29 (7,9)	47 (12,8)	115 (31,4)	94 (25,7)	66 (18)
Eat diet foods	4 (1,1)	15 (4,1)	27 (7,4)	118 (32,2)	106 (29)	96 (26,2)
Feel that food controls my life	10 (2,7)	17 (4,6)	39 (10,7)	80 (21,9)	76 (20,8)	144 (39,3)
Display self-control around food	24 (6,6)	41 (11,2)	90 (24,6)	140 (38,3)	56 (15,3)	15 (4,1)
Feel that others pressure me to eat	10 (2,7)	8 (2,2)	21 (5,7)	58 (15,8)	110 (30,1)	159 (43,4)
Give too much time and thought to food	3 (0,8)	24 (6,6)	51 (13,9)	93 (25,4)	84 (23)	111 (30,3)
Feel uncomfortable after eating sweets	14 (3,8)	29 (7,9)	33 (9)	108 (29,5)	102 (27,9)	80 (21,9)
Engage in dieting behaviour	10 (2,7)	15 (4,1)	32 (8,7)	116 (31,7)	102 (27,9)	91 (24,9)
Like my stomach to be empty	8 (2,2)	12 (3,3)	38 (10,4)	113 (30,9)	81 (22,1)	114 (31,1)
Enjoy trying new rich foods	22 (6)	34 (9,3)	74 (20,2)	121 (33,1)	85 (23,2)	30 (8,2)
Have the impulse to vomit after meals.	1 (0,3)	5 (1,4)	4 (1,1)	16 (4,4)	40 (10,9)	300 (82)

The EAT-26 consists of 26 items. The scores of the participants from the scale range from 0 to 45, with an average of 9.77 ± 7.51. The internal consistency level of the items that make up the scale was found to be 0.769 (Table 2).

Table 3. Eating Attitude Behaviour Disorder Risk Evaluation Depending on EAT-26 Scale

	n	%
No Risk (<20)	334	91,3
Risky (≥20)	32	8,7

According to the scores of the EAT-26 scale, 91.3% of the participants (n = 334) had no risk of eating attitude behavior disorder, while 8.7% (n = 32) had (Table 3).

Table 4. Distribution of Responds for the BCS

	Don't like at all	Don't like	Indecisive	Like	Like very much
	n (%)	n (%)	n (%)	n (%)	n (%)
My feeling/thought about my hair :	12 (3,3)	53 (14,5)	93 (25,4)	162 (44,3)	46 (12,6)
My feeling/thought about the color of my face :	7 (1,9)	40 (10,9)	83 (22,7)	192 (52,5)	44 (12)
My feeling/thought about my appetite :	47 (12,8)	83 (22,7)	95 (26)	129 (35,2)	12 (3,3)
My feeling/thought about my hands :	9 (2,5)	57 (15,6)	79 (21,6)	162 (44,3)	59 (16,1)
My feeling/thought about my nose :	7 (1,9)	72 (19,7)	65 (17,8)	159 (43,4)	63 (17,2)
My feeling/thought about my physical power:	13 (3,6)	69 (18,9)	80 (21,9)	162 (44,3)	42 (11,5)
My feeling/thought about my urine&stool patterns:	14 (3,8)	37 (10,1)	65 (17,8)	184 (50,3)	66 (18)
My feeling/thought about my muscle power :	21 (5,7)	92 (25,1)	84 (23)	139 (38)	30 (8,2)
My feeling/thought about my waist :	40 (10,9)	101 (27,6)	80 (21,9)	118 (32,2)	27 (7,4)

My feeling/thought about my energy level :	38 (10,4)	64 (17,5)	94 (25,7)	141 (38,5)	29 (7,9)
My feeling/thought about my back :	40 (10,9)	98 (26,8)	76 (20,8)	133 (36,3)	19 (5,2)
My feeling/thought about my ears :	2 (0,5)	20 (5,5)	42 (11,5)	200 (54,6)	102 (27,9)
My feeling/thought about my age :	6 (1,6)	34 (9,3)	62 (16,9)	177 (48,4)	87 (23,8)
My feeling/thought about my jaw :	6 (2,1)	25 (8,6)	57 (19,5)	204 (69,9)	0 (0)
My feeling/thought about my body structure :	18 (4,9)	72 (19,7)	97 (26,5)	149 (40,7)	30 (8,2)
My feeling/thought about my profile :	5 (1,4)	45 (12,3)	80 (21,9)	191 (52,2)	45 (12,3)
My feeling/thought about my height :	10 (2,7)	69 (18,9)	57 (15,6)	170 (46,4)	60 (16,4)
My feeling/thought about the sensitivity of my senses:	7 (1,9)	41 (11,2)	69 (18,9)	183 (50)	66 (18)
My feeling/thought about my endurance for the ache :	23 (6,3)	44 (12)	61 (16,7)	158 (43,2)	80 (21,9)
My feeling/thought about my arms :	19 (5,2)	66 (18)	68 (18,6)	167 (45,6)	46 (12,6)
My feeling/thought about the shape of my eyes :	7 (1,9)	21 (5,7)	38 (10,4)	188 (51,4)	112 (30,6)
My feeling/thought about my digestive system :	26 (7,1)	59 (16,1)	73 (19,9)	156 (42,6)	52 (14,2)
My feeling/thought about the shape of my teeth:	31 (8,5)	64 (17,5)	53 (14,5)	160 (43,7)	58 (15,8)
My feeling/thought about my teeth :	18 (4,9)	48 (13,1)	61 (16,7)	177 (48,4)	62 (16,9)
My feeling/thought about my sleeping patterns :	41 (11,2)	82 (22,4)	78 (21,3)	128 (35)	37 (10,1)
My feeling/thought about my voice :	20 (5,5)	57 (15,6)	96 (26,2)	140 (38,3)	53 (14,5)

My feeling/thought about my health :	5 (1,4)	39 (10,7)	106 (29)	175 (47,8)	41 (11,2)
My feeling/thought about my knees :	24 (6,6)	61 (16,7)	81 (22,1)	163 (44,5)	37 (10,1)
My feeling/thought about my posture :	32 (8,7)	94 (25,7)	81 (22,1)	134 (36,6)	25 (6,8)
My feeling/thought about my weight :	60 (16,4)	118 (32,2)	75 (20,5)	89 (24,3)	24 (6,6)
My feeling/thought about my resistance for disease:	19 (5,2)	49 (13,4)	68 (18,6)	181 (49,5)	49 (13,4)

The BCS consists of 31 items. The scores of the participants from the scale range from 1 to 4.9, with an average of 3.43 ± 0.51. The internal consistency level of the items that make up the scale was found to be 0.892 (Table 4).

Table 5. Comparison of EAT-26 and BCS Scores According to Descriptive Statistics

		EAT-26	**BCS**
Age	**r**	-0,005	0,184
	p	**0,923**	**<0,001***
BMI	**r**	0,017	-0,187
	p	**0,742**	**<0,001***
		Avg±sd	**Avg±sd**
Gender			
Female		10,32±7,79	3,41±0,51
Male		6,53±4,37	3,52±0,48
[a]t		**5,092**	**-1,394**
p		**<0,001***	**0,164**
Marital Status			
Married		9,55±7,34	3,45±0,46
Single		10,39±8,76	3,33±0,68
Divorced		10,71±5,95	3,39±0,46

[b]F	**0,516**	**1,440**
p	**0,598**	**0,238**
Educational Status		
High School and below	8,49±6,93	3,49±0,54
Undergraduate	9,97±7,55	3,41±0,5
Graduate	10,06±7,75	3,44±0,49
[b]F	**0,941**	**0,595**
p	**0,391**	**0,552**
Exercise Status		
Always	13,59±8,82	3,69±0,49
Usually	10,36±7,49	3,46±0,50
Hardly ever	8,22±7,05	3,35±0,50
Never	7,74±5,3	3,24±0,44
[b]F	**7,777**	**8,428**
p	**<0,001***	**<0,001***

r=Pearson correlation coefficient [a]Independent groups t test [b] One Way ANOVA
*p<0,05

There was no statistically significant relationship between the participants' ages and EAT-26 scores (p> 0.05). A statistically significant positive correlation at the level of 0.184 was found between the participants' ages and the BCS scores (r = 0.184, p <0.001). There was no statistically significant relationship between BMI values and EAT-26 scores of the participants (p> 0.05). A statistically significant negative correlation was found between the BMI values and BCS scores of the participants at the level of 0.187 (r = -0.187, p <0.001).No statistically significant difference was found in terms of EAT-26 scores according to the gender of the participants (p <0.001). Women's scores are higher than men's scores. No statistically significant difference was found in terms of BCS scores according to the gender of the participants (p> 0.05). There was no statistically significant difference in terms of EAT-26 and BCS scores according to the marital status of the participants (p> 0.05). No statistically significant difference was found in terms of EAT-26 and BCS scores according to the educational status of the participants (p> 0.05). A statistically significant difference was found in terms of EAT-26 scores according to the frequency of exercise of the participants (p <0.001). As a result of the evaluations performed using the Bonferroni test, it was found

that the scores of those who stated that they always exercised were higher than those who stated that they did usually or hardly ever and never did (p = 0.045, p <0.001, p = 0.001, respectively). There was no significant difference between other exercise frequencies (p> 0.05) (Table 5).

A statistically significant difference was found in terms of BCS scores according to the frequency of exercise (p <0.001). As a result of the evaluations performed using the Bonferroni test, it was found that the scores of those who stated that they always exercised were higher than those who stated that they did it usually or hardly ever and never did (p = 0.025, p <0.001, p <0.001, respectively). It was determined that the scores of those who stated that they exercised usually were higher than those who stated that they never did (p = 0.046). There was no significant difference between other exercise frequencies (p> 0.05).

Table 6. Relationship Level Between EAT-26 and BCS Scores

		EAT-26
BCS	r	-0,100
	p	**0,056**

r=Pearson correlation coefficient

There was a very weak and negative relationship between the participants' EAT-26 scores and the BCS scores (r = -0.100, p> 0.056) (Table 6).

4. Discussion

In our study, which is a descriptive and cross sectional research, we investigated the relationship between eating attitude behaviors and body image perception by using internationally used and confidential scales. In order to achieve reliable results of through our study, we paid attention to assure sufficient number of samples and chose our scales meticulously. We have also been throughly careful about the correct scoring and interpretation of the scores obtained from the test results. Body image perception includes how the individual perceives his / her own body in a general and short definition, and is measured by Body Cathexis Scale (BCS) worldwide. The Body Cathexis Scale was composed by Secard & Jourard in 1953 and adapted to Turkish society by Hovardaoğlu in 1986 (Demir and Bilgin, 2021).

As the correct perception of body weight is the consistency between the perceived and measured body weight of the person, inaccurate perception of body weight makes individuals more concerned with having slim body images and dieting. Having an impaired and negative body image and not having an idealized weak body can lead people to aggressive and

unconscious diets, and the desire to lose weight, which is subliminally based on body image perception disorder indeed, can cause eating disorders. So, supports our “there is a relationship between body image perception and eating attitudes” and “both disorders are linked” hypothesis.

Eating disorder is accompanied by psychological and physiological problems in the individual, which occurs with the occurrence of visible disruptions and disorders in the individual's eating attitudes and behaviors and causes behavioral disorders in the individual. In clinical studies, it has been observed that individuals with eating disorders started dieting before eating disorder behavior and behavior began (Ogur et al.,2016). Studies conducted in recent years; Not only one reason in eating disorders, but also social conditions such as biological and psychological predisposition, family and business life, and multiple perceptions such as body perceptions that they consider their body too big and fat play a role. At the beginning of these, individuals' fear of gaining weight and being fat is excessive, there is an excessive obsession with slimming and thinning (Costa et al.,2019) The eating attitudes was measured by EAT-26, which is an internationally valid scale also, was developed in 1982 to determine the risk of eating disorders. EAT-40, the previous version of the EAT-26 scale, was composed by Garner & Garfinkel in 1979 for the detection of Anorexia Nervosa, and then EAT-26 was developed for the detection of all kinds of eating disorders risk.

In our study, where we investigated the relationship between eating attitude behaviors and body image perception, we would like to share the following remarkable data that we think may contribute to future studies as a result of examining these scales and their relationship with other descriptive statistics. A number of data from the USA, Italy and Australia have shown that 13% of women and 6% of men have eating disorders such as Anorexia Nervosa, Binge Eating, Bulimia Nervosa.(Stice et al., 2021) In a study conducted in the western provinces of Turkey, the probability of having an eating disorder was found to be 9.5%(Ünsal et al., 2010). According to the scores of the EAT-26 scale through our analysis, 91.3% of the participants (n = 334) had no risk of eating attitude behavior disorder, while 8.7% (n = 32) had. So the eating disorder risk was found 8.7%. Therefore, the percentage we found in our analysis, is consistent with both foreign and domestic literature.

In our study, a statistically significant positive correlation at the level of 0.184 was found between the participants' ages and the BCS scores ($r = 0.184$, $p < 0.001$). Although many studies have been conducted on body image perception in youth and adolescence, I did not find any striking findings about body image perceptions of elderly individuals. Therefore, the positive correlation found in our correlation analyses between age and

BCS score can be a starting point for future studies. This findings bring with it the thought even if exercising is usually a sign of good health and is a recommended activity, the risk turning into an obsession may occur. As we shared above, the risk of eating behavior disorder has been observed especially in individuals who do aesthetic sports. Eating disorders may develop in individuals who exercise excessively due to weight loss obsession.

Following this result, we would like to share the information that individuals who do exercise have higher BCS scores. According to our analysis, a statistically significant difference was found in terms of BCS scores according to the frequency of exercise ($p < 0.001$). As a result of the evaluations performed using the Bonferroni test, it was found that the scores of those who stated that they always exercised were higher than those who stated that they did it usually or hardly ever and never did ($p = 0.025$, $p < 0.001$, $p < 0.001$, respectively). It was determined that the scores of those who stated that they exercised usually were higher than those who stated that they never did ($p = 0.046$). There was no significant difference between other exercise frequencies ($p > 0.05$).

In a randomized control study in which the effects of exercise training on mental health and well-being were investigated and compared on individuals with sedentary life, it was observed that the exercises performed on the participants positively affected the participants' quality of life, depression and body image. In particular, resistance exercises have been found to further improve body image perception.(Taşpınar et al., 2014). The relationship between eating attitudes and body image perception, which is the starting point of the study, was measured by EAT-26 and BCS tests, and a very weak negative relationship was found in accordance with our initial hypothesis. Although the EAT-26 test, developed differently from the EAT-40 test, claims to measure the risk of all kinds of eating disorders, when the questions are examined, it is seen that it is still closer to measuring the risk of Anorexia Nervosa. I believe it would be beneficial increasing the sample size and adding different scales that can measure nutrition habits to examine these cases for future studies.

Since the concepts of body perception and self esteem generally occur during adolescence, nutritional education should start from childhood and adolescence. The important thing is that physical and mental health should be in good health as a whole, not that the weak is beautiful, but to instill a positive body perception in one's own healthy body composition both socially and personally. At the social level, children and students should be educated about body perception and healthy nutrition, and awareness should be created in media that can affect people's body perception such as big brands, television programs, advertisements, social media.

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CHAPTER XIII

COMPARISON OF EATING ATTITUDES AND BEHAVIORS BETWEEN OBESE AND NON-OBESE FEMALE INDIVIDUALS

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1. Introduction

Obesity is defined by the World Health Organization (WHO) as abnormal or excessive fat accumulation in the body as disrupting health. Mild overweight and obesity leads to adverse metabolic effects on blood pressure, cholesterol, triglyceride, and insulin resistance. High body mass index (BMI) is an important risk factor for non-contagious diseases (cardiovascular, diabetes, musculoskeletal diseases, and some types of cancer) (Hajian-Tilaki, 2006). In 2016, World Health Organization determined that more than 1.9 billion adults aged 18 and over were overweight or obese, of which 650 million were obese. It isreported that 39% of the adult population in the world were slightly overweight and 13% were obese in 2014. The prevalence of obesity had increased more than double worldwide between 1980 and 2014. According to the data of Nutrition and Health Survey of Turkey- 2010 (TBSA2010), it has been reported that while the prevalence of obesity was 30.3% among all the adults in Turkey, the prevalence of mild overweight was 34.6% (Hajian-Tilaki, 2006). It has been stated that the increase in the prevalence of obesity in many countries cannot be attributed only to the genetic factors, instead, environmental changes interacting with the biological structure lie behind the obesity pandemic. Eating attitude is the tendency of a person forming the behavior, emotion, and thoughts of eating and nutrition (Yılmaz, 2017). Eating behavior is also related to emotional life and it is not only to ensure the biological and physiological development of the person (Semiz et al.,2013). In addition to physical hunger, psychological reasons also affect a person's desire to eat.In order to have a positive eating attitude, it is necessary to adopt adequate, balanced, thus, healthy eating habits. The positive eating attitudes acquired in pre-school period in children lead also in the future (Ünlü et al.,2011). However, poor and

unhealthy eating attitudes are also the main factors revealing eating disorders in their future lives (Batıgün et al., 2006).The present study is planned to determine the eating attitudes and behaviors of overweight/non-overweight women between the ages of 19 and 65 in order to evaluate the eating disorders and the relationship between BMI and some anthropometric measurementLütfen yazınızı bu boş şablona kopyalayıp yapıştırınız. Düzelttikten sonra web sayfasına yükleyiniz.

2. Material and Method

2.1. Study Design and Participants

After the approval of the Ethics Committee with date 29.05.2019 and KAEK Decision No: 1031, this study was conducted on 200 overweight or non-overweight female individuals between 19 and 65 years old who admitted to a private clinic, interviewed face to face. The data is collected by the eating attitude test (EAT-26) and eating habits. A data collection form was used for participants' sociodemographic characteristics including age, employment status, any health problems in the family, and the use of any medication regularly used upon the recommendation of the doctor were questioned as well as their anthropometric measurements (body weight and height). Socio-economic status of individuals was not mentioned.

2.2.The Eating Attitude Test (EAT-26) Scale

The Eating Attitude Test (EAT-40), originally in English, is an assessment scale based on self-report developed by Garner and Garfinkel (Garner and Garfinkel, 1976) in 1979 to measure the symptoms of anorexia nervosa and bulimia nervosa. In clinical evaluation, besides providing the detailed information for the determination of the individuals with eating disorders, it also determines the changes that occur as a result of the treatment. On the other hand, the scale is a screening tool that is also used to identify individuals with anorexia nervosa previously undiagnosed in populations with a high risk of disease (Gören, 2015). EAT-26 Eating Attitude Test consists of 26 questions and each item of EAT-26 is consisted of 5-point likert scale from "Always" to "Never". The evaluation of the scoring is the total score obtained: > 20 There is a risk (there is a risk of eating attitude behavior disorder), < 20 No risk.Min. score is 0 points. Max. score is 78 points.

2.3. Sociodemographic Characteristics and Anthropometric measurements

Sociodemographic characteristics including age, employment status, and the use of any medication regularly used upon the recommendation of the doctor by a data collection form; anthropometric measurements such as body weight and height was measured. Body mass index (BMI) was

calculated with weight/(height)^2 formula. According to the World Health Organization (WHO) BMI classification was as: BMI <18.5 kg/m^2 as underweight; 18.5-24.0 kg/m^2 as normal body weight;25-29.9 kg/m^2 as overweight;>30 kg/m^2 as obese.

2.4. Statistical Analyses

NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) program was used for statistical analyses. While the study data were being evaluated,besides descriptive statistical methods (mean, standard deviation, median, frequency,ratio, minimum, maximum), Mann Whitney U test was used for the comparison of the variables that did not show a normal distribution in the comparison of quantitative data. Pearson chi-square test and Fisher's Exact test were used to compare qualitative data. Significance was evaluated at p <0.05 levels (Karagöz,2014).

3. Results

The weight measurements of the cases ranged from 40 to 114 kg, with an average of 63.06 ± 11.97 kg, their height ranging from 143 to 176 cm, and the average was found as 163.47 ± 6.11 cm. their BMI measurements varied between 15,6 and 48,2 kg/m^2 and the average was found to be 23.65 ± 4.64 kg/m^2. Of the cases, 8% (n = 16) were underweight, 62.5% (n = 125) were normal weight, 21% (n = 42) were overweight, 6% (n = 12) were obese, 1.5% of them (n = 3) were 2nd degree obese, and 1% (n = 2) were 3rd degree obese. Of the cases, 45.5% (n = 91) were employed, 26.5% (n = 53) had a chronic disease, 34.5% (n = 69) had a chronic disease in their family, and 25.5% (n = 51) were observed to use drugs regularly.

