# Modern Medical and Health Sciences

Editor

Halit DEMİR

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Health Sciences

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**Modern Medical and Health Sciences**

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## PREFACE

We are pleased to have published the book, “CModern Medical and Health Sciences, which consists of 21 chapters. Chapters containing scientific studies conducted in the field of health sciences. It is our greatest wish that this book will be an important resource for all scientific readers doing scientific research in the field of health.

I would like to thank to coordinators, referees and authors for their contributions. I would like to thank the publishing house that contributed to the writing, format, design and preparation of this edition for printing.

Best regards

Prof. Dr. Halit DEMİR

Editor

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# CHAPTER I

# ARTERIAL BLOOD GAS INTERPRETATION AND ACID-BASE BALANCE

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## 1. Introduction

Arterial blood gas is a valuable laboratory diagnostic method that can provide important information about pulmonary and metabolic functions when evaluated together with the clinical status of the patients. Arterial blood gas provides information about gas exchange, oxygenation, ventilation and acid-base balance in the lungs. Arterial blood gas is also used to determine the diseases that cause impairment in gas exchange in the lungs, diuresis and acid-base balance in the kidneys and to determine their severity.

While alveolo-arterial gradient is calculated for gas exchange, partial oxygen pressure (PaO2) and oxygen saturation (SaO2) for oxygenation, and partial carbon dioxide pressure (PaCO2) for ventilation. Acid-base balance is interpreted roughly by evaluating pH, PaCO2 and HCO3-. After these are analysed, electrolytes and metabolites are checked and the interpretation is completed.

Nowadays, thanks to technological developments, various parameters such as glucose, haemoglobin, electrolytes, bilirubin and lactate can be included in blood gas analysis in addition to the values mentioned above and these data

are used as a guide in the diagnosis and differential diagnosis of various diseases and in the evaluation of response to treatment.

Arterial blood gas is mostly performed by invasive puncture of the artery percutaneously or with a catheter and then sampling, but noninvasive methods such as transcutaneous gas monitors can also be used, although they are not very common today. (1)

While radial, brachial and femoral arteries are generally preferred for arterial blood gas sampling, dorsalis pedis and axillary arteries can rarely be used. The radial artery travels above the distal radius. The radial artery is the most preferred artery because it is superficial, easy to palpate, there is no vein nearby, easy to apply pressure after the procedure, and less risk of infection. Before sampling the radial artery, the collateral circulation must be checked with Allen test. The ulnar artery is evaluated with collateral circulation. The ulnar artery and radial artery are the two arteries responsible for the blood supply of the hand. Any undesirable situation that may occur while sampling from the radial artery in a patient with impaired collateral circulation may cause major complications in the hand.

When performing the Allen test, firstly the patient makes a fist and then the radial and ulnar arteries are pressed with the thumbs where they are felt the most. Afterwards, the patient opens his/her hand and it is observed that the hand looks progressively whiter and paler. While the pressure on the radial artery continues, the thumb on the ulnar artery is lifted and the hand is expected to get its old colour with blood supply in about 10-15 seconds. This is evidence that the ulnar artery acts as a collateral in the circulation of the hand. The same test can be performed for the radial artery. Allen tests are abnormal in approximately 1-25% of cases. Ulnar artery circulation may be impaired in peripheral arterial diseases such as Raynaud's disease and in the presence of arteriovenous fistula. In such cases, the radial artery should not be used. (1,2)

Although it may vary depending on the clinical condition of the patient, a platelet count below 30000 is generally considered a contraindication for arterial blood gas. When the platelets are above 50000, the procedure can be performed safely. Anticoagulant, antiaggregant therapies and coagulopathy of the patient do not constitute a contraindication for blood gas, but caution should still be exercised in terms of bleeding risks and these patients should be closely monitored. (2)

The patient should be given detailed information about the procedure before arterial blood gas sampling. If the radial and brachial arteries are to be

sampled, the patient should be lying, semi-lying or sitting, and if the femoral artery is to be sampled, the patient should be lying down. Before sampling from the brachial artery and femoral artery, the circulation should be evaluated by checking the distal pulses, and care should be taken for anatomical abnormalities and regional infections. The vessel should be felt with the pulp of the second and third fingers and the area should be cleaned with antiseptic solutions (containing 70% alcohol), povidone iodine or chlorhexidine. Wait for a while to ensure sterility with the solution used and then start the procedure. The radial and brachial arteries are entered at an angle of 30-45°, whereas a 90° angle is usually required to reach the femoral artery. Although pre-prepared heparinised syringes are mostly used for blood gas, a heparinised syringe obtained by drawing 0.5-2ml heparin (1000units/ml) into a standard syringe and then emptying it can also be used.

When the artery is entered, the syringe usually fills spontaneously with the pulse in the artery without the need for aspiration. If the syringe does not fill spontaneously, reasons such as shock, hypovolemia, heart failure, peripheral vascular disease, venous access instead of arterial access should be considered. A blood sample of approximately 2-3 ml is sufficient. The colour of the sample usually does not indicate artery or vein. Dark colour may indicate polysystemia or hypoxia. After the sample is taken, the puncture site should be pressed with sterile gauze for at least 5 minutes. This period should be prolonged in patients receiving anticoagulant, antiaggregant treatment or in those who are prone to bleeding. (2,3)

The sample taken should be examined within 5 minutes and if it cannot be examined in this time, it should be kept in the ice battery. With the ice battery, the metabolism of the samples is slowed down, oxygen consumption and carbon dioxide production are reduced. In this way, samples can be stored for up to 30 minutes-1 hour. The PaO2 and pH values of the samples that are not stored in an ice battery are lower and the PaCO2 value is higher and they are not suitable for healthy evaluation.

If the resting oxygen-free blood gas values of the patients are to be analysed, the patient should be in a sitting or lying position for 30 minutes and should not receive oxygen support.

Some complications may rarely develop due to arterial blood gas collection. These include pain, bleeding, haematoma, paresthesia, local infections and nerve damage at the puncture site. Patients should be evaluated after the procedure for

early recognition of possible complications and any complications should be intervened rapidly. (4)

### 2. Interpretation of Arterial Blood Gas

When interpreting arterial blood gas, it is necessary to be familiar with the clinical and laboratory data of the patients and previous blood gas values, if any. It may be misleading to make comments about the patient and diseases only with blood gas. At the same time, factors such as whether the patient is receiving oxygen support, whether he/she is in a sitting or lying position or how long he/she has been resting may be important when taking blood gas.

Analysing previous blood gas values may give us information about whether the current picture is acute or chronic, and may also help us to learn the basal values of the patient. In the sitting position, lung function is often assessed much better.

When interpreting blood gases, a systematic approach is important to prevent possible overlooked pathologies. When we start interpretation, PaO2, SaO2, pH, PaCO2 and HCO3 are the basic parameters we look at, and other parameters should be reviewed after evaluating them. With the basic parameters we look at, we have information about oxygenation, ventilation, gas exchange and acid-base balance of the patients. Normal blood gas values are shown in Table 1.

**Table1:** Normal Values of Arterial Blood Gas in Room Air (Under 21% Oxygen Pressure)

| | |
|---|---|
| pH | 7.35-.7.45 |
| $PaO_2$ | 80-100 mmHg |
| $SaO_2$ | %94-100 |
| $PaCO_2$ | 35-45 mmHg |
| $HCO_3^-$ | 22-26 mEq/L |
| $P(A\text{-}a)O_2$ | 5-15 mmHg |
| Baz Excess | -2 ± 2 |

### 3. Oxygenation

One of the most basic tasks of the respiratory system is to ensure that the oxygen molecules in the air are taken by inhalation and pass from the alveolo-

capillary membrane to the capillaries in the lungs by passive diffusion and to introduce oxygen into the systemic circulation. This journey of oxygen is called oxygenation. In this way, the oxygen demand of tissues is met.

The solubility of oxygen in liquid solutions such as blood is not good. However, it is very important to provide the oxygen required for tissues. For this reason, oxygen is mainly transported to tissues by haemoglobins to which it is reversibly bound. 100ml of blood contains approximately 15grams of haemoglobin. Each 1gram haemoglobin can carry approximately 1.34ml oxygen. In this way, an average of 20ml of oxygen is carried in 100ml of blood. Approximately 98% of oxygen is found in haemoglobin and 2% is dissolved in the blood. While dissolved oxygen is represented by the PaO2 value, the saturation value shows what percentage of haemoglobin is filled with oxygen.

The standard dissociation curve (Figure 1) shows the relationship between partial oxygen pressure and the total amount of oxygen in the blood under optimal conditions of pH 7.40, temperature 37C° and atmospheric pressure 760 mmHg. As can be seen in this curve, the amount of dissolved oxygen constitutes a very small part of the total amount of oxygen. The PaO2 value required to fill 50% of the haemoglobins is called the P50 value and is 26.5mmHg on average. P50 value is one of the parameters used to evaluate the affinity of haemoglobin to oxygen.

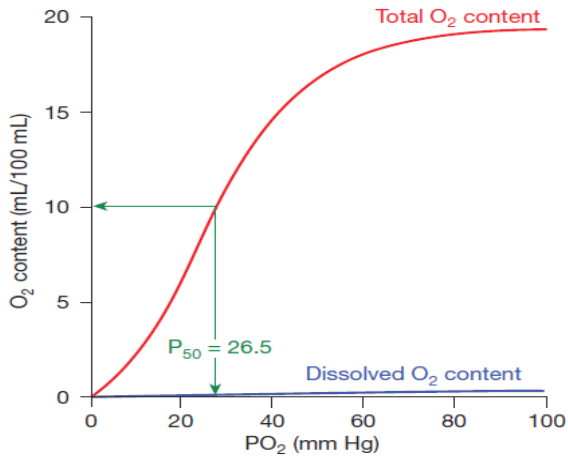


**Figure 1:** Oxygen dissociation curve, red line shows total O2 amount, blue colored line shows dissolved oxygen (PaO2), green line shows P50 value.(5)

The curve in which the relationship of partial oxygen pressure (PaO2) with hemoglobin is evaluated is the oxyhemoglobin dissociation curve (Figure 2).

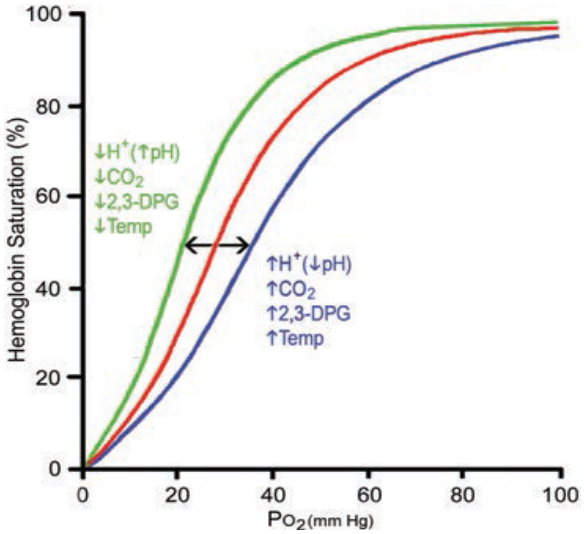


**Figure 2:** Red line shows normal dissociation curve, green line shows left shift, blue line shows right shift. (5)

Although the percentage of dissolved oxygen in the blood is low compared to the percentage of oxygen bound to haemoglobin, dissolved oxygen has a very important function for our body because the haemoglobin molecule cannot leave the erythrocytes.

When oxygen binds to a haem group of haemoglobin, some changes occur in different haem groups of the same haemoglobin. With these changes, the interest of haemoglobin to oxygen increases and the oxygen haemoglobin dissociation curve becomes sigmoidal. The sigmoidal shape of this graph helps us to understand the difference in oxygen transfer between the lungs where PaO2 is high and peripheral tissues where PaO2 is low.

When PaO2 is around 80-100mmHg, almost all haemoglobins are filled with oxygen. However, when PaO2 falls to 60mmHg and below, the curve steepens and it becomes easier for haemoglobins to give oxygen, so that haemoglobin is easily separated from oxygen in peripheral tissues where PaO2 is low.

At the same time, carbon dioxide (CO2), 2-3diphosphoglycerate, hydrogen (H+) and heat resulting from metabolism in peripheral tissues make different changes in the structure of haemoglobin and shift the curve to the right and thus the interest of haemoglobin to oxygen decreases. When the oxyhaemoglobin dissociation curve is examined when the curve shifts to the right, it will be seen that the same PaO2 values correspond to a lower saturation percentage. Decreases in CO2, 2-3 diphosphoglycerate, H+ and heat have the opposite

effect, shifting the curve to the left and increasing the affinity of haemoglobin to oxygen. The normal value of the P50 value is around 26.5mmHg. When there is a left shift, the P50 value decreases, while the P50 value increases in the right shift. (2,4)

The absence of sufficient partial oxygen pressure in arterial blood is called hypoxaemia, while the absence of sufficient oxygen in tissues is called hypoxia. PaO2 value changes with age.

The ideal PaO2 value is calculated with 109-(0.43xyage).The critical PaO2 value for hypoxaemia is 80 mmHg. PaO2 below 80 mmHg in arterial blood gas indicates hypoxaemic respiratory failure.

60-79 mmHg mild hypoxaemia,

40-59 mmHg moderate hypoxaemia,

<40 is classified as severe hypoxaemia.

When PaO2 falls below 55-60 mmHg, i.e. moderate hypoxaemia, oxygenation of tissues is significantly impaired and symptoms and signs of hypoxia begin to be observed. These are complaints such as dyspnoea, fatigue, headache, dizziness, lack of attention, visual and hearing problems, muscle contractions and examination findings such as cyanosis, tachycardia and tachypnoea.

Causes of hypoxia:

Hypoxic hypoxia (arterial hypoxia):

It is due to the decrease of PaO2 in arterial blood, it can be caused by pulmonary or nonpulmonary causes, it is the most common cause of hypoxia.

Anaemic hypoxia:

It is a type of hypoxia caused by haemoglobin pathologies. It is most commonly caused by a decrease in the amount of haemoglobin (anaemia) or pathologies such as carboxyhaemoglobin, methaemoglobinemia.

Ischaemic hypoxia:

It may be caused by circulatory disorders such as shock, heart failure, left-to-right shunt diseases, hypovolemia.

Cytotoxic hypoxia:

It occurs as a result of impairment in the metabolism of oxygen by cells. It may be caused by causes such as disorders in the electron transfer chain due to cyanide poisoning. (6)

Peripheral saturation is indicated by SpO2 and measured by pulse oximetry. Arterial saturation is indicated by SaO2 and is one of the blood gas parameters. The SpO2 value estimates the SaO2 value. In daily practice, these two terms are often used with the same meaning. While SpO2 or SaO2 values between

95-98% are considered normal, 88-92% should be determined as the target value in diseases with a tendency to hypercarbia such as chronic obstructive pulmonary disease. (7)

**4. Ventilation**

Ventilation is the inhalation of air into the lungs and the exhalation of air out of the lungs. Some of the air taken in by breathing remains in the conducting airways and some of it reaches the alveoli. The inlet and outlet of the air that reaches the alveoli and plays a role in gas exchange is called alveolar ventilation.

Under normal conditions, fixed amounts of oxygen are used and carbon dioxide is produced during the metabolism of tissues. The blood gas parameter that shows ventilation most accurately is PaCO2 value. The amounts of carbon dioxide produced and carbon dioxide removed from the lungs are similar and are around 200ml per minute. Since the diffusion capacity of CO2 is much higher than oxygen, the difference between alveolar and arterial CO2 pressure is very small. CO2 is normally present in very small amounts in the air.

The volume of air entering and leaving the airways during one minute is called minute ventilation.

Minute Ventilation (VE) = Tidal Volume (TV) x Number of Respirations (F)

Although tidal volume varies according to height and weight, it is 400-600ml on average. Approximately 150 ml of 500 ml remains in the conducting airways and 350 ml reaches the alveoli. The air remaining in the conductive airways does not participate in gas exchange.

Minute Ventilation (VE) = Alveolar Ventilation (VA) + Dead Space Breathing (VD)

CO2 levels are controlled by peripheral and central chemoreceptors and the respiratory centre located in the medulla oblangata. With minute ventilation, CO2 level is tried to be kept between 35-45 mmHg. In other words, minute ventilation is regulated by changes in PaCO2 level. PaCO2 >45mmhg is called hypercapnia and PaCO2<35mmhg is called hypocapnia. CO2 is transported in 3 forms in the blood.

1- As dissolved (PaCO2)
2- Depending on haemoglobin
3- In the form of bicarbonate (most common)

Causes of hypercapnia:

1-Hypoventilation caused by a decrease in tidal volume or respiratory rate

- Weakness in the respiratory muscles
- Central hypoventilation, which may be caused by causes such as destructive brain lesions
- Use of drugs that suppress the respiratory centre
- Incision or damage to the medulla spinalis

2-Dead cavity increased respiration

- Diseases with lung parenchymal involvement (e.g. ventilation-perfusion imbalances and anatomical shunts)
- Rapid and superficial respiration (2)

**5. Evaluation of Gas Exchange**

In order to evaluate the gas exchange in the lungs and to have general information, the alveolo-arterial oxygen gradient, P(A-a)O2, is calculated. PAO2: refers to alveolar oxygen pressure. The partial oxygen pressure in the alveoli is subtracted from the partial oxygen pressure in the arterial blood gas and this value is expected to be between approximately 5-15mmHg (average 12mmHg). A P(A-a)O2 value above 15 roughly indicates that there is a problem in gas exchange due to a pathology in the lungs. P(A-a)O2 may vary according to age.

It is calculated with the formula P(A-a)O2=2.5+(0.21xyage) which should be according to age.

$$P(A\text{-}a)O_2 = FiO_2(Patm - PH_2O) - (PaCO_2/R) - PaO_2$$

FiO2: It is the oxygen ratio in the inspired air, in other words, it is expressed as oxygen fraction. It is 21% in room air. Patm: 760mmHg, PH2O: 47mmHg, R: Respiratory constant and its numerical value is 0,8.

Alveolaarterial oxygen gradient increases in ventilation-perfusion imbalances, diffusion disorders and shunts. In the presence of alveolar hypoventilation, no increase in gradient is expected. P(A-a)O2 evaluation facilitates the differential diagnosis of some diseases.

**6. Acid-Base Balance**

PH is a scale we use to measure the acidity or alkalinity of the blood. Its range varies between 0-14 and normal values are between 7.35-7.45. The range

compatible with life is thought to be between 6.8 and 7.8. PH is basically the negative logarithm of hydrogen ion (H+) concentration. A one unit decrease or increase in pH causes about 10-fold change in H+ ion concentration.

PH:<7.35=Asidosis, >7.45=Alcoholase.

Thanks to PH, we can comment on the general acid-base balance in our body and it becomes easier to intervene quickly in any disorder.

Many volatile and nonvolatile acids are produced in our body as a result of metabolism or from food. These acids must be buffered and removed in order to maintain acid-base balance. CO2 is the most important volatile acid and is removed through the lungs, while the removal of non-volatile acids is mainly provided through the kidneys. Our body uses buffer systems to maintain the acid-base balance within a very narrow range. The most important of these buffer systems are bicarbonate-carbonic acid system, erythrocyte buffer system, ammonium, phosphates and proteins. The most important buffer system of extracellular fluid is carbonic acid (H2CO3)-bicarbonate (HCO3-) buffer system. CO2, which is an acid, dissolves in a very large proportion of H2O and forms carbonic acid (H2CO3). Carbonic acid is rapidly converted into H+ and HCO3-. Although these reactions are normally very slow, they take place rapidly thanks to the catalysing action of the enzyme carbonic anhydrase.

$$CO_{2+}\,H_2O \longleftrightarrow H_2CO_3 \longleftrightarrow HCO_3^- + H^+$$

Melt CO2 is approximately one 20th of HCO3 in plasma. Changes in these ratios lead to acid-base imbalances.

PH=pK+ log [HCO3-] /[PaCO2]

The pK value was determined as 6.10 at body temperature.

The above equation, called Henderson-Hasselbach equation, shows that pH is positively correlated with HCO3 and negatively correlated with CO2. While HCO3 changes are mainly due to metabolic causes, CO2 changes suggest respiratory pathologies in the foreground.