Table 1. Distribution according to the feeding habits

No. of main meals	*Min-Max (Median)* *Mean±Sd*
No. of snacks	*Min-Max (Median)* *Mean±Sd*
Consumption habits	**Morning** **Noon** **Evening** **Snacks**
Home	**Morning** **Noon** **Evening** **Snack**
Out of home	**Morning** **Noon**

	Evening
	Snack
Meal skipping	**Yes**
	No
	Sometimes
Skipped meal (n=170)	**Morning**
	Noon
	Evening
Reason for skipping meal (n=170)	**Insufficient time**
	Loss of appetite
	Absence of ready-to-eat meals
	Desire to lose weight
	Not having such a habit
	Other
Points considered in food consumption	**Easy to prepare**
	Cooking method (Grilled, fried, boiled)
	Economic
	Saturating
	Being delicious

·***More than one option is marked***

The number of main meals of the subjects included in the study ranged from 1 to 3, the average number of snacks was 2.54 ± 0.52, the number of snacks ranged from 0 to 4, and the average was found to be 1.17 ± 0.88. Of the subjects, 86.5% (n = 173) consumed the morning meal, 74.5% (n = 149) consumed the lunch, 97% (n = 194) consumed the evening meal and 72.5% (n = 145) consumed snacks. When the meals consumed at home are examined, 72% of the subjects (n = 144) stated that they consumed the morning meal, 28.5% (n = 57) had lunch, 87% (n = 174) had the evening meal, 35.5% (n = 71) stated that they consumed snacks. When the meals consumed outside the home were examined, 14% (n = 28) of the subjects had morning meal, 46.5% (n = 93) lunch, 10.5% (n = 21) evening meal, and 27% (n = 54) consumed snacks (Table 1).

Table 2. Assessment of Internal Consistency of Eating Attitudes Test (EAT-26)

	No. of items	**Cronbach's Alpha**	**Eating behavior**	
			Normal	**Abnormal**

EAT-26	26	0.848	137 (68.5)	63 (31.5)

EAT scoring; less than 20 is normal; >=20 abnormal

Internal consistency of the eating attitudes test (EAT-26) of the cases was determined as α=0.848. Abnormal eating behavior was observed in 31.5% (n=63) of thecases (Table 2).

Table 3. Assessment of Eating Habits According to Demographic Characteristics

		Eating Behavior		
		Normal (n=137)	**Abnormal (n=63)**	***p***
Age (year)	*Min-Max (Median)*	19-65 (31)	19-64 (35)	***[a]0,612***
	Mean±Sd	33.92±11.53	36.30±14.34	
BMI (kg/m^2)	*Min-Max (Median)*	15.6-36.5 (22.76)	17.7-48.2 (23.46)	***[a]0,039****
	Mean±Sd	23.11±4.11	24.82±5.48	
	Weak	14 (10.2)	2 (3.2)	
	Normal weight	88 (64.2)	37 (58.7)	
	Overweight	26 (19.0)	16 (25.4)	
	1st degree obese	7 (5.1)	5 (7.9)	
	2degree obese	2 (1.5)	1 (1.6)	
	3rd degree obese	0 (0.0)	2 (3.2)	
Employment Status	**No**	70 (51.1)	39 (61.9)	***[b]0,154***
	Yes	67 (48.9)	24 (38.1)	
Chronic Disease	**No**	104 (75.9)	43 (68.3)	***[b]0,254***
	Yes	33 (24.1)	20 (31.7)	
Chronic disease in the family	**No**	90 (65.7)	41 (65.1)	***[b]0,932***
	Yes	47 (34.3)	22 (34.9)	
Drug use	**No**	103 (75.2)	46 (73.0)	***[b]0,744***

Yes	34 (24.8)	17 (27.0)

[a]Mann Whitney U Test *[b]Pearson Chi-Square Test* **p<0,05 **p<0,01*

The BMI value of the subjects with abnormal eating behavior was found to be significantly higher than the subjects with normal eating behavior (p = 0.039; p <0.05) (Table 3).

Table 4. Assessment of Eating Habits According to Feeding Habits

			Eating Behavior	
		Normal (n=137)	**Abnormal (n=63)**	***p***
No. of eating meals	*Min-Max (Median)*	2-3 (3)	1-3 (3)	***[b]0,771***
	Mean±Sd	2.55±0.5	2.51±0.56	
No. of eating snacks	*Min-Max (Median)*	0-3 (1)	0-4 (1)	***[b]0,503***
	Mean±Sd	1.14±0.90	1.24±0.84	
Consumption habits	**Morning**	114 (83.2)	59 (93.7)	***[b]0,045****
	Noon	107 (78.1)	42 (66.7)	***[b]0,085***
	Evening	134 (97.8)	60 (95.2)	***[c]0,382***
	Snack	96 (70.1)	49 (77.8)	***[b]0,257***
Place where the meals are consumed				
Home	**Morning**	94 (68.6)	50 (79.4)	***[b]0,116***
	Noon	38 (27.7)	19 (30.2)	***[b]0,725***
	Evening	120 (87.6)	54 (85.7)	***[b]0,714***
	Snack	42 (30.7)	29 (46.0)	***[b]0,035****
Out of home	**Morning**	19 (13.9)	9 (14.3)	***[b]0,937***
	Noon	73 (53.3)	20 (31.7)	***[b]0,005*****
	Evening	12 (8.8)	9 (14.3)	***[b]0,236***
	Snack	39 (28.5)	15 (23.8)	***[b]0,491***
Skipping meals	**Yes**	55 (40.1)	28 (44.4)	***[b]0,848***
	No	21 (15.3)	9 (14.3)	
	Sometimes	61 (44.5)	26 (41.3)	

Skipped meal (n=170)	**Morning**	40 (34.5)	12 (22.2)	[b]***0,028****
	Noon	71 (61.2)	34 (63.0)	
	Evening	5 (4.3)	8 (14.8)	
Reason of skipping meals(n=170)	**Insufficient time**	53 (45.7)	23 (42.6)	[b]***0,705***
	Loss of appetite	48 (41.4)	19 (35.2)	[b]***0,442***
	Absence of no ready-to-eat meal	31 (26.7)	7 (13.0)	[b]***0,045****
	Desire to lose weight	17 (14.7)	14 (25.9)	[b]***0,076***
	Absence of habits	18 (15.5)	9 (16.7)	[b]***0,849***
	Other	7 (6.0)	7 (13.0)	[c]***0,142***
Points considered infood consumption	**Easy to prepare**	105 (76.6)	42 (66.7)	[b]***0,138***
	Cooking method (Grilled, fried, boiled)	78 (56.9)	41 (65.1)	[b]***0,276***
	Economic	56 (40.9)	36 (57.1)	[b]***0,032****
	Being delicious	124 (90.5)	51 (81.0)	[b]***0,058***
	Taste, consistency and color	109 (79.6)	46 (73.0)	[b]***0,303***
	Absence of additives	82 (59.9)	46 (73.0)	[b]***0,072***
	Being low-fat	84 (61.3)	43 (68.3)	[b]***0,344***
	Low in calories and high in nutritional value	63 (46.0)	39 (61.9)	[b]***0,036****
	Being an organic food	72 (52.6)	35 (55.6)	[b]***0,693***
	Consuming herbal foods	67 (48.9)	29 (46.0)	[b]***0,706***
	Generally home consumption	99 (72.3)	43 (68.3)	[b]***0,562***

[a]Mann Whitney U Test Test
[b]Pearson Chi-Square
[c]Fisher's Exact Test
**p<0,05*
***p<0,01*

The rate of consuming the morning meal of the subjects with abnormal eating behavior was found to be statistically significantly higher than the subjects with normal eating behavior (p = 0.045; p

<0.05). The rate of consuming lunch outside the home was found to be statistically significantly lower in patients with abnormal eating behaviors than those with normal eating behaviors ($p = 0.005$; $p < 0.01$). The rate of skipping the evening meal in the patients with abnormal eating behavior was found tobe higher than those with normal eating behavior ($p = 0.028$; $p < 0.05$). The rate of the subjects answered as the absence of ready-to-eat meals as the reason for skipping meal with abnormal eating behavior was found to be statistically significantly lower than those with normal eating behavior ($p = 0.045$; $p < 0.05$). The ratio of the cases with abnormal eating behaviors paying attention to being economical in food consumption was found to be significantly higher than the subjects with normal eating behaviors ($p = 0.032$; $p < 0.05$). The ratio of patients with abnormal eating behaviors for paying attention to low calorie and high nutritional values was found to be significantly higher than the patients with normal eating behaviors ($p = 0.036$; $p < 0.05$) (Table 4).

4. Discussion

Obesity is the most common nutritional public health problem encountered in the society. Struggling with obesity actually means preventing many diseases caused by obesity. At the present time, the prevalence of obesity is increasing rapidly in the world every year. Many organizations all over the world, especially the World Health Organization, develop and lead various projects regarding gaining adequate and balanced nutritional habits in struggling with obesity and encouraging a lively life (Aslan and Cengiz, 2007).

The ages of the individuals participating in the present study varied between 19 and 65 years old, and the average age was found to be 34.67 ± 12.49 years. In a study conducted on 218 women regarding depression, self-perception and eating attitudes of obesity, the mean age was found as 44.8 ± 11.56 years (Engin, 2014). The present study was conducted among a wide range of overweight or normal-weight individuals, who applied to a private clinic for any purpose. In the study examining the relationship between weight and eating behavior of the individuals, the mean age was found to be compatible with the literature.

In a study investigating the eating attitudes, dietary intakes, and mild obesity levels of French families, a negative correlation was found between energy consumption($p \leq 0.001$) and carbohydrate intake ($p \leq 0.001$) and a positive correlation was found with energy consumption and protein intake ($p \leq 0.001$) inwomen having an average age of 40.4 years and a BMI of 23.6 ± 4 kg/m². In the studies, it was found that women, who were housewives or had an irregular working life, had high risk of being obese. Factors such as a sedentary lifestyle, a decrease in

energy expenditure, a slowdown in basal metabolic rate as the age progresses, and the fact that women were more desk-bound, increased the risk of obesity in women (Helen, 2004). Healthy nutrition depends on the daily eating attitudes and behaviors of the individuals. In order to gain correct eating habits, it is necessary to determine the stimuli causing unhealthy nutrition and then to conduct the treatment on behavior change. Eating disorders threaten public health around the world, especially in western countries. Eating attitude test is a screening tool for eating attitude and behavior disorders. Scores of 20 or more in this test are indicative for eating disorders. Clinically, the eating attitude test can detect the disease in the individual, but also determines the susceptibility level of the individual to eating disorders (Akbulut and Özmen, 2007). When the meals consumed at home were examined, 72% of the subjects stated that they consumed the morning meal, 28.5% consumed lunch, 87% consumed evening meal, and 35.5% consumed snacks. When the meals consumed outside the home were examined, 14% of the subjects stated that they consumed morning meal, 46.5% had lunch,10.5% had evening meal, and 27% had a snack. In the treatment of obesity, meal frequency and the order of the meals are also important. It is thought that regulation of the number of meals as 4-6 meals will prevent excessive food intake and snacks and reduce food intake in later periods (Yardımcı and Özçelik, 2010). In addition, it is highlighted that at least three meals a day should be consumed in order for the basal metabolism to work properly (Mattson, 2005). However, there are few studies showing how the meal frequency affects health (Song et al.,2005).

Of the cases participated in the study, 41.5% stated that they skipped meals, 15% did not skip meals, and 43.5% sometimes skipped meals. Among the subjects who skipped meals, 30.6% stated that they skipped the morning meal, 61.8% skipped lunch, and 7.6% skipped evening meal. In a study conducted on American adults, the relationship between BMI value and breakfast consumption was examined. At the end of the study, it was observed that people with the habit of consuming breakfast had low rate of being overweight and obese(Yılmaz, 2010). In another study, the results were similar to the results in this study, and it was determined that the most skipped meals were breakfast and lunch (Mattson, 2005). Although itwas stated for the study that skipping meals was a factor increasing the risk of obesity and that the basal metabolic rate and energy expenditure could decrease depending on the meal skipped, the thermal response due to diet may also decrease, however, the results of other studies on the matter are not clear. In addition, it was stated that skipping meals could lead to an increase in hunger and more energy intake in the next meal (Wright and Louris, 2012).

Of the individuals participating in the this study, 73.5% stated that they pay attention to food consumption to be easy to prepare, 59.5% pay attention to the cooking method, 46% to being economical, 72.5% to be saturating, 87.5% to be delicious, 77.5%to its taste, consistency, and color, 64% to the absence of additives, 63.5% to the low fatcontent, 51% to low calorie, high nutritional value, 53.5% to be organic food, 48% to consuming herbal foods, and 71% to generally consuming meals at home. When a study conducted was considered, 41.4% of individuals stated that they did not eat regularly, 53.6% of them consumed excessively junk food, and 70.7% consumed foods with high calories. Thus, the relationship between the dietary habits of the individuals (irregular diet, high-calorie, fat- and sugar-containing processed foods) and obesity is shown (Kundakçı and Hovardaoğlu, 2005). Since nutrition has a psychological aspect as well as a physiological aspect, eatingdisorders have led to the need for discussing the psychological aspect of nutrition today (Aydemir and Köroğlu, 2000). Eating Attitude Test (EAT-26), which is used in screening and evaluating the eating attitudes, plays an important role by allowing the individuals to answer their eatinghabits in the most appropriate form of each item (Ulaş et al., 2013). The internal consistency of the Eating Attitude Test (EAT-26) of the subjects included in the study was found to be $\alpha = 0.848$. It was observed that 31.5% of the caseshad abnormal eating behavior. In a similar study conducted on 384 individuals, the rate of eating disorders was found as 4.2% and the mean score of the eating attitude test was found as 14.8 ± 7.4 (Ulaş et al., 2013). In another study conducted on 600 university students, the mean eating disorder eating test score was found as 60.32 ± 22.1 (Köroğlu,2019). The BMI value of the subjects with abnormal eating behavior was found to be significantly higherthan the subjects with normal eating behavior ($p = 0.039$; $p < 0.05$). In the literature, a positive correlation was found between BMI values and eating attitude scores in obese individuals in the results of a study examining the eating attitudetest score distributions of individuals with different age and body mass indexes ($r = 0.39$,$p = 0.000$) (Şengül and Hekimoğlu, 2005). As the body mass index of individuals increased, it was considered that the significant increase in the scores obtained from the eating attitude scale could cause the eating attitude disorder of the individuals in addition to the factors such as hormonal and genetic reasons causing obesity. Thus, implementation of this test in obese individuals aswell as the anorexia and bulimia nervosa patients will help to plan their treatment.

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CHAPTER XIV

STEM CELLS CLASSIFICATION AND ROLES ON SKIN WOUND HEALING

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1. Introduction

Factually, many human tissue have ability to repair their damages. The reason is these tissues possess specific type of cells called "Stem Cells", these unspecialized cells can differentiate into specific tissues or organs (Simón and Pellicer, 2007; Dupta, 2009; Hongbao et al., 2010). Also, these cells can make up the different types of human tissues like nerves, bone, muscles, skin, and other organs (Nikolic et al. 2009; Hongbao et al., 2010; Sharma et al., 2014). However, most organs in our bodies contain a population of stem cells that could have a potential to repair many injuries (Simón and Pellicer, 2007; Hongbao et al., 2010; Sharma et al., 2014). Likewise, during the normal development, these cells restore their damaged and worn-out tissues by some normal processes (Nikolic et al. 2009). For instance, the epithelial tissue contains a normal population of stem cells which are administrator for their generation and continuous regeneration (Ojeh et al., 2015). These tissues are termed as "Self-renewing tissues" such as, skin, hair follicle, blood, lung, liver, *etc.* These tissues and organs contain stem cells that are called adult stem cells which serve to maintain and repair these tissues where they are resident (Simón and Pellicer, 2007), but for some people who suffer from delayed or stopped repairing mechanism, these cells are not enough to heal their injuries, so they need support from donors stem cells (Nikolic et al. 2009). Especially, from several years, the disease rate has significantly increased, but stem cells provide great promises for those patients due to their potential roles and abilities in self-renewal and differentiation for a life time (Nikolic et al. 2009; Tartarini and Mele, 2016), this make the therapy by stem cells is successful treatment because stem cells support tissue functions, and have treated the damaged organs in humans (Nikolic et al. 2009).

The recent researches about stem cell therapy have attracted the scientific, clinical, and public attention (Nikolic et al. 2009; Kucharzewski et al. 2019; Golchin et al. 2022). Also, there are many researches around the world have illustrated the tremendous roles of stem cells from many origins in cure of some disorders.

Stem Cells

Stem cell is medical term was offered by "**Alexander Maksimov**"- Russian histologist - in 1908 (Sharma et al. 2014; Kalra and Tomar, 2014). Stem cells are the basic cells of all multicellular organisms. Indeed, stem cells are those cells that able to proliferate and give rise to more differentiated and more specialized cells. Also, they self-renew and replace themselves for a life time because they undergo a symmetric cell division. Additionally, they possess plasticity phenomena because they hold all the genetic information of the living cells, and they can develop into mature cells (Simón and Pellicer, 2007; Dupta, 2009; Hongbao et al., 2010; ISSCR, 2011; Kalra and Tomar, 2014; Sharma et al., 2014). Self-renewal is ability of stem cells to produce identical daughter cells - another stem cells - and more differentiated daughters - progenitors or specialized cells - by symmetric, and asymmetric divisions. A symmetric division just causes increase in number of cells whereas an asymmetric division leads to generate cells with different properties without alteration in number (Simón and Pellicer, 2007). Stem cell is firstly divided by symmetric division to two identical daughter stem cells. Then the daughter stem cells are divided by asymmetric division to one cell is identical to the previous generation (i.e. stem cell), and the other is different cell that does not have the same properties of stem cells, and it is called progenitor cell. Then progenitor cell is divided to give rise to more specialized cells for one type of tissue cells by terminal differentiation (Sharma et al. 2014).

2.1 Stem cells classification

Stem cells are classified according to the origin and according to the differentiation potency (Simón and Pellicer, 2007; Can, 2008; Dupta, 2009; Hongbao et al., 2010; Kalra and Tomar, 2014; Sharma et al., 2014).

2.1.1 Classification of stem cells according to the origin

As a matter of fact, there are two origins of stem cell embryonic and adult stem cells.

2.1.1.1 Embryonic stem cells

They are pluripotent stem cells that are derived from inner cell mass of the blastocyst (after the fourth day of development and before the implantation), and they have ability to give rise to any cell of the body. On the other hand, these cells are usually cultured under *in vitro* conditions, and the treatment by using these cells is ethically restrictive (Simón and Pellicer, 2007; Can, 2008; ISSCR, 2011; Kalra and Tomar, 2014; Sharma et al., 2014). Although they give promising outcomes and widespread clinical use due to their potential for immunogenicity and tumorigenicity, they are restricted (Duscher et al., 2016).

2.1.1.2 Adult stem cells

Somatic stem cells, postnatal stem cell, multipotent mesenchymal stromal stem cells, or tissue-specific stem cells (TSSCs) all of these are nomenclatures for the adult stem cells (Simón and Pellicer, 2007; Can, 2008; Hongbao et al.,2010; Sharma et al.,2014). The adult stem cells are multipotent undifferentiated stem cells that are found in many adult tissues and organs. Additionally, they have self-renewal capacity, they can produce large numbers of at least one differentiated cell type, and can differentiate into just specific lineages that are only related to the origin of body's tissue (Simón and Pellicer, 2007; ISSCR, 2011; Sharma et al., 2014). Similarly, they are undifferentiated cells present in the tissues to replace the worn-out and lost-functional cells of the same tissue of origin, where they can specialize to all cell types of this tissue (Simón and Pellicer, 2007). Almost all adult tissues have stem cells, but they represent a very little percentage compared with the total tissue mass (Simón and Pellicer, 2007), and they have been isolated from many tissues like liver, heart, lungs, nervous system, skin, gastrointestinal epithelium, skeletal muscles, cornea, kidneys, and endometrium. That mean humans have unlimited sources of stem cells which is located in many tissues (Simón and Pellicer, 2007; Can, 2008; Dupta, 2009; Hongbao et al.,2010; Kalra and Tomar, 2014; Sharma et al.,2014). Adult stem cells are multipotent as general, but in fact, some of adult stem cells are multipotent with various potency degrees and the others are bipotent or unipotent (Simón and Pellicer, 2007). Adult stem cells are very beneficial in the regenerative medicine. (Hasegawa and Ikeda, 2015). The multiple sources of adult stem cells give the clinical significant importance for stem cell therapy because adult stem cells represent a fresh source of different cells (Simón and Pellicer, 2007; Hongbao et al., 2010).

2.1.1.2.1 Adult stem cell sources

Adult stem cells can specialize for many tissues and reside for long time within a specific niche. Besides, the adult stem cells can subdivide according to the tissue type – niche – and the differentiation rate (Simón and Pellicer, 2007). All tissues and organs of our bodies have stem cells to replace the worn-out and damaged cells in these regions, so stem cells found throughout our bodies (Can, 2008; Hongbao et al., 2010), but not all of them are used in stem cell therapy because they cannot isolate and use all of them in the treatment.

2.1.2 Most Common Stem Cells

2.1.2.1 Mesenchymal stem cells (MSCs)

They are adult stem cells and they are multipotent self-renewing stem cells (ISSCR, 2011; Tartarini and Mele, 2016). Also they can differentiate into various cell types such as osteoblasts, chondrocytes, adipocytes, and myocyte (Kirby et al., 2015). Mesenchymal stem cells can be isolated from bone marrow and other tissues including; umbilical cord as umbilical cord-derived stem cells (UC-MSCs), amniotic fluid as fetal stem cells, placenta as placental-derived stem cells, bone marrow as bone marrow-derived stem cells (BM-MSCs) and as hematopoietic-derived stem cells (HSCs), adipose tissue as adipose-derived stem cells (ASCs), nerve tissue as neural stem cells (NMSCs), and dermis as skin-derived stem cells (SD-MSCs) (Sharma et al., 2014; Kirby et al.,2015; Tartarini and Mele, 2016; Duscher et al., 2016; Maxson et al., 2012). Moreover, MSCs are capable to repair all mesenchymal tissues, bone marrow, muscle, bone, cartilage, tendon, and ligament. In addition to, nervous tissue, heart, liver, and skin (Kirby et al., 2015; Maxson et al., 2012). Furthermore, placental membrane is a rich source of mesenchymal stem cells for tissue regeneration and repair (Maxson et al., 2012).

2.1.2.2 Bone marrow mesenchymal stem cells (BM-MSCs)

They are adult stem cells, which are located in the bone marrow of the adult bones, they are easily obtained from younger donors for clinical transplantation because those cells can give rise to bone, cartilage, blood, and adipose stem cells (Sharma et al., 2016).

2.1.2.3. Hematopoietic stem cells (HSCs)

They are multipotent stem cells, that are derived from adult stem cells, have limited differentiated rate, and self-renewal ability. HSCs represent 99% of bone marrow and they can differentiate into all mature circulating blood cell types including erythrocytes, leukocytes “granulocytes and lymphocytes”, and platelets (Simón and Pellicer, 2007).

2.1.2.4 Adipose-derived stem cells (ASCs)

They are multipotent mesenchymal stem cells from the adipose tissue and they are another potential source of adult stem cells (Nikolic et al., 2009; Telci et al., 2013; Tartarini and Mele, 2016; Duscher et al., 2016). Adipose stem cells can differentiate into endodermal and ectodermal beside mesodermal lineages, and they can make up osteogenic, periodontogenic, and angiogenic. In addition, ASCs can differentiate into keratinocytes, hepatocytes, and neural cells (Hasegawa and Ikeda, 2015).

2.1.2.5 Amniotic fluid (Fetal stem cells)

These cells are obtained from the aspiration in the amniotic sac of course during pregnancy. These cells are similar to the ESCs, so they are pluripotent stem cells, but their isolation is easier than ESC isolation because they are obtained during genetic screening without damage in the embryo, yet they are also ethically limited because their isolation may cause loss of the pregnancy. Furthermore, these cells can engender neuron-like cells, osteoblasts, chondrocytes, adipocytes, myocytes, liver, and endothelial cells (Dupta, 2009; Sharma et al., 2014). Therefore, these cells represent an alternative stem cell source, but to avoid immune rejection and genetic diseases, they need critical careful during donor selection (Duscher et al., 2016).

2.1.2.6 Umbilical cord blood stem cells (UC-MSCs)

These cells are obtained directly after birth from the blood of the umbilical cord. However, these cells can specialize to various types of body's cells such as neurons, skeletal muscle, and liver cells. So that, UC-MSCs have successfully been used to treat blood disorders because they could be stored and frozen (Sharma et al., 2014). Additionally, the UC-MSCs are a source for hematopoietic and mesenchymal stem cells (Duscher et al., 2016).

2.1.2.7 Skin-derived mesenchymal stem cells (SD-MSCs)

They are type of adult stem cells that undifferentiated and self-renewal cells which participate in wound healing and found in basal layer of epidermis "epidermal stem cells", bulge region of the hair follicle "hair follicle stem cells", base of the sebaceous glands "sebaceous gland stem cells", as well as interfollicular stem cells. In addition, some other types of stem cells reside within hair follicle like, mesenchymal-like stem cells, melanocyte stem cells, and nestin-positive stem cells (Ojeh et al., 2015).

2.1.2.8 Induced Pluripotent stem cells (iPSCs)

These are adult stem cells that behave like embryonic stem cells where they can engender all cell types of the body, but the treatment by these cells may be carcinogenic. (Sharma et al., 2014), but autologous induced pluripotent stem cells are nonimmunogenic (Duscher et al., 2016). In fact, induced pluripotent stem cells are resulted from the engineering and manipulating of some genes by process called "reprogramming" where they convert somatic cells to pluripotent embryonic stem cells (ISSCR, 2011; Kalra and Tomar, 2014). Likewise, these cells can differentiate into keratinocytes, melanocytes, and fibroblasts. Nevertheless, iPSC-based therapy for wound healing requires improvement of their safety (Ojeh et al., 2015).

2.1.3 Classification of stem cells according to the differentiation potency

The stem cells classified according to their differentiation capacity or their plasticity into five classes are totipotent, pluripotent, multipotent, unipotent, and oligopotent (Simón and Pellicer, 2007; Can, 2008; Hongbao et al., 2010).

2.1.3.1 Totipotent stem cells

The totipotent stem cell is a fertilized egg "Zygote", it can produce all cell types in the embryo and extraembryonic tissues "placenta and umbilical cord". However, it is believed that the totipotent stem cells can produce a new embryo if these cells are supported by appropriate microenvironment (Simón and Pellicer, 2007; Can, 2008; Dupta, 2009; Hongbao et al.,2010; ISSCR, 2011; Kalra and Tomar, 2014; Sharma et al., 2014). Totipotent mean total potency (Dupta, 2009). So that, these cells can give rise to any and all cell types of the individual, such as heart, liver, brain, skin, or blood (Hongbao et al., 2010; Sharma et al., 2014).

2.1.3.2 Pluripotent stem cells

They are the inner cell mass cells of the blastocyst after the fourth day of the embryonic cell division. Also these cells are termed as human embryonic stem cells (hESCs), and they have high proliferative rate with ability to differentiate into all cell types of the three embryonic "germ" layers; endoderm, mesoderm, and ectoderm "proper embryo" (Simón and Pellicer, 2007; Can, 2008; Dupta, 2009; Hongbao et al.,2010; ISSCR, 2011; Kalra and Tomar, 2014; Sharma et al., 2014). The pluripotent stem cells involve all embryo tissues except the extraembryonic tissues "placenta and umbilical cord" (Dupta, 2009).

2.1.3.3 Multipotent stem cells

They are stem cells that can differentiate into several cell lineages (Simón and Pellicer, 2007). Thus, these cells are able to differentiate into more than one mature cell type (Hongbao et al., 2010). Hence, multipotent stem cells have ability to produce a limited number of mature cell lineages. For example, hematopoietic stem cells are multipotent blood stem cells that can produce all cell types of normal blood component, red blood cells, white blood cells and platelets (Can, 2008; Dupta, 2009; Hongbao et al.,2010; Kalra and Tomar, 2014; Sharma et al., 2014).

2.1.3.4. Unipotent stem cells

These stem cells can just differentiate into a single, mature end-stage cell type (Simón and Pellicer, 2007; Sharma et al., 2014). In addition, these cells have ability to produce only one lineage of cells such as germ stem cells, myosatellite cells of muscles, corneal epithelial cells, and endothelial

progenitor cells (Hongbao et al., 2010; Kalra and Tomar, 2014). So that, they possess the lowest differentiation rate when they are compared with other stem cell classes (Sharma et al., 2014).

2.1.3.5. Oligopotent stem cells

These stem cells can specialize into only a few cells like, lymphoid and myeloid stem cells (Kalra and Tomar, 2014; Sharma et al., 2014).

2.2 Stem Cell Therapy

Stem cell therapy has a tremendous interest for more than thirty years, but not all stem cell types are used in the curative applications (Sharma et al., 2014). The aim of stem cell therapy is supporting and repairing the worn-out and damaged tissues that failed to heal themselves, and that give hope to patients who want just reduce their disease symptoms rather than the final cure from these illnesses (Kalra and Tomar, 2014). Therefore, due to the properties of stem cells to renew themselves, differentiate, and specialize, the stem cell therapy has been used to treat and replace the lost-functional tissues (Sharma et al., 2014). However, the most common type that is exactly used to treat human diseases is Hematopoietic stem cells where HSCs have treated leukemia, lymphoma, and several inherited blood disorders. Moreover, bone marrow transplantation (BMT) is a well-known clinical transplantation of stem cells (Nikolic et al., 2009; Telci et al., 2013). Stem cell therapy is considered as an existing alternative treatment for many diseases by using patient's stem cells "Autologous sources" instead of using organ transplantation (Sharma et al., 2014). As a matter of fact, we must use stem cells as alternative treatment for organ transplantation because the number of patients who need transplantation is more than the number of available organs (Dupta, 2009).

It is worth to be mentioned, the last few years, the national policies, the government officials, as well as the religious groups have put a set of laws governing the scientific researches and therapeutic purposes regarding to stem cells in order to safeguard the public from unethical stem cell researches and uses (Kalra and Tomar, 2014). The ethical concept of stem cell therapy is usually related with utilizing of the embryonic stem cells and human embryonic stem cell trails are ethically limited Telic et al. (2013) because these trails cause destruction of human blastocysts when they remove the inner cell mass (Can, 2008).

2.2.1 Most Common Medical Applications of Stem Cell

(1) Treatment of degenerative neurologic disorders such as Alzheimer's, Parkinson's diseases, as well as motor neuron disorders like stroke and multiple sclerosis (MS). In addition to spinal cord injuries (Nikolic et al., 2009; Telci et al., 2013; Sharma et al., 2014; Tartarini and Mele, 2016).

(2) Immunological diseases such as Bubble boy disease, Wisko H-Aldrich syndrome, and autoimmune diseases (Dupta, 2009; Sharma et al., 2014).

(3) Cure of musculoskeletal regeneration problems such as the repair of non-healing bone fractures and rebuilding of degenerated cartilages or tendons like osteogenesis and imperfect chondrodysplasias. In addition to treat myocardial infarction, heart failure, cardiac, and muscular diseases (Nikolic et al., 2009; Sharma et al., 2014).

(4) Treatment for diabetes type-1 and diabetes type-2 (Kalra and Tomar, 2014; Sharma et al., 2014).

(5) Mitigation lung diseases like chronic pulmonary obstruction, and pulmonary idiopathic (Nikolic et al., 2009; Sharma et al., 2014).

(6) Treatment of diverse disorders such as scleroderma, retina degeneration, inner ear, and renal disorders (Nikolic et al., 2009). Additionally, Arthritis, Baldness, Deafness, Blindness, and Cancer (Sharma et al., 2014).

(7) Remedy of liver diseases Nikolic et al. (2009), and chronic liver injuries (Sharma et al., 2014).

(8) Enhance wound healing in case of delayed wound healing, chronic non-healing wounds, and skin cancer (Nikolic et al., 2009; Telci et al., 2013; Tartarini and Mele, 2016).

(9) Medication for digestive system disorders like Cohn's disease (Sharma et al., 2014).

(10) Alleviate Age-related functional defects (Sharma et al., 2014).

(11) Medicament for reproductive system disorders and infertility (Dupta, 2009; Sharma et al., 2014).

(12) Curative for some congenital defects (Dupta, 2009; Sharma et al., 2014).

2.2.2 Most Common Stem Cells Used in Therapeutic Purposes

The stem cell therapy is giving promising results for many disorders, and the most common uses are:

(1) Stem cells for liver diseases: The liver possesses mature, regenerative hepatocytes which have a property to regenerate themselves as stem cells, but in the case of liver disease, this regenerative property is insufficient or blocked for liver repair. In this case the stem cells provide a great alternative treatment instead of liver transplantation by using ESCs, HSCs, and BMSCs which can convert into liver cells (Nikolic et al., 2009).

So that the stem cell therapy for the liver is an alternative to liver transplantation.

(2) Stem cells for cardiovascular applications:ESCs and BM-derived SCs have been used to treat heart failure and myocardial infarction, by transdifferentiation of BM-derived SCs into cardiomyocytes to repair cardiac function (Nikolic et al., 2009).

(3) Neurologic diseases: The neural stem cells and progenitor cells of the nervous system are astroglial cells. MSCs can give rise to neuronal cells and they have been used to treat nervous system diseases. Additionally, BM-derived MSCs can create neurons. In order that, stem cell therapy has been treated neurologic disorders such as Parkinson's, Alzheimer's, and MS, by BM-MSCs, (UC-SCs) umbilical cord blood stem cells through promotion of neurogenesis, synaptogenesis, and angiogenesis rather than transdifferentiation of stem cells to functional neurons. Likewise, umbilical cord blood stem cells have been treated stroke (Nikolic et al., 2009).

(4) Stem cell therapy for diabetes mellitus: Stem cell therapy is a promising alternative treatment for pancreatic transplantation. ESCs can convert to β-like cells to cure diabetes. Also, BM-derived SCs and HSCs can transform to functional islet cells including "insulin-expressing cells or endocrine pancreatic cells" (Nikolic et al., 2009).

(5) Stem cells support reproductive system and fertility: Stem cells are potential therapy for reproductive tract disease and infertility. Actually, there are extra gonadal Germ Stem Cells (GSCs) that capable to long-term support for oogenesis and spermatogenesis, these cells are located in adult bone marrow, where germ stem cells are released from bone marrow into peripheral blood circulation, but due to many circumstances, these cells are not sufficient, so in these conditions, the patients need to support their reproductive organs by stem cell therapy to stimulate the organs functions. Therefore, BM-derived MSCs and HSCs have potentially contributed in reproductive functions by differentiation into germ progenitor cells (Simón and Pellicer, 2007). Also, BM-MSCs contribute in menstrual cycle by renewal of endometrium (Telci et al., 2013). So that BM-MSCs may be used to treat some endometrial diseases like Asher man's syndrome and infertility. Moreover, ESCs can transdifferentiate into oocyte-like cells under certain conditions. So the stem cell therapy supports reproductive system by transformation of GSCs from bone marrow to the ovary in female and TSCs "Testicular Stem Cells" transplantation in male (Simón and Pellicer, 2007).

(6) Stem cell therapy for skin disorders: BM-MSCs and skin-derived mesenchymal stem cells "SD-MSCs" with collagen are used for full-thickness wound treatment. Also, BM-MSCs with matrix rich by collagen

and fibrin have been used to treat many cases and caused complete recovery. Additionally, ASCs combined with scaffolds of natural biomaterials “collagen and polysaccharides” have greatly influenced the wound repair (Tartarini and Mele, 2016). Similarly, ASCs from autologous origin represent a safe source to treating inherited and acquired skin disorders (Hasegawa and Ikeda, 2015; Ojeh et al., 2015). To give a concrete example, autologous ASC transplantations are safe without evidence of cancer formation (Duscher et al., 2016).

(7) MSCs have successfully treated skin chronic non-healing wounds, endometrial diseases, bone defects, peripheral arterial and coronary diseases (Nikolic et al., 2009). In addition, they may treat brain, liver, and lung injuries as well as kidney, cardiovascular diseases, and cancer (Kirby et al., 2015).

(8) iPSCs participate in cutaneous wound healing by optimizing inflammation and promotion of angiogenesis “new blood vessels formation” and collagen synthesis. In addition, iPSCs can give rise to keratinocytes and melanocytes (Ojeh et al., 2015; Duscher et al., 2016). Angiogenesis occurs naturally in normal situations, but is often insufficient to allow for wound healing (Nikolic et al., 2009). But stem cells produce Vascular Endothelial Growth Factor “VEGF” which regulates new blood vessels formation and induce angiogenesis (Simón and Pellicer, 2007).

(9) Stem cells propose a novel therapeutic modality for advanced aged by releasing of appropriate cytokines and growth factors. For instance, human embryonic stem cells form a new therapy for regenerating tissue damage, injury, and aging process (Hasegawa and Ikeda, 2015; Ojeh et al., 2015).

(10) ASCs have ability to differentiate into kerationcytes-like cells when they are cultured in suitable scaffolds, environment, and growth factors. ASCs are easily obtained from donor with high population of stem cells and progenitor cells. These cells can differentiate into a various cell types, and have a potential to give rise to epithelial cells. Furthermore, they serve an important role in the treatment of different kinds of diseases, especially skin diseases. Also, BM-MSCs can differentiate into epithelial-like cells, but using of ASCs has many advantages than the utilization of BM-MSCs (Hasegawa and Ikeda, 2015).

2.3 Stem Cells in Wound Healing

2.3.1 Skin

The skin is considered as the largest and most available organ in the human body, and also it is a highly complex organ, it represents 10% of the human body weight and with a surface area 1 - 2 m^2 (Vaughan, 2002; Pakurar and Bigbee, 2004; Pavelka and Roth, 2005; Moran and Rowley,

2009; PSDDS, 2009; Ojeh et al., 2015; Kirby et al., 2015). The skin composed of three distinct layers are the superficial one is “epidermis”, then “dermis”, and the last is subcutis or called “hypodermis” (Pakurar and Bigbee, 2004; Moran and Rowley, 2009; PSDDS, 2009).

2.3.2 Epidermis

The epidermis is stratified Squamous keratinized epithelial cellular layer consists of five regions “stratum corneum”, “stratum lucidum”, “stratum granulosum”, “stratum spinosum”, and “stratum germinativum or basale” from outer to inner, and each region is separated from the other by a thin water sheet. However, the thickness of this layer ranges from 0.5 mm as in eyelid to 1.5mm on the palms and soles (Vaughan, 2002; Pakurar and Bigbee, 2004; Pavelka and Roth, 2005; Moran and Rowley, 2009; PSDDS, 2009). Memorable, this layer is continuously regenerated or self-renewed every 15-30 days due to the differentiation of kerationcytes in stratum basale “germinativum” region of the epidermis which serve as stem cells, and the skin tissue houses also another types of stem cells such as stem cells of hair follicles, these natural stem cells participate in wound healing and skin restoration after skin injuries (Vaughan, 2002; Pakurar and Bigbee, 2004; Pavelka and Roth, 2005; PSDDS, 2009). The ability of keratinocytes in the differentiation is not only part of periodically regeneration of the skin, but also part of the wound healing after injuries (Moran and Rowley, 2009).

The epidermis has many cell types including:

(1) Keratinocytes are the major cells in the epidermis (PSDDS, 2009). Keratinocytes are arranged in five layers “strata” and their functions are formation the skin barrier as well as keratinization. (Pakurar and Bigbee, 2004; Pavelka and Roth, 2005; Kirby et al., 2015).

(2) Melanocytes is called melanin pigment-producing cells located in stratum germinativum and spinosum (Pakurar and Bigbee, 2004; Pavelka and Roth, 2005; PSDDS, 2009; Kirby et al., 2015).