In acid-base disorders, compensation mechanisms are activated to bring pH to normal range. However, compensation is usually insufficient to bring the pH into the normal range. The amount of compensation varies according to whether the event is acute or chronic. In pathologies caused by metabolic disorders, the lungs are activated within half an hour and reach a maximum level within -12-24 hours. In pathologies caused by respiratory disorders, the kidneys are activated between 6-24 hours, while the maximum level can reach 4 days. (2,3,8)

When analysing the acid-base balance, a systematic approach is important and a certain sequence should be followed.

Stepwise approach

-Is the measurement compatible with the Hendersan-Hasselbach equation?
-Is there acidosis or alkalosis by looking at pH?
-Is the primary problem respiratory or metabolic?
-Has compensation developed?
-Is there an increase in anion gap in case of metabolic acidosis?
-If anion gap is increased, what is the relationship with HCO3?

Sometimes, if PaCO2 and HCO3 are not in the normal range although pH is in the normal range, there may be a mixed acid-base disorder. It is also important to look at this aspect during blood gas evaluation.

### *6.1. Respiratory Acid-Base Disorders:*

#### *6.1.1. Respiratory Acidosis*

It is a condition that occurs with pH< 7.35 and PaCO2 >45mmHg. The CO2 produced is more than the CO2 removed through the lungs. The bicarbonate-carbonic acid system is disrupted towards the carbonic acid side. CO2 retention occurs and is usually caused by alveolar hypoventilation. Compensation is tried to be provided by excretion of hydrogen ion by the kidneys and by reducing the elimination of bicarbonate. In the acute period, every 10 mmHg PaCO2 increase causes a 1mEq/lt increase in HCO3, whereas in acidosis lasting 3-5 days, every 10 mmHg PaCO2 increase causes a 3-4mEq/lt increase in HCO3. The causes of respiratory acidosis are shown in Table 2.

| **Table 2:** Causes of Respiratory Acidosis | |
|---|---|
| Use of sedatives | Central Nervous System Depression |
| Brain stem diseases | Hypothermia |
| Encephalitis | Uncontrolled Oxygen Therapy |
| Neuromuscular Diseases | Chest wall deformities |
| COPD | Obesity |
| Restrictive Lung Diseases | Pulmonary Edema |
| Fever | Thyrotoxicosis |

### *6.1.2. Respiratory Alkalosis*

PaCO2 <35 mmHg and pH >7.45. The bicarbonate-carbonic acid system is impaired towards the bicarbonate side. It usually occurs with excessive increase in alveolar ventilation as a result of hyperventilation and hypocapnia appears. Compensation is tried to be provided by reducing the excretion of hydrogen ions by the kidneys and excretion of bicarbonate. In the acute period, every 10 mmHg PaCO2 decrease causes a decrease of 2 mEq/lt in HCO3, while in the chronic period, every 10 mmHg PaCO2 decrease causes a decrease of approximately 5 mEq/lt in HCO3. The causes of respiratory alkalosis are shown in Table 3.

| **Table 3:** Causes of Respiratory Alkalosis |
|---|
| Use of drugs and toxins that stimulate the respiratory system |
| Intracranial pathologies |
| Pain |
| Fever |
| Anxiety |
| Hyperthyroidism |
| Respiratory pathologies such as pneumothorax, pulmonary embolism |
| Pregnancy |
| Mechanical hyperventilation |

### *6.2. Metabolic Acid-Base Disorders*

In the absence of respiratory pathologies, anions and cations are in balance in our body thanks to the kidneys. If this balance is disturbed, metabolic acid-base disorders occur. The main cations that can be measured in our body are sodium and potassium, while the main anions are chlorine and bicarbonate. However, there are some anions such as protein, sulphate, phosphate, lactate that we cannot measure in the blood. The difference between the cations and

the anions we can measure gives us information about the anions we cannot measure and this difference is called anion gap.

Na++ K+=HCO3- + CI- + unmeasurable anions

[Na++K+]-[HCO3- + CI-]= Unmeasurable anions

The value of potassium can be neglected in this formula because it is numerically lower than the others.

Anion gap should normally be 12±4 mEq/lt. Increased or normal anion gap helps us in differential diagnosis.

Base excess shows the amount of deviation of the total base from the required value. Since the most important base is HCO3-, base excess is calculated by the difference between actual and standard HCO3-. Actual bicarbonate is the actual bicarbonate value in the blood at that time and averages 22-26 mEq/lt. Standard bicarbonate is the HCO3 value resulting from the neutralisation of bicarbonate changes caused by PaO2 and PaCO2 and shows the direct metabolic component. Base excess should normally be between ± 2 mEq/l. BE > +2 mmol/L indicates metabolic alkalosis and BE < -2 mmol/L indicates metabolic acidosis.

### *6.2.1. Metabolic Acidosis*

HCO3- <22 mEq/L and pH <7.35. It usually develops due to a strong acid intake or loss of bicarbonate from the gastrointestinal system and kidneys. Anion gap is used to determine the aetiology. The lungs are activated in the first 30 minutes to compensate for the decrease in HCO3 and rapid and deep breathing is observed. Thanks to rapid and deep breathing, alveolar ventilation increases and CO2 level is reduced. The expected PaCO2 value can also be calculated with [1.5 x HCO3-+ 8 ] ± 2. 12-24 hours may be required for complete compensation. The lowest value that PaCO2 can reach is 10-15 mmHg. The causes of metabolic acidosis are shown in Table 5.

Table 5 Causes of Metabolic Acidosis

| Increased Anion Gap | **Normal Anyon Gapli** |
|---|---|
| Lactic acidosis | Gastrointestinal bicarbonate loss |
| Ketoacidosis | Böbreklerden bikarbonat kaybı |
| Uremia | Type 2 Renal tubular acidosis |
| Methanol, salicylate, acetraminophen poisoning | Carbonic anhydrase inhibitors |

### *6.2.2. Metabolic Alkalosis*

HCO3- >26 mEq/lt and pH >7.45. It usually occurs as a result of intake of a strong base or loss of a strong acid. In metabolic alkalosis, PaCO2 increases by 0.7 mmHg for every 1 mEq/L increase in HCO3-. The highest value PaCO2 can reach is 50-55 mmHg. The causes of metabolic alkalosis are shown in Table 6.

**Table 6** Causes of Metabolic Alkalosis

| |
|---|
| Diuretic use (loop and thiazide group) |
| Vomiting, emptying of stomach contents with nasogastric |
| Hipokloremi |
| Hypomagnesaemia |
| Primary hyperaldosteronism, Cushing's syndrome, Mineralocorticoid intake |
| Milk-alkali syndrome |
| Cystic fibrosis |
| Use of some penicillins |

## 7. Conclusion

Arterial blood gas is a valuable laboratory diagnostic method that can provide important information about pulmonary and metabolic functions when evaluated together with the clinical status of the patients. Arterial blood gas provides information about gas exchange, oxygenation, ventilation and acid-base balance in the lungs. Arterial blood gas is also used to determine the diseases that cause impairment in gas exchange in the lungs, diuresis and acid-base balance in the kidneys and to determine their severity.

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CHAPTER II

# HYPERSENSITIVITY PNEUMONITIS

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## 1. Introduction

Hypersensitivity pneumonitis (HP) is a disease that occurs in susceptible individuals as a result of repeated inhaled exposure to various environmental or occupational agents and is based on immunological mechanisms. It may cause the involvement of lung parenchyma and small airways. It is also called "Hypersensitivity Pneumonitis" and "Extrinsic Allergic Alveolitis". Although many agents are thought to cause HP, organic dust particles smaller than 5μm are blamed as the causative agent. It is most commonly seen in bird feeders and farmers. Due to the variety of agents causing HP and the fact that the disease is caused by the individual immunological response to these agents, the clinical presentation may vary greatly from patient to patient. HP is a complex disease with similar clinical, radiological, and histopathological findings that are thought to be caused by a common pathogenesis. (1,2)

Although the disease was classified as acute, subacute, and chronic in the past, this classification had limitations in predicting prognosis. In addition, the determination of the duration of the disease often causes difficulty and confusion. It is thought that the association with radiological and/or histopathological fibrosis rather than the duration of the disease is more meaningful in determining the prognosis. Currently, HP is classified as "nonfibrotic HP" and "fibrotic HP". While nonfibrotic HP usually corresponds to acute HP, fibrotic HP is mostly the result of a chronic process. (2)

## 2. Epidemiology and Etiology

Although the epidemiology may vary depending on age, geographical factors, life style, seasons, risk factors such as occupation, and the intensity of exposure to antigens, the annual prevalence was found to be 1.67- 2.71/100000 in a cohort study published in the USA in 2018. One of the reasons for the differences in prevalence values between studies may be the lack of a gold standard diagnostic method. At the same time, confusion with diseases such as asthma, infections, especially in the acute period, and other interstitial lung diseases in the chronic period may cause the diagnosis to appear less than it is. (3–6)

The prevalence of HP increases with age, especially after the 5th decade. Farmer's lung, which is more common during the harvest season, can be shown as seasonal differences.Occupational HP may occur due to various low molecular weight chemicals or organic animal antigens. In one study, the prevalence of HP among pigeon keepers was found to be 5-21%. (7,8)

Despite similar antigenic exposure in the lungs of smokers, the risk of HP has been found to be reduced due to less immunological response. However, the prognosis of HP is worse and is characterized by attacks. (9)

HP has been recognized since 1700 and more than 300 etiological agents have been identified. The most common causative agent is thermophilic actinomycetes in moldy hay and cereals, usually found in farmers. Non-tuberculous mycobacteria such as M.avium complex and contamination of hot water areas such as showers and saunas may also be responsible for HP, especially in patients with underlying lung disease. This condition is called hot tub lung. Similarly, a condition called humidifier or air-conditioner lung occurs with contaminated humidification systems. In addition, it can be seen in many occupational groups such as mushroom picking,woodworking, paper industry, wine and cheese production, textile, and food. Those who work in the bird and poultry industry or have contact with them, such as veterinarians may develop occupational HP due to antigenic materials such as feathers, urine, feces and serum of these animals.

Occupational HP can also be seen in painters and workers in contact with chemical materials, who have occupational exposure to inorganic antigens such as isocyanates and anhydride. Similarly, various drugs may be causative agents in HP. (1)

### 3. Pathogenesis

Basically, genetic and environmental factors are thought to cause the disease. The fact that some people who are similarly exposed to the same factors have the disease and the detection of HP clusters in monozygotic twins raised in different environments suggests that the patients are genetically predisposed. Similarly, the fact that some of the patients with similar exposure resulted in fibrosis may be related to genetic predisposition. The underlying immunological mechanism is complex and has not been clearly elucidated. Most people exposed to antigens develop immunotolerance and disease does not occur. Insome individuals, humoral and cellular excessive immunoreaction develops against the antigen and the disease occurs after inflammation. In the chronic period, granulomas are formed as a result of delayed-type hypersensitivity in which Th1 cells play a role. In cases with fibrosis, fibroblasts are activated, and extracellular matrix accumulation is observed. There are studies suggesting that major histocompatibility complex (MHC) plays a role in genetic predisposition. (8,10)

### 4. Clinical Features

While the specific agent can be detected in some of the HP patients, the antigen can not be detected in approximately 50-60% of them. While multiple agents may have caused HP at the same time, contact with the agent may have ended at the time of diagnosis. Respiratory symptoms of patients with HP vary in both non-fibrotic and fibrotic types. The most common symptoms are shortness of breath, chest pain, and cough. Symptoms may be in the form of recurrent attacks. On physical examination, inspiratory rales and squeak can be heard in the middle of inspiration. Generally, acute onset within days and weeks is associated with the nonfibrotic type, while insidious onset is compatible with fibrotic HP. However, there is no definite relationship between the duration of symptoms and fibrosis. The presence of fibrosis and the detection of the triggering agent are very important in predicting diagnosis, treatment, and prognosis. (2)

Patients with fibrotic HP are generally older and have lower pulmonary function test and diffusion test values, as well as fewer detected triggering agents than patients with nonfibrotic HP.

Acute hypersensitivity pneumonitis usually presents with a flu-like picture 4-12 hours after exposure to a triggering agent. Symptoms may mimic

acute infections such as upper respiratory tract infection and pneumonia. Physical examination findings and occasional hypoxemia may be present. Symptoms usually regress within a few days when the agent is removed. Chest radiography is usually normal. Chronic HP, like other chronic interstitial lung diseases, progresses more slowly and with nonspecific symptoms such asmalaise and fatigue. manifests itself. Progressive dyspnoea, velcro rales, clubbing, pulmonary hypertension, and respiratory failure may be present during physical examination. Lesions may be irreversible even if the agent is removed. Sometimes acute and chronic differentiation can not be made clear. In addition, chronic/fibrotic HP may be frequently confused with other chronic interstitial lung diseases. Therefore, identification of the causative agent is very important and patients with suspected HP should be evaluated in detail in terms of occupational and environmental exposure. (1)

**5.Diagnosis**

HP should be considered in patients who have contact with an agent known to cause HP in the presence of appropriate clinical and radiological findings and the absence of specific findings in alternative diagnoses. The diagnosis of HP has been a controversial issue for a long time and the most emphasized issue recently is that multi disciplinary evaluation is very important. There is no gold standard diagnostic test for the diagnosisof HP.

In the diagnosis, it is important to try to determine antigen exposure, radiological findings to be compatible with HP, and lymphocytosis dominance in bronchoalveolar lavage (BAL) fluid. Detailed environmental, occupational, and hobby inquiry is very important for antigen exposure. Detailed anamnesis forms can be prepared in accordance with the patient profilein the study area. The prognosis is generally better in patients in whom the triggering agent is identified. For diagnosis, it is sometimes recommended to expose the patient to the suspected agent and observe the appearance of symptoms and signs compatible with HP. After this application, differential diagnosis is facilitated by using objective tests such as chest radiography, blood count and pulmonary function test.

If there is a relationship between history, suspected agent, and respiratory symptoms, specific immunoglobulins (Ig) can be analyzed. However, since the sensitivity and specificity of IgGs analyzed against certain antigens are low, their use is controversial. (10)

Pulmonary function tests may be normal in acute HP, whereas restrictive type orobstructive type disorder may appear in chronic HP. However, it is often not useful in differentiating non-fibrotic HP and fibrotic HP. In fibrotic HP, DLCO is the first parameter affected and a decrease is expected. SFT can be used to exclude other possible diagnoses. (11)

The examination of cell types and numbers (percentages) with BAL does not diagnose HP but helps in the differential diagnosis. BAL shows the inflammation in the alveoli best. BAL sample should be taken from the place with the highest radiological involvement. Withmicrobiological examination, diseases such as pneumonia can be excluded. In addition, the percentage of lymphocytes in the BAL sample of more than 20% (mostly more than 50%) increase in CD8 and decrease in CD4/CD8 ratio is a finding supporting the diagnosis in patients with clinically and radiologically suspected HP. Infibrotic HP, lymphocytosis is detected less frequently in BAL.

High-resolution computed tomography (HRCT) used in the diagnosis of HP should be performed in two sessions, the end of deep inspiratory and end of deep expiratory. HRCT may be normal in acute HP. HRCT image types of fibrotic and nonfibrotic HP patients are shown in Table 1 and Table 2.

**Table 1:** Typical HRCT findings for non-fibrotic HP

| HRCT Pattern | Typical HP | Compatible HP | Indeterminate HP |
|---|---|---|---|
| Description | At least one of the signs of middle, upper zone distribution of parenchymal infiltration and at least one of the signs of small airway | Nonspecific patterns have been described in HP | not applicable |
| Radiological Findings | Parenchymal infiltration:<br>-GGOs<br>-Mosaic Attenuation(Figur 1)<br>Small Airway Disease:<br>-<5mm centrilobüler nodüles(Figure2)<br>-Air Trapping | Parenchymal infiltration:<br>Lower-mid lobe and peribronchovasküler predominance<br>-Uniform GGO<br>-Airspace<br>-Cysts | not applicable |

Definition of abbreviations: GGO = ground-glass opacity; HP = hypersensitivity pneumonitis; HRCT = high-resolution computed tomography

Examples of HRCT images of HP patients are shown in figures 1 and 2.

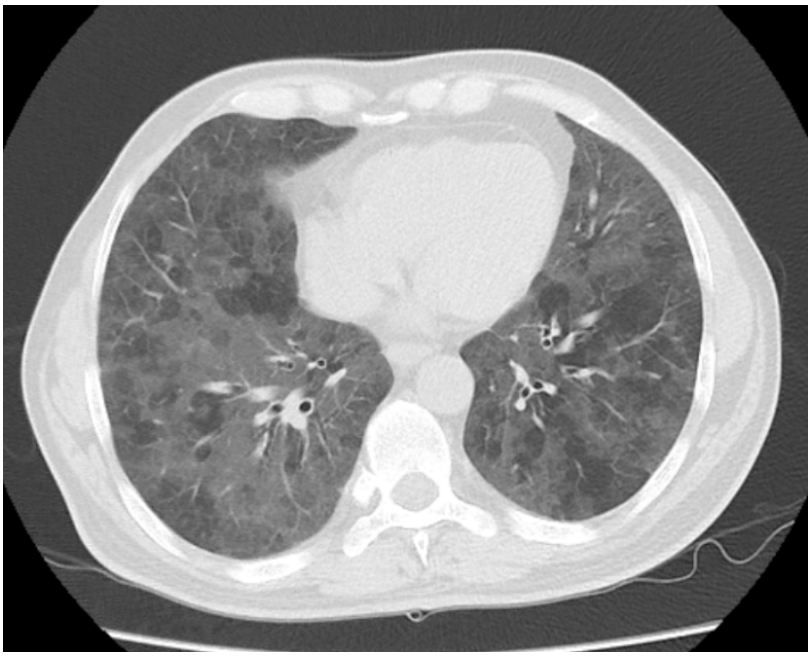

**Figure 1 :** Mosaic Attenuation

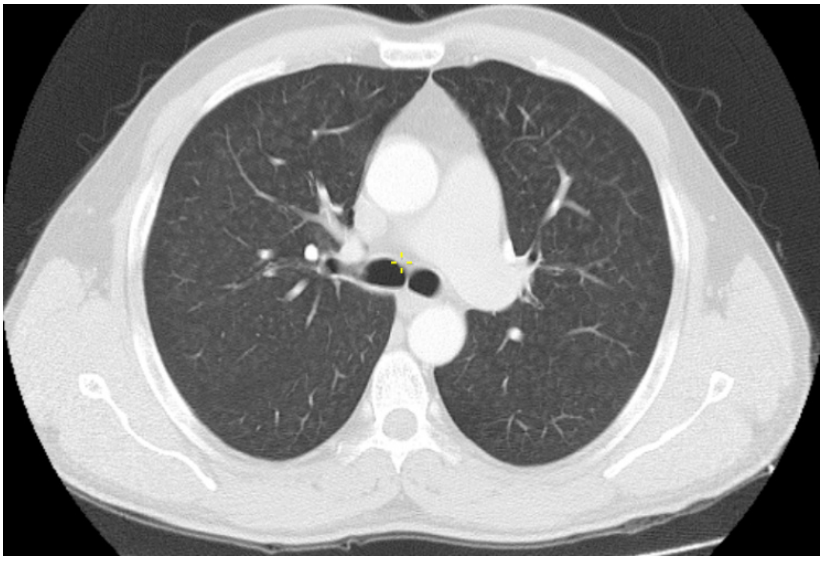

**Figure 2:** Centrilobuler nodules

Table 2: Typical HRCT findings for Fibrotic HP

| HRCT Pattern | Typical HP | Compatible HP | Indeterminate HP |
|---|---|---|---|
| Description | At least one of the signs of fibrosis and small airway should be present. | Small airway disease accompanied by atypical, variable signs of fibrosis | Absence of typical and compatible findings |
| Radiological Findings | Fibrosis findings:<br>Septal thickenings, reticular scars, traction bronchiectasis and minimal honeycomb in the middle zone<br>Airway Disease:<br>-Centrilobular nodules<br>-GGOs<br>-Mozaik atenüasyon<br>-Three density pattern, air trapping | Various fibrozis:<br>-UİP<br>-Extensive GGOs with lung fibrosis<br>- Upper lobe and peribronchovasc distribution<br>Small Airway Disease:<br>Centrilobular nodules three density patterns, air trapping | UİP |