(3) Langerhans cells are macrophages that have immunological function in skin reactions (Vaughan, 2002; Pakurar and Bigbee, 2004; Pavelka and Roth, 2005; PSDDS, 2009; Kirby et al., 2015). Moreover, Langerhans cells are the most important part in the skin associated lymphoid tissue “SALT”, they participate in transference the pathogenic materials to the lymphatic system (Vaughan, 2002; Pakurar and Bigbee, 2004).

(4) Merkel’s cells are touch receptors (Vaughan, 2002; Pakurar and Bigbee, 2004; PSDDS, 2009). Besides, Merkel’s cells are innervated by myelinated sensory fibers, these cells are numerous in the most sensitive

regions to touch like the fingertips (Vaughan, 2002; Pakurar and Bigbee, 2004).

2.3.3 Dermis

The dermis is a dense irregular connective tissue layer that contains blood and lymphatic vessels, nerves, hair follicles, sweat and sebaceous glands. In addition to, sensory receptors including Pacinian corpuscles, Meissner's corpuscles, Ruffini ending, and Merkel's cells (Vaughan, 2002; Pakurar and Bigbee, 2004; Moran and Rowley, 2009; PSDDS, 2009).

The dermis composed by two regions; the papillary layer and deeper reticular layer. Also, dermis connective tissue is supported by collagen and elastic fibers which their nature, arrangement, and density vary according to the location, gender, age, and the nutritional state of the individual (Pakurar and Bigbee, 2004; Moran and Rowley, 2009).

2.3.4 Hypodermis

The hypodermis is a layer of connective tissue and adipose tissue which can accumulate in this layer and the amount of fat in this layer is depended on body location, age, gender, and the nutritional and physical states of the person. Moreover, this layer may contain the base of sweat glands, hair follicles, and many sensory receptors, especially Pacinian corpuscles (Vaughan, 2002; Pakurar and Bigbee, 2004; Moran and Rowley, 2009; PSDDS, 2009).

2.3.5 The Structures associated with skin

The structures associated with skin are called "Skin derivatives" and they are:

(1) Glands (sweat and sebaceous).

(2) Hair follicles.

(3) Nails.

(4) Sensory structures including Pacinian corpuscles, Meissner's corpuscles, Ruffini ending, and Merkel's cells (Vaughan, 2002; Pakurar and Bigbee, 2004; Pavelka and Roth, 2005; Moran and Rowley, 2009; PSDDS, 2009).

These skin appendages represent 0.1% of the total skin surface (PSDDS, 2009).

2.3.6 Skin Wounds

The skin wound is any injuries that lead to break down in the normal structure and function of the skin tissue. However, the degree of wound ranges from superficial cutaneous wounds to the deep wounds which

extend into subcutaneous tissue with damage in the other structures like muscles, nerves, and blood vessels (Velnar et al.,2009).

Forms and types of wounds differ according to the causes and in turn the causes of wounds vary from injuries by small sharp objects to hard motor vehicle accidents or as the result of diseases. Furthermore, the wounds might be acute or chronic, as well as they might be open or closed wounds (Velnar et al., 2009).

2.3.7 Wound Healing

The wound healing consists of a series of linked, sequential steps that must be well performed to ensure the integrity of the wound structurally and functionally. However, the normal wound healing involves bleeding, vessel contraction with coagulation, activation of complement and inflammatory response, cell migration, proliferation, differentiation, angiogenesis, matrix formation, and reepithelialization. Finally, increasing wound strength. All of these complex events are arranged into four major phases (Dipietro and Burns, 2003; Maxson et al., 2012). The successful wound healing requires an adequate population of some cell types, suitable extracellular matrix "microenvironment", and presence of some appropriate soluble mediators such as cytokines and growth factors (Velnar et al., 2009). On the other hand, the non-healing wound is resulted due to unsuccessful wound healing processes and this lead to chronic wounds which may be caused by some genetic changes in the natural stem cells of the patient (Ojeh et al., 2015).

In fact, there are many suggested therapies for wound healing such as Debridement, skin dressing, skin graft and flaps, but the most potential one is stem cell therapy for non-healing wounds and the other skin disorders. Moreover, the stem cell therapy is beneficial for acquired and congenital disorders like debilitating and difficult treated skin defects. For example, adult stem cells, hair follicle stem cells, and epidermal stem cells are the most common potential candidates for skin disorders (Ojeh et al., 2015).

2.3.7.1 Cutaneous wound healing phases

At the time of injury, the wound healing starts directly where the wound healing process divided into four main phases and the first phase is coagulation which begins immediately after the injury, then the inflammatory phase begins shortly after this injury. After that, the resident and migratory cells play their role in the proliferative phase of the wound healing. Finally, the wound remodeling and scar tissue formation (Velnar et al., 2009; Maxson et al., 2012; Kirby et al., 2015).

2.3.7.1.1 Coagulation phase

Coagulation phase takes place immediately after the injury and this is the function of vascular system to protect itself from exhaustion and

minimize blood loss. In addition to provide a suitable microenvironment for inflammatory cells. This phase starts when the neuronal signals lead to contraction of smooth muscle cells in the vascular wall to constrict the injured vessels, but this is not effective for long time. However, the platelets contact to the exposed collagen fibers, this trigger the platelets to release clotting factors such as fibrin, fibronectin, thrombospondin, vitronectin, which lead to clot formation. After that, platelets release also cytokines and growth factors including platelet-derived growth factor "PDGF", transforming growth factor-β "TGF-β", insulin-like growth factor "ILGF", and epidermal growth factor "EGF", which are very important to the second phase "Inflammatory phase" (Velnar et al., 2009; Maxson et al., 2012; Kirby et al., 2015).

2.3.7.1.2. Inflammatory phase

Inflammatory phase begins shortly after the wounding, and it is immune reaction that is initiated when cytokines and growth factors such as PDGF, TGF-β, ILGF, and EGF released by platelets, activate and attract the inflammatory cells including neutrophils, then macrophages, fibroblasts, and endothelial cells (Dipietro and Burns, 2003). In addition, these cells are also attracted by complement components C3a and C5a. Likewise, platelets release also vasodilator molecules such as serotonin that cause extravasation of fluids which lead to edema (Velnar et al., 2009). Besides, mast cells are also activated and release histamine, and other active amines that are responsible for inflammatory signs like redness, heat, pain, and swelling (Maxson et al., 2012). The first event in the inflammatory phase is neutrophils infiltration to the site of injury where they remove and destroy the bacteria and the other foreign particles by phagocytosis. Then the neutrophils adhere to and induce the endothelial cells of the blood vessel to secrete chemokines. After that, some neutrophils migrate out of the blood vessel and the others are eliminated by apoptosis and neutrophil's apoptotic bodies are removed or phagocytosed by macrophages. Additionally, monocytes are attracted from blood to give rise to macrophages in the wound site where the macrophages continue the process of phagocytosis for longer time than neutrophils. Later in the inflammatory phase, the lymphocytes are attracted by the complement components include C3a and C5a. In addition to interleukin-1 and immunoglobulin G "Ig-G" to start the immune response. In the end of this phase, the cytokines and the growth factors activate fibroblasts, keratinocytes, and endothelial cells to replace the destroyed tissue and create the new blood supply to the wounding, and to start the next phase (Velnar et al., 2009; Maxson et al., 2012; Kirby et al., 2015).

2.3.7.1.3 Proliferative phase

Proliferative phase involves fibroblast migration, collagen synthesis, angiogenesis and granulation tissue formation "matrix formation" which is also called "epithelialization". As well as reepithelialization. The proliferative phase starts when the fibroblasts migrate, proliferate, and synthesize collagen fibers that play important roles in all wound healing phases. Besides, the fibroblasts produce also the extracellular matrix components to restore the normal structure of the tissue because the matrix components support the migration of cells. Then, the fibroblasts change to myofibroblasts which have pseudopodia that attach to fibronectin and collagen in this matrix to lead to wound contraction. Furthermore, there are numerous angiogenic factors including FGF, VEGF, PDGF, TGF-α, TGF-β, and EGF that are secreted by platelets and other inflammatory cells. These factors induce the formation of new blood capillaries during the all wound healing phases to supply the injured skin by oxygen and nutrients that promote the cellular migration, proliferation, and differentiation. At the end of this phase the epithelialization "granulation tissue formation" is stimulated by EGF and TGF-α. The epithelialization is the migration of keratinocytes to the wound edges and formation of new basement membrane to preface the remodeling phase (Velnar et al., 2009; Maxson et al., 2012; Kirby et al., 2015).

2.3.7.1.4 Remodeling phase

Remodeling phase is the last phase of wound healing that responsible for reepithelialization "development of new epithelium" and scar formation (Velnar et al., 2009; Maxson et al., 2012; Kirby et al., 2015). This phase starts when the epithelial cells that line the hair follicles sweat, and sebaceous glands migrate to the surface of the wound where they differentiate into epidermal keratinocytes, and this represents the reepithelialization (Dipietro and Burns, 2003). Moreover, this phase represents the homeostatic balance between degradation and synthesis to produce normal healing and this occurs because the collagen fibers are synthesized and degraded by matrix metalloproteinase enzymes produced by fibroblasts, neutrophils and macrophages. Then, this leads to new matrix formation, accumulation, and tensile strength of the wounding (Velnar et al., 2009; Kirby et al., 2015). Furthermore, the underlying connective tissue shrinks in size and the wound margins close together due to the interactions between fibroblasts and extracellular matrix and by help of some growth factors and other factors. At the end of wound healing, the excess fibroblasts and macrophages are eliminated by apoptosis as well as the capillary growth is stopped (Maxson et al., 2012).

2.3.7.2 The Role of Stem Cells in Wound Healing

These days many people are affected by especially cancer and diabetes which affect millions of people all around the world. Unfortunately, these diseases increase the incidence rate of delayed healing of the injured tissues, this in turn causes contamination of wounds and worsening of the condition. So that we need a new therapeutic strategy to solve these situations, and that is represented in utilization of stem cells because stem cells abilities for self-renewing and potential differentiation give the significant importance for use them in delayed wound healing, chronic non-healing wounds, skin cancer, after skin non-melanoma cancer surgical excision, and after radiation burns (Tartarini and Mele, 2016).

For these reasons, it is suggested that, there is a new interest that focuses on stem cell as a tremendous therapeutic agent.

2.3.7.3 Most Common Stem Cells Involved in Wound Healing

(1) MSCs that can produce complete wound healing and tissue repair because they have roles in granulation tissue formation, accelerate epithelialization, promote angiogenesis "new vessels formation" and vascularization of the scaffolds (Maxson et al., 2012; Kirby et al., 2015). Besides, MSCs reduce the local inflammation, induce the cell migration and proliferation, and stimulate the formation of extracellular matrix "ECM" components (Telci et al., 2013; Maxson et al., 2012; Duscher et al., 2016). Likewise, MSCs induce immune system cells such as B and T-lymphocytes to increase their surface receptors that encourage phagocytosis (Telic et al., 2013; Tartarini and Mele, 2016). Moreover, MSCs secrete antimicrobial proteins, so they have antimicrobial activity, all of these functions are during wound repair when they also accelerate wound closure and increase the rate of healing as well as reduce scarring and increase tensile strength (Maxson et al., 2012; Telci et al., 2013; Kirby et al., 2015; Duscher et al., 2016). MSCs are involved in all wound healing phases because they can control the necessary cellular functions by producing paracrine signaling by releasing growth factors including PDGF, VEGF, KGF, bFGF, TGF-β, EGF, ILGF, Stromal cell-derived factor-1 and Matrix metalloproteinase-9 (MMP-9) (Maxson et al., 2012; Telci et al., 2013; Kirby et al., 2015; Duscher et al., 2016). In addition to cytokines such as interleukin-6 (IL-6), interleukin-8(IL-8), Seprin E1, growth-regulated protein-α (GRO-α) and Macrophage migration inhibitory factor (MIF) (Kirby et al., 2015). All of these mediators control the proliferation of the regulatory cells of wound healing like fibroblasts, endothelial cells, and keratinocytes to successfully complete the wound healing process. So that, MSCs have effective therapeutic potential to treat many diseases (Telci et al., 2013; Maxson et al., 2012; Duscher et al., 2016).

(2) BM-MSCs are adult stem cells, located in the bone marrow of adult bones, and there are two distinct terms for this type, the first is BM-MSCs "bone marrow-derived stem cells" which are isolated from iliac crest and have faster rate of healing than BM-MNSCs which is the second term that are derived from the other body bones (Kirby et al., 2015). Otherwise, BM-MSCs participate in many phases of wound healing because they are source of fibroblasts which synthesize the granulation tissue. Also, BM-MSCs can differentiate into myofibroblasts in presence of connective tissue growth factor "CTGF" and transferring growth factor-β "TGF-β", as well as induce the differentiation of tissue-derived stem cells into fibroblasts in presence of paracrine signaling from MSCs (Telci et al., 2013; Tartarini and Mele, 2016). Moreover, BM-MSCs decrease inflammatory cell permeation, improve vascularization, enhance angiogenesis, promote epithelialization, enhance reepithelialization, accelerate the wound closure, and ensure the integrity of wound healing by increasing the tensile strength (Kirby et al., 2015; Duscher et al., 2016).

(3) ASCs are called adipose-derived stromal stem cells, and they are multipotent adult stem cells located in adipose tissues. ASCs can differentiate into endothelial progenitor cells "EPCs" that assist in endothelial repair, and angiogenesis because they have capability to differentiate into fibroblastic, endothelial, epithelial, osteogenic, chondrogenic, myogenic, and adipogenic lineages in wound area, as well as endogenous skin cells, and keratinocytes. Moreover, ASCs secrete cytokines, angiogenic factors, and growth factors such as insulin-like growth factor, Hepatocyte growth factor, and vascular endothelial growth factors that induce the differentiation capacity, facilitate the formation of new blood vessels, and enhance fibroblasts and epithelial migration and proliferation after paracrine signaling from MSCs. Furthermore, ASCs have role in acceleration the wound closure and reepithelialization (Nikolic et al., 2009; Telci et al., 2013; Tartarini and Mele, 2016; Duscher et al., 2016).

(4) HSCs are blood progenitor cells that able to give rise to all types of mature blood cells "erythrocytes, leukocytes, platelets, and lymphocytes", and these cells are isolated from bone marrow or peripheral blood (Kirby et al., 2015; Tartarini and Mele, 2016). Otherwise, these cells are suggested to migrate to the wounding site and play critical roles in regulation, proliferation, and migration of epithelial stem cells, and improve healing (Kirby et al., 2015). HSCs participate in early stages of wound healing where they are able to differentiate into long-term repopulating cells "LT-HSCs", short-term repopulating cells "ST-HSCs", and restricted progenitor cells known as multiprogenitors. Also, HSCs take part in inflammatory phase by producing of the inflammatory cells, especially neutrophils, macrophages, and mast cells. In order that, HSCs can be

utilized in the stem cell therapy of wound healing. For instance, HSCs isolated from bone marrow enhance the wound healing by acceleration the proliferation and migration of fibroblasts, angiogenesis, and tissue repair, as well as reepithelialization (Telci et al., 2013). To share a real life example, Autologous HSCs are clinically used for treatment of many diseases such as leukemia, sickle cell anemia, lymphoma, myeloma, neuroblastoma, germ cell tumors, auto-immune disorders, blood sicknesses, and chronic wounds (Nikolic et al., 2009; Kirby et al., 2015).

(5) SD-MSCs "Skin-derived Mesenchymal Stem Cells" have a great capacity for self-renewal and they are the primary source of keratinocytes, hair follicle stem cells, and interfollicular epidermal stem cells "IFESCs" that are involved in the early stages of wound healing and they are essential in the complete reepithelialization and wound repair, but not in the wound closure (Telci et al., 2013). Moreover, SD-MSCs possess the ability for skin regeneration where the hair follicle and interfollicular stem cells participate in reepithelialization of wounds and full-thickness wounds and there are many evidential studies suggested that hair follicle graft is a potentially effective alternative therapy for hard-to-heal wounds and burns. Additionally, there are some epidermal substitutes are commercially available to treat diabetic and venous ulcers as well as burns. Furthermore, there are multipotent stem cells within the skin that can give rise to adipocytes, myocytes, neurons and glial cells, and all of these cells contribute in dermal repair during wound healing (Ojeh et al., 2015). In addition, the hair follicle stem cells can also differentiate to myofibroblasts, keratinocytes, adipocytes, osteocytes, chondrocytes, and they have renewal ability to give rise to all the epithelial cells of the skin layers. Similarly, interfollicular stem cells have the self-renewal capacity to generate all the cells of the stratified epithelium in response of epidermal injury (Telci et al., 2013).

2.4 Conclusions

Human skin is the largest and the most complex organ in the body (URL-1, 2009; Tartarini and Mele, 2016), that is responsible for touch, feeling "pain, heat, cool, and burns", and also regulate body temperature. In addition to, it plays a significant role as barrier against infections, dehydration, thermal, mechanical, and chemical conditions (Vaughan, 2002; Pakurar and Bigbee, 2004; Pavelka and Roth, 2005; Moran and Rowley, 2009; URL-1, 2009; Ojeh et al., 2015).

If the skin is injured, many interconnected events will start to assure wound healing and in turn the healing of skin wounds involves complex events that are controlled by molecular signaling and many interactions between different cell types within the wound site (Dipietro and Burns, 2003; Ojeh et al., 2015), but in case of delay or failure of the restoration of

injury, many complications will occur such as excess inflammation or pathogenic invasion (Dipietro and Burns, 2003).

The failure of wound healing associates with numerous cases include; diabetes, tumor, ischemia, ulcers, and severe infections, and in turn the impaired healing can cause decreasing the quality of life, disability, and sometimes death due to severe complications, but stem cells are giving promising results for many patients (Tartarini and Mele, 2016).

Recent clinical trials focus on the use of stem cell therapy for different organs and systems in the body because the stem cells from many origins can give rise to various specialized and fully functional cell types. As a result, stem cell therapy may soon become a routine clinical treatment in many countries (Nikolic et al., 2009; Kucharzewski et al. 2019; Golchin et al. 2022).

Unfortunately, stem cell research is still poorly developed regarding to the utilization of stem cells in gene therapy because of the stem cells have many properties like multiply, migration, and communication with adjacent cells. On the other hand, stem cells can produce cancer, if they are transferred into the patient without a previous subtype-specific cell differentiation (Nikolic et al., 2009). Nevertheless, there is a new attempt to accelerate the skin repair is equipping the wound site by directory biomaterials as scaffold to imitate the physiochemical and biochemical properties of the skin. This attempt depends on combination of stem cells with biomaterials to provide a suitable microenvironment for cell differentiation and proliferation in order to effective treatment because this scaffold provide mechanical support and protect the injured area from external stresses (Tartarini and Mele, 2016). Additionally, the researchers and scientists are still trying how to control the usage of adult stem cells because all stem cells might be beneficial for medical researches and applications, but each one with different restrictions and promises. For example, ESC researches are active, but they are complicated technically and ethically (Simón and Pellicer, 2007). Notwithstanding, it is believed that just adult stem cells could extensively be used as a stem cell therapy (Hongbao et al., 2010).

The Abbreviations

ASCs	Adipose Stem Cells
BM-MSCs	Bone Marrow-derived Mesenchymal Stem Cells
BM-MNCs	Bone Marrow Mononuclear Cells
CTGF	Connective Tissue Growth Factor
ECM	Extracellular Matrix

EGF	Epidermal Growth Factor
ESCs	Embryonic Stem Cells
FGF	Fibroblast Growth Factor
HGF	Hepatocyte Growth Factor
HSCs	Hematopoietic Stem Cells
IGF	Insulin-like Growth Factor
iPSCs	Induced Pluripotent Stem Cells
IFESCs	Interfollicular Epidermal Stem Cells
KGF	Keratinocyte Growth Factor
MSCs	Mesenchymal Stem Cells
PDGF	Platelet-derived Growth Factor
TGF-β	Transforming Growth Factor-β
TSSCs	Tissue Specific Stem Cells
VEGF	Vascular Endothelial Growth Factor

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CHAPTER XV

CURRENT UPDATES OF EPIGENETICS INTERACTIONS FOR GAINED CHEMOTHERAPEUTIC RESISTANCE IN ACUTE MYELOID LEUKEMIA

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1. Basics of epigenetics

The work by a group of scientists, including Conrad H. Waddington and Ernst Hadorn, aimed at combining genetics with developmental biology in the mid-20th century has evolved into a comprehensive field now called epigenetics. This term that was introduced to the literature by Waddington in 1942, is derived from the Greek word "epigenesis"that describes the effect of genetic processes in development, and it is defined as somatic changes that can be inherited through cellular divisions, that are not associated with the changes in the DNA sequence (https://www.whatisepigenetics.com/fundamentals/) , (Ivanov et al., 2014).

The field of epigenetics is growing, and this has led to the notion that both the environment and the individual lifestyles can directly interact with the genome in order to influence the epigenetic changes. These changes are observed at various phases throughout the individual's life and even throughout generations. For example; human epidemiological studies show that prenatal and early postnatal environmental factors in adults effect the risk to develop several chronic diseases and behavioral disorders (https://www.whatisepigenetics.com/fundamentals/). Based on this, the biological nature of the organisms is specified with genomic characteristics such as DNA sequence and epigenetics (Fardi et al., 2018).

The unique characteristics of each cell arranged in morphological and functional, is emerging as a function of epigenetic system and this way, each cell gains the potential to fulfill its own function.

The epigenetic profile of a cell is determined with the state of DNA methylation, covalent modifications of histones, chromatin structure, and non-coding RNAs, and the state of network creation with each other. The

significance of this regulatory system will human diseases caused by disorders in the epigenetic system are being described (Fong et al., 2014).

As epigenetic mechanisms identify which genes and which signal pathways to be activated, it is known that it will play an important role to determine the best treatment and monitoring approach for some human diseases. The epigenetic mechanisms functional in human diseases include diseases that occur with damaged epigenetic systems (eg. cancer, diabetes, lupus, asthma, and neurological diseases). Also, these mechanisms can initiate the disease as well as direct the clinical consequences of the disease. Currently, the relationship between the genome and the chemical compounds that change it continues to be investigated. Genome changes; is examined what the effects generated on protein production, gene function, and human health (Fardi et al., 2018). For this purpose, with the Human Genome Project (IGP), which was initiated to fully discover the nature of heredity, the studies gained a different scientific dimension. Although the human genome project started as an American-based project, many laboratories around the world contributed to the Project (Fidanoğlu et al., 2013).

1.1. The methylation of DNA, the modifications of histone and the remodeling of chromatin

The epigenetic mechanisms induce DNA to relax and to compress, which lead to transcriptional activation and inactivation. A chromatin consists of histone units, each consisting of 8 subunits of histone core and DNA around the histone nucleus. Histones are proteins surrounding DNA so as to form nucleosomes. Each nucleosome consists of DNA that contains 2 copies of the histones H2A, H2B, H3, and H4 (heterochromatin and euchromatin). Nucleosomes are the units responsible for the packaging of DNA located in the nucleus (Hatzimichael et al., 2013). While histone proteins provide a structure for DNA to be stored in the nucleus of the eukaryotic cells. These histone proteins and the macromolecular complex of DNA include the chromatin structure (Bewersdorf et al., 2019). By compressing 146 base pairs of DNA helix around a histone, DNA can be put in the nucleus. Chromatin can change one of the forms of tight or loose packed in a replaceable manner. This situation is called heterochromatin and euchromatin. The heterochromatin is a complex form resistant to bind various proteins like transcriptional mechanisms. The euchromatin is a loose form of chromatin that is open to modifications and transcriptional processes (Shahid et al., 2020) (Zhou et al., 2019).

Chromatin modification, which alters the interaction between DNA and histones, is quite a dynamic process in cells to effect transcription, DNA repair, and replication, and plays a critical role to regulate of all DNA-based processes (Bewersdorf et al., 2019) (Dawson et al., 2012).

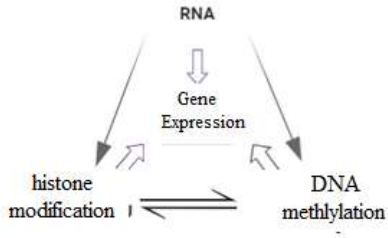

Figure 1. Schematic drawing of the epigenetic mechanism (Created by me through biorender)

Histone modifications are functional in a variety of biological functions, consisting of the suppression of transcriptional, the activation of gene, and the repair of DNA, except chromatin packaging, and three kinds of them, of histone-interacting proteins are identified depending on the functionality: In histone changes, functional writers (e.g. methyltransferases, histone acetyltransferases (HATs) and histone methyltransferases) catalyze the integration of epigenetic markers to histones or DNA. Erasers that detect these changes (such as histone deacetylase (HDACs), histone demethylase) catalyze the separation of epigenetic markers from histones or DNA. Thirdly, readers (like bromodomain proteins) who recognize changes help to recognize epigenetic markers as secondary chromatin modifiers or elements of transcriptional mechanisms (figure 2) (Nettersheim et al., 2019).

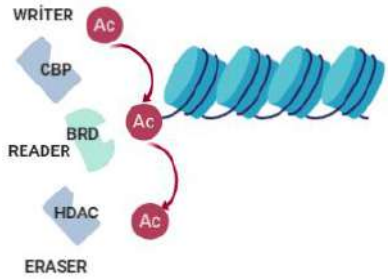

Figure 2. Histone-interactive protein classes (Created by me through biorender)

Histone acetylation is quite a dynamic process that modifies the transcription of gene, which is densely coordinated by the competitive activity of histone acetyltransferases and histone deacetylase (HDACs), which leads to a more reachable open chromatin structure promoting gene transcription (Bewersdorf et al., 2019).

Histone acetylation is checked by two groups of inverse-functional enzymes. These are histone acetyltransferase (HAT) and histone deacetylase (HDAC). HAT causes the positive form o lysine to neutralized by adding acetyl to histone at the position of Lys. Consequently, the connection between histone and DNA is loosen. HDACs with anti-HAT function take the Lys group away. They keep the histones form and cause chromatin stability in the relevant status (Fardi et al., 2018).

The connection of methyl groups to the tails of histone proteins causes histone methylation. It results the formation of a densed chromatin structure, it is called "heterochromatin". The heterochromatin structure leads to transcriptional suppression by inhibiting to bind DNA transcription mechanism. Adding acetyl groups to lysine residues in the histone tails at the N-terminus results histone acetylation. It leads to the formation of an open chromatin status which is called "euchromatin" (Figure 3). Thus, transcription factors and other proteins can be linked to the DNA linking sites and proceed with active transcription (Kim et al., 2017).

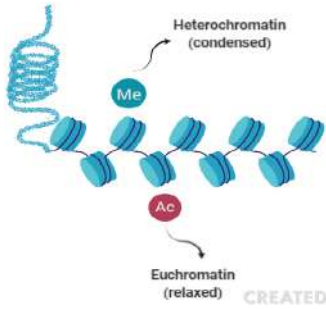

Figure 3.Schematic drawing of the histone methylation and the acetylation (Created by me through biorender)

In other studies on methylation after histone methylation, the importance of DNA methylation was defined as a result of situations like embryonic progress, X chromosome inactivity, gene silencing and gene expression in various evolution processes (Fardi et al., 2018). DNA methylationis formed in the promoter region of the genes in somatic cells, by adding cytosine 5carbon atom to a methyl group. The DNA methylation formed in dinucleotide CpG islands (Hatzimichael et al., 2013). DNA methylation is formed by the DNA methyltransferase group (DNMTs). This group includes DNMT1, DNMT2, DNMT3A, DNMT3B, and DNMT3L (Cheng et al., 2008).

Although DNA methylation in 5'-promoter regions has been studied quite well and shown to suppress the expression of gene, it has been noted

that the methylation of DNA appears in the downstream regions of the promoters, intra- and intergenic, and regions with low CpG density.

Damages in DNA methylation are related to leukemia, lupus, muscular dystrophy, and several congenital anomalies. Hypomethylation of DNA occurs in most cancers; (Hatzimichael et al., 2013) DNA hypomethylation triggers the transcription of oncogenes to tumorgenesis. The methylation results in the stability of genome. Furthermore, hypomethylation causes genetic mutations in the DNA sequence, increasing genetic instability (Fardi et al., 2018). Therefore, DNA methylation and hydroxymethylation are epigenetic pathways that cause malignant transformation by inactivating tumor suppressor genes. Gene mutations effect DNA methylation (e.g. DNMT3A) and demethylation (e.g. TET2). They frequently result in silencing target genes. Mostly they are seen in 22% and 23% of patients with acute myeloid leukemia, respectively.

Chromatin remodeling complex proteins play a role in regulating epigenes and adaptation with DNA methylation and histone modifications. Among the various chromatin precursors that are remodeling there is SWI / SNF complex (Miesfeld et al., 2015), nucleosome remodeling factor (NURF), Mi-2 / NuRD (nucleosome remodeling and deacetylase) complex, and Polycomb suppressor complex (PRCs) that regulate many aspects of retinal proliferation and differentiation and also have important functions in cellular differentiation. These are known to play a role in cellular reprogramming. They are large protein complexes to use the energy of ATP hydrolysis to activate and to restructure nucleosomes (Ponnusamy et al., 2019) (https://www.nature.com/scitable/topicpage/chromatin-remodeling-in-eukaryotes-1082/)

1.2. Co-ordination among DNA methylation, histone modifications and chromatin remodeling

Chromatin remodeling is an active modification of chromatin architecture. It provides gene expression control of proteins in the regular transcription mechanism of genomic DNA, is mainly carried out by histone modifications (histone acetyltransferases (HATs), deacetylases, kinases) and ATP-dependent chromatin remodeling complexes (Clapier et al., 2009).

Abnormal promoter hypermethylation or histone modifications are known to be important mechanisms in the initiation and progression of cancer. These epigenetic regulations can influence to express genes regardless of genetic changes, by recognizing them the "third way" in Knudson's double hit the inactivation of tumor suppressor gene model (Kondo et al., 2009).

It is known that epigenetic regulations that are DNA methylation and histone modifications etc., interact in order to achieve their effects at general and specific levels, in a tightly regulated manner. It is known that histone acetylation is protected against DNA methylation through isolators (insulation compounds). These insulation compounds found in genes, while limiting DNMTs, mediate the regular integration of MBD protein and Mi-2 deacetylase complex; to allow chromatin to bind to transcription factors, with the relaxation of the chromatin structure of the lines are included in the structure (Ponnusamy et al., 2019).

The continuous interacting structure of DNA and histones ensures the coordination between them. The specific combination of modified amino acids located in the histone tail helps to control the density of chromatin, its stability or instability for transcription, replication and repair(Luger et al., 1997).

Studies on the interaction of DNA methylation and histone modifications have been carried out through a group of proteins with methyl DNA binding activity. these proteins include Methyl CpG binding protein 2 (MeCP2), Methyl-CpG binding domain protein 1 (MBD1) and ZBTB 33. these proteins are localized in DNA methylated promoter regions. It forms a protein complex that includes histone deacetylases (HDACs) and histone methyltransferases. Through these studies, it has been shown that changes in DNA methylation and histone modifications induce chromatin structural changes (Kondo, 2009).

2. Epigenetic approaches in leukemia treatment and epigenetic regulators in the AML mutational landscape

Leukemias are a life group that threatens malignant diseases of the blood and bone marrow. While factors related to more aggressive disease biology increase with age, the tolerability of treatment strategies decreases (Juliusson et al., 2016). Acute myeloid leukemia (AML), characterized by clonal expansion and differentiation of myeloid progenitor cells, is known as a malignant disease of the bone marrow (Shallis et al., 2019). In addition, AML is a highly heterogeneous disease in terms of pathobiology and clinical aspect (Sun et al., 2018).

AML (Acute myeloid leukemia) is the most common type of leukemia (Gardin et al., 2017). AML is a heterogeneous disease that presents with different molecular markers, therapeutic responses and survival rates. It occurs as a result of abnormal accumulation of blasts in the bone marrow leading to bone marrow failure. There are myeloid lineage blasts in the peripheral blood at a concentration of about 20%. Different DNA methylation markers have been identified as suitable markers for leukemogenesis and prognosis. These markers contribute to understanding the course of the disease.

AML treatment is divided into 3 phases as induction, consolidation and protection (figure 4). Treatment of AML is divided into 3 phases (consolidation and maintenance) due to removal of leukemia cells from the circulation by cytotoxic chemotherapy (induction) followed by removal of leukemia cells from the circulation (Dexheimer et al., 2017).

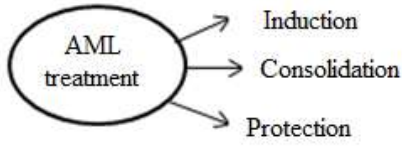

Figure 4. AML treatment methods (Created by me through biorender)

The characterization of genomic AML regulation was established by detecting repetitive mutations in several genes not previously defined in AML. These mutated genes; includes transcription factors, kinases, cell cycle regulators, spliceosomal genes, and epigenetic regulators. The genes which are encoding epigenetic regulators are the factors to be mutated in AML. The observation highlights the role of epigenome dysregulation in the pathogenesis of AML (Sun et al., 2018).

Anthracyclines and cytarabine arabinoside (AraC), are mostly the basic drugs therapeutic regimes. Their aim is for complete improvement in health and survival. Treatments using a these agents signify response rates in the complete improvement of 70 to 80% for patients belong the age of 60.

Epigenetic therapy may cause sensitivity both to standard chemotherapy and to emerging immunotherapy strategies. Also, clinical trials involving both of the epigenetic drugs and immunotherapy are still ongoing to cure several types of cancer such as metastatic melanoma, metastatic kidney cancer, peripheral neuroectodermal tumors, especially leukemias (Roberti et al., 2019). Until 2000, researchers realized that hypomethylation agents can turn around drug resistance to platinum chemotherapy in vitro. Based on the results, a synergistic effect between decitabine and platinum agents was seen. Then, various mixture trials were tested clinically. Another study observed that AML patients given decitabine had significantly improved outcomes before chemotherapy (Kelly et al.,2017).

Interactions of epigenetic agents and other immunological or small molecule inhibitors, have been reported to produce additive or synergistic effects on the survivals of the cells with cancer. The epigenetic treatment process in the field of cancer improves patient outcomes by correcting the molecular disorders in a particular malignancy (Kelly et al., 2017).

The development of new treatments requires both time and high cost. Therefore, using a molecular approach, current therapeutic regimens can be optimized, improving response levels, reducing prognosis and probably toxicity (Dexheimer et al., 2017).

3. Approaches to epigenetic therapy

When epigenetic therapies are used in combination with immunotherapy, it emerges as a promising treatment approach for advanced malignancies. The use of epigenetic therapy agents, DNMT inhibitors and HDAC inhibitors (alone/in combination) has been highlighted by clinical trials in multiple cancer types. Histone deacetylase inhibitors can affect the tumor myeloid compartment by causing myeloid-derived suppressor cell differentiation and functional antagonism. The combination of epigenetic drugs and immunotherapy is emerging as a essential therapeutic paradigm in various malignancies. (Topper et al., 2020).

There are epigenetic treatment methods that include bromodomain-containing protein inhibitors, histone demethylase inhibitors and mutant isocitrate dehydrogenase inhibitors. These treatment methods offer promising possibilities for epigenetic modulation in acute myeloid leukemia (Table 1).

Table 1. Samples of epigenetic targeted therapy in AML (Wouters et al., 2016)

Class of epigenetic regülatör	***Target***	***Compound***
Cell cycle inhibition	DNMTs	Azacitidine Decitabine
Histon acetyl reader	Bromodomain containing proteins (BET proteins)	BET inhibitors
Histone deacetylase	HDACs	HDAC inhibitors
Regulator of methylation	IDH1, IDH2	Inhibitors of mutant: IDH1/2
Histone lysine acetyltransferase	CREBBP(CBP) EP300(p300)	CREBBP inhibitors EP300 inhibitors
Histone arginine methyltransferase	PRMTs	PRMTs inhibitors
Histone lysine demethylase	LSD1	LSD1 inhibitors

DNA methylation, histone acetylation, and related epigenetic changes associated with the pathophysiology of acute myeloid leukemia have made epigenetic regulation an active area of research in AML treatments. Epigenetic mechanisms and heterogeneity of various treatment target areas, are being investigated. AML is known as a complex disease characterized not only by a significant genetic mutation, but also by deleterious epigenetic differentiation, which has allowed the development of therapies targeting epigenetic modifications in AML. Targeted epigenetic therapy applications are still at an early stage. Therefore, various strategies can be used for appropriate targeted therapy applications.

The first strategy is the application of high efficient compound screening approaches. There are a large number of compounds and small molecules involved in certain known epigenetic processes. By performing MTT analysis of these molecules, large-scale titration susceptibility experiments performed on primary AML cells in vitro will provide composite response signatures of each AML cell. AML patients will be classified according to their response signature.The mechanisms of action of the compounds identified by biochemical, molecular and cellular biological studies will be revealed (Wouters et al., 2016).

Another approach uses chemical-based engineering techniques to design new molecules that can affect specific epigenetic regulation. Such approaches are often combined with computer-based modeling is based on chemical processes such as crystallography (Wouters et al., 2016).

4. Epigenetic regulators in AML pathogenesis

There are limited data on the genomic modification of largely epigenetic regulators for the pathogenesis of acute myeloid leukemia. NGS (next generation sequencing)-based studies highlighting the role of epigenetic regulators in the pathogenesis of AML have shown that the pathogenesis of AML includes one of the most frequently mutated gene classes. In this way, mutations in some new genes that were not previously in the pathogenesis of AML could be identified. These include human homologues of the Drosophila polycomb complex such as DNA methyltransferases (DNMTs), isocitrate dehydrogenases (IDH1/IDH2) and EZH2, in AML and myelodysplastic syndromes, and in myeloproliferative neoplasms (MDS/MPN) (Dexheimer et al., 2017). Besides these genes, there are other examples of epigenome modulators that are not directly mutated but still play a role in the pathogenesis of AML. These epigenetic regulators are functional in the pathobiology of AML. Studies examining the appropriate targets of these regulators are still ongoing.

Epigenome-based strategies aimed at regulating altered epigenomic configurations in AML cells focus on large-based epigenomic

reprogramming. Because these epigenetic processes are involved in both suppression and transcription activation dependent on epigenetic markers and chromatin content, determining which AML subset can benefit from broad-based epigenomic reprogramming treatments can be challenging. There is a need specifically repressed or activated oncogenes to identify TSG-targeted therapeutics.

Several classes of anticancer drugs are functional in epigenetic regulation, including inhibitors of DNA methyltransferase, histone deacetylase (HDAC), lysine-specific demethylase 1, zest homolog 2, and bromodomain and extra-terminal motif (BET) proteins. BET protein inhibitors, which are anticancer agents to BET proteins that are functional in most biological processes from transcription to cell cycle regulation, have been developed. These inhibitors show that selectivity for tumor cells by preferentially binding to super-enhancers, which are non-coding regions of DNA. (Doroshow et al., 2017).

However, inhibition of DNA methylation and histone deacetylation is being examined in detail as a therapeutic strategy in AML using DNMT and HDAC inhibitors (Sun et al., 2018). Azacitidine (AZA) and decitabine (DAC) is a DNMT inhibitor and gives an effective result in patients with myelodysplastic syndrome and AML patients. HDAC inhibitors valporic acid and vorinostat are approved for clinical use.

Studies for target-specific epigenetic therapies are in earlier stages; However, the expectations are very promising direction. Epigenetic therapies, some of the challenges that need to be taken into account before they become the basis of AML treatment strategies are available. Initial, much remains to be done in terms of preclinical and fundament research to explain the consequences of mutations discovered in AML based on epigenetic regulators. With a few exceptions, it is not fully known which subsets of AML could benefit from a particular epigenome-based therapy. Characterization and susceptibility studies are required for epigenome-based studies, including in vitro and in vivo inhibitors/genetic screens/specific “epigenetic lesions” and epigenomic studies to identify their respective progenitors (Sun et al., 2018).

5. Combined epigenetic therapies

Epigenetic drugs used in combination are seen as potential therapeutic agents in some diseases due to epigenetic disorders. Learning the genetic and epigenetic profiles specific to each patient results in optimal performance of these treatments.

The combination of DNA inhibitors and DNA deacetylation inhibitors azacitidine and entinostat, used at low doses in most patients with non-small cell lung cancer, has been shown to produce an effective response.

In addition, studies have shown that these two drugs have a synergistic effect when the efficacy of these two drugs is evaluated in metastatic colorectal cancer (mCRC) (Juergens et al., 2011).