Definition of abbreviations: GGO: Ground-glass opacity, HP: Hypersensitivity pneumonitis, HRCT: High-resolution computed tomography

In patients with HP, the diagnosis is based on clinical, radiological, BAL and sometimes histopathological findings. Diagnostic criteria of HP patients are shown in figure 3. The presence of typical radiological findings, detection of the causative agent, predominance of lymphocytosis in BAL examination and clinical improvement after the possible causative agent is removed often lead to a diagnosis without the need for histopathological examination. However, in suspicious patients, transbronchial biopsy, cryobiopsy and surgical lung biopsy can be performed after discussion in multidisciplinary councils. (1,2)

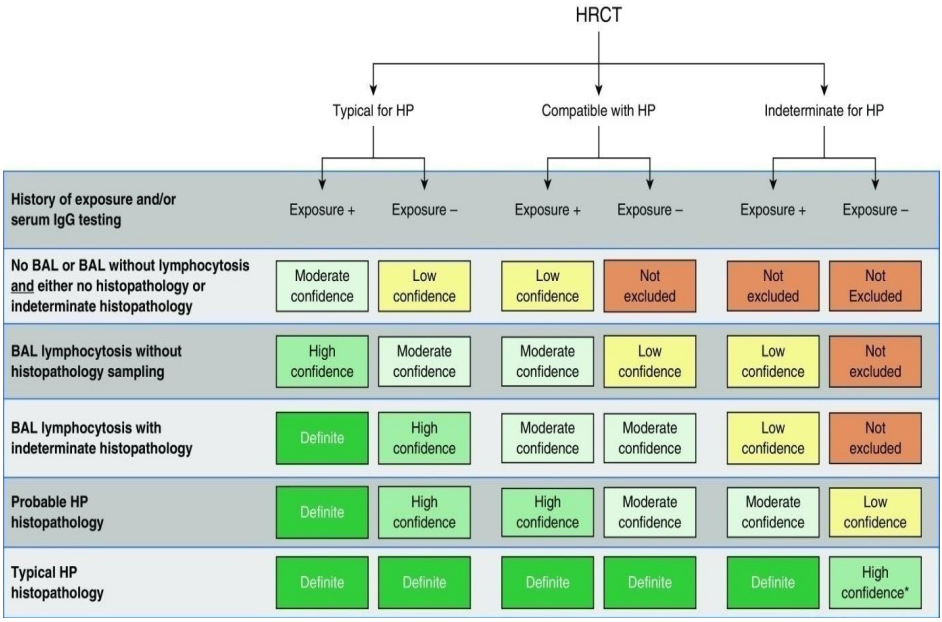


**Figure 3:** Diagnostic criteria for hypersensitivity (2)

The diagnostic algorithm in a patient with suspected interstitial lung disease on lung imaging is shown in Figure 4.

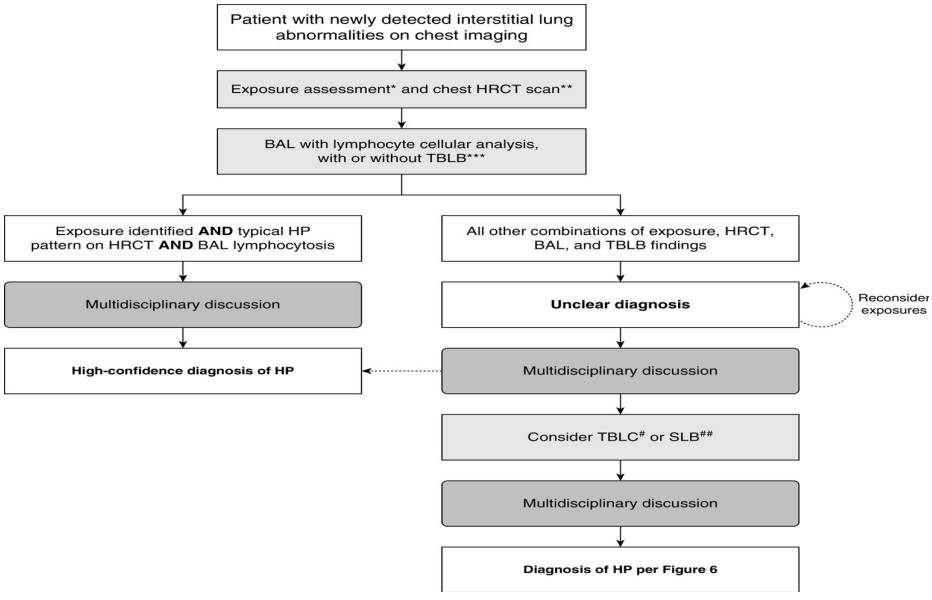


**Figure 4:** Algorithm for the diagnostic evaluation of hypersensitivity pneumonitis (2)

### 6. Differential Diagnosis

• Chronic bronchitis and asthma

• Interstitial lung diseases with fibrosis, especially IPF

• Diseases causing centrilobular nodules such as sarcoidosis, pulmonary langerhans cell histiocytosis

• Organic dust toxic syndrome

• Inhalation fever

### 7. Treatment

Patients with HP usually improve with avoidance of the exposed antigen, but patients with severe symptoms and progressive disease may require additional treatment.

Glucocorticoid treatment may be started if symptoms such as shortness of breath and cough are persistent, if there are serious findings in respiratory test, blood gas and radiological imaging and if there is progression in the existing findings. The dose is 0.5mg/kg prednisone daily. After 1-2 weeks of treatment, the dose can be decreased at 2- 4 week intervals. Caution should be exercised during treatment in terms of possible side effects of corticosteroids. (12,13) Immunosuppressive therapy is less effective in patients with fibrotic HP than in patients with nonfibrotic type. If progression occurs under corticosteroid treatment, if long-term treatment is required or if steroids cannot be used due to side effects, other immunosuppressive agents such as azathioprine, mycophenolate mofetil can be switched to.

Antifibrotic therapy should be considered in patients with progressive fibrotic HP. There are studies showing that nintedanib reduces FVC decline in non-IPF fibrotic ILD patients.

In addition, oxygen therapy, pulmonary rehabilitation, smoking cessation, vaccination and lung transplantation should be kept in mind.

### 8. Conclusion

The prognosis of HP varies depending on the type and intensity of the agent, the duration of exposure and, most importantly, whether fibrosis is associated. In the nonfibrotic/acute form, the prognosis is generally good and complete remission is usually observed. (14)

Failure to detect antigen, prolonged antigen contact, male gender, advanced age, crackles on lung examination, low pulmonary function test and diffusion values, exacerbations and attacks are indicators of poor prognosis (6)

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CHAPTER III

# DIAGNOSIS AND TREATMENT OF AORTIC VALVE REGURGITATION

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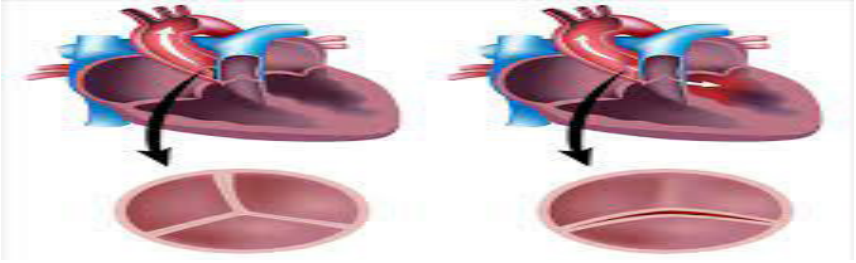
## 1. Introduction

Aortic regurgitation (AR), also named aortic insufficiency defined as retrograde blood flow from the aorta into left ventricle during diastolic phase. Inefficient closure of the aortic valve leads to this clinical condition. It is one of the causes of cardiovascular morbidity and mortality and affects up to 13% of the males and 8.5% of the females (1). Therefore, early diagnosis and appropriate treatment are important to prevent this undesirable results.

## 2. Anatomy of the Aortic Valve and Associated Structures

Aortic valve is a kind of semilunar valve and has three leaflets normally. It is approximately 20 mm of diameter. Bicuspid valve can be detected in some congenital clinical conditions (Figure 1). It located between two highest pressure diffrences such as right ventricle and aorta (2).

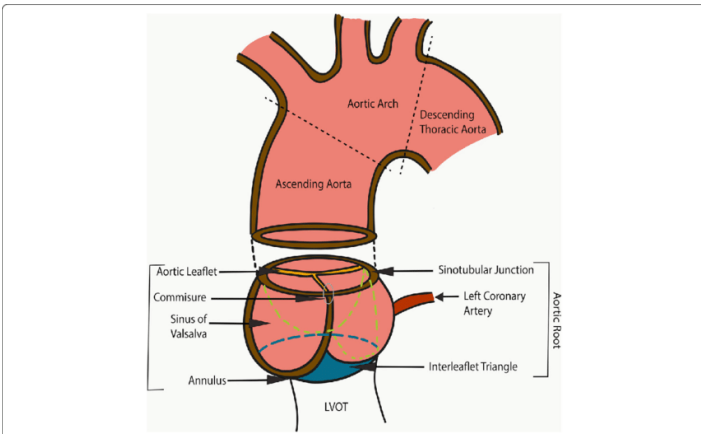
**Figure 1.** Normal trileaflet anatomic structure
and abnormal bicuspid structure of the aortic valve
https://www.achaheart.org/your-heart/educational-qas/types-of-heart-defects/bicuspid-aortic-valve-bav/#vue_joinnow



Aortic annulus provides the connection between the leaflets and aortic root. Commisures are kind of fibrous structures and suspend the leaflets. The term "cusp" can be used instead of the "leaflet". The leaflets are traditionally named as left coronary, right coronary and non-coronary. Several structures are associated with the aortic valve and described as belows (3).

Aortic annulus acts as an mainstay for the valve (4). Intervalvular trigone is located between the bases of sinuses and attached to the wall of the left ventricle. It consists of three triangles and seperates the sinuses (2). Sinus of Valsalva are the aortic sinuses that prevent the occlusion of the coronary arteries during systolic phase by the aortic leaflets (5). Sinotubular junction is a stucture found at the top of the sinuses. It is the transition site from the artic root to the ascending aorta (6). All these structures are visualized in figure 2.

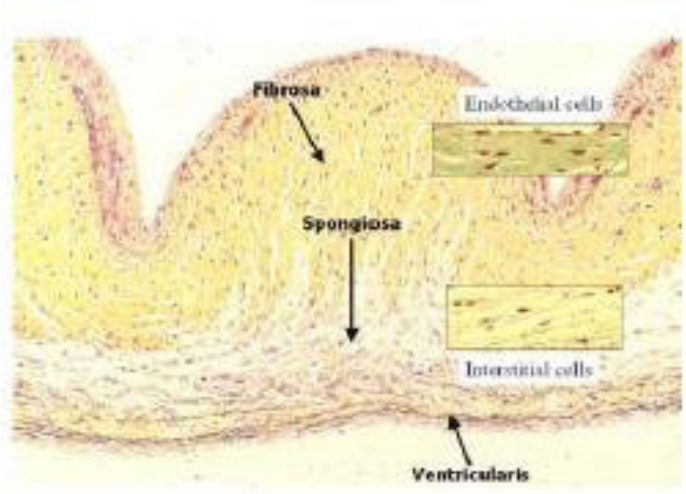
**Figure 2.** Aortic valve and associated structures
Nagpal P, Agrawal MD, Saboo SS, Hedgire S, Priya S, Steigner ML. Imaging of the aortic root on high-pitch non-gated and ECG-gated CT: awareness is the key! Insights into Imaging 2020;11(51):1-14



### 3. Histology of the Aortic Valve

The aortic leaflets are composed of three layers; fibrosa, spongiosa and ventricularis and covered by an endothelial layer externally. Fibrosa is made of collagen which provides tensile strength, flexibility and extensibility. Ventricularis is composed of elastin and maintains the opening and closure of the valve. Spongiosa is a viscous structure in nature and provides flexibility and resists compression. The external structure that covers the leaflet called endothelial layer, plays a little role directly on aortic valve mechanics but affects the interstitial cell function of the valve (7). Histologic layers of the aortic valve were given in figure 3.

**Figure 3.** Histologic layers of the aortic valve.
https://www.researchgate.net/publication/325360294_Heart_valves




### 4. Etiology of tyhe Aortic Regurgitation

AR occurs as a result of mal-coaptation of the leaflets due to disorders of the cusps or associated structures, or both. Calcification of the aort usually results into aortic stenosis but also can be the cause of AR. Infective endocarditis alters the anatomical strucrure of the leaflets. Laceration or tearing of the ascendan aorta disrupts the commisural support and gives rise to prolapse of the aortic leaflets. Bicuspid aortic valve leads to incomplete closure of the leaflets and may result into AR. Ventricular septal defect (VSD) is a congenital defect of the heart and may associated with AR. Fibrous infiltration of the cusps may ocur due to rheumatologic disease and disorders in the opening and the closure of the valve

may become related to retraction. Secondary AR may result due to scarring and thickening of the aortic valve as a complication of membraneous subaortic stenosis. AR can also be seen after TAVI (transcatheter aortic valve implantation) or percutaneous aortic balloon valvulotomy. Occasionally, trauma may lead to AR. Whipple disease, Crohn disease, syphilis and apetite-suppressing drugs are the other rare causes of AR (8-10).

There are some atypical causes of AR were reported in the literature. Bromocriptine, a dopamine agonist, increases the cardiac contraction and stres on the aortic valve, then valvular fibrosis may ocur and it increases the risk of AR development (11).

In a study conducted by Sachdev et al. including patients with Turner syndrome, severe AR was detected 15% of the patients (12).

Dilation of aortic annulus may cause the separation of the leaflets and leads to AR. Age related aortic root changes or cystic medial necrosis related to Marfan syndrome or osteogenesis imperfecta may the reasons of AR. Similarly, higher arterial hypertension levels play a role in the progression of AR (8,11).

## 5. Epidemiology of the Aortic Regurgitation

Men are affected more than women from AR (13% versus 8.5%). Advanced age is a predisposant to the disease and is most seen above the age of 50. Prevalence of AR was reported to be 4.9% - 10% in different studies (13). It is predicted that 2% of the population above 70 years old, have AR. Presentation of AR is different between developing countries and industrialized countries. Younger patients are affected mostly in developing countries and initiation is rapid in nature. Infective endocarditis and rheumatic heart disease are two major contributors to AR. In industrialized countries AR is more common in older individuals as a result of degeneration (14,15).

## 6. Clinical Signs and Symtons of the Aortic Regurgitation

Anamnesis and physical examination are important parts of the diagnosis like in all other diseases. Dyspnea especially with excertion, orthopnea, chest pain, paroxysmal nocturnal dyspnea, lightheadedness, cough, palpitation and syncope are the main presenting symptoms of AR. During sleeping heart rate becomes slower and arterial diastolic pressure falls to low levels. This situation causes nocturnal angina (16-18).

AR presents with widened pulse pressure because of higher systolic and lower diastolic blood pressures. The apical left ventricular impulse displaced inferolaterally. Systolic thrill may be detected over the carotid arteries and base of the heart. Despite a normal S1, S2 can be changeable, increased or decreased due to the aortic root dilation or thickened aortic leaflets. Diastolic murmur with the characteristics of decrescendo and high frequency is heard on the border of third intercostal space and left side of the sternum. Murmur is heard in early diastolic phase in mild AR and holosystolic type in severe AR (19).

There are several signs which can be detected in physical examination related to AR. Although these all were described in the literature, these may not meet always in patients. These signs can be listed as; Austin Flint murmur, bisferiens pulse, Duroziez sign, Hill sign, de Musset sign, Quincke sign, Traube sign, Rosenbach sign, Corrigan sign, Gerhardt sign, Muller sign and Mayne sign (20).

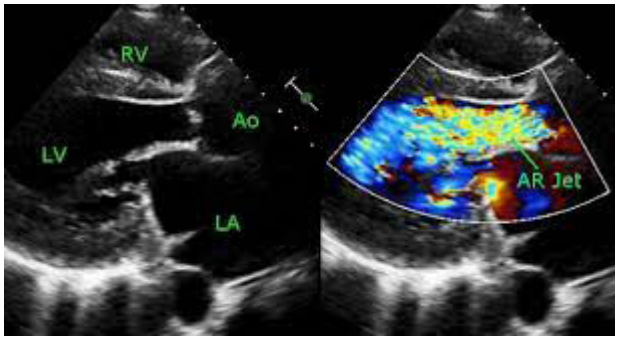
Decreased stroke volume is responsible from the signs and symptoms in acute AR. Pulmonary edema, tachypnea and tachycardia are presented in patients. Clinical signs and symptoms of acute AR are not as apparent as those in chronic form, therefore clinical suspicion in patients with acute dyspnea and shock is essential for rapid and accurate diagnosis (21).

## 7. Diagnosis of the Aortic Regurgitation

Chronic AR leads to left ventricular volume overload which reflects left ventricular hypertrophy and lateral precordial narrow Q waves. T wave and ST segment are usually normal. Vector of QRS complex shows left axis deviation (22). In a study included the ECG data of patients with AR designed by Recke, R peak delay which is a marker used in detection of left ventricular function was found in patients with severe AR (23). Sinus tachycardia is another finding that can be found in ECG monitoring (16).

Echocardiography provides the evaluation of aortic valve anatomy, left ventricle and aortic root, therefore it is the primary diagnostic tool in AR (Figure 4). Chronic AR manifests with a left ventricular dilation. Systolic functions are preserved until late stages and decreased ejection fraction (EF) or increased end systolic dimension may reflect the deterioration (8).

**Figure 4.** Detection of Aortic Regurgitation jet in echocardiography
https://johnsonfrancis.org/professional/severe-aortic-regurgitation-echo/




AR can be classified as mild, moderate and severe according to the echocardiographic criteria. In severe AR, central jet width to left ventricular outflow tract ratio is over 65%, effective regurgitatnt orifice area (EROA) is over 0.3 $cm^2$, regurgitant volume and fraction is equal or over 60 ml/beat and 50%, respectively and vena contracta is above 6 mm. In the proximal descending aorta, reverse diastolic flow is found (24). Echocardiographic criteria used in the classification of AR were given in table 1.

**Table 1.** Echocardiographic criteria used in the classification of Aortic Regurgitation
https://echobyweb.com/homepage/echo-lab/normal-values/4/

**Echocardiographic Criteria to Grade Aortic Regurgitation**

| | | Mild | Moderate | | Severe |
|---|---|---|---|---|---|
| | | | Mild to moderate | Moderate to severe | |
| **PHT** | ms | >500 | 500-200 | | < 200 |
| **Vena contracta** | mm | < 3 | 3 – 6 | | > 6 |
| **Jet / LVOT** | % | < 25 | 25-45 | 46-64 | >65 |
| **Regurgitant Volume** | ml | < 30 | 30-44 | 45-59 | ≥ 60 |
| **Regurgitant Fraction** | % | < 30 | 30-39 | 40-49 | ≥ 50 |
| **EROA** | $cm^2$ | < 0.10 | 0.10-0.19 | 0.20-0.29 | ≥ 0.30 |
| **Aortic Backflow** | cm | Early diastolic | | Holodiastolic > 15 | |

A rapid deceleration time in patients with severe AR can be shown in continuous wave doppler profile of the regurgitation jet. Pressures of the aorta and left ventricle in diastolic period become rapidly equal (25).

Cardiac magnetic resonance imaging (CMRI) is an another diagnostic procedure in AR and can be used in suboptimal evaluation obtained from echocardiography, or data incompatible with clinical situation. It gives the most accurate results about left ventricle end systolic volume, mass and

diastolic volume. Quantification of the severity of AR can be achieved with this method by evaluating retrograde and antegrade flow volumes in the ascending aorta (26).