Conventional chemotherapy treatments are ineffective in patients with Relapsing-Refractory Diffuse Large B-Cell Lymphoma (RR-DLBCL) due to its aggression and resistance (Pera et al., 2016). Another study addressing the combination of DNMTi and HDCI recommends this therapy as an effective therapeutic strategy for the treatment of RR-DLBCL. Thanks to these two drugs, the combination therapy synergistically enhancing the anti-lymphoma effect against RR-DLBCL functions in vitro and in vivo without any toxicity. (Pera et al., 2016).

Basic research showed that the synergy of different therapeutics in combination can target the apoptosis mechanisms of leukemia cells that disrupter therapeutic success with single - agent treatments (Bewersdorf et al., 2019)

6. Clinical reflection of epigenetics

Cancer biomarkers and cancer treatment are two main topic in the clinical use of epigenetics.

6.1. Cancer biomarkers

Molecules act as predictors of cancer response to immunotherapy and are called biomarkers. It is also widely used in personalized cancer immunotherapy: These include PDL1 expression, tumor-associated antigens, HLA expression, tumor burden, and neoantigen detection, lack of mismatch repair, tumor-associated macrophages, and the presence of cells that could potentially inhibit polymorphonuclear myeloid-derived suppressor cells, as well as the incidence of genetic changes together with treatment response. With epigenetic control of these mechanisms, the use of specific epigenetic changes as potential biomarkers for immunotherapy is feasible. These cancer cell-certain epigenetic changes are together with resistance to therapy in consequence of lineage in carcinogenesis, tumor progression, B-cell lymphoma, and leukemia (Villanueva et al., 2020).

Certain biomarkers which make attractive the use of a molecule are related features methylated genomic DNA. It is stable in biological fluids like blood, urine and saliva. Techniques used to recover methylation in CpG and methylated DNA during malignant transformation are appropriate to automation (Hatzimichael et al., 2013).

Given that changes in DNA methylation may be measured in liquid biopsies and body fluids, additional advantages can arise, such as low patient invasiveness. Besides, a flow of information about the lifestyles of

patients can be provided and details about the origin and progress of a particular disease can be revealed (Villanueva et al., 2020).

Therefore, DNA methylation for the identification of CpG hypermethylation that can be used as a cancer biomarker holds promise as a potential biomarker for early cancer screening. DNA methylation of certain gene sequences mainly reflects clinicopathological characteristics such as disease subtype, patient outcome, and cancer treatment response (Karin-Kujundzic et al., 2019).

HSF1 (Heat shock factor 1), which can be used as a cancer biomarker that is functional in cancer-specific transcriptional regulation, which is associated with poor prognosis and supports malignancy, has a pleiotropic effect on malignancy in many functional processes from tumor biology, DNA repair to angiogenesis. HSF1 functions as a possible biomarker for metastatic tumors by promoting the malignancy of cancer cells. The potential of HSF1 as a biomarker is to provide an understanding of its fundamental function in heat shock and cancer. Studies have shown that HSF1 mRNA and protein levels in more than one tumor type are predictable for patient outcomes and also have a prognostic biomarker function. For example, HSF1, which has an increased expression level in hepatocellular carcinoma (HCC), is associated with overall and metastasis-free survival of HCC patients (Carpenter et al., 2019).

Cancer biomarker studies conducted in a research setting use complex instrumentation and sample preparation techniques that are incompatible with daily operations in a clinical laboratory, require highly efficient, reproducible methods, and are easy to perform. For example, Proteomics-based cancer biomarker studies are based on mass spectrometers that have a low production capacity and require extensive staff training. This makes it difficult to fully automate clinical laboratories and integrate them with a multiplex test platform (Hristova et al., 2019) .

6.2. Cancer therapeutics

Research on epigenetic changes in cancer has led to the development of new anticancer drugs and attractive biomarker candidates called epigenetic modifiers. Unlike genetic changes that are therapeutically compelling, these epigenetic changes are reversible and make them attractive therapeutic targets. (Jung et al., 2020).

Epigenetic proteins and protein markers are emerging as good targets for the development of new anticancer therapies. Treatment of MDS, AML and some types of lymphoma, demethylating agents and histone acetylase (HDAC) inhibitors must be FDA and EMEA approved so that epigenetic treatments can be applied. (Hatzimichael et al., 2013).

DNA methyltransferase and histone deacetylase inhibitors are among the cancer therapeutics. The two best studies of cancer therapeutics in clinical use are DNA methyltransferase inhibitors (DNMTi), aza-nucleoside azacitidine (5-azacytidine) and decitabine. The agents used in both studies were approved for use in myelodysplastic syndromes and low blast number AML. The therapeutic activities of these agents are not limited to hematological malignancies, but are also used in the treatment of other tumors. HDACi, which catalyzes the removal of lysine residues from acetyl groups and is a functionally transcriptional suppressor, not only deactivates histones, but also deacetylates transcription factors, signal transducers, and even other non-histone proteins that are oncogene or TSG products involved in oncogenesis (Hatzimichael et al., 2013).

In order to increase the clinical success of the treatment, it is necessary to determine which cells have undergone epigenetic changes, to ensure the continuity of therapeutic agents, to target their ability to penetrate the tumor mass, and to target malignant cells. When epigenetics is used as a contributing factor, it will lead to the emergence of different therapeutic approaches; It will bring new insights into the development of normal and abnormal cells (Fardi et al., 2018).

7. Acquired chemoresistance from epigenetic regulation

Tumorogenesis is regulated by epigenetic defect and involves cellular reprogramming. Therefore, epigenetic disorders have significant benefits in acquired cancer drug resistance. DNA methylation, post-translational histone modifications and chromatin remodeling regulate epigenetic signaling and inherited gene expression (Ponnusamy et al., 2019).

DNA methylation and histone modifications that regulate a variety of fundamental cellular physiology, an aberration in epigenetic regulation lead to tumorigenesis and the development of resistance.

DNA mutations that cause chemotherapy resistance are irreversible mechanisms; However, it is known that changes resistant to epigenetic therapy have reversible mechanisms. There is new data that epigenetic therapy has the efficacy of overcoming chemotherapy resistance and sensitizing cancer cells to therapy. Among these data, it appears that epigenetic agents may help overcome chemotherapy resistance and increase sensitivity to chemotherapy, with promising clinical outcomes for acute myeloid leukemia and a range of malignancies, including colorectal, ovarian, lung and breast cancer.

With epigenetic agents in overcoming chemotherapy resistance, these treatments can be utilized when it is determined that the drugs used cause tumor-specific chemosensitivity and provide high target-directed toxicity at low doses (Strauss et al., 2016). In order to reverse drug-resistant tumors,

certain treatments can be offered by combining epigenetic treatments and traditional treatments, and this approach can eliminate the side effects of treatment depending on the dose of the drug. In this way, it will be possible to improve the patient's quality of life. (Fardi et al., 2018).

Abnormal DNA methylation conditions that trigger genetic/epigenetic changes occur early in tumor development and can reverse epigenetic aberrations by contributing to the carcinogenesis process.

Potential therapeutic opportunities arise thanks to the dynamic nature of abnormal DNA methylation. Unlike target cancer cells, epigenetic modifying agents targeting epigenetic enzymes that regulate the genetic programming of the cell are shown as potential therapeutic approaches. This approach is promising for inducing cell differentiation and resensitizing chemotherapy-resistant cells when cancer stem cells are in a stable situation. This can be achieved by using DNA demethylating agents, histone deacetylase (HDAC), histone methyltransferase (HMT) and histone demethylase (HDM) inhibitors. DNA demethylating agents and HDAC inhibitors alone or in combination with chemotherapeutic agents can be used to re-sensitize to chemo-resistance and show that their effect through cellular reprogramming. Minimal dose DNA methylating agents and HDAC/HMT/HDM inhibitors appear to decrease tumor formation and prohibit CSC invasiveness and tumor metastasis, besides reactivate silenced tumor suppressor genes and induce cancer stem cell (CSC) differentiation. Moreover, the combination of DNA methylation and histone-modifying agents may work synergistically to arrange the cross-interaction between the two mechanisms. (Ponnusamy et al., 2019). Addressing cellular programming is crucial to initiating transient drug tolerance leading to resistance development.

Although epigenetic agents are functional in overcoming chemotherapy resistance, they may not be effective in patients who do not tolerate additional chemotherapy. Therefore, if epigenetic drugs are determined to produce tumor-specific chemosensitivity and provide the low dose and extremely low toxicity, patients will continue to benefit from these treatments (Strauss et al., 2016). Also, epigenetic changes can be accurately identified with data from advances in genome-wide sequencing by RNA data profiles, chromatin immunoprecipitation (ChIP) or bisulfate transformation. Patients can be screened or grouped according to genetic modifications in driver genes using sensitive techniques with a personal therapeutic approach to treating each patient. The application of therapeutic programs by grouping the tumors according to their molecular properties and the use of higher dosages may improve efficacy of epigenetic therapy in solid tumors (Fardi et al., 2018).

As a result, determining which cells are undergoing epigenetic changes allow therapeutic agents to maintain their persistence, ability to permeate the tumor mass. The ability to target malignant cells will enhance the clinical achievement of the treatment. Also, in light of advances in scientific research, the road to personalized therapies and clinical applications in diagnosis, prognosis and prevention, a major advance in cancer epigenetics, will transform our views on chromatin structure, DNA methylation and gene expression, and on carcinogenesis and classification, as well as on chromatin structure, DNA methylation and gene expression. Epigenetic modifications can become useful biomarkers for prognosis and treatment of the disease, gaining the focus of epi-data. Given a large number of potential targets, a systematic approach that identifies and validates potential drug targets is needed to focus on drug development and achieve the promise of this strategy.

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Abstract

No matter how well the chemical and molecular structure of DNA has been resolved, with the advancement of technology, it has begun to be understood that everything is not just DNA. Changes occur in gene expressions in the process that starts from the embryo and lasts until the end of life. These changes have included the concept of "epigenetics" in our lives. With this concept, we are talking about a process that does not cause any change in the base sequence and is often reversible. “Epigenetics” is of great importance in controlling gene regulation, determining the differentiation processes of cells, and also elucidating how cells become carcinogenic. The biological events observed in living organisms regularly occur thanks to the interaction of genetic and epigenetic events. Defects occurring between these two systems to a number of diseases (leukemia, neurodegenerative diseases etc.) is inviting. In this review, epigenetics in which changes in gene expression are

examined, cancer treatment and the use of biomarkers for cancer are discussed, and how to find solutions to diseases using epigenetic therapy, and the functions of epigenetic regulations in gaining chemoresistance are emphasized. The effects of the drugs used in epigenetic therapy have also been shown in studies, and the only problem is that the specificity is limited for each patient in this process. Therefore, the limited specificity of drugs used in epigenetic therapy is a limiting factor in studies. In conclusion, in our review, we wanted to emphasize the importance of "epigenetics" in our lives by gathering together the concept of epigetic and its changes in epigenetic process, the therapies performed, and their effects on AML pathogenesis, which is one of the types of leukemia.

Keywords: Epigenetics; therapy; leukemia, biomarker

CHAPTER XVI

MICROBIOTA IN DISEASE FORMATION AND HEALTH PROTECTION

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1. Introduction

Intestinal flora, or with its known name, intestinal microbiota refers to the microbial community living in the intestines of mammals and humans. The microbiota is shaped after a long-term evolution and establishes a mutually beneficial relationship with the host (Li et al., 2021). Studies show that the intestines host approximately 10 times as many microbial cells as human body cells and that there are more than 500 billion species. *Bacteroidetes* and *Firmicutes* are dominantly located at the phylum level in the intestine. Aside from these, there are also *Proteobacteria*, *Actinobacteria*, *Fusobacteria*, *Spriochaetes*, *Verrucomicrobia*, and *Lentisphaerae* phyla (Carding et al., 2015). Generally, each of these takes part in many functions in the body. They also play roles in the maturation of the intestines and the stability of the intestinal structure after birth. Although this microbial community plays roles in the formation of some intestinal-borne diseases, they also undertake some functions in the prevention or treatment of some diseases (Natividad and Verdu, 2013). They take part in the expression of some genes in the body and participate in daily digestion. They also ferment various substrates and convert them into fibrous short-chain fatty acids. It was also reported in previous studies that they have some functions on the immune system (Zoetendal et al., 2008).

Most of the microbiota members are non-culturable microorganisms, and for this reason, Next-Generation Sequencing Genetic Technology (NGS) is used in its analysis (Kamps et al. 2017). This sequencing

technology is based on the enzymatic fragmentation of the selected target area of the genomic DNA that is obtained from the biological material to be examined and creating a library with a large number of DNA fragments. Microbiota analysis can be performed in many living things with metagenomic analyzes and can be associated with diseases (Kchouk et al., 2017; Bruijns et al., 2018). This also provides important evidence regarding their roles in the host. Although the idea that these microbial partners can support human and animal health is not a new concept, the extent to which the microbiota controls all physiological systems has recently become more understandable with NGS (Kashyap et al., 2013). The main function of the groups that exist in the microbiota is the protection of the host against pathogen invasion and colonization together with the immune system. However, they have been associated with many diseases from Alzheimer's to diabetes in recent studies. Similarly, the microbiota is seen as a factor that directly affects animal health in recent years. For all these reasons, they are also called the second brain (Lloyd-Price et al., 2019). In fact, opinions are arguing that the human enteric nervous system is a brain on its own, both structurally and neurochemically (Ridaura and Belkaid, 2015). Previous studies show that there is a correlation between microbiota changes and diseases such as mental disorders, obesity, metabolic diseases, autoimmune diseases, allergies, irritable bowel syndrome (IBS), acute chronic intestinal inflammation, and gastroenteritis (Goulet, 2015; Roquetto et al., 2015; Huang et al., 2018). In the present study, the current status of the relationship between microbiota and some diseases in animals and humans was discussed.

2. Intestinal Microbiota and Human Biology

The association of microbiota with health and disease occurs at every stage of human life. Any change in the healthy structure of the microbiota, which is considered to have a great say in vital activities, is called dysbiosis, and there are many intestinal diseases shaped by dysbiosis. It was reported in previous studies that the microbiota is generally affected by life-long environmental factors along with variables such as age, genetics, and drug use. Also, studies on how effective dysbiosis in childhood is in shaping the formation of disease in older ages are still underway (Saari et al., 2015). Scientific evidence shows that microbial flora is one of the factors governing human biology at every stage of life. Previous studies show that *Clostridium* replaces *Bacteriodetes* with aging. When the presence of *Bifidobacterium* was examined in newborns, it was reported that it colonized the neonatal steps 6 months after cesarean delivery. In vaginal delivery, it was shown that the predominant species in newborn babies was *Bifidobacterium* (Fouhy et al., 2012). Similarly, the ratio between dominant families (*Bacteriodetes* and *Firmicutes*) is constant under normal conditions. There are opinions that various metabolic

diseases occur if this ratio shifts in favor of one of these (Carding et al., 2015). Unlike the view that the microbiota, whose healthy structure is deteriorated, deteriorates body health and that the resulting form of dysbiosis affects the form of the disease, debates continue that the response of the intestinal microbiota creates dysbiosis in every disease (Ni et al., 2017).

2.1. The Role of Microbiota in the Protection of Intestinal Health

It has been emphasized in recent years that microbiota changes affect human health in general. The most important point that will be accepted indisputably in this respect is the relation between microbiota and intestinal health (Louis et al., 2014). Aside from metabolic diseases caused by microbiota whose general structure is deteriorated, they also cause serious health problems directly such as constipation, diarrhea, colitis, and IBS (Carding et al., 2015).

Ulcerative colitis, IBS, and Crohn's Disease are chronic and inflammatory diseases with unknown etiologies progressing in the form of attacks and showing a wide distribution worldwide with increasing incidence. These are inflammatory diseases that change the dynamics of the intestinal microbiota, and then trigger some important diseases such as dysbiosis and colon cancer (Ibrahim et al., 2019). It is considered that nutrition, genetic factors, immune system, antibiotic use, and microbial flora play roles in shaping such intestinal diseases (Manichanh et al., 2012). The general belief is that abnormal microbiota colonization in the intestines of individuals who have genetic susceptibility causes these diseases. It was observed in the microbiota analyzes in patients that there were significant differences in the taxa when compared to the healthy individuals. For example, it was reported that *Firmicutes* members are reduced considerably in Crohn's Disease. However, members of *Proteobacteria* such as *E. coli* increased. Analyzes in the same family members showed that intestinal diseases are caused by dysbiosis rather than genetic factors (Halfvarson et al., 2017; Ni et al., 2017). For this reason, it is considered that modulations in this microbial ecosystem will be very effective in preventing and treating diseases. Also, the immune system is among the important factors playing roles in intestinal inflammations and related diseases. The immune system has important effects on microbial colonization, and it is considered that abnormal communication between the microbiota and the mucosal immune system is the main factor causing chronic intestinal inflammation (Asquith et al., 2010; Ni et al., 2017). Animal studies elucidated the basic immunological pathways in the pathogenesis of diseases. The microorganisms in the intestines regulate the immune system and pro-inflammatory response by ensuring the release of some cytokines in the body. Previous *in vitro* and *in vivo* studies showed that some bacterial species in the intestine protect

individuals from intestinal inflammation by causing the regulation of pro-inflammatory cytokines or the stimulation of anti-inflammatory factors (Bringiotti et al., 2014). Aside from this, it was also observed that commensal species in the intestine produce metabolites that inhibit the settlement of pathogens from the outside in the intestines and the excessive increase in opportunistic ones in the microbiota. In this way, intestinal inflammation is prevented. It was also reported that the microbiota contributes to the benefit of the body in some cases frequently faced in bowel syndromes. In this respect, it was observed that it provides the induction of T-cells, which are among the basic cells of the immune system, synthesizes molecules that will prevent the immune system from reaching abnormal sizes and damaging the intestines, and modulates the mucosal immune response (Becker et al., 2015; Eminler et al., 2017). For this reason, it is foreseen that the microbiota must be balanced in the prevention or treatment of inflammatory bowel diseases. Also, the microbiota, which colonizes a large part of the gastrointestinal tract, has a great say in the basic functions of this system. For this reason, a balanced microbiota is necessary for a healthy digestive function, high utilization of nutrients, and removal of wastes from the body (Alkan, 2017; Ni et al., 2017).

2.2. Can Microbiota Cause Obesity?

Obesity is an important and growing public problem worldwide with a multifactorial etiology. It is generally defined as a disease characterized by uncontrolled fat accumulation (WHO). It was reported that approximately 39% of individuals over the age of 18 have had obesity problems since 2016 worldwide. This shows a very high rate of global healthcare problems (Cao et al., 2019).

It is a long-known fact that many factors play roles in the formation of obesity. Also, recent studies have shown the role of a new partner in the formation of obesity in the intestinal microbiota. According to the microbiota analysis performed in individuals diagnosed with obesity, the ratio of two dominant *Bacteriodetes/Firmucutes* phyla was found to be impaired. In our present day, obesity is described as a healthcare problem characterized by increasing intestinal dysbiosis. Various studies show an association between intestinal microbiota composition and body weight (Everard and Cani, 2013; Moreno et al., 2020).

In previous studies that were conducted with obese individuals in a certain age range, it was observed that bacterial lipopolysaccharides and cell wall residues that originate from microbiota are present in the circulation. This stimulates the inflammatory response allowing the release of chemotactic substances. This process, which is called metabolic endotoxemia, causes muscle loss in the body, increases intestinal

permeability, and results in damage to other tissues (Everard and Cani, 2013; Duranti et al., 2017). This forms the basis of the decreased muscle tissue and increased adipose tissue in obese individuals. Based on these findings, various studies are conducted on the treatment of obesity with microbiota modulations. It was found in studies that investigate probiotic supplements for therapeutic purposes in experimental animals that *Bifidobacterium* spp., *Lactobacillus* spp., *F. prausnitzii*, and *A. muciniphila* supplements had positive effects on lipid ratios and inflammatory processes in obese subjects. Although these experimental animal studies suggest that probiotic and prebiotic interventions are very important in the treatment of obesity, more studies are required in this respect (Everard and Cani, 2013; Duranti et al., 2017; Moreno et al., 2020).

However, it is already known that the daily diet plays active roles in inflammatory processes. A diet that is rich in fat modulates the intestines affecting the permeability of the intestines by changing the composition of the microbiota. Also, since the relation between obesity and diet is indisputable, it would not be wrong to argue that the daily diet-microbiota-obesity triangle is directly associated with each other. Previous studies showed that low fiber and high fat compounds affect the glycemic index and microbiota structure negatively (Foley et al., 2018). On the other hand, the microbiota plays roles in the metabolism of various oligosaccharides and fatty acids affecting energy metabolism. For this reason, it is still a matter of debate whether the microbiota which changes depending on daily diet and physical activity causes obesity or whether dysbiosis appears with the onset of obesity. However, scientific evidence shows that the intestinal microbiota plays very important roles in the pathogenesis of obesity.

2.3. Diabetes and Microbiota

Diabetes is a chronic disease that is characterized by increased amounts of sugar in the blood, which occurs because of the problems with the production of the insulin hormone by the pancreas or the effective use of this hormone produced. It is a disease in itself, and it can also be a triggering factor for the formation of other diseases such as neuropathies, kidney degenerations, including cardiovascular diseases (Glovaci et al., 2019). The International Diabetes Federation has reported that diabetes, which affects human health in many ways, has become a pandemic increasing with each passing day all around the world. In this regard, it has important effects not only on health but also on social and economic problems (Chami and Khaled, 2022).

On the other hand, the number of genes included in the microbial community is approximately 100 times greater than the number of human body cells. For this reason, the expression of these genes is highly likely to play roles in many functions of the body. There is some evidence that the

microbiota, which has recently been associated with many diseases, plays roles in the formation of diabetes. Physiological changes in the digestive system occurring because of the development of dysbiosis cause increased energy that is provided from short-chain fatty acids, decreased levels of Fasting-Induced Adipose Factor (FIAF), and Adenosine Monophosphate-Activating Protein Kinase (AMPK) signaling. In this respect, Lipopolysaccharides (LPS) activate the immune system increasing the production of pro-inflammatory cytokines. In this way, dysbiosis plays important roles in the pathogenesis of obesity, diabetes, and insulin resistance (Everard and Cani, 2013; Tavares da Silvia et al., 2013; Özsoy, 2019). It was reported in a previous study that blood sugar was regulated and insulin resistance decreased in mice that were fed with symbiotic yogurt (Ban et al., 2020). In another experimental animal study, it was reported that linseed oil modulates the intestinal microbiota, and therefore, the findings of diabetes decrease (Zhu et al., 2020). In general, it was observed in microbiota analyzes performed in diabetic patients that the ratio of the two dominant phyla, *Bacteroidetes* and *Firmicutes*, was impaired (Özsoy, 2019). However, here, the basic question of the relationship between many diseases and the microbiota is also on the agenda; Does diabetes develop in individuals with dysbiosis, or do significant reactions occur in the microbiota with the onset of diabetes? Further studies are needed to answer this question. However, it is generally believed that microbial change precedes diabetes (Dunne et al., 2014).

2.4. Is Microbiota the Cause of Depression? Collaborator?

It is already known that the microbiota interacts with many systems in the body, it is especially related to the nervous system closely. Studies conducted on the important roles of microbiota in the gut-brain axis are increasing with each passing day (Cheung et al., 2019).

This microbial community that is hosted in the intestines produces neurologically active substances e.g. Gamma-Aminobutyric Acid (GABA), as well as performing the digestion of indigestible foodstuffs and the producing of micronutrients. These are important molecules affecting the hypothalamic-pituitary-adrenal axis in the host (Mayer et al., 2015; Cheung et al., 2019). Also, many experimental animal studies are showing the relation between inflammatory conditions, altering intestinal permeability, microbiota, and depression. Previous studies showed that intensive use of antibiotics causes dysbiosis causing neuronal changes, and shaping depression-like behaviors in animals (Maes et al., 2008; Maes et al., 2012). However, there are also findings that *Lactobacilllus* spp. supplementation has therapeutic effects, some stimuli occur in the hippocampus, and some hormones are released (Clarke et al., 2013; Kelly et al., 2016). Although anxiety and major depression-like behaviors were observed when unhealthy microbiota transplantation was performed to

germ-free animals, similar conditions were not observed in healthy microbiota transplantation (Kelly et al., 2016; Zheng et al., 2016). Similarly, although major depression symptoms were observed when opportunistic agents such as *Clostridium* and *Klebsiella* metabolized carbohydrates, it was reported that the findings of major depression after feeding decreased with the increase of probiotic members such as *Bifidobacter* (Macfabe, 2012; Vindigni et al., 2013; Derya Ipek and Özgün Yılmaz, 2018). For this reason, it is argued that the intestinal microbiota-brain axis plays roles in the formation of conditions such as stress and depression. However, it can also be argued that a single type of diet is a marker for depression because it affects the microbiota composition. Especially in recent years, some studies have reported that unhappiness and depression are more common in individuals who eat carbohydrate-heavy diets (Sommer & Bäckhed, 2016).

2.5. Cancer and Microbiota

Uncontrolled and abnormally-dividing cells make up the cancer tissue. Cancer, which is one of the most feared diseases of the 20th century, continues to be a global healthcare issue with an increasing incidence in the 21st century (Roy and Saikia, 2016). Although the causes of cancer include genetic factors as well as environmental factors such as chemical factors and radioactivity, it was also reported that infectious agents can also cause cancer. Microorganisms such as bacteria and viruses can cause cancer, and the change in the microbial load in the intestines plays important roles in the formation of cancer, especially in the intestines (Park et al., 2018). However, the microbiota has a complex system and play roles in the biology, health, and disease formation in the host, both transcriptomically and metabolically along with the genetic characteristics of the host. Researchers argue that an intact microbiota must exist for the most favorable cancer treatment. Studies are underway on how the microbiota affects the person with cancer and cancer tissue. The current general opinion is that immune responses against cancer cells are mediated by microbiota (Dzutsev et al., 2014).

Studies in germ-free animals showed that there is an interaction between microbiota and cancer formation (Klimesova et al., 2013; Raza et al., 2019). Microbial metabolism can cause the activation or inactivation of carcinogens. For example, it was shown that bacteria-mediated acetaldehyde production has vital importance in oral cancer tissue because of its limited metabolism. Similarly, the effects of microbiota, which also affects hormonal metabolism, were reported in estrogen-related cancers. In this respect, it was also reported that the microbiota modulates the development of cancer. However, findings show that members of the microbiota that undergo dysbiosis suppress chemotherapeutic drugs used in cancer treatment (Plottel and Blaser 2011; Raza et al., 2019).

3. Conclusion

The microbiota and the human body develop together. Colonization, which begins at birth, continues throughout human life. For this reason, disruptions in the microbial community likely affect the body. Many studies show that the current state and changes of the intestinal microbiota have more than expected effects on the human body. In previous studies, debates continue whether or not the microbiota is a collaborator of diseases or whether it is a cause or a result of diseases. However, scientific evidence shows that the microbiota is among the important factors that affect most functions of the host playing roles in the pathogenesis of diseases.

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CHAPTER XVII

HOMEOPATHY IN PHARMACOLOGY

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Homeopathy is formed from the combination of the Greek words homoeo (similar) and pathos (pain) (Ruddock, 2007; Walach et al., 2005). It is one of the most popular areas of alternative medicine (Nair et al., 2014). According to homeopathy, a substance that shapes disease symptoms or causes pain in non-patients is based on the principle of healing in patients with the same findings (Kural Cigerli and Ilhan, 2021; Hahnemann, 1982). It also proposes to use a wide variety of substances to stimulate the physiological reactivity of the organism by directly combating diseases (Bianchi, 2017). Based on the report published by the World Health Organization (WHO) (World Health Organization, 2022), homeopathic medicines are widely used in over 100 countries.

1. History

Homeopathy is a form of treatment that has existed in various forms since ancient times. Sources for the use of homeopathic principles date back to the Ancient Egyptians, Chinese, Aztecs, and Native Americans (Ullman, 1998).

German Doctor Friedrick Samuel Hahnemann, while translating Materia Medica into German in 1790, saw that he treated malaria using cinchona bark, and this did not make much sense to him. He drank four sips of cinchona-containing water twice a day for several days to fully

appreciate the potency of the treatment. After a while, malaria-like symptoms appeared in his body. When he performed these trials in other healthy people, he saw the same results, and he thought that if the same drug was given to sick people who had similar findings in healthy people, they could be treated. Homeopathy was discovered based on this principle.

The full discovery of homeopathy was between 1796-1843 and it was developed over time. This period coincided with the time when epidemic diseases (such as rabies, smallpox, flu, diphtheria, tuberculosis, scarlet fever, syphilis, gonorrhea) were common in European societies. In this period, when bacteria and viruses were not fully known, the concept of infectious disease was still unknown. Primitive theories based on superstitions had a significant impact on the treatment approaches of the period. Draining the patient's blood (hijama), leech therapy, and applications with metals such as arsenic and mercury were among the main treatment methods (Kate, 2007). Homeopathy has found use because of its success in the prevention and treatment of many epidemic diseases (Kural Cigerli and Ilhan, 2021).

2. Basic Principles of Homeopathy

2.1. Similarity

Hahnemann explains as “a weaker dynamic influence is eliminated by a similar and stronger influence” (Hahnemann, 2013). In other words, it is based on the Latin "Similia Similibus Curantur" meaning "like cures like" principle. According to this rule, it is important to strengthen the patient's life force by producing similar symptoms instead of eliminating the symptoms (Kayne, 2006). In this rule, there is the idea that a disease can be cured with the substance that causes it. For example, when caffeine is taken in excessive, it causes symptoms such as insomnia, irritability, palpitation however, caffeine can become a homeopathic remedy that can be used to treat insomnia, palpitations and irritability (Kural Cigerli and Ilhan, 2021). In many primitive societies it has been reported that they could be used in histamine-mediated situations such as insect stings of bee or by vaccinating them several times with substances made from snake

venom to protect themselves from snake poisoning (Kural Cigerli and Ilhan, 2021; Kayne, 2006).

2.2. Single Drug

There is a principle in homeopathy, only a single drug is used that fits the severity, appearance and symptoms of the disease, different drugs cannot be mixed with each other. This theory is applied in studies examining the efficacy of homeopathic medicines. The reason for this is that only one drug is similar to the patient's condition, and it is not known which drug will cause the effects that occur in the use of more than one drug. It is suggested that the total effect will not increase as a result of the administration of many drugs on the contrary, they will prevent the effects of each other (Ruddock, 2007).

2.3. Life Force

This theory reveals that 'the body is not a machine in which organs are kept together, but inside every body there is its own physician who heals it'. Hahnemann referred to this healing power as the "vital force". For the application of any treatment, the body's response power to the treatment must be sufficient. It is thought that the ability to bodily sensation, function and protect oneself cannot be fulfilled without the vital force. In short, it is explained that the life force completely directs the bodily organism (Hahnemann, 2013; Kizil and Atam, 2016). The purpose of applying a similar drug is to stimulate this power and provide healing. In other words, the drug gives the life energy the opportunity to do its job in the best way (Owen, 2007).

2.4. Minimum Dose

According to this theory, it means that the lower dose of the drug, it will be more effective (Kural Cigerli and Ilhan, 2021). Since high doses will affect the healing power above the detection capacity, treatment failure may occur. This is especially important for patients with low vitality (Owen, 2007). The aim is to perform the treatment without tiring the patient. The low but sufficient efficacy of the drug to be administered ensures that the undesirable effects of the drug are reduced. Although

permanent undesirable effects are not seen in homeopathy, it can minimize the side effects that may occur (Kayne, 2006; Moore, 2007).

3. Homeopathic Substance Selection and Preparation of Medicines

In homeopathy, all symptoms should be taken into account when choosing a medicine. Disease-specific symptoms are considered in traditional (conventional) medicine, while patient-specific symptoms are considered more in homeopathy. In addition, it is aimed to evaluate not only the symptoms occurring in certain organ/system but also the symptoms in the whole body and to deal with them as a whole. For this reason, a detailed anamnesis should be taken, the patient's condition should be observed very well, and the most appropriate drug should be selected and used (Baehr, 2004; Vockeroth, 1999).

Substances used in homeopathy can be of vegetable (Table 1), animal, mineral origin as well as acid, salt, enzyme and synthetic (Table 2). There are harmless natural substances that can activate certain sensitivity mechanisms in living organisms and do not interfere with natural defense reactions (Ortiz-Cornejo, 2017). Sometimes, it can also be dog saliva with rabid, vaccines, scabie insects, tuberculin, and substances originating from cancerous formations.

Raw materials (vegetable, animal, etc.) are cut and shredded after being washed, dried, and then sent to the laboratory for many examinations. It is kept in a solvent for a while, then the main substance (tincture, powder, extract etc.) is obtained by separating the dissolved parts (Ullman, 1998). Homeopathic medicine is obtained by diluting the main substance. The degree of dilution is known as the strength of ten. While water, alcohol, aqueous alcohol (10%), spirit, aqueous spirit (10%) and glycerol are used as liquid diluents in dilution processes, substances such as lactose and sucrose are used as solid diluents (Clausen and Albrecht, 2010). Dilutions can be made in the form of D potency (Decimal), C potency (Centimal) and Q potency (Quinquagiesmillesimal) dilutions. D potency dilution is 1/10, C potency dilution is 1/100, and Q potency dilution is 1/50000 dilution (Baehr, 2004; Chatterjee, 2003).

Table 1: Some Plants Used in Homeopathy

	Name	Use of drug
PLANTS	Aconitum napellus	Anxiety, antipyretic, and pain reliever (Bhat et al., 2020)
	Atropa belladonna	Mydriasis, tachycardia, and nervous system activation (Oniszczuk et al., 2013)
	Caulophyllum thalictroides	Viral diseases, female reproductive system diseases (Riley, 2018)
	Agnus castus	Postpartum depression, female reproductive system diseases
	Urtica	Anti-inflammatory, antifungal, benign prostatic hyperplasia (Safarinejad, 2005)
	Pulsatilla	Infertility (BalajiDeekshitulu, 2020)
	Caulophyllum	Viral infections, allergy (Riley, 2018)
	Calendula	Dental infections (Mourao et al., 2020)
	Euphrasia	Hay fever, sinusitis (Wandile, 2017)
	Drosera rotundifolia	Spasmolytic, antitussive (Allaert et al., 2017)

Table 2: Other Substances Used in Homeopathy

	Name	Use of drug
ANİMAL	Sepia	Gynecological diseases, ringworm (Dixit and Giri, 2020)
	Apis Mellifica	Leg edema, anti-inflammatory (Bigagli et al., 2014)
MINERAL	Sulphur	Depressive disorders (Oberai et al., 2013)
	Phosphor	E. cuniculi infection (Nagai et al. 2019)
	Kalium bichromicum	Treatment of peptic ulcer (Ratnaparikh and Adkine, 2021)
	Ferrum Phosphoricum	Antioxidant, immunomodulator (Tasinov et al., 2021)
ENZYME	Bromelain	Periorital edema, ecchymosis (Sakallioglu et al., 2021)

4. Uses in Veterinary Medicine

Homeopathics have found use because they are obtained from natural sources, are economical, and do not have undesirable effects when used with other treatment applications (Braghieri et al., 2007; Rajkumar et al., 2006). In veterinary medicine, it helps in the treatment of many diseases such as allergies, uterus/urinary tract/breast diseases, infertility, retention of puppies, joint-muscle inflammations and pains, smooth muscle spasms, hepatitis, fatty liver, heart failure (Ruddock, 2007). Some herbal, animal and mineral origin homeopathic substances used in veterinary medicine are as follows;

Comfrey grass: It accelerates the joining of broken pieces. In other words, it stimulates faster recovery and better recovery.

Tarantula cubensis (Theranecron): It is used in the treatment of breast tumors. It has been observed to be quite effective in preventing the formation of new tumors. In addition, it reduces the severity of vaginal discharge, accelerates uterine involution, and can prevent retention of secundinarum (Gultiken and Vural, 2007; Kacar et al., 2007).

Aloe vera: Positive effects have been observed as a result of intramammary use in cases of mastitis (Duval, 2021).

Chasteberry: It is effective on the female and male genital system.

Honey bee: It is effective in acute or chronic edema. In addition, it can also be used for joint inflammation, ovarian dysfunction and breast inflammation.

Beautiful horsetail (Atropine): Especially mares are sensitive to this substance. It is more effective on the central nervous system. Response can also be obtained in very painful abscesses.

Wind rose: It is one of the most important homeopathics. It is effective on the circulatory system, skin, mucosa, digestive system, liver and muscles. It also has effects on the central nervous system and pituitary. It can be preferred in animals that are mostly calm but can suddenly become aggressive and have behavioral disorders. It helps the contractions to be regular and the opening of the cervix during birth.

Cuttle fish: It has an effect both the genital organs and blood-lymph system. It can also be used to regulate these behavioral disorders in cows, in case of sexual cycle disorders, liver failures, dogs that do not take care of their puppies after birth, or dogs that eat their puppies.

Lion ear: It has a regulatory effect at all stages of the birth process, before, during or after.

Tailless frog (Buforana): It is effective in central nervous system disorders, paralysis and excessive sexual desire. It is used especially in cases of motor disorders due to viral infections.

Stinging nettle: It helps to remove milk from the mammary gland and urticaria.

Witch hazel (Hamamelis): It is used in bleeding perforated wounds.

Eye herb: It helps many eye diseases, including conjunctivitis caused by cold winds. It is used in cases of sneezing and nasal allergies, and also as a first aid treatment for eye ulcers.

Citrillus colocynthis: It can be used for first aid purposes in case of pain in horses.

Calendula/Garden: Used as a lotion to accelerate the healing of cuts, scrapes or open wounds. It also helps him fight the septic infection caused by such injuries.

5. Conclusions

Since there are not enough studies on the use of homeopathic medicines in veterinary medicine in our country, their effects on the tissue are not fully understood. However, it is known that homeopathic medicines can activate many bioenergy systems in the body, as they have strong effects, even if the intensity is low. It will have a more widespread use in the future due to its advantages such as being obtained from natural substances, being economical and not addictive. It is thought that this information will provide a source for studies on homeopathy.

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CHAPTER XVIII

HIGH-RISK PREGNANCIES AND CASE MANAGEMENT IN MARE

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1. Introduction

Average gestation period in mares is between 330-345 days and varies between 310-370 days according to warm and cold blooded breeds. The mating season begins in the northern hemisphere in late winter or early spring and lasts until conception occurs or autumn. The mating season is usually between April and October. Sexual activity is most intense in June. Although mares generally reach puberty when they are 12-24 months old, regular cyclic activity can only be seen from the age of 2 and the age of first insemination is 3 (England, 2005, Kaymaz et al., 2015). While risk is the possibility of occurrence of undesirable situations with the presence of one or more factors, "risk in terms of pregnancy" is the possibility of occurrence of some pre-existing complications that are not expected under normal conditions but may develop during pregnancy (Kuru, 2007). Three main case groups are used in the evaluation of risky pregnancies in mares (Santchi & Vaala, 2011). In the first group, there are mares with pathologies that have the potential to recur in previous pregnancies, such as premature placental abruption, placental abruption, premature birth and dystocia. In the second group, there are mares with suspicious findings in their current pregnancy. Although there is no reproductive problem in the past seasons in the anamnesis of these mares, abnormal findings such as general weakness, exposure to anesthesia, systemic diseases, acute colic, vaginal discharge, early mammary gland development or excessive abdominal growth are accompanied in advanced pregnancy. Although there is no definite pathology in the mares in the third group, a suspicious situation is mentioned in the observations of experienced breeders and physicians. When all groups are evaluated, it is important to monitor the mares with periodic examinations, to maintain the well-being of the mother and the fetus, and to continue the pregnancy (Santchi & Vaala, 2011, Macpherson, 2012). In twin pregnancies in mares, fetal count can be considered as the first step in terms of risk detection, considering the circumstances such as insufficient nutritional environment and immunological rejection of each other by fetuses. Twin pregnancies in

mares carry a 65-70% risk of abortion. For protection purposes, one offspring is reduced in mothers who have twins after an early pregnancy test (Whitwell, 2011). Early diagnosis and effective treatment of possible pathologies may be possible with careful follow-up until delivery, following the detection of a single sac in ultrasonographic examinations. Again, since intrauterine growth retardation, hypoxia and various infections will be very effective on neonatal vitality in the offspring, ultrasonographic examinations are performed for the morphology and hemodynamics of the fetoplacental structure in these animals. In this way, it may be possible for newborns to get the right support in the intensive care units as soon as possible by taking the necessary precautions before birth. Neonatal mortality will be high in advanced cases and in pregnancies where proper management cannot be performed (Vaala & Sertich, 2006). The main thing in the management of risk pregnancies is the treatment of the primary disease and the continuation of the pregnancy. The main goal is to control the health of mares and foals without threatening them. In applications that serve this purpose, sometimes the same and sometimes independent approaches may be in question. The management of risk pregnancies should be carried out effectively in the presence of follow-up findings. If a choice between mother and offspring has arisen in the management of some cases with high perinatal mortality and poor prognosis, the expectation of the owner (mare or foal?) is decisive on the treatment protocol (Tibary & Pearson, 2012). Another approach in the evaluation of risk cases during pregnancy is to define the tissue from which the pathology originates. Accordingly, the cases may be of maternal or feto-placental origin. From this point of view, pathologies that can be seen in high-risk pregnancies and the management of these cases can be summarized as follows:

2. Non-pregnancy related (Non-obstetric) pathologies: Findings of varying severity, such as general health problems originating from maternal tissues and stress due to secondary pathologies not related to childbirth, malnutrition, anorexia, high fever, pain, irreversible destruction of the skeleton and internal organs, reduce the mother's quality of life and cause risk pregnancies. The main non-birth related problems and treatment practices that may adversely affect pregnancy in mares are summarized below.