Cardiac catheterization is an alternative method in the diagnosis of AR when noninvasive methods like echocardiography or imaging modalities contraindicated, unavailable or provide insufficient data. It gives data from the left and right anterior oblique positions about the severity of AR, anatomy of the coronary arteries and hemodynamics (27).

## 8. Treatment of the Aortic Regurgitation

In acute aortic regurgitation controlling the hypertension with calcium channel blockers, angiotensin receptor blockers (ARB) or angiotensin converting enzyme inhibitors (ACEI) is required. Beta blockers can be used in aortic dissection but shoul not be used in severe aortic regurgitation. Because they increase the diastolic filling time which causes increase in regurgitatnt blood flow. In addition, they prevent compensatory tachycardia which is required for maintaining adequate cardiac output. Intravenous vasodilators and diuretics can be used for afterload reduction. Inotropes are helpful to increase the cardiac output. If the etiology is infective endocarditis, suitable antibiotics according to the blood culture results should be given. Echocardiographic results should be checked for additional surgical intervention beside aortic valve replacement (AVR). Patients should be urgently operated when the etiologies are aortic dissection, trauma with deterioration in hemodynamic stability or infective endocarditis (28-30).

In chronic AR, medical therapy is arranged according to the stages of AR. Chronic AR has four stages; Stage A means patients at risk for AR. In Stage B, patients have progressive mild or moderate AR. The patients involved in Stage C have severe AR, but they are asymptommatic. Stage C is divided into two according to the EF. In C1, EF is more than 50%, and in C2, EF is less than 50%. In Stage D, patients are symptommatic and have severe AR (11).

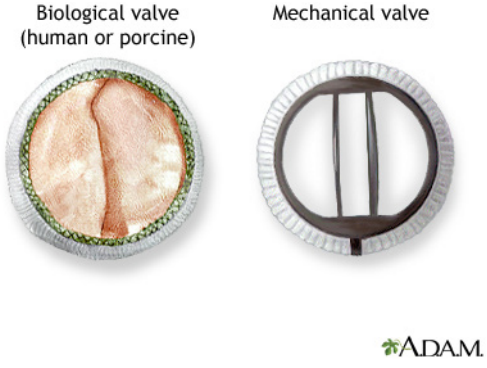
Similar antihypertensive medication has class I recommendation for the patients in stage B and C. Patients in stage C2 and D, and with comorbidities that prevent the the surgery, ACEI, ARB and beta blockers have class IIA recommendation. Patients involved in stage D, stage C2 and stage C1 with other cardiac disorders are candidates for AVR with class I recommendation. Timing of the surgery for AR was given in table 2 (31).

**Table 2.** Recommendations of surgery for aortic regurgitation

| Recommendations for Timing of Intervention for Chronic AR Referenced studies that support the recommendations are summarized in Online Data Supplement 15 to 17. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | B-NR | 1. In symptomatic patients with severe AR (Stage D), aortic valve surgery is indicated regardless of LV systolic function.[1–7] |
| 1 | B-NR | 2. In asymptomatic patients with chronic severe AR and LV systolic dysfunction (LVEF ≤55%) (Stage C2), aortic valve surgery is indicated if no other cause for systolic dysfunction is identified.[3,5,8–12] |
| 1 | C-EO | 3. In patients with severe AR (Stage C or D) who are undergoing cardiac surgery for other indications, aortic valve surgery is indicated. |
| 2a | B-NR | 4. In asymptomatic patients with severe AR and normal LV systolic function (LVEF >55%), aortic valve surgery is reasonable when the LV is severely enlarged (LVESD >50 mm or indexed LVESD >25 mm/m²) (Stage C2).[10,11,13–24] |
| 2a | C-EO | 5. In patients with moderate AR (Stage B) who are undergoing cardiac or aortic surgery for other indications, aortic valve surgery is reasonable. |
| 2b | B-NR | 6. In asymptomatic patients with severe AR and normal LV systolic function at rest (LVEF >55%; Stage C1) and low surgical risk, aortic valve surgery may be considered when there is a progressive decline in LVEF on at least 3 serial studies to the low–normal range (LVEF 55% to 60%) or a progressive increase in LV dilation into the severe range (LV end-diastolic dimension [LVEDD] >65 mm).[12,16,17,20,25–28] |
| 3: Harm | B-NR | 7. In patients with isolated severe AR who have indications for SAVR and are candidates for surgery, TAVI should not be performed.[29–32] |

The prosthetic valves used in AVR can be classified into two groups; mechanical prosthesis and bioprosthesis (Figure 5). They have both advantages and disadvantages. One of the main advantages of the mechanical prosthetic valves is to be long lasting than bioprosthetic valves. They are usually preferred in patients below 60 years old. Life long requirement of warfarin treatment is the disadvantage of this group. If the therapeutic range of INR can not be achieved stenosis of the valve or bleeding may happen. Although life long anticoagulant therapy is not required, bioprosthetic valves are short-lived than mechanical valves (32,33).

**Figure 5.** Types of prosthetic valves used in aortic valve replacement
https://medlineplus.gov/ency/presentations/100161_4.htm



Although it is not the part of the standart care, TAVI has to be considered as a treatment choice in patients with severe native pure AR who have high surgical risks and accepted as inoperable (34).

Risk of operation in sudden, severe AR is higher than chronic, severe AR. Additional conditions such as dissecting aneurysm or infective endocarditis are associated with poor prognosis (35).

Even if severe, asymptomatic and chronic AR usually has favorable long term prognosis. Left ventricular systolic function and size are predictors of clinical outcomes like the severity of AR. If left ventricular dysfunction can be detected earlier, it may reversible. Surgery should be performed before the initiation of irreversible changes to reduce mortality. Four year survival without replacement in patients with NYHA Class III or IV is about 30% (36).

## 9. Conclusion

Despite the on of the most important valvular disease, severe AR can be treated successfully in current era. Early diagnosis is important before the development of irreversible symptoms suc as decreased LV EF, enlarged LV and increased severity of AR.

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CHAPTER IV

# OBSTRUCTIVE SLEEP APNEA SYNDROME: ETIOLOGY

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## 1. Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is a prevalent sleep disorder that impacts the quality of life for many individuals (1). The cause of OSAS encompasses various factors such as anatomical features, physiological conditions, and genetic traits (2). This condition is marked by recurring airway obstructions, leading to decreased oxygen levels and repeated sleep disturbances (3).

The origins of apnea are multifaceted. Anatomical factors may be a contributing cause of the narrowing and closure of the pharyngeal airway (4), potentially due to abnormal size or position of the tongue, tonsils, and soft palate (5). Physiological factors may be related to changes in respiratory-related muscle activity, which could lead to decreased airway tone and backward movement of the tongue (6). Moreover, obstructive sleep apnea risk may increase due to inflammation and edema in the airway (7).

Studies on the etiology of OSAS indicate that genetic components may contribute to the development of this disorder (8). It is believed that certain genes may raise an individual's risk for OSAS by impacting the structure and function of pharyngeal tissue recently (9). Additionally, lifestyle and environmental factors may also influence the risk of OSAS. For instance,

obesity is a significant risk factor for OSAS since fat tissue buildup can lead to the narrowing of airways around the upper airway. Other factors that increase the risk of apnea are smoking, alcohol consumption, and the use of sedatives, which promote airway relaxation or constriction (10,11).

Additionally, sleep position might also contribute to OSAS etiology. Sleeping on the back may cause obstruction in the airway due to the tongue moving backward, thereby increasing the risk of apnea in individuals sleeping in that position (12). Additionally, postmenopausal women and the elderly have a higher risk of OSAS, suggesting that hormone changes and age-related textural changes may play a role in the etiology of the condition (13).

As a brief, the etiology of OSAS is complex and multifactorial. Anatomic, physiological, genetic, lifestyle, and environmental factors might all contribute to the development of this disorder. Hence, a comprehensive grasp of the etiological factors could aid in diagnosing and treating the disorder more effectively (14).

## 2. Etiology

Obstructive Sleep Apnea (OSAS) is a multifaceted condition linked with multiple risk factors. OSAS, which has a broad range of causative factors such as anatomical anomalies and neuromuscular control changes, is prevalent in the community. This chapter will provide a detailed analysis of the etiology of OSAS.

### *2.1. Anatomical Factors*

Multiple factors need to be examined to understand the etiology of OSAS. Anatomical causes are at the top of these factors (15). Differences in the structure of the respiratory tract between individuals cause anatomical factors. Abnormalities in upper airway anatomy may increase the risk of OSAS (16).

- Pharyngeal Stenosis: Stenosis in the pharynx is one of the most common anatomical causes of OSAS (2). This stenosis may occur due to enlargement of the posterior part of the tongue or the soft palate and uvula.
- Mandibular Retrognathia: The lower jaw (mandible) being further back than normal can cause the tongue to be in a position where it can obstruct the airway (17). This increases the risk of airway obstruction.
- Nasal Obstruction: Obstruction or narrowing of the nasal passages may contribute to developing OSAS (18). This obstruction may result from many causes, such as enlarged turbinates, nasal polyps, or deviated septum.

- Adenotonsillar Hypertrophy: Enlarged adenoids and tonsils, especially in children, may cause narrowing of the airway (19). This is a common etiologic factor of OSAS in the pediatric population.
- Craniofacial Abnormalities: Congenital abnormalities in facial and cranial structure may cause airway narrowing and development of OSAS (20). It is especially associated with syndromes such as Pierre-Robin syndrome or Down syndrome.
- Obstructive Lingual Tonsil Hypertrophy: Enlargement of the lingual tonsil may lead to obstruction of the tongue root (21). This condition is usually a rare cause of OSAS in adults, but it is important to recognize and treat.

The anatomical etiology of OSAS results from structural defects in the upper airway. However, these anatomical factors alone are not the cause of OSAS. For OSAS to develop fully, these anatomical factors must be combined with neurologic, physiologic, and other etiologic factors (22). However, recognizing and treating anatomical factors is critical in OSAS management (23).

### *2.2. Functional Factors*

The etiology of OSAS is a combination of both anatomical and functional (or structural) factors. Functional factors are elements related to the dynamics of respiratory functions and the airway (2,12,13). These factors are affected by the physiologic characteristics of individuals, such as airway resistance, muscle tone, neuromuscular reflexes, and ventilation control mechanisms.

- Upper Airway Resistance: Upper airway resistance may increase in OSAS patients compared to healthy individuals (24). This increase may be caused by factors such as loss of elasticity of the airway wall or inflammation.
- Genioglossus Muscle Activity: The genioglossus is the main muscle that moves the anterior part of the tongue. In OSAS patients, there may be changes in the activity of the genioglossus muscle, which may cause airway closure (25).
- Neuromuscular Reflexes: In OSAS patients, upper airway reflexes may be impaired (26). These impairments may lead to ineffective functioning of the airway muscles and cause obstruction.
- Ventilation Control: In OSAS, abnormalities in central ventilation control mechanisms may be present (27). These abnormalities may cause changes in the sensitivity of chemical receptors that regulate oxygen and carbon dioxide levels.

- Arousal Threshold Arousal threshold refers to the level of disruption of an individual's sleep. In OSAS patients, this threshold may be lowered, which may cause wakefulness as a rapid response to airway obstruction (28).
- Respiratory Drive: The respiratory drive is the mechanism that determines the individual's need to breathe. In OSAS patients, there may be abnormalities in this drive, which may lead to airway obstruction or irregular breathing (29).

The functional etiology of OSAS is closely related to the dynamic and physiologic characteristics of respiration. Together with anatomical factors, these functional factors play an essential role in the development and severity of OSAS (30). The combination of anatomical and functional factors constitutes the complex etiology of OSAS, and these factors need to be fully understood when determining treatment approaches (24).

### *2.3. Neurological Factors*

OSAS etiology is also closely related to neurologic factors (31). Neurologic factors can be defined as central nervous system abnormalities that affect the activation of respiratory muscles and the function of the respiratory drive.

- Neuromuscular Function Disorders: Impairments in the neuromuscular function of the pharyngeal muscles have been found in OSAS patients (32). These disorders may reduce the ability of these muscles to keep the airway open.
- Anomalies in Respiratory Control Centers: Respiratory control centers in the brain stem may not function properly in OSAS patients (33). Irregular activation of these centers may cause fluctuations in respiratory rhythm and apnea episodes.
- Changes in Arousal Threshold: In OSAS patients, the arousal threshold may be higher in response to airway obstruction (34). This means that the threshold to wakefulness is raised in response to airway obstruction.
- Abnormalities in Chemoreceptor Sensitivity: Chemoreceptors that monitor arterial oxygen and carbon dioxide levels may be hypersensitive in OSAS patients (35). This can cause a rapid respiratory response as a rapid response to airway obstruction.
- Neurotransmitter Disequilibrium: Neurotransmitter imbalance in the brain has been linked to the etiology of OSAS (36). Neurotransmitters, especially serotonin, norepinephrine, and GABA, are important in respiratory control, and their imbalance may contribute to the development of OSAS.

Neurological factors are significant in developing OSAS and should be considered while developing treatment approaches (2,33,36). Due to the complicated etiology of OSAS, various treatments may be appropriate depending on patients' characteristics (37,38). Thus, it is crucial to comprehend neurological factors thoroughly for the effective management of OSAS.

### *2.4. Endocrine and Metabolic Factors*

Among the factors, endocrine and metabolic factors have a significant role in the development and progression of OSAS (38). An in-depth understanding of these factors enables precise identification and effective treatment of OSAS.

- Insulin Resistance and Type 2 Diabetes: A strong association has been found between OSAS and insulin resistance and type 2 diabetes (39). The decreased sensitivity of cells to insulin may be due to repeated oxygen deprivation during the night. At the same time, treatment of OSAS may reduce insulin resistance and help manage diabetes (40).
- Polycystic Ovary Syndrome (PCOS): The incidence of OSAS is increased in women with PCOS. This suggests that the hormonal changes of PCOS may increase the risk of OSAS by affecting the function of airway muscles (41).
- Growth Hormone and Cortisol: Changes in growth hormone and cortisol levels have been found in individuals with OSAS (42). These hormonal changes may be part of the body's stress response to airway obstruction.
- Metabolic Syndrome: OSAS has been associated with components of the metabolic syndrome, including high blood pressure, high triglyceride levels, low HDL cholesterol levels and abdominal obesity (43). These components may increase the risk of airway obstruction and influence the severity of OSAS.
- Leptin and Ghrelin: These two hormones regulate hunger and satiety. An imbalance of these hormones has been found in individuals with OSAS, possibly contributing to OSAS being more common in overweight or obese individuals (44).

The etiology of OSAS is complex and involves endocrine and metabolic factors. Effective management of OSAS necessitates consideration of these factors and the adoption of individualized treatment approaches (45,46). The etiology of OSAS is complex and involves endocrine and metabolic factors. A comprehensive grasp of endocrine and metabolic factors is crucial for optimal OSAS treatment outcomes.

### *2.5. Drug and Substance Use*

Studies on the role of drug and substance use in increasing the risk of OSAS) have shown that certain substances may affect OSAS risk due to their stimulant or depressant effects on the respiratory center (47). The increase in OSAS risk or change in severity due to drug and substance use results from direct and indirect effects of these agents on the respiratory system.

- Alcohol: The sedative properties of alcohol may relax the muscles of the upper airway, especially in the first few hours after consumption (48). This may cause the tongue and soft palate to obstruct the airway more easily. The risk of OSAS may increase, especially in individuals who fall asleep immediately after alcohol consumption.
- Benzodiazepines and Sleeping Drugs: Sedatives and sleeping pills such as benzodiazepines can affect respiratory function. Especially in individuals who use these drugs continuously or take them in high doses, the risk of OSAS may increase (49).
- Opioids: Long-term opioid use may cause respiratory depression (50). Opioids may inhibit the respiratory drive, leading to increased severity of OSAS.
- Some Antidepressants: Some antidepressant drugs may affect respiratory function and increase the risk of OSAS (51). However, this effect may vary depending on the dose and type of drug used.
- Smoking: The stimulant effect of nicotine and other toxic substances can cause edema and inflammation in the airway. This can lead to the narrowing of the airway and an increased risk of OSAS (52).

Awareness of drug and substance use and its impact on the risk of OSAS is crucial for effectively managing this disorder. Individuals should be mindful of their drug and substance use habits and comprehend the potential risks of these substances in both diagnosis and treatment (53). It is highly advisable that people using particularly high-risk drugs or substances communicate with their physicians regarding this matter.

### *2.6. Inflammation and Allergic Factors*

The development of OSAS is better understood through clinical and experimental studies, revealing the role of inflammation and allergic factors. Individuals with OSAS show increased inflammatory responses in the upper respiratory tract and systemic inflammation indicators (54).

- Upper Respiratory Tract Inflammation: In patients with OSAS, increased inflammatory cell infiltration has been observed in the nasopharyngeal and oropharyngeal mucosa. This inflammatory response may lead to edema and narrowing of the upper airway, thus facilitating airway obstruction (55).
- Systemic Inflammation: OSAS is known to be associated with a systemic inflammatory state. Increased inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) have been found in individuals with OSAS (56). This is thought to be one reason for the association of OSAS with cardiovascular diseases.
- Allergic Reactions: Allergic rhinitis is a factor that may increase the risk of OSAS. Swelling and inflammation in the nasal passages due to exposure to allergens may cause obstruction in the respiratory tract (57).
- Adenoid and Tonsil Hypertrophy: It is known that adenoid and tonsil hypertrophy may increase the risk of OSAS in children. Adenoids and tonsils may enlarge in response to inflammation and allergic reactions, obstructing the airway (58).
- Gastroesophageal Reflux Gastroesophageal reflux (GERD) can trigger an inflammatory response, leading to laryngeal edema. This can lead to increased severity of OSAS (59).

Understanding the relationship between OSAS and inflammation and allergy is crucial for developing treatment options and patient management strategies. Controlling these causal factors of OSAS may enhance patients' quality of life and reduce the risk of complications (58,59,60).

### *2.7. Age and Gender-Related Factors*

Age and gender have essential effects on the prevalence and severity of OSAS. OSAS is a prevalent condition among adults, with the risk escalating with age (61). There is also a potential link between sex and the occurrence and severity of OSAS.

- Age-Related Factors: Understanding how OSAS changes in relation to age is critical for the correct diagnosis and treatment of this disorder. There is an increase in the prevalence of OSAS in adults, especially in middle age and beyond (62). This is associated with changes in the mechanical properties of the upper airway, muscle tone and neurologic controls with age (63).
- Gender-Related Factors: Gender-specific features of OSAS are characterized by higher prevalence and severity in men. It is thought that

factors such as the anatomical structure of the upper airway, hormones and fat distribution may increase the risk of OSAS in men (64). An increased risk of OSAS has been observed in postmenopausal women, which may be associated with changes in hormone levels (13,64).

- Hormonal Factors: Testosterone levels in men and estrogen and progesterone levels in women may have an impact on the gender-specific prevalence and severity of OSAS (65). Estrogen deficiency, especially in postmenopausal women, may increase the risk of OSAS by causing a decrease in upper airway tone (66).
- Life Periods and OSA: Clinical symptoms and severity of OSAS may differ in childhood, adulthood and old age. While OSAS usually develops in children due to enlarged tonsils and adenoids, decreased muscle tone and impaired neurologic control are more prominent in elderly individuals (67).

Understanding the age- and gender-related factors of obstructive sleep apnea (OSAS) is crucial in identifying individuals at risk and in treating this disorder. Identifying age- and gender-specific causal factors can aid in developing the most suitable treatment approach for individuals (66,67,68).

### *2.8. Genetic Factors*

OSAS is a syndrome that affects a considerable portion of the population. Studies investigating its causes have indicated that genetic factors may play a role in its development. Analyzing such factors provides valuable insight into the etiology of OSAS, paving the way for advances in disease diagnosis and treatment (69).

- Familial Predisposition: In families of individuals with OSAS, it has been observed that this disorder is more common in other members. Family studies show that OSAS has a familial characteristic (70). This indicates that a genetic predisposition contributes to the development of the disease.
- Genetic Polymorphisms: Certain gene variants have been shown to be associated with OSAS risk. These genes are linked to different pathways associated with OSAS, such as inflammatory responses, respiratory muscle function, fat storage and upper airway structure (71).
- Genome-Wide Studies (GWAS): GWAS is a powerful method used to identify specific gene regions associated with OSAS risk. Such studies can help identify genetic markers that increase the risk of OSAS (72).
- Epigenetic Changes: Epigenetic mechanisms such as DNA methylation and histone modifications that can cause changes in gene expression may play

a role in the etiology of OSAS (73). Environmental factors affecting the course of OSAS may lead to changes in gene expression and affect the severity of the disease.

Understanding the genetic origin of OSAS may facilitate the early identification of at-risk individuals and the developing personalized treatment approaches. However, it is important to note that genetic factors' exact contribution to OSAS remains unknown, highlighting the need for further research. Additionally, to inform clinical practice, robust studies, and ethical discussions on the employment of genetic information are required (70,72-74).

### *2.9. Movement Disorders and Other Associated Sleep Disorders*

OSAS is a prevalent sleep disorder that results in repeated breathing cessation during sleep. Nonetheless, aside from OSAS, individuals may also encounter other sleep disorders and movement disorders. These concomitant disorders can influence the severity, signs, and symptoms of OSAS (1).

- Sleep Leg Movement Disorder (RLS/PLMD): A condition characterized by involuntary movements of the legs during sleep. The prevalence of RLS in OSAS patients has been found to be higher than in the general population. The coexistence of RLS and OSAS may affect response to treatment and quality of life (75).
- Narcolepsy It is a sleep disorder characterized by excessive sleepiness, cataplexy, and hypnagogic hallucinations. OSAS has also been observed in some patients with narcolepsy. This may affect treatment strategies and may require evaluation of narcolepsy patients in terms of OSAS (76).
- Sleep Terrors and Sleepwalking: OSAS may contribute to the development of parasomnia forms such as sleepwalking and sleep terrors, especially in children. Respiratory disturbances during sleep may trigger such sleep events (77).
- Idiopathic Central Sleep Apnea: While OSAS develops due to upper airway obstruction, central sleep apnea occurs as a result of improper transmission of brain signals to the respiratory muscles. In some patients, a combination of both types of apneas may be observed, this condition is called mixed sleep apnea (2).

These co-occurring disorders of sleep and movement can complicate the diagnosis and treatment of OSAS. Additionally, the existence of these comorbid

disorders can have an adverse effect on the patient's quality of life as well as their response to treatment. Therefore, it is crucial to evaluate patients with OSAS for other potential sleep disorders (78).

## 3. Conclusion

OSAS is a complex disorder where respiratory arrest occurs due to repeated upper airway obstruction during sleep. The etiology of OSAS involves multiple factors, demanding a comprehensive approach to treatment and management (69).

Anatomical factors are vital to OSAS etiology, with evidence pointing to structural features of the upper airway, facial and jaw structure, tonsil size, and tongue position as key players (23). In addition, functional factors play a critical role in developing OSAS. Specifically, impaired functional activity of the upper airway muscles may increase OSAS risk (24).

While neurologic factors may be less significant, they still contribute to the etiology of OSAS. Evidence suggests that activation or inhibition of certain brain regions may influence respiratory muscle function (37). Endocrine and metabolic factors can significantly increase the risk of OSAS, especially when associated with factors such as obesity and insulin resistance (46). Therefore, patients' history of drug and substance use should be thoroughly evaluated because it may have direct and indirect effects on the etiology and severity of OSAS (53).

Studies on the role of inflammation and allergic reactions in the etiology of OSAS indicate that these factors may contribute to an increased risk of upper airway obstruction (60). Additionally, the potential impact of demographic factors, such as age and gender, on OSAS etiology is examined. While OSAS is more prevalent in men, postmenopausal women face an increased risk (68). Studies also suggest that OSAS may be linked to genetic predisposition. This implies that OSAS is more prevalent in individuals with a family history (74). Treatment strategies and patients' quality of life may be affected by movement disorders and other sleep disorders associated with OSAS (78).

Overall, the cause of OSAS is intricate and results from the interplay of various factors. Patients' personal risk factors, lifestyle choices, genetic predispositions, and comorbid health conditions can significantly affect the severity and signs/symptoms of OSAS. This requires adopting a patient-centric approach in the treatment and management of OSAS (69,78).

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# CHAPTER V

# CLASSIFICATION OF SLEEP DISORDERS

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## 1. Introduction

Sleep is a biologically and psychologically restorative process that takes up almost a third of our lives. It is a vital factor that impacts individuals' overall health, quality of life, daily functioning, and even life expectancy. Sleep disorders are a prevalent issue many people confront at some point in their lives, and recent studies have shed better light on the prevalence of these disorders (1). These disorders can lead to chronic fatigue, difficulty concentrating, memory problems, and, in some cases, accidents or serious medical complications (2).

To diagnose a sleep disorder, doctors should use laboratory tests, as well as specialized tests such as polysomnography in addition to clinical evaluation (3). The most widely accepted classification system for sleep disorders is the International Classification of Sleep Disorders, ICSD-3 (4). In this classification, sleep disorders are evaluated under the main headings of Insomnia, Sleep Related Breathing Disorders, Central Disorders of Hypersomnolence, Circadian Rhythm Sleep-Wake Disorders, Parasomnias, and Sleep Related Movement Disorders (5).

Sleep related breathing disorders, characterized by respiratory interruptions or difficulty breathing during sleep, are a common health problem. It is important to address these issues in order to improve overall health and quality of life. This

category comprises several disorders, with obstructive sleep apnea being the most common (6). Insomnia is defined by symptoms such as difficulty falling or staying asleep, and early awakening, and may have a significant impact on one's quality of life (7). Hypersomnia is a disorder in which individuals experience excessive sleepiness and is exemplified by narcolepsy (8).

Circadian rhythm sleep-wake disorders arise from a mismatch between an individual's biological clock and the external environment's light-dark cycle. This includes the condition known as jet lag experienced after long flights (9). Parasomnias include events such as sleepwalking and talking during REM or non-REM sleep periods (10). Sleep-related movement disorders generally refer to conditions like restless leg syndrome (11).

It is important to emphasize that treating sleep disorders should involve a multidisciplinary approach. Sleep disorders may arise due to a combination of psychological, physiological, neurological, and environmental factors. Hence, treatment strategies should be tailored to individual needs by considering the etiology and symptomatology of sleep disturbances (12).

## 2. Classification of Sleep Disorders

Sleep disorders are prevalent societal issues and can negatively impact individuals' health, quality of life, and functionality (13). The most current and extensive classification system for sleep disorders is ICSD-3 (International Classification of Sleep Disorders, 3rd Edition) (4). This system divides sleep disorders into various main categories.

### *2.1. Insomnia*

Insomnia is defined as the inability of individuals to fall asleep or stay asleep and is a common sleep disorder in society (14). According to ICSD-3, insomnia is a condition in which individuals complain of unsatisfactory sleep due to inadequate sleep duration or quality, and daytime functioning is affected accordingly (15).

ICSD-3 provides more specific definitions by dividing insomnia into several subtypes.

- Acute Insomnia: Acute insomnia is a sleep disorder that typically lasts less than one week and results from stress, health issues, or life events (16). Subjective evaluations are excluded unless clearly marked. This type of insomnia is usually temporary and resolves by removing the triggering factor (17).

- Chronic Insomnia: Chronic insomnia is defined as experiencing trouble sleeping or staying asleep three or more nights a week for at least three months (18). It may develop from underlying health issues, lifestyle factors, or side effects of certain medications (19).
- Co-morbid Insomnia: In some individuals, insomnia occurs concurrently with another health condition. This type of insomnia is referred to as co-morbid insomnia (20). For instance, insomnia frequently occurs in individuals with depression or anxiety disorders (21).

The treatment of insomnia may vary depending on the underlying causes of the disorder. Cognitive behavioral therapy (CBT) is acknowledged as an effective approach to treating insomnia (22). Additionally, attention to sleep hygiene and incorporating some lifestyle changes may also alleviate insomnia (23, 24). In certain situations, short-term medication may be necessary. Insomnia is a prevalent sleep disorder with considerable implications for quality of life. Early detection and effective treatment methods can contribute to overcoming this condition (4).

### *2.2. Sleep-Related Breathing Disorders*

Sleep-related breathing disorders hold a significant position in the ICSD-3 classification and encompass conditions arising from respiratory issues during sleep (4). This classification is further divided into multiple subcategories.

- **Obstructive Sleep Apnea (OSAS): O**SAS is the most commonly diagnosed breathing disorder associated with sleep (25). It causes temporary cessation of breathing during sleep due to partial or complete blockage of the upper airway. These interruptions are often accompanied by symptoms including snoring, night sweats, dry mouth or throat (26). People may awaken without realizing it, resulting in symptoms like excessive daytime fatigue, lack of focus, and memory problems (27).
- **Central Sleep Apnea (CSA):** Unlike OSAS, CSA is a condition in which breathing is interrupted due to a disturbance of brain signals. In other words, physical obstruction is absent in this condition. CSA arises from the faulty performance of the central nervous system (CNS) regions responsible for respiratory control (28). This condition can be induced by several factors, including heart failure, stroke, or opioid use (29).
- **Sleep Related Hypoxic Hyperventilation Disorders (SRHHD):** This category encompasses breathing disorders caused by neurological, cardiovascular, or pulmonary conditions that lead to low oxygen levels during

sleep (30). SRHHD typically arise due to insufficient respiration related to an underlying illness (31).

Sleep related breathing disorders can adversely affect an individual's overall health, quality of life, and daily functionality. Early diagnosis and management of these disorders using appropriate treatment strategies can enhance individuals' quality of life and prevent other health complications (32).

### *2.3. Central Disorders of Hypersomnolence*

Central disorders of hypersomnolence comprise a group of sleep disorders defined by symptoms of excessive sleepiness or daytime insomnia (33). These disorders can result in an irresistible need to sleep even after obtaining satisfactory and adequate sleep at night (34). The ICSD-3 categorizes central disorders of hypersomnolence into various subtypes.

- **Narcolepsy:** Narcolepsy constitutes a sleep disorder that exhibits sudden and compelling urges to sleep during awake periods (35). Narcolepsy is categorized into two main types in accordance with ICSD-3, based on hypocretin deficiency and clinical diagnosis: Type 1 and Type 2 (4).
- **Idiopathic Hypersomnia:** Idiopathic hypersomnia is a disorder characterized by excessive daytime sleepiness of an unknown cause (36). In this condition, individuals experience long and uninterrupted nighttime sleep but still feel extremely tired during the day (37).
- **Kleins-Levin Syndrome:** This condition is characterized by individuals experiencing extended periods of sleepiness lasting for days or weeks, which is rare (38). During these episodes, individuals awaken only to consume food and sleep excessively during the daytime (39).

The treatment of central disorders of hypersomnolence may vary depending on the type of underlying disorder. Although stimulant drugs are often administered for narcolepsy, treatment for idiopathic hypersomnia and Kleins-Levin Syndrome typically focuses on symptom management (40). Central disorders of hypersomnolence can significantly impact an individual's daily life, work performance, and social interactions (41). By diagnosing these disorders early and utilizing effective treatment methods, it is feasible to overcome them and enhance the individual's quality of life (42).

### *2.4. Circadian Rhythm Sleep-Wake Disorders*

Circadian rhythm sleep-wake disorders are sleep issues that arise due to a mismatch between the internal circadian clock and the 24-hour cycle of the

external environment (43). These disorders are linked to how the body's internal clock manages physiological functions and behaviors at different times of the day (44). ICSD-3 classifies circadian rhythm sleep-wake disorders into various subcategories.

- *Delayed Sleep Phase Disorder:* This disorder is identified by the tendency of individuals to stay up late at night and wake up late in the morning (45). Individuals with delayed sleep phase disorder often face issues due to work or school commitments early in the morning (46).
- *Early Sleep Phase Disorder:* In this disorder, individuals tend to fall asleep in the early hours of the night and wake up early in the morning (47). This is more prevalent in older individuals (48).
- *Conversion Disorder:* It is a frequently encountered issue among shift workers. These individuals experience irregularities in sleep and wakefulness periods due to the constant change in working hours (49).
- *Social jet lag:* This is the incompatibility that arises from the difference between the weekday and weekend sleep habits of individuals. This difference can result from the habit of waking up early on weekdays and going to bed late on weekends (50).

Approaches like light therapy and melatonin supplements are often used for treating circadian rhythm disorders (51). Additionally, lifestyle adjustments such as improving sleep hygiene and regulating the individual's circadian rhythm are recommended. Circadian rhythm sleep-wake disorders can adversely affect an individual's daily life, work performance, and overall quality of life. However, it is possible to overcome these issues with accurate diagnosis and efficient treatment methods (51, 52, 53).

### *2.5. Parasomnias*

Parasomnias refer to undesired events or movements that occur during the sleep cycle. These disorders are mainly caused by rapid eye movement (REM) sleep or non-REM sleep (4). ICSD-3 divides parasomnias into two primary categories: *REM-related parasomnias* and *non-REM-related parasomnia*s (54).

- *REM-Related Parasomnias* include REM sleep behavior disorder (RBD), which is a common and notable example of this category. Normally, individuals remain still during REM sleep, but this is not observed in those with RBD. These individuals may physically act out their dreams, leading to injuries upon awakening (55,56).

- *Non-REM Related Parasomnias* generally occur in the deeper stages of sleep, with examples including sleepwalking and night terrors. Sleepwalking is defined as an individual walking, talking, or performing complex tasks while asleep. During these episodes, the individual is not fully awake and typically does not remember these actions (57). Night terrors are characterized by sudden and severe bouts of fear. Although the person appears to be awake, they usually do not react during these episodes and do not remember the event afterwards (57,58).

The cause of these disorders is not yet fully understood, but it is believed that genetic factors, abnormalities in brain structures, and neurological diseases play a role in their development (59). Treatment options may vary depending on the underlying cause, including medication, behavioral therapy, or a combination (60). Both individuals and their families can find it challenging to cope with such disorders. However, early diagnosis and proper treatment can enhance the quality of life for these individuals and prevent potential complications (61).

### *2.6. Sleep-Related Movement Disorders:*

Sleep-related movement disorders consist of various conditions characterized by involuntary movements that disturb individuals' sleep. These movements typically take place when falling asleep or whilst asleep (4). ICSD-3 has provided a comprehensive classification by separating these disorders into categories (62).

- **Periodic Limb Movement Disorder (PLMD):** PLMD refers to involuntary movements at regular intervals during sleep, particularly in the legs. These movements typically repeat every 20-40 seconds and may disturb the individual's sleep. Although a specific cause of PLMD is generally unknown, it is believed that neurologic and physiologic factors may play a role (61,62,63).
- **Restless Legs Syndrome (RLS):** It can be defined as feelings of discomfort usually experienced in the legs. This sensation generally decreases with movement and typically worsens in the evening. The causes of RLS may include an imbalance of dopamine, genetic factors, and iron deficiency (62,63).
- **Bruxism (*Clenching and/or Grinding Teeth*)**: Bruxism is a parafunctional activity which is characterized by clenching and grinding of teeth unconsciously (64). It can cause jaw pain and myofascial pain syndrome (MPS) when it becomes chronic. The condition is believed to be often attributed to stress, anxiety, side effects of several medications that affect dopamine metabolism and OSAS (65).

- **Sleep-Related Leg Cramps:** This condition is characterized by the sudden onset of severe muscle cramps in the legs (66). The cramps usually last for a few seconds to a few minutes. Electrolyte imbalance, dehydration, or certain medications are believed to be the leading cause of these cramps (67).
- **Sleep-Related Rhythmic Movement Disorder:** It is also characterized by rhythmic movements of the head, neck, or other body parts while falling asleep. These movements are more common in childhood and may decrease in adulthood. Treatment for sleep-related movement disorders may vary depending on the underlying causes, severity of symptoms, and age of the individual. Approaches like drug therapy, behavioral therapies, or physical therapy may prove efficacious in managing these disorders (68,69,70).

## 3. Conclusion

Sleep is an essential part of the human daily life cycle. It has been proven that qualified sleep has a significant impact on overall health (80). *Classifying sleep disorders* aims to provide clinicians and researchers with a more systematic and effective approach for both diagnosis and treatment of the conditions that arise from lack of quantity and quality of sleep (71). Therefore, the classification of sleep disorders aims to provide a more systematic and effective approach to clinicians and researchers (72). Among the current classifications, ICSD-3 offers a detailed classification of sleep disorders as a guide (4,72,73).

*Central Disorders of Hypersomnolence* are the conditions which are characterized by sudden episodes of daytime sleepiness (42,68). It is known that these kinds of sleep disorders can impact individuals' daily lives negatively, reduce work productivity, and potentially cause accidents (74).

*Circadian Rhythm Sleep-Wake Disorders* arise when an individual's biological clock struggles to adjust to environmental factors (75). Diagnosis and treatment of these disorders may enhance the quality of life and positively impact overall health status (76).

*Parasomnias* are defined by unusual behaviors, emotions, and movements that manifest during particular sleep stages or while awake (77). This group encompasses potentially hazardous conditions such as sleepwalking, which can result in actions that may be detrimental to the individual (77,78).

*Sleep-Related Movement Disorders* are involuntary movements that occur during sleep (89). These disorders can potentially reduce sleep quality and negatively impact daily life (80).

*The classification of sleep disorders* aids in understanding, recognizing, and treating these disorders adequately (81). Clinicians and researchers benefit from ICSD-3's reflection on the accumulation of knowledge in this field (81,82,83,84).

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# CHAPTER VI

# FETAL SURGERY FOR MYELOMENİNGOCELE-WHERE DO WE STAND TODAY?

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## 1. Introduction

Spinal dysraphism, the most common type of neural tube defect, is caused by failure of the spinal neural tube to close during the first 3 weeks of pregnancy (1). The mildest form of it, closed spinal dysraphism (spina bifida occulta), involves a hidden vertebral defect with a lesion that is covered by the skin with no exposure of the spinal cord. Meanwhile, open spinal dysraphism (spina bifida aperta) involves an exposed neural tissue to its surrounding environment, with or without a protruding sac, and no skin coverage (2, 3).

The prevalence and incidence of spinal dysraphism vary across geographical regions with socio-demographic characteristics and socio-economic status of the populations having a significate influence over its epidemiology (4).

Myelomeningocele, an open form of spinal dysraphism, has an incidence rate around 0,2-0,4/1000 live births. However, higher rates have been reported in Latino population, in some regions of China, Africa, Middle East, India and Thailand (5, 6).

## 2. Historical Considerations

Descriptions of what appears to be spinal dysraphism has been discovered in different writings that belong to Greco-Roman era. But, the earliest definitive description of spinal dysraphism is attributed to the Dutch clinician Peter van Forest (1522-1597). In his work, published after his death in 1610, van Forest

reported a 2-year-old child with a neck malformation that appears to have been a form of spina bifida. Surgical ligature at the base of the lesion was performed and resulted in the death of the patient (7).

Almost 300 years later, a German surgeon, C. Bayer introduced the concept of placing the neural structures within the spinal canal, followed by layered covering of the surrounding tissues using various rotating flap techniques (8). Following Bayer's principles, Antoine Chipault reported good surgical outcomes in patients with myelomeningocele using multi-layered closure of the neurological structures (9). Charles H. Frazier (1870-1936), one of the early pioneers in American Neurosurgery, had great contributions in the field of surgery for myelomeningocele, with his techniques that would become

the primary modality of surgical repair used in the first half of the 20$^{th}$ century- excision of small myelomeningocele sacs followed by a primary closure of the neck after overlying the spinal erector muscles, while in larger and more complex defects, mobilization of the aponeurosis and paraspinal muscles in order to cover the defect in a multilayer manner was performed (7, 10).

### 3. Pathophysiology

Between the second and sixth week of pregnancy, development of normal spinal cord takes place in three stages; gastrulation, primary neurulation and secondary neurulation. Open and closed spinal dysraphisms are typically the result of defects occurring in the stage of primary neurulation.

At the end of the third week of gestation, during the stage of gastrulation, the neural plate is formed. Once the bilaminar embryonic disk is composed, embryonic disc's cells quickly divide, migrate, and eventually transform into a trilaminar disc.

Following the interaction of the notochord with the ectoderm, neuroectoderm is formed and neural plate which begins at the midline, then proceeds cranially and caudally. The neural groove, which is a small central depression, appears as the neural folds emerge during the primary neurulation phase. Furthermore, the neural folds will gradually fuse in order to form the neural tube. Closing of the neural tube's cranial and caudal ends marks the end of the primary neurulation stage. Any defect in closure of the caudal part of the neural tube's closure would will lead to exposure of the neural tissue known as placode (11, 12).

Meningeal lining and neural placode are associated with myelomeningocele lesions and are one of the most crucial characteristics that help to distinguish from myelocele.

## 4. Fetal Surgery for Myelomeningocele

### *4.1. Background*

For decades management of myelomeningocele consisted of early postnatal surgery in order to cover the exposed spinal cord; However, the purpose of postnatal myelomeningocele surgery was not to reverse or prevent any neurologic injury, rather to palliate (13).

As a consequence of incomplete primary neurulation combined with chronic in utero damage (mechanical and amniotic-fluid induced chemical trauma) to the exposed neural tissue, neurologic deficits associated with myelomeningocele lesions occur.

Development of fetal surgery for myelomeningocele is based on the ‘‘two-hit hypothesis’’ concept- early fetal surgical repair in order to reduce the secondary damage (amniotic-fluid exposure, hydrodynamic pressure, direct trauma) to the exposed neural structures (14, 15).

### *4.2. Trials and Tribulations*

In 1984, Michejda used a primate animal model (Macaca mulatta monkeys) in order to test the hypothesis according to which intrauterine intervention can prevent further neural tissue damage and the consequent neurologic deficits. A fetal L3–5 laminectomy was performed in the 32 week of gestation in eight primates. Five monkeys underwent immediate repair of the laminectomy in utero using allogeneic bone paste to reconstruct the resected dorsal arches. Primate fetuses that underwent in utero repair were neurologically normal at birth. The other group of primates that did not underwent repair of the induced defect had associated deficits at birth, such as paraplegia, incontinence and somatosensory deficits (16).

Heffez et al (17) reported similar conclusions using a fetal rat and a pig model of induced spinal dysraphism. Their study concluded that both mechanic trauma and toxic injury may contribute to the spinal cord injury.

In 2007, Stiefel et al (18) used a mouse genetic model in which spinal dysraphism developed spontaneously. Observing the fetuses with spinal dysraphism in a later gestational stage, the study reported degenerative changes within the pathologically exposed spinal cord tissue. Nerves connecting the open spinal cord to the hindlimbs were identifiable up to embryonic day 15.5 showing development of intact neuronal continuity between spinal cord and periphery despite failure of neural tube closure. However, after embryonic

day 17 neural projections from the spinal dysraphism lesion to the hindlimbs were barely visible, suggesting a more complex disrupted neuronal continuity between spinal cord and periphery at this stage in mice fetuses with spinal dysraphism lesions. The study concluded that these degenerative changes progress with ongoing gestation and culminate in sub-total or complete loss of all exposed neural structures by birth due to traumatic and/or toxic destructive processes occurring within the amniotic environment during late gestation.

Different studies showed a gradual loss of neurological function with advancing gestation in correlation with the increasing tissue damage of the exposed spinal cord (18, 19).

### *4.3. Anesthesia and Maternal/Fetal Considerations*

Perioperative management of these cases is complex and multidisciplinary approach represents the key to optimal patient outcomes due to potential anesthetic, obstetrical, neurosurgical and fetal surgical and neonatal risks that a fetal surgical procedure carries. Anesthesia and analgesia for the mother and for the fetus, provision of uterine relaxation and fetal immobilization need to be ensured in order to offer proper conditions conducive to surgical access (20). These are achieved with maternal general anesthesia, transplacental delivery of anesthetic agents to the fetus and further tocolytic agents administered as required (21, 22). Different studies concluded

that supplemental fetal analgesia with intramuscular injection of fentanyl may lead to fetal bradycardia and should best be avoided (20, 23). The risks of placental and fetal hypoperfusion, fetal acidosis, maternal and fetal sepsis and maternal fluid overload should not be ignored.

### *4.4. Modern Analysis, Finding and Researches, Controversies*

In 1997, Dr. Joseph Brunner performed the first human fetal myelomeningocele repair at Vanderbilt University, in Nashville, Tennessee (24). Lack of complex information regarding the potential maternal/fetal risks and benefits led to the development of the notorious multi-center Management of Myelomeningocele Study (MOMS); the study was proposed by Dr. Diana Farmer, a pediatric and fetal surgeon. The study was funded in 2002 by the National Institute of Health and aimed to compare the outcomes of patients after prenatal open repair of myelomeningocele versus postnatal repair. The trial was ended in 2010 due to demonstrated efficacy of the prenatal repair.

Published in 2011 in New England Journal of Medicine, the multi-center randomized controlled trial Management of Myelomeningocele Study (MOMS) reported that, prenatal repair of spinal dysraphisms decreases the rate of shunted hydrocephalus, reverses the hindbrain herniation and improves developmental, motor and ambulation outcomes compared to postnatal surgical intervention (25). The rates of ventriculo-peritoneal shunt placement were 40% in the prenatal-surgery group and 82% in the postnatal-surgery group, patients being evaluated at 12 months.

Favorable results were reported also in terms of hindbrain herniation; incidence of patients who had no evidence of hindbrain herniation in the prenatal group was 36%, compared to only 4% in the postnatal surgery group. Furthermore, prenatal surgery group had a lower rate of moderate or severe hindbrain herniation (25%) versus postnatal surgery group (67%) and also a lower incidence of brainstem kinking (moderate or severe 14% with prenatal surgery and 37% with postnatal surgery). Syringomyelia was observed in 39% of the patients that underwent prenatal surgery and in 58% of the children included in the postnatal surgery groups (25). The incidence of cord tethering requiring surgical intervention was however higher in the prenatal surgery group (8% vs 1%).

MOMS trial addressed also maternal and neonatal complications.

Pregnancy complications were more common among women in the prenatal-surgery group. Pregnancy complications and maternal morbidity associated with prenatal surgery included chorioamniotic membrane separation, oligohydramnios, placental abruption, spontaneous membrane rupture, pulmonary edema, chorioamnionitis, spontaneous membrane rupture, spontaneous labor. Fetuses that were treated prenatally were delivered at an average gestational age of 34.1 weeks and 13% were born before 30 weeks of gestation. In the postnatal-surgery group the children were born at an average

of 37.3 weeks of gestation with none delivered before 30 weeks. Two fetal deaths were reported in the prenatal surgery group and a neonatal death due to prematurity (25).

Different studies published after the MOMS trial reported similar results in terms of patients' outcome (26, 27, 28).

The criteria used to qualify myelomeningocele patients for prenatal repair are (25):

- Myelomeningocele with the upper boundary located between T1 and S1, with hindbrain herniation

- Maternal age ≥18 years-old
- Gestational age 19 0/7 weeks to 25 6/7 weeks at the time of prenatal surgical intervention
- Singleton pregnancy
- Normal karyotype or FISH.
- Normal fetal echocardiogram

In parallel, major exclusion criteria are represented by (25):

- Severe kyphosis in fetus (more than 30 degrees)
- Risk of early delivery (incompetent or short cervix-less than 20 mm, previous preterm birth)
- Maternal body-mass index≥35 kg/$m^2$
- Maternal Hepatitis B, C and HIV
-Maternal hypertension increasing the risk of preeclampsia or preterm delivery, maternal insulin-dependent pregestational diabetes
- Placental abruption
- Previous history of hysterotomy in the active uterine segment
- Maternal – fetal Rh isoimmunization

Worldwide expansion of fetal surgery, especially after the publication of MOMS trial brought with it controversies of the prenatal myelomeningocele repair. One of the current controversies addresses the inclusion/exclusion criteria for fetal myelomeningocele repair. Some fetal centers started to perform fetal myelomeningocele repair in patients that have a body-mass index of up to 40 kg/$m^2$ (29, 30). Moehrlen et al (31) reported a fetal myelomeningocele repair in a Hepatitis B positive mother; the fetus remained Hepatitis B negative at the 24-month follow-up.

Another controversy refers to the type of surgical approach- open versus fetoscopic myelomeningocele repair. The open myelomeningocele repair is performed via a maternal laparotomy followed by exteriorization of the uterus and then a hysterotomy. The fetoscopic repair is performed by placing the fetoscopic ports through the maternal abdominal wall and uterus (32).

The surgical principle of myelomeningocele repair consists of multilayer closure of the neural placode, dura mater, lumbar fascia,

subcutaneous tissue and skin. Closure of the neural placode and dura mater remained unchanged over decades, however different soft tissue closure methods are still topics of debate in medical literature. Materials used as scaffolds and/or defect coverings in animal models include collagen- or gelatin-based scaffolds,

small intestinal submucosa, and polymeric materials including silicone, high density polyethylene, and polypropylene (33). The utilization of pericardium bovine patch combined with fibrin sealant at the fascial level-between the dural sac and the skin had successful results in a study reported by Gürer et al (34).

Fetoscopic repair technique using a biocellulose patch (Bionext) over the neural placode with good neurological outcome was also reported by other authors (35).

Heye et al (36) recognized the advantages of fetoscopic repair in terms of independent ambulation in myelomeningocele patients; However, their study reported that 30% of the patients included in the study developed inclusion cysts in the first two years of life. The authors also concluded that inclusion cysts might lead to loss of neurologic function and considered them as the so called "third hit".

Pathophysiology of the inclusion cysts after myelomeningocele repair and whether their origin is dysembryogenic or iatrogenic remains a topic of debate and research in the medical literature. The exact impact of the inclusion cysts on the clinical outcome of the patients remains uncertain.

Danzer et al (37) reported that after fetoscopic repair inclusion cysts were determined in 10 over 54 patients at a median age of 27 months. After surgical removal of the inclusion cysts, loss of normal bladder function and clean intermittent catheterization requirement was determined in 4 patients, while loss of normal motor function in low extremities was seen in 1 patient.

Mazzola et al (38) reported 3 patients that underwent open repair. Neurological examination at birth revealed normal motor function in the low extremities and no bladder dysfunction. Spinal MRIs performed because 2 patients later developed loss of motor function in both legs and one patient bladder dysfunction, showed the presence of inclusion cysts associated with spinal cord tethering. The authors concluded that patients who have undergone prenatal repair of spina bifida should be carefully observed for any signs of deterioration in motor or bladder function.

In a recently published study, Patel et al (39) investigated the effect of allograft patch closure on incidence of spinal inclusion cyst formation following open fetal myelomeningocele repair. Patients that underwent prenatal myelomeningocele repair were found to be at a higher risk for development of inclusion cysts those who underwent postnatal repair. The presentation of symptoms was also earlier in these patients than previously reported after postnatal repair. The study concluded that use of a dural

allograft patch appears to have a positive correlation with the formation of spinal inclusion cysts.

Long-term urological outcome of patients following fetal meningomyelocele repair is still under research. MOMS trial questioned the bladder function of patients 30 months after their birth and at their school age. Despite some beneficial results in terms of need for catheterization, decreased bladder trabeculation and increased volitional voiding in patients after fetal repair, the urodynamic results were found to be similar when compared to patients with postnatal repair (40, 41).

Pastuszka et al (42) reported that prenatal repair ensures improvement

of the degree of social urinary continence, reducing the risk of urinary tract infection and constipation. Other studies mentioned a lower incidence of high-risk bladders in patients that underwent fetoscopic repair with a trend toward clinically significant improvement compared to patients that underwent open repair. Gerber et al (43) concluded that larger, prospective, long-term studies are required in order to further evaluate the potential benefits on fetal myelomeningocele repair on bladder safety.

## 5. Conclusion

In this group of pediatric patients larger and homogenous study groups combined with multidisciplinary long-term follow-up periods including evaluation of the cranial and spinal MRIs are necessary in order to have a better perspective over the consequences and efficacy of each of these neurosurgical techniques, but the preliminary results are encouraging.

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CHAPTER VII

# APPLIANCE OF STEREOTACTIC SURGERY IN THALAMIC ABSCESSES

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## 1. Introduction

The incidence of intracerebral abscess is considered to be around 8% of all the intracranial lesions. Thalamic abscesses are considered to be relatively rare lesions, with an incidence that varies in the literature between 1.3%-6% of the intracerebral abscesses (1). In pediatric patients, intracranial abscess lesions localized in the deep gray matter structures such as basal ganglia, and thalamus are not frequently seen. Though potentially curable, they still carry a high level of mortality and morbidity. The 5% mortality rate is mainly due to brain herniation or abscess rupture into ventricles (1).

## 2. Historical Considerations

The beginning of stereotaxy goes back to 1908 when British neuroscientist and surgeon Sir Victor Horsley and British physiologist Robert Henry Clarke described the first stereotactic frame that was used in order to study the structures and functions of the cerebellum in monkeys. The principle of the device' functioning was based on the reproducibility of the relationships between skulls' landmarks such as inferior orbital rims, external auditory canals, midline and anatomical structures within the cerebrum of the animal model. The cranial fixation points established the baselines of a 3-dimensional Cartesian stereotactic coordinate system (2).

Ten years later, in 1918, Canadian neuroanatomist and neurophysiologist Aubrey Thomas Mussen designed the first stereotactic device for humans;

However, Mussen's device did not received the expected interest and was never used clinically (3).

In 1946, Austrian-American neurologist Ernst A. Spiegel and his student and later collaborator Henry T. Wycis, described the first stereotactic device used in human subcortical surgery. The landmarks used were represented by the pineal gland and the foramen of Monro, visualized by preoperative or intraoperative pneumoencephalograms (4).

### 3. Modern Analysis, Finding and Researches

For the last decades there is an increasing emphasis on minimally invasive and robotically-assisted surgeries in all medical fields. Development of more sophisticated and complex radiological imaging techniques has initiated a renewed interest in stereotactic devices and their application field (5).

Methods like stereotactic aspiration, stereo-endoscopic aspiration, ultrasound-guided or neuronavigation guided aspiration are minimally invasive, carry low morbidity and can be performed on compromised patients under local anesthesia. Different studies reported a major improvement in the management of intracerebral abscesses, especially in the last thirty years.

An insight into the etiopathogenesis of the intracerebral abscesses reveals that the most common route involved is hematogenous, which accounts for 25% of all abscesses. A second common etiology is from a contiguous source such as a paranasal sinus, middle ear, dental root, osteomyelitis, or emissary vein. The third route is direct through trauma or post-surgery, especially post-sinus breach. The most common pathogens are represented by Streptococcus viridians, Streptococcus milleri, Staphylococcus aures, Staphylococcus epidermis and anaerobes. However, in many cases a predisposing factor cannot be determined (6).

Different studies reported low level of postoperative complications after stereotactic thalamic abscess aspiration, which lead to the conclusion that this minimally-invasive technique, when it comes to deep brain lesions is accurate, safe, and has a high postoperative success rate. Small, deep localized, multiple, poorly defined, inflammatory lesions are considered to be feasible for a stereotactic approach. Auvichayapat et al (7) analyzed the location of the intracerebral abscess lesion in 107 cases. Thalamic abscesses were found in 3.3% of all of the patients. The reported mortality rate was 10.7% and attributed to late presentation and furthermore a delayed diagnosis. The classic triad consisting of headache, fever, and focal neurological deficits was found in only 9.4% of all of the patients.

Kocherry et al (8) reported 22 patients diagnosed with abscess located either in deep gray matter regions of the cerebrum or in the eloquent cortex, in which stereotactic aspiration was performed. Mortality rate was zero and postoperative intracerebral hemorrhage rate was 13.6%. Nishihara et al (9) studied the safety of stereotactic biopsy analyzing 56 patients operated between 1997 and 2007. The morbidity rate in this study was 2.4%. The only intraoperative complication reported was intracerebral hemorrhage (5.2%).

A detailed review of the studies published in the medical literature regarding stereotactic aspiration for thalamic abscess reveal an incidence of complications around 7.2%. Procedure-related hemorrhage ranges from 0 to 5.3% (10). Stereotactic aspiration carries the risk of incomplete abscess evacuation, recurrence of the abscess and spillage of infected material in the

ventricle. The risk of abscess recurrence after stereotactic aspiration varies between 0 and 24% according to different authors (11, 12).

Progress in technology, associated with the development of neuronavigational systems, has made stereotactic aspiration and drainage of thalamic abscesses effective and valid alternatives to traditional methods- conservative medical treatment/open surgical excision (11). Successful results reported in the literature after Computed-tomography (CT)-guided stereotactic abscess aspiration, combined with the low rate of procedure related complication determined stereotactic surgical interventions to be considered the treatment of choice in all cerebral abscess except for large and superficial one as early as 1987 (13, 14).

Widespread use of CT and MRI (Magnetic Resonance Imaging) has made it possible to detect abscesses in very early stages. This may be in the form of multiple small lesions in patients without acquired immunodeficiency syndrome (AIDS), or nonenhancing hypodense lesions in the stage of acute cerebritis (15). The course of brain abscess evolution is as follows; Nonenhanced CT scans may be normal or show a vague hypodense lesion in the phase of early cerebritis. Variable contrast- enhancement pattern may be identified. Lesion demarcation and mass effect seem to be more pronounced in late phase of cerebritis, with more distinct rim-like contrast enhancement. In the early capsule phase, a heavily enhancing collagen capsule surrounding the necrotic center is present. The cortical side of the capsule will be thicker than the ependymal side, a detail quite suggestive of abscess. Abscess shrinkage and regression of edema can be seen during late capsule stage. During all stages, Magnetic resonance Imaging (MRI) is more sensitive than Computed Tomography (CT) to edema and contrast enhancement (16,17).

In 1999, Barlas et al (17) in their study also accepted image guided stereotactic surgery to be the best way of approaching intracerebral abscess. The study reported zero mortality rate and one case of iatrogenic intracerebral hematoma.

Development of robotic-assisted surgery and progresses made in the ‘‘virtual reality’’ field in the last years has truly been remarkable. Robot-guided stereotactic puncture with drainage in the treatment of thalamic abscess has already been reported by Chen et al (18) in a patient with a left thalamic abscess with no history of prodromal infection Stereotactic puncture and drainage were performed under the guidance of the Ruimi robot. The patient was discharged after 4 weeks of antibacterial treatment.

## 4. Conclusion

The management of thalamic abscesses has significantly improved in the recent years, and this is due to modern non-invasive neuro-radiological imaging; Deep gray matter abscess lesions can be successfully managed via minimally invasive procedure such as CT/MRI-guided stereotactic aspiration, stereo-endoscopic aspiration, ultrasound-guided aspiration, neuronavigation-guided aspiration or robot-guided stereotactic aspiration, procedures that carry low rates of complication, recurrence and intraoperative mortality.

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CHAPTER VIII

# PROPRİOCEPTİON, THE SİXTH SENSE, DURİNG DİFFERENT EXERCİSES

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## 1. Introduction

Proprioception was derived from the Latin words "proprius" and "perception", which refer to a person, by the famous neurophysiologist Charles Sherrington. Sherrington proprioception is defined as understanding joint and body movements and accurately perceiving their position in space (1). Proprioception is often used together with the Greek term kinesthesia, which means movement. These terms are used to refer to the ability to evaluate the movements and configuration of the body (2).

## 2. Peripheral and central pathways in proprioception

Kinesthesia is the ability to perceive the movement of the body. However, proprioception is the ability to perceive the body's position in space rather than the ability to perceive movement (3). When proprioception is examined in more depth, it becomes apparent that it is a very complex sense. It has been considered part of the sense of somatosensation (sixth sense). It has been stated that it includes not only the sense of movement, but also the sense of tension (resistance), the sense of joint position, and the sense of change in velocity (Figure 1). Joint movement sensation includes understanding the speed, direction, acceleration, amplitude, and timing of movement; The feeling of resistance indicates the ability to understand the force produced by the joint; joint position sense; the person's ability to understand the angle of motion of the joint and then capture the same position; sense of change in velocity represents the ability to detect vibration in the body (3, 4).

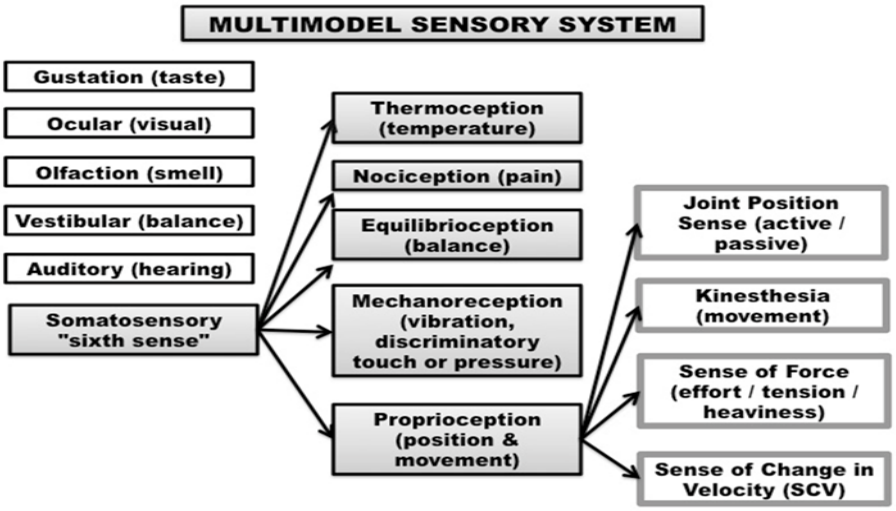


**Figure 1:** Sensory Systems (4)

The peripheral nervous system and the central nervous system play a joint role in the perception of proprioception. Proprioceptive information is sensed by receptors in an organism's muscles, tendons, skin, fascia, and joints. It is thought that not a single receptor, but multiple receptors play an active role in afferent signaling (5). Although it is known that proprioception is signaled by structures such as muscle spindles and Golgi tendon organs in muscle tissue, the role of different mechanoreceptors is still actively discussed in the literatüre (6). In afferent transmission, muscle spindles play an active role throughout the entire movement, while mechanoreceptors carry important signals in the middle of the movement and cutaneous receptors carry important signals at the end ranges and contribute to interoceptive perception (7, 8). Afferent signals coming from the periphery are processed in the central nervous system in the spinal cord, brainstem cerebral cortex, and cerebellum. It is divided into two: conscious and unconscious, according to the way it is transmitted and the way it works. The dorsal column transmits afferents from conscious proprioception to the cerebrum via the medial lemniscal system. In unconscious proprioception, it is transmitted to the cerebellum together with the dorsal spinocerebellar system and ventral spinocerebellar system. Spinocerebellar pathways provide the fastest transmission in the central nervous system. Stimulations coming from afferents contribute to joint stability by creating direct motor responses in the form of reflexes at the spinal level (5) (Figure 2).. Afferent impulses to the brainstem act together with the visual and vestibular systems to maintain

postural control and balance . Information coming to the cerebral cortex plays a role in the occurrence of voluntary movement by contributing to the perception of conscious proprioception (9).

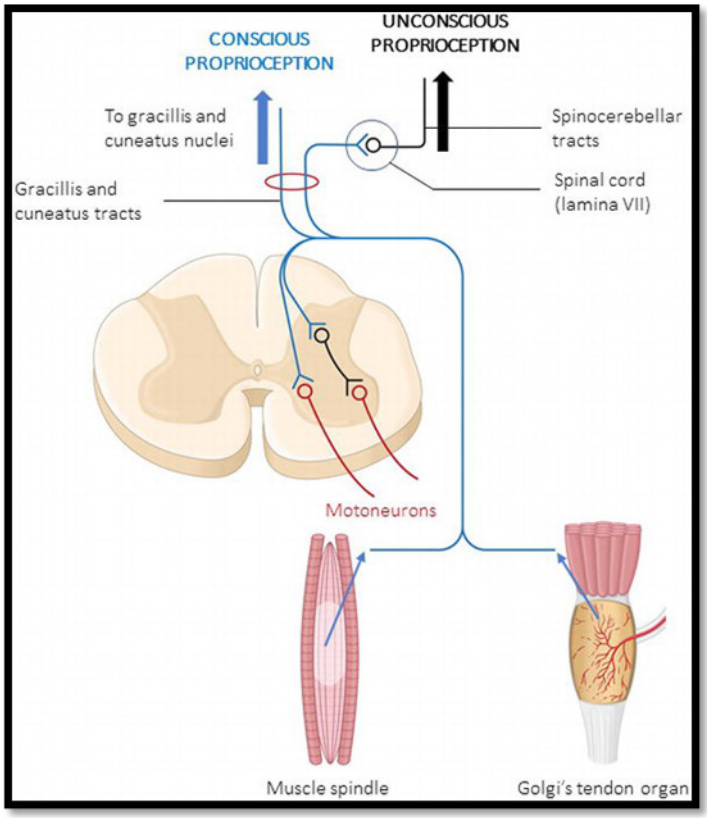


**Figure 2:** Proprioceptive Pathways (5)

The proprioceptive system plays a critical role in the body's balance and stability. It can be affected by many factors such as aging, muscle weakness, various neurological diseases, orthopedic injuries, brain traumas, diabetes, and neuropathies. The proprioceptive acquisition is considered as a basis in the symptomatic treatment of many of the mentioned diseases. Based on this, we examined the effect of proprioception during different exercises .

### *2.1. Warm up exercise*

Warm-up exercises increase the visco-elastic properties of the structures around the joint, reduce muscle stiffness, increase metabolic efficiency, and have a positive effect on physical performance. Proprioceptive training increases

automatic control of movement and reduces the risk of injury, as do warm-up exercises. However, there are very few studies examining the contribution of warm-up exercises and proprioception in reducing the risk of injury. However, when the studies in the literature were examined, it was concluded that joint proprioception increased after warm-up exercises (3). Bartlett et al. examined the effect of a warm-up program including running and stretching exercises on knee joint position sense. As a result of the study conducted on 12 athletes, it was concluded that knee proprioception sensation improved after the warm-up exercise (10). A different study examined the effect of different warm-up periods on proprioception in healthy individuals. As a result of the study, it was found that the group given 10 minutes of warm-up exercise improved proprioception more than the group given 5 minutes of warm-up exercise (11).

### *2.2. Neuromuscular exercises*

Neuromuscular exercises are exercise programs that include dynamic joint stabilization, proprioceptive sense, reactive neuromuscular control, and functional movements. In most studies in the literature, neuromuscular control exercises have been seen as one of the effective exercise methods for gaining proprioceptive control. Neuromuscular exercise training is also used prophylactically to prevent injuries. Caraffa et al. stated that after a 5-part neuromuscular exercise training in football players, injuries decreased significantly compared to others (12). Hewett et al. investigated the effect of neuromuscular exercises on knee injury in high-risk female athletes. According to the measurements taken at the end of the study, the injury rate of trained women was lower than untrained women; He found that educated women were no different from uneducated men (13). Studies have shown that proprioceptive training is included in neuromuscular training.

Neuromuscular training is one of the effective exercise methods both during treatment and prophylactically. During training, the patient may be exposed to different and difficult conditions to improve his proprioceptive abilities. It is thought that this type of proprioceptive input loading on the patient is a faster and more effective way to convert it into voluntary muscle movements, which are received from the periphery by appropriate afferents, carried to the upper centers, and from there again with efferents (14).

### *2.3. Eccentric exercises*

After eccentric exercise, some changes occur in the skeletal muscle. Muscle fatigue and stiffness occur after exercise in people who are not

accustomed to eccentric exercise(15). It has been suggested that delayed muscle stiffness and pain resulting from minimal damage to muscle fibers may also affect the sensory receptors of the muscle, leading to impairment of proprioception(16).

### 3. Conclusions

These exercises and neuromuscular exercises are effective in improving proprioceptive sense; It is developed that eccentric training will negatively improve the proprioceptive sense.

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# CHAPTER IX

# COMPLEMENTARY THERAPY APPROACHES IN PATIENTS WITH PARKINSONS

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## 1. Introductıon

Parkinson's is among the most common neurological diseases worldwide [1]. Parkinson's is a neurodegenerative disease that causes motor and non-motor disorders. Loss of dopaminergic neurons in the substantia nigra has an important place in the pathogenesis of the disease [2]. As a result of damage to these cells, dopamine loss occurs. The decrease in dopamine causes the activity of the direct pathway to the cortex to decrease and the activity of the indirect pathway to the cortex via the thalamus to increase. As a result, inhibition occurs [3].

The incidence rate in men is higher than in women. It is stated that 4.2% of all women and 6.1% of men between the ages of 55 and 85 develop Parkinson's disease [4]. The symptoms seen in Parkinson's disease are divided into motor and non-motor symptoms. Motor symptoms are bradykinesia (slowing of movements), postural reflex disorder (balance and coordination disorders), and rest tremor (tremor). Non-motor symptoms can be listed as psychiatric disorders, sleep problems, sensory disorders, and disorders of the autonomic system [5].

In patients with Parkinson's disease, impairments in walking speed, step length and rhythmic pattern of movement are observed. Disorders in the frequencies of the steps stand out. This walking style is basically called festination walking. Additionally, freezing while walking is one of the main problems [1]. Lack of gait automaticity and other disorders in gait cause an increase in the number of falls [6]. Balance problems may also occur in the early stages of the disease. As the disease progresses, balance problems may become more severe and may be an important cause of falls. Balance problems were observed to increase at the 5-year follow-up [7].

Treatment of Parkinson's disease focuses on slowing or stopping the progression of the overall disease [8]. Treatment approaches can be classified as medical, surgical, and rehabilitation approaches. The gold standard in medical treatment is levodopa treatment. Surgical approaches are mainly based on brain stimulation. Rehabilitation supports medical and surgical treatment in order to maximize the patient's physical function [9]. Side effects occurring during medical treatments and non-motor symptoms that affect the extra quality of life caused by the disease direct patients to complementary therapeutic approaches. Complementary approaches include manipulative approaches, mind-body exercises, and approaches to increase physical activity [10]. There is evidence that physical activity improves balance and functional activities in patients with Parkinson's. In addition, there are complementary approaches to increase the physical activity of patients by making them more enjoyable [11]. Various approaches such as pilates, yoga or tai chi exercises are recommended, especially to improve balance performance [12]. However, there is limited research on complementary approaches. Therefore, this section aims to summarize the literature on complementary therapeutic approaches.

## 2. Action Observation Training

Action observation training is based on observing videos of actions performed by a person. This view is usually followed by execution of the same action, but this last step may not be performed [13]. The person performing the action in the video may be the patient himself or a third party. Videos are often recorded from different perspectives [14-16] and although treatment applications do not exceed 30 minutes, the most appropriate application protocol has not been established [17]. Patients with Parkinson's disease experience a deficit in the cerebral network that prepares movements, which later manifests as symptoms such akinesia and bradykinesia [18].

However, by modifying cortical plasticity, action observation can be employed as sensorimotor integration, peripheral feedback and can give them the right cues to enhance their motor abilities [19-21].

Seven studies involving 227 participants were examined in the systematic review examining the effectiveness of action observation training in Parkinson's patients. As a result of these studies, it was reported that action observation training in Parkinson's disease had positive effects on typical motor symptoms of Parkinson's, such as walking ability and freezing of gait. Action observation training has generally been found to be a treatment that enhances motor control, functional mobility and clinical features in Parkinson's patients; nevertheless, the visual stimulus characteristics and training dose have a significant impact in the interventions' efficacy. Although there is a consensus among studies on the use of stimuli with transitive movements, it is emphasized that the use of intransitive movements should also be taken into account in future studies [22].

Another systematic review looked at 7 research to determine the benefits of action observation training for Parkinson's disease patients and to talk about the qualities of visual stimuli that were utilized in clinical studies and their efficacy. The outcomes demonstrated that action observation training improved walking abilities and gait-related issues in Parkinson's disease patients, as well as motor and functional performance. However, original research comparing the usage of a first-person versus third-person perspective or the watching of video clips with both Parkinson's patients and healthy participants has demonstrated to provide extra benefits on recovery [23].

In a study on the effects of a single session of action observation on bradykinesia in finger movements in Parkinson's disease, participants were randomly split into two groups: 20 people with the condition and 14 healthy controls. Those in the acoustic group listened to acoustic signals paced at 3 Hz, while those in the action group saw video clips of repetitive finger movements paced at 3 Hz. All individuals' spontaneous speed increased following both video and acoustic training, but the improvement was in favor of the video group. The results showed that action observation training may be a promising approach in the rehabilitation of bradykinesia [24].

Studies in which action observation and motor imagery were integrated into a single method for rehabilitation in Parkinson's disease were systematically examined. Both practices taken together show that they can improve or slow down the deterioration of motor abilities [25].

### 3. Motor Imagery

Motor imagery is basically the mental rehearsal of the activity without physically performing it. Imagination of movement can be kinesthetic or visual [26]. It has been reported that the centers activated in motor imagery are similar to the neuronal centers activated during movement execution. Areas commonly activated by normal movement can be listed as premotor cortex, supplementary motor area and areas of the inferior parietal lobe [27]. The advantages of motor imagery are its low risk of injury, easy applicability, and low cost and equipment requirement [28]. Its disadvantages are that it causes mental fatigue [9].

It has been stated that adding motor imagery training to a neurorehabilitation program will have beneficial effects on Parkinson's patients. Although there are more studies in the literature evaluating the motor imagery ability of patients with Parkinson's disease, there are limited studies investigating the effect of motor imagery training [29].

In Liakat et al.'s study, one group was given walking exercises, while the other group was given motor imagery in addition to walking exercises. Effects on walking, balance and movement disorders have been investigated. Motor imagery program added to routine treatment has been shown to have positive effects on walking, balance and movement disorders compared to routine physiotherapy [30].

In a recent study, the effect of kinesthetic motor imagery on Parkinson's patients was investigated, based on the idea that different forms of motor imagery would cause activation of different regions in the cortex. In one of the groups, participants were asked to first perform the movements and then feel these movements. In the other group, the program included visual visualization of motionless objects through audio notification. Motor imagery was performed via fMRI-based neurofeedback. As a result, despite failures in neurofeedback, it has been shown that both visualizations cause improvements in motor function in mild Parkinson's patients [31].

In the study of Kashif et al., the effects of virtual reality training and motor imagery training on balance, motor function and quality of life were examined. In fact, as motor imagery is based on explicit learning and virtual reality is based on implicit motor learning, it was thought that the combination of the two would improve learning. As a result of the research, it was shown that motor imagery and virtual reality training applied in addition to traditional rehabilitation significantly improved motor function, balance and activities of daily living compared to traditional rehabilitation alone [28]. In a study conducted in 2022,

the effect of the combination of action observation therapy and motor imagery was investigated in patients with Parkinson's disease, considering that it would increase the activation in the brain. One of the groups was given action observation, motor imagery and walking training. In addition to walking training, the other group was shown informative videos about Parkinson's disease. As a result of the study, significant changes were observed in balance and gait characteristics in both groups. However, no difference was found between groups [1].

In the systematic review conducted by Kashif et al. in 2023, the effect of motor imagery on motor function and balance in Parkinson's patients was investigated in a total of 6 studies. The included studies were of good to moderate methodological quality. Motor imagery has been shown to produce beneficial results when applied in addition to other therapeutic approaches, compared to physical therapy alone [32].

### 4. Pilates

Pilates exercises are structured exercises combined with breathing exercises to strengthen the muscles in the core area and provide flexibility [33]. The use of Pilates for therapeutic purposes in rehabilitation is based on increasing the stability of the lumbar region through the development of the muscles in the core area and, as a result, improving posture and movement control. It is basically carried out by two different methods. Mat pilates, as a classical pilates method, includes exercises performed on the mat. Instrumental pilates are performed with the help of auxiliary equipment. [34]. It is reported that Pilates exercises are suitable for all ages and physical fitness levels [11]. In Göz et al.'s study, the effects of pilates and elastic taping on balance and postural control in patients with Parkinson's disease were investigated. Pilates exercises and elastic banding were applied to one group, only pilates exercises were applied to the other group, and no treatment was applied to the control group. As a result, taping applied together with pilates training did not have a significant advantage over other groups. However, it has been shown that pilates exercises cause important results in improving dynamic balance. [35].

In a study, the effects of pilates exercises performed for 8 weeks on balance, lower extremity muscle strength, fall risk and functional mobility were investigated. As a result of the research, it was found that clinical pilates exercises caused a significant improvement in dynamic balance compared to traditional rehabilitation [33]. In the study of Cardalda et al., the effect of therabant-based pilates exercises on the balance of Parkinson's patients was investigated. Mat

pilates exercises were applied to one of the groups with therabant. The other group was given classical gymnastics exercises. A significant improvement was shown in dynamic balance measurements in the pilates exercise group performed for 12 weeks. However, when this improvement was evaluated 4 weeks after the completion of the treatment, it was found that there was no improvement. [36]. In a single-arm study conducted in 2013, reformer pilates exercises were applied to patients with Parkinson's disease. The 6-week exercise program consisted of exercises to increase trunk flexibility, step exercises and reformer pilates exercises. As a result of the research, a significant improvement was observed in balance score, walking time, balance confidence and posturographic measurements. [37].

In another study, pilates exercises were added to the classical physiotherapy program in patients with idiopathic Parkinson's. The other group was given only the classical physiotherapy program. As a result, it was found that the conventional program combined with pilates exercises was more effective in improving functional balance, confidence level and functional activities [12]. Similarly, in a study conducted in 2017, the effect of 8-week pilates exercises on balance and fall risk in patients with idiopathic scoliosis was examined. The control group applied standard protocols such as walking exercises only. While no significant improvement was observed in balance and fall risk in the control group, a significant improvement was observed in the pilates exercises group. There was a significant difference between the groups in favor of the pilates group [11].

In the 2023 study, the effect and feasibility of mat pilates exercises of two different intensities based on strengthening exercises were examined in participants with Parkinson's disease. According to the Borg Perceived Exertion Scale, a "3" intensity protocol was applied in the low-intensity exercise group and a "7" intensity protocol was applied in the high-intensity exercise group. Despite the significant improvement in walking speed and lower extremity muscle strength in both exercise groups, it was determined that there was a greater improvement in the high-intensity exercise group [38].

In a systematic review examining studies conducted until 2019, including 4 randomized controlled studies and four non-randomized controlled studies of poor to medium methodological quality, it was found that pilates training had beneficial effects on condition, balance and functional mobility. Additionally, as a result of meta-analysis of randomized controlled studies, it has been shown to improve lower extremity function [39]. In a meta-analysis published in

2023, the effect of different exercise types on postural instability in patients with Parkinson's disease was investigated. As a result, it was found that pilates exercises were significantly effective on proactive balance [40].

### 5. Dance Therapy

Dance engages multiple somatosensory systems through whole body movements [41]. Dance is a multitasking practice that combines aerobic capacity, balance, postural control, gait and cognitive skills with music and rhythmic signals and its benefits have been stated in Parkinson's patients [42,43] [44]. It has been stated that during dance interventions in patients with Parkinson's disease, rhythmic stimulation increases the activity in the putamen and facilitates movement [45]. The cortico-basal ganglia controls posture, movement and action selection and is very important in dance [46,47]. He combination of dance and music activates the anterior cerebellar vermis [48]. Additionally, the right putamen is involved in voluntary metric movements [48].

Dance parameters vary according to different dance styles. systematic reviews have shown that various dance styles improve functional fitness in older adults [49,50]. In addition, various certified dance programs such as NeuroTango®, Dance for PD®, Dance Movement Therapy® are used in Parkinson's patients. These applications use different music speeds [51-53].

In an analysis of 372 patients to evaluate the effect of dance on patients with Parkinson's disease, dance was found to improve symptoms and outcomes, especially motor symptoms, in patients with Parkinson's disease compared to other types of exercise or control groups with no activity. It has also been reported to have positive effects on balance, functional mobility and cognition [54]

Nine literature studies with 307 patients were assessed as part of a systematic review that examined the benefits of dance therapy in alleviating non-motor symptoms in Parkinson's disease patients. The analysis showed that dance therapy significantly improved cognitive status in Parkinson's disease, but was not effective in improving depression, fatigue and apathy [55].

Another review examined the effects of dance interventions on the severity of the disease and cognitive and physical outcomes in people with Parkinson's disease. Dance therapy has been shown to enhance some parts of balance and moderately lessen the severity of motor diseases, but there is little research on the effects of dance therapy on other outcomes, such as agility, motor function, cognition, mood, social outcomes, quality of life, and adverse events, such as the risk of falling [56].

In a meta-analysis conducted in 2023, the effectiveness of dance-based interventions and the effectiveness of different dance styles and durations in improving balance in patients with Parkinson's disease were examined. It has been reported that dance therapy, especially for 12 weeks or longer, can safely and effectively improve balance in individuals with Parkinson's. However, there is not enough evidence to support that any one dance style is superior to others in improving balance. Additionally, dance therapies lasting 60 and 90 minutes have been shown to be similarly effective in improving balance among individuals with Parkinson's [57].

In a meta-analysis examining the effect of dancing on postural control in people with Parkinson's disease, it was shown that 211 individuals with Parkinson's disease in the dancing group had better postural control than 182 individuals with Parkinson's disease in the control group. The results showed that dance can improve postural control in a short time in people with Parkinson's and therefore contribute to the prevention of falls [58].

A systematic review of the effects of dance therapies on cognition, gait, and dual tasking in Parkinson's disease was undertaken in another study. Results showed that gait speed, timed up and go test performance, six-minute walk test times, and cognitive dual task were significantly improved after the dance intervention compared to controls. There is not enough data to establish the best dance interventions' intensity, frequency, duration, or musical composition [59].

The meta-analysis completed in 2022 examined 60 randomized controlled trials with 2037 individuals to identify the best kind of mind-body training (yoga, Tai-Chi, Pilates, Qigong, and dance) for enhancing functional performance and quality of life in Parkinson's patients. Pilates has been shown to be most effective in improving functional mobility and balance performance, dance has been shown to be most effective in improving motor function and when considering HRQoL, and Qigong has been shown to be most effective in improving walking speed [60].

### 6. Tai Chi

Tai Chi has a broad mass base in China, particularly among older groups. Tai chi is both a mental and physical workout. The movement is gradual and fluid. The practitioner can lower stress and control negative emotions by breathing rhythmically and exerting control over their bodies. [61]. In its most basic form, Tai Chi is a fusion of cardiovascular exercise and mental stimuli [62]. Regular tai chi practice considerably improves the volume of the entire brain and prevents

the decrease of brain function [63]. A faster heartbeat can supply the brain with more blood, glucose, and oxygen as well as the energy necessary for the brain's neurons to quickly mobilize. Tai chi practitioners' typical heart rates can rise to 121 beats per minute during practice, which is the ideal heart rate range for enhancing cognitive abilities [64]. The brain's capacity to manage and control various bodily functions can be strengthened by combining Tai Chi movements and ideas. To sum up, the moderate intensity and gentle rhythm of Tai Chi make it a favorite among seniors. [65].

Within the scope of the meta-analysis, which examined the effects of different Tai Chi exercises on motor function in individuals with Parkinson's disease, 996 individuals with Parkinson's disease were analyzed. Simplified Tai Chi with 24 forms, Tai Chi exercise program, simple Yang style Tai Chi with 8 forms and simplified Chen style Tai Chi with 8 forms were applied. It has been reported that the most effective Tai Chi program on motor function is simplified Tai Chi with 24 forms, and the least effective is simplified Chen style Tai Chi with 8 forms [66].

In the meta-analysis that examined the studies conducted to evaluate the effect of Tai Chi on functional mobility, balance and falls in Parkinson's disease, it was reported that Tai Chi had significant effects on functional mobility, balance and falls in Parkinson's patients [67]. Similar to this, a meta-analysis of Tai Chi's effects on falls, balance, and functional mobility in Parkinson's patients found that it may be an effective physical training method for reducing falls and enhancing balance and functional mobility in these patients [68].

In the meta-analysis examining the effectiveness of Tai Chi on the lower extremity function of Parkinson's patients, 10 randomized controlled studies including 532 Parkinson's patients were examined. Tai chi significantly improved motor function, balance function, functional walking capacity, and walking speed, but did not improve walking endurance, step length, and walking pace [69].

Studies evaluating Tai Chi's impact on motor function, balance, and quality of life in Parkinson's disease were examined in a different meta-analysis. The analyses' findings indicate that Tai Chi is a reasonably safe activity that can enhance bradykinesia, balance, and general motor function but it does not have a statistically significant advantage in terms of quality of life and functional mobility [70].

In a study that systematically evaluated the motor and non-motor effects of Tai Chi/Qigong, it was shown that Tai Chi was effective in improving motor

function, quality of life and depression in patients with Parkinson's disease, but was not effective in cognitive recovery [71].

Within the scope of the study, which systematically examined the effects of Tai Chi on physical function and well-being in individuals with Parkinson's, 7 randomized controlled studies and 4 quasi-experimental studies were included. Overall, participants who took Tai Chi were reported to have better balance and well-being [72].

Tai chi, resistance training, and dancing all significantly enhanced physical function and functional mobility, according to a meta-analysis that looked at the impact of various interventions on improvements in motor symptoms. Additionally helpful for balance are Tai Chi and dance. However, research has found that dancing enhances walking capacity more than weightlifting and tai chi [73].

### 7. Yoga

Yoga, a particular type of mind-body intervention, has been demonstrated to lessen anxiety symptoms, notably in the adult population and in persons with Parkinson's [74,75]. It has the ability to ease both motor and non-motor symptoms in people with Parkinson's. 22 About 20% of participants in a study looking at the use of complementary therapies for people with Parkinson's had tried yoga, and more than 70% of those who did felt that it was useful [76].

A systematic review and meta-analysis study conducted in 2022 looked at the effects of yoga on people with Parkinson's disease. 14 randomized controlled trials were systematically reviewed. Yoga interventions have been shown to be safe for people with mild to moderate Parkinson's disease. In addition to providing physical and psychological benefits, yoga has been shown to be comparable to exercise. A subsequent meta-analysis of 5 randomized controlled trials reported that yoga was more effective than passive control in improving motor symptoms [77].

In a study examining 7 studies in 2021, data on the changes observed in motor function, gait, balance parameters, anxiety, depression and quality of life scores in Parkinson's patients after Yoga were compiled. It has been shown that the society's regular adoption of Yoga practice can help reduce the risk of Parkinson's, especially in people at risk of Parkinson's, and is beneficial in improving gait, balancing freezing and falls, and improving depression, anxiety and memory disorders [78].

In a study conducted to identify randomized controlled studies evaluating the effects of yoga on depression and motor function in Parkinson's patients, 3 studies were examined. In the first randomized controlled study, yoga performed every two weeks resulted in a decrease in depression scores. In the second study, weekly yoga caused a significant decrease in depression and its therapeutic effects were shown to be long-lasting. In the last study, no significant difference was found between the control and experimental groups in terms of depression after yoga performed every two weeks. However, yoga has been reported to protect against worsening depression [79].

The advantages of mindfulness yoga compared to regular physical activity on health-related facets of life were investigated in persons with Parkinson's disease. In this study, 138 patients with Parkinson's disease were randomized into 2 groups: eight weeks of yoga and stretching. Yoga has been showed to be more efficient at decreasing both motor and non-motor symptoms of everyday living than conventional stretching exercises [80].

Another study examined how yoga affected Parkinson's sufferers' involvement outcomes. Participants reported improvements in attendance [81].

The impact of yoga on teaching oral hygiene practices and tooth brushing skills in 100 Parkinson's patients was investigated because Parkinson's patients also struggle with fine motor skills when performing basic tasks like brushing their own teeth, taking a bath, remembering small details, and writing skills. Results showed that yoga practice improved tooth brushing skills and oral hygiene in Parkinson's patients [82].

A study of feasibility was conducted to investigate the effect that a home-based yoga program with mHealth might have on Parkinson's patients' functional balance, motor symptoms, psychological wellness, and quality of life. Parkinson's patients have found the mobile health-based, at-home yoga program to be a practical, secure, and well-liked alternative, particularly in pandemic situations [83].

### 8. Aquatherapy

Exercises performed in water are increasingly being added to rehabilitation programs. Exercises performed in water cause the development of motor functions. Additionally, it provides improvements in terms of quality of life, sociability and communication skills [84]. Exercises performed in water cause a decrease in body weight, thus reducing the risk of fall injuries [85]. The basic properties of water are its buoyancy and fluidity. Thanks to these features, the

stress on the joints is reduced. For this reason, while making some movements easier, it also creates resistance for some movements [86].

The important results of physical exercises in patients with Parkinson's are known. In this regard, the combination of exercises performed in water and on land has been shown to have significant results in terms of balance, motor function and quality of life [87]. In a study conducted in 2023, a program was created to provide dual-task training in water, which has an important place in the rehabilitation of patients with Parkinson's disease. Dual-task training in water may be preferred as it reduces the risk of falling. The exercises in the program consisted of activities of increasing difficulty, such as counting while walking sideways or throwing a ball during the exercises. Significant improvements were observed in both motor functions and quality of life in the dual-task training group in water [84]. In another study, it was observed that exercises performed in water caused a significant improvement in the average strength and functional performance of the knee flexors and extensors of the most affected side compared to the pre-treatment period [88].

Non-motor symptoms such as insomnia are important problems affecting the quality of life of Parkinson's patients [89]. The effect of water exercises in solving the problem of insomnia has been examined. A different method was used. The program generally involves the participant doing dance exercises in warm water. It is also based on an approach that integrates manipulative therapy approaches such as myofascial stretching, rotational movements and traction. The control group was subjected to a program that included exercises performed on land. As a result, a significantly different improvement in sleep and quality of life was observed in the water exercise group compared to the control group [90].

The effect of exercises performed in thermal water on patients with Parkinson's disease was also examined. Exercises were performed in a 1.4 m deep pool at 32-36 degrees. It can provide pain relief and muscle relaxation through the temperature of thermal water and the minerals it contains. A study was designed considering muscle tensions that affect the quality of life in patients with Parkinson's disease. As a result, significant results were observed in terms of balance and quality of life [85].

In a systematic review-meta-analysis conducted in 2020, the effects of water exercises on balance, mobility, functional independence, functional performance, fear of falling and quality of life were examined. As a result of examining the results of 15 randomized controlled studies and 435 individuals,

exercises performed in water resulted in greater improvements in balance, mobility and quality of life than exercises performed on land. No difference was observed in terms of functional performance. In terms of fear of falling, exercises performed on land were found to be more effective [91].

The effects of water exercises in terms of body structure and function, activity and participation in patients with mild and moderate Parkinson's disease were examined within the scope of ICF.

In a systematic review that included 12 studies, it was found that while positive effects were shown on patients' body structure and function (postural balance), no significant improvement was noticed in activity and participation results [92]. In a systematic review examining 24 exercise types, aquatic exercises were found to be more effective than other exercise types in improving static balance [40]. The results of a recently published systematic review examining the results of 10 randomized controlled trials showed that exercises performed in water caused significant improvements in balance, walking and quality of life compared to traditional rehabilitation. In addition, no significant results were found in terms of motor function [93].

## 9. Conclussion

There appear to be various complementary therapeutic approaches in addition to rehabilitation in Parkinson's disease. Therapeutic approaches frequently encountered in the literature can be listed as action observation therapy, motor imagery, pilates, dance therapy, tai chi, yoga, and aqua therapy. However, in general, it has been observed that there are limited studies in the literature on the effect of these complementary approaches and future research is needed.

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# CHAPTER X

# EVALUATION OF PARTICIPATION IN INDIVIDUALS WITH CEREBRAL PALSY

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## 1. Introduction

Cerebral Palsy (CP) is defined as a permanent but non-progressive disorder that occurs as a result of the impact of the immature brain for various reasons in the prenatal, birth or postnatal period. (1) CP is the most common cause of childhood disability, and while its incidence is 4.4 per 1000 live births in Turkey, this rate is determined to be 2.5 per 1000 live births on average in European countries. (2, 3)

ICF is a classification system developed by WHO in 2000 to determine people's health-related conditions. The ICF provides a versatile perspective for evaluating and using health outcomes. According to ICF, participation is being a part of life and symbolizes the social dimension of functioning. Participation is viewed as a dynamic interaction between the individual and their environment. The purpose of rehabilitation practices; The patient achieves his/her rehabilitation goals and thus increases his/her participation. (4, 5) Participation is an important outcome component of health for all children; It is reported as being in life. Developing participation occurs through the maturation and development of the child's abilities and involvement in activities in the social and environmental

context. (6) Home, school and social participation of children with CP decreases due to their inadequacy in physical functions and limitations in mobility. In addition, they also experience difficulties in personal care and recreational skills. (7) Again, chronic disorders such as CP can reduce children's ability to participate in meaningful and purposeful activities. These children have various clinical symptoms and exhibit motor deficits and activity limitations. (8, 9) Children with disorders experience more limitations in participation compared to their peers, and children with CP or neurological disorders are more restricted in this group. (10, 11) Children with CP often participate in home-based activities but have difficulty turning this into friendships with their peers. (12) Participation in school or community-based activities; It is challenging because children's communication or social skills are limited, their inability to maintain physical relationships with their peers, and parents' avoidance of arrangements for the child's physical needs. (12)

The ICF states that there are nine areas in which activity and participation can be assessed, including learning and applying knowledge, general tasks, demands, communication, mobility, self-care, domestic life, interpersonal interaction and relationships, and major living spaces as well as community, social, and civic life. In ICF-CY, which is the adapted version of ICF for youth and children, the same nine domains are defined, but in addition to these nine domains, there are age-appropriate behavioral goals, tasks and developmental stages. (6, 13) Participation includes some subjective aspects in addition to the 9 life domains in ICF-CY. Participation develops within the child's sociocultural environment and refers to the child's purposeful and meaningful efforts within environmental factors. (11, 14) Children with CP have been reported to have limited participation in selective and social activities compared to their peers, and evaluation scales have been developed to understand and improve the relationship between children's activities and participation. (15) In evaluating participation, scales prepared within the framework of the fields in ICF-CY are used, but existing scales to evaluate children's activities and participation, especially in SP, are limited. Additionally, many of these scales do not fully represent all dimensions of the ICF-CY. (16) In this section, it is planned to examine in detail the scales that evaluate participation in children with CP.

### 2. Child and adolescent scale of participation (CASP)

Gary Bedell created the CASP ordinal scale to measure social participation in many contexts and activities, such as home, community, and school

involvement, as well as daily activities. The interviewer or the respondent may administer this scale. (17) There are 20 questions and 4 subsections in total. In sections; 6 questions ask about Home Participation, 4 questions about Neighborhood and Community Participation, 5 questions about School Participation, and 5 questions about Home and Community Activities. Grading to identify constraints and participation; cannot and cannot be applied, very limited, somewhat limited, full participation expected from age. Scoring is given between 0 and 4 points. Survey responses are as stated below:

***Expected for age (full participation):*** The child participates in activities at the same level or more than his/her peers. (with or without auxiliary devices). (4 points)

***Somewhat limited:*** The child participates in activities slightly less than his peers. (may need occasional help or observation) (3 points)

***Very limited:*** The child participates in activities much less than his peers. (may need a lot of help or observation) (2 points)

***Cannot:*** The child cannot participate in activities even though his/her peers do. (1 point)

***Not applicable:*** The child's peers are not expected to participate in the activity. (0 points)

The survey form is filled out by the primary caregiver. When primary caregivers complete the survey, they are asked to select the best answer that indicates the child's participation and the situations that help or interfere with the child's participation. The total score is obtained by converting the sum of the scores for each item into a 100-point system. This score is first divided by the total number of items, 80, and then multiplied by 100, thus obtaining a total score out of 100. The total scores of the subsections can be used for more specific results. Here again, the scores are converted to a 100-point system in a similar way and a score out of 100 is obtained. (18) 80 points is the maximum score that can be obtained from the survey. Low subsections of the survey or total score indicate low participation; High scores indicate high participation. (18) Atasavun Uysal S. et al. carried out the Turkish reliability and validity of the survey; the test-retest correlation coefficient for the class was reported to be 0.954. (19)

CASP has been used to assess participation in several studies. Using CASP, Sahoo et al. evaluated participation in their study to look at the association between the severity of motor disability and social participation in kids with CP. According to the severity levels of their motor problems, children with CP had

limited social participation in a variety of situations and activities, according to the study's findings, which involved 80 participants between the ages of 6 and 12. (20) In the study conducted by Bingöl and Günel, where the effects of bimanual training and modified restrictive forced movement therapy were compared in terms of certain parameters in children with hemiplegic cerebral palsy who were educated in normal schools, the participation results were evaluated with CASP. Improvement in participation has been reported to be greater in modified restrictive forced movement therapy. (21) Children with cerebral palsy who underwent botulinum toxin were evaluated using the CASP in Akyuz et al.'s study to determine changes in the activity and participation domains of the ICF, Disability and Health a procedure used in conjunction with thorough rehabilitation to enhance balance when sitting. The study's findings demonstrated that functional enhancements in sitting balance with integrated BoNT-A treatment had a positive impact on patients' levels of activity and participation. (22)

### 3. Children's assessment of participation and enjoyment (CAPE)

It is a survey consisting of 55 items. It was developed for healthy and disabled individuals between the ages of 6 and 21. The test is completed between 30 and 45 minutes. Each question in the survey has its own picture (black and white). In accordance with the survey procedure, all questions are asked to children by showing them black and white pictures. It measures how children participate in daily activities outside of school. The survey evaluates 5 types of activities: recreational activities, social activities, physical activities, personal development activities and skill-based activities. These 5 types of activities assess the various dimensions of participation listed below.

1. Activity variety (number of activities performed)
2. Activity frequency (frequency of participation in the activity)
3. Degree of entertainment
4. With whom the activity was done
5. Where the activity takes place. (23, 24)

CAPE has 3 scoring levels: (1) Comprehensive scoring, (2) Scoring regarding whether it is planned or unplanned, (3) Scoring related to the type of activity. (24)

A cross-cultural adaptation study of the Portuguese, Arabic and Spanish versions of the CAPE was conducted in children with CP. (25-27) The impact

of cerebral palsy and gender on young people's involvement in extracurricular activities was examined in a study. The Children's Engagement and Enjoyment Assessment was completed by 30 peers without developmental disabilities and 22 participants with CP. The findings revealed that participants with CP participated in a smaller range of activities and did so less frequently than normally developing children. The amount of enjoyment for both groups was comparable. (28) In their study where Mehraban et al. evaluated 30 children with CP and 30 normal children with CAPE, it was shown that children with CP took part individually in skill-based activities and general activities compared to their normal peers, and that they carried out most activities at home. It was found that the main effect of gender and the interaction between gender and groups were not statistically significant in any variable of the CAPE test. (29) In another study, participation in leisure activities was assessed with the CAPE to verify whether participation in leisure activities affects domains of quality of life in children and adolescents with Cerebral Palsy in Spain. Participation in leisure activities had a positive impact on the quality of life of Spanish adolescents and children with CP. (30) King et al examined geographic differences in leisure time participation of children/young people with cerebral palsy using Children's CAPE data from Australia, Canada and the USA. Children/youth in the US participated in the least physical activity, while Ontarians participated in the most personal development activities. (31)

### 4. Frequency of participation questionnaire (FPQ)

SPARCLE Questionnaire developed by the working group and derived from Life-H using 14 optional activities. FPQ is only about frequency (not difficulty) of participation. (32) Because the Life-H instrument for participation does not capture the frequency of participation in discretionary activities such as leisure activities, an instrument called the FPQ was developed to capture the frequency of Life-H items that are meaningful. It was also applied to children in the general population in the relevant age range in each country to provide comparative normative data. (33)

In their study by Parkes et al., FPQ was used to measure the frequency of participation. Children with cerebral palsy and severe co-disorders were found to be significantly less likely to experience higher levels of participation in most aspects of daily life. (34) In the study examining the participation in daily activities and quality of life in pre-adolescent children with cerebral palsy in South West Ireland, the frequency of participation was evaluated with the

FPQ