2.1. Colic: Although it does not make a significant difference in colic management in mares in terms of the current pregnancy treatment protocol, the prognosis in advanced pregnancies gradually worsens (Santchi & Vaala, 2011). The presence of pregnancy-related discomfort and gastrointestinal lesions is important in the differential diagnosis of advanced pregnant women. In treatment, a double dose of altrenogest (0.088mg/kg) can be used every 24 hours to reduce uterine contractions

that may start due to colic. Against fetal hypoxia, the circulatory system should be supported with intravenous fluid therapy. Antibiotics can be used against endotoxemia, enteritis and other bacterial infections. Again, anti-inflammatory drugs are effective in colic of gastrointestinal origin. (Macpherson, 2012). A surgical approach is required in the treatment of colic in advanced pregnant mares after large colon abnormalities and small bowel lesions. However, the increasing effect of surgical procedures on fetal risk should not be forgotten. The pressure caused by the pregnant uterus on the aorta and diaphragm in mares lying on their back during the operation causes hypotensive picture in mother and foal. Researchers report that approximately 20% of abortion cases are encountered after colic surgery (Santschi & Vaala, 2011). In a similar study, an increase in fetal mortality was observed in operations performed in the last 60 days of pregnancy (Santschi et al., 1991). The results of performing laparotomy-cesarean section together, which can be recommended in such cases, are controversial. Since the disruption of the maturation process of the fetal lungs will reduce the neonatal vitality, determining the correct operation time is the most critical point (Silver et al., 1984). The gestation period in mares lasts 335-345 days, but it may vary in some mares (Rossdale & Ricketts, 1980). Therefore, the duration of pregnancy alone is not decisive for induction of labor or cesarean section. Cervical softening, mammary development and the presence of colostrum should be investigated and it should be evaluated whether the offspring is ready for the external environment (Ousey et al., 1984). Chemical analyzes in the presence of colostrum are very decisive. A milk calcium level of 40 mg/dl and a potassium level of 30 mEq are accepted as threshold values for fetal maturation (Ousey et al., 1984). In the presence of compelling conditions such as inability to reach the fetus during the operation, the source of the pain (such as distal small colonic lesions) should be primarily focused on. If the foal is removed from the uterus within 20 minutes after anesthesia, the effect of anesthesia on the foal decreases and the chance of survival increases (Watkins et al., 1990). In addition, controlling hypoxemia, which may occur intraoperatively and postoperatively, is effective in prognosis. Maternal blood pressure should be kept above 80 mmHg and oxygen support should be provided. The signs of metritis and endotoxemia should be controlled with postoperative flunixin meglumine injections. In such cases, premature cesarean section operations should be avoided as much as possible, since it will not be possible to keep the offspring alive without supportive care and monitoring in neonatal intensive care units (Santschi et al., 1991, Santschi & Vaala, 2011).

2.2. Laminitis: Increasing body weight during pregnancy is one of the factors that increase the incidence of laminitis. It is considered to be an important risk due to its progressive nature and severe pain in the mother.

Exercise limitation should not be applied to reduce complications in laminitis cases in pregnant mares. Thanks to the exercises to be done at a low tempo, edema and other signs of inflammation will decrease. Nonsteroidal anti-inflammatory use is recommended in all cases of laminitis. There are also opioid and intravenous lidocaine applications for analgesic effect, but the effect on the fetus is not known for certain (LeBlanc, 2008, Santschi & Vaala, 2011).

2.3. Endotoxemia: The primary cause of the disease is mostly the toxins of gram-negative agents in the gastrointestinal tract (Santschi & Vaala, 2011). Free cytokines in the general circulation can cause coagulation and decrease tissue (especially placental) perfusion, leading to fetal losses (Werners et al., 2005). Intravenous isotonic, hypertonic fluids, colloid and plasma administration are effective in supportive treatment. Again, cyclooxygenase inhibitor drugs such as flunixin meglumine and endotoxin binding agents such as polymyxin B are recommended (Barton et al., 2004). In the specific treatment, the use of progesterones in pregnant mares and oxygen support during endotoxic crisis are essential. Treatment should be continued until clinical findings disappear or improvement in feto-placental follow-up findings is confirmed (Santschi & Vaala, 2011).

2.4. Various infectious cases: The use of nonsteroidal anti-inflammatory drugs is effective for high fever in equine herpes virus (EHV-1) or equine arteritis virus infections. In addition, acyclovir applications provide prophylaxis by preventing the release of the EHV-1 agent into the environment (Wilkins et al., 2005). However, it should not be forgotten that acyclovir carries a risk of abortion, since the effect of acyclovir on the development of the fetus is not certain. In recent years, researchers have stated that the use of valaciclovir (27 mg/kg peros, two days at 8-hour intervals, and 18 mg/kg at 12-hour intervals in the following days) causes a day-to-day decrease in nasal discharge. They also reported that neurological findings caused by the neuropathic strain of EHV-1 and findings in the viremia stage decreased (Maxwell et al., 2009). It has been reported that especially penicillin applications and isolation measures are effective in the treatment of leptospirosis infections in mares (Bernard et al., 1993).

2.5. Toxication of meadow grass*:* Consumption of meadow grass infected with the endophyte named Acremonium coenophialum in mares should be avoided and infected pastures and dry grasses should be avoided for the last 60-90 days. If this is not possible, starting from day 300 of pregnancy, domperidone (1.1 mg/kg, every 24 hours), sulpiride (3.3 mg/kg, 12 hours apart) or perphenazine (0.3-0.5 mg) containing D2 dopamine receptor antagonists /kg, peros, every 12 hours) can reduce clinical and endocrine findings (Redmond et al., 1994). Domperidone use

is preferred over other D2 antagonists because it does not cross the blood-brain barrier. Treatment should be continued for at least 1-2 weeks after delivery (Redmond et al., 1994). Caesarean section is indicated for mares affected by meadowgrass toxicity (Santschi & Vaala, 2011).

2.6. Pelvic abnormalities: Existing pelvic abnormalities in mares are an important risk factor for mother and fetus in the second phase of labor. Fracture healing and callus formation in pelvic injuries narrow the pelvic canal and cause dystocia (Santschi & Vaala, 2011). In such cases, hysterectomy is preferred. Fetal survival rate has been reported in the range of 66-88% in pregnant mare with abnormal pelvis structure (Watkins et al., 1990, Santschi & Vaala, 2011). In order to determine the correct time for hysterectomies, the condition of the pelvic canal and signs of delivery should be carefully investigated.

2.7. Prepubic tendon rupture and abdominal hernia: Abdominal wall or prepubic tendon ruptures may be encountered in advanced pregnant mares. Shooting horses and out-of-form mares are more likely to have these conditions. In mares with prepubic tendon rupture, edema in the lower abdominal wall and characteristic sawhorse posture are observed (Macpherson, 2010). In protection, the mare's movements should be limited and overfeeding should be avoided. In order to support abdominal contractions during labor, the abdomen should be wrapped with a large cotton-filled support. When labor begins, extraction force can be applied by assisting the mother (Macpherson, 2007). In very painful cases, analgesics intravenous flunixin meglumine or phenylbutazone may be recommended. In addition, fluid therapy, antibiotics and applications that support placental functions or fetal health (altrenogest, pentoxifylline and vitamin E) can be applied (Ross et al., 2008). If high-dose dexamethasone (100 mg) is administered for three consecutive days starting from the 315th day of pregnancy, delivery can be initiated within 1-8 days following the last administration (LeBlanc, 2008). In cases of abdominal hernia, complications such as death of the mare due to internal bleeding or intestinal damage, intestinal evisceration following the rupture of the body wall, intra-abdominal adhesion and intestinal trauma, and postpartum colic are encountered (Vaala & Sertich, 2006). Emergency laparotomy should be performed in cases of suspected intestinal obstruction. While surgical intervention gives successful results in small tears in the body wall, the prognosis is poor in larger tears. Colts born from mares with prepubic tendon rupture or hydrops develop problems associated with chronic placental insufficiency, such as hypoxic ischemic encephalopathy. As the births associated with these disorders will be hard and long, neonatal stress occurs as a result of acute hypoxia. Most of these foals are weak puppies that have difficulty in standing, require special care, have insufficient

absorption of colostrum antibodies and are susceptible to early sepsis (Vaala & Sertich, 2006).

2.8. Urinary bladder rupture: Urinary bladder ruptures seen in pregnant mares are cases that require urgent intervention and have a high mortality. In limited cases, an economical and successful treatment can be performed with catheter application, peritoneal lavage and supportive treatment (Beck et al., 1996). 0.9% NaCl, broad-spectrum antibiotics and nonsteroidal anti-inflammatory drugs can be used in hyperkalemic and hyponatremic patients (Lillich & DeBowes, 1999). However, in many cases, surgical approach is inevitable. In such cases, a fluid sample should be taken from the peritoneal cavity after incision from the median line and a bacterial culture should be performed, and postoperative antibiotic selection should be made. After sampling, the urinary bladder is emptied, the tear is located, and the wound lips are sutured (Lillich & DeBowes, 1999). Considering the risk of stone formation in closing the tear, it should be sutured in two layers with synthetic absorbable suture material (Kaminski et al., 1978). The uterus should be carefully examined before the abdominal wall is closed. In the ruptures formed in the neck of the urinary bladder, the operation to be performed from the median line usually cannot reach the relevant area. For this reason, urethral sphincectomy is performed in the outpatient mother under lower epidural anesthesia. After the operator reaches the bladder, he should return the bladder to the vagina and repair the tear. Then, the urinary bladder should be brought to its anatomical position and the urethral incision should be closed (Higuchi et al., 2002). Cases of the operator's hand advancing through the atonic urethral sphincter and performing a single-layer suture in the pouch have been reported. However, during the closing process, intestines etc damage to tissues should be avoided (Jones et al., 1996).

3. Pregnancy-related (Obstetric) pathologies: Pathologies originating from the uterus, offspring membrane/waters and fetus that will occur during pregnancy are the main findings for the diagnosis of risk pregnancy. Early diagnosis and prompt implementation of the correct treatment protocol in obstetric-related problems are very important for the continuation of pregnancy. Treatment practices related to the main obstetric pathologies seen in risky pregnant mares are summarized below.

3.1. Endometrial dysfunction: Mares with placental insufficiency and weak endometrium structure are faced with varying complications such as abortion or delayed delivery. Currently, there is no effective treatment protocol for endometrial insufficiency in mares. However, treatment with altrenogest, pentoxifylline and oxygen support can be tried. In the management of the cases, the general health status of the mare should be

monitored throughout the pregnancy due to the prolongation of the gestation period (Santschi and Vaala, 2011).

3.2. Uterine torsion: In cases of torsion formed after the 320th day of pregnancy, the survival rate of mother and fetus decreases significantly. External maneuvers or surgical correction are used to correct the torsional uterus (Chaney et al., 2007, Kaymaz et al., 2015). External rotations are ineffective if the mare also has a gastrointestinal lesion or uterine rupture. In mid-term pregnancy torsions, in cases where the animal owner cannot afford the surgical intervention, in cases where the birth has started, the cervix is open, and less than 270° torsion, external correction can be made (Riggs, 2006). In the operative treatment of torsion, an incision is made from the median line under general anesthesia or from the standing hunger trough with sedatives. Laparotomies to be made from a hunger cup are recommended for mid-term pregnant mare. In the treatment of cases in advanced pregnancies, celiotomy to be performed from the median midline under general anesthesia would be more appropriate. In this way, the intra-abdominal situation can be examined (Chaney et al., 2007). In the postoperative period, fetoplacental tissues should be examined with B-mode and Doppler ultrasonography, and whether the uterine thickness and blood flow in the artery uterina are within normal limits should be monitored. Nonsteroidal anti-inflammatory and progestagens are useful for stabilizing the condition (Ousey, 2006).

3.3. Placentitis: In the management of placentitis, it is essential to initiate appropriate antibacterial therapy after the isolation and identification of the causative agent and to support fetal life at this time (Santschi & Vaala, 2011). Streptococcus equi zooepidemicus, Escherichia coli, Pseudomonas aeruginosa, Klebsiella and Nocardia species are often isolated in the bacteriological culture to be performed on samples taken from vaginal discharge or cervix. Most bacteria enter via the cervix and spread along the caudal part of the placenta in the cervical star region, and some (especially Nocardia species) along the base of the uterine horns (Christensen et al., 2008, Kaymaz et al., 2015). Placental infections in early pregnancy either result in fetal infection or increase the release of cytokines due to chronic inflammation (Santschi & Vaala, 2011). In addition to antibacterial treatment, nonsteroidal anti-inflammatory drugs and cytokines are suppressed with pentoxifylline in treatment. Cervical tone and uterine immobility are tried to be achieved with altrenogest, and hypoxic tissue damage is reduced by maternal oxygen and antioxidant therapy (Macpherson, 2005). A combination of beta-lactam and aminoglycosides (usually penicillin and gentamicin) has been reported to be effective in the treatment of mares affected by placentitis. Although the effect of these antibiotics on the fetus is not known exactly, it should be noted that they migrate to the allantoic fluid (Murchie et al., 2003).

Similarly, the combination of trimethoprim-sulfametazole (30 mg/kg, every 12 hours) is effective in controlling placenitis, but it has not been fully investigated in terms of pharmacokinetics (Macpherson, 2005, Kaymaz et al., 2015). It has been reported that the use of antibiotics, pentoxifylline and tocolytics in the treatment of placentitis cases diagnosed only by transrectal ultrasonography resulted in 75% of healthy foal births (Troedsson & Zent, 2003, Kaymaz et al., 2015).

3.4. Early placental separation (Red bag): Medical treatment of premature separation of the placenta is risk for both mother and offspring. In such cases, the chorioallantois should be immediately ruptured with a hand or a blunt object, and the foal should be delivered without wasting time. When the foal is taken out, massage is done with a towel and respiratory support is given. The severity of aspiration varies depending on the time elapsed from placental separation (Vaala & Sertich, 2006). In the management of the case, oxygen should be given to the foals, and if the heartbeat cannot be obtained, the circulation should be stimulated by massaging the chest area. Due to fetal hypoxia, the fetus may be contaminated with meconium during delivery. In such cases, the mouth and nose of the foal should be cleaned to prevent aspiration, and oxygen support should be provided with a nasal cannula or mask. Affected foals should be closely monitored for signs of hypoxic ischemic encephalopathy. (Vaala & Sertich, 2006).

3.5. Hydroamnion/Hydroallantois: Hydroamnion/Hydroallantois is usually caused by excessive accumulation of allantois or amniotic fluid in the last three months of pregnancy (Slovis et al., 2013). Hydroallantois increases the risk of mortality in mares due to excessive and rapid accumulation of fluid. Hydroamnion, on the other hand, develops more slowly, causing difficult delivery or umbilical cord anomalies (Vaala & Sertich, 2006, Kaymaz et al., 2015). The success rate in the treatment of calf membrane hydrops in mares is low. Hydrops; It increases the incidence of hypovolemic shock during delivery as it will suppress respiration by causing an increase in intra-abdominal pressure. Again, in these cases, the possibility of abdominal hernia, prepubic tendon and uterine rupture increases (Christensen et al., 2008). In cases of mild hydroallantois where the mare's condition is normal and the fetus is alive, the mother should be supported with fluid therapy. Dextrose, laxative diets, vitamin B, oral vitamin E, nonsteroidal anti-inflammatory drugs (NSAI), and altrenogest (0.088 mg/kg, 24 hours apart) help maintain gestation until adequate fetal maturation and reduce the likelihood of shock (Santschi & Vaala, 2011, Kaymaz et al., 2015). Since the possibility of abdominal hernia and prepubic tendon rupture will increase in mares with hydrops, early signs of muscle damage should be investigated and serum creatine kinase (CK) concentration should be monitored. Prophylactically, antibiotics and

NSAIs are effective in preventing metritis, endotoxemia and laminitis (Santschi & Vaala, 2011). Mistakes to be made in the management of the case when labor begins carry a high risk of mortality. In cases of advanced hydrops (with 100-200 L accumulation), sudden discharge of fetal fluids causes hypovolemic shock in the mare. To reduce the risk of shock, intravenous crystalloid (20 L bolus) and hypertonic saline (kg/4L) or other colloid fluids (hetastarch 10 mL/kg) should be administered prior to fluid drainage, followed by maintenance crystalloids (10-40 mL/kg). The most swollen part of the allantois sac is identified and incised with a trocar advanced from the cervix, and the allantochorion fluid is emptied in a controlled manner (Santschi & Vaala, 2011). Oxytocin injections to be made before drainage of the fluid may not be effective due to uterine inertia. In order to reduce fetal hypoxia and maternal stress during delivery, the mother should be helped by pulling offspring and flunixin meglumine should be administered to the mother after birth (Vaala & Sertich, 2006, Kaymaz et al., 2015). Restless mares should be followed closely after delivery of the fetus. Retentio secundinarum is common in this type of mare and there is a delay in involution.

3.6. Umbilical cord abnormalities: Prenatal umbilical cord abnormalities have no known cure and are rarely diagnosed. These abnormalities cause fetal losses (Giles et al., 1993). The excessively long umbilical cord causes kinks and circulatory disorders by wrapping around the fetal limbs, while the short cord increases the pulling force on the offspring membranes and causes premature placental separation (Santschi and Vaala, 2011).

3.7. Fetal anomalies: It is not possible to cure fetal anomalies such as schistosoma reflexum, arthrogryposis and hydrocephalus during pregnancy and fetal death occurs in almost all cases. This type of abnormality is usually detected in the second half of the birth and results in a dystocia (Santschi & Vaala, 2011, Kaymaz et al., 2015). Broad-spectrum antibiotics and NSAIs should be used, since uterine contamination and retention are high in relation to dystocia (Vaala & Sertich, 2006).

4. Conclusion

A healthy colt that will be born with an uncomplicated birth following a healthy pregnancy is one of the most important goals for horse breeders and working physicians. In recent years, developments in the field of perinatology and innovations in examination techniques have enabled veterinarians to obtain more detailed information about intrauterine life, and have enabled new steps to be taken in the diagnosis and treatment of risk pregnancies. It is noteworthy that the first research in the field of veterinary perinatology was carried out on foals, which are the most

expensive offspring. Today, with the innovations in imaging techniques reducing the examination costs, pregnancy follow-ups can be performed in other species as well. In the future, it is aimed to create many types of similar scans and follow-up protocols. Again, the importance of these studies is better understood in the early diagnosis and management of related diseases in pregnant animals to be obtained during the production of endangered species and transgenic animals. The fact that pregnant mares are not monitored routinely between the first two and the last two months in field conditions is an important obstacle in terms of possible mother and offspring losses. It will be beneficial for physicians to follow up-to-date studies against various pregnancy pathologies that may arise from fetal, placental or maternal factors in terms of reducing the losses that may be encountered in this type with a long gestation period.

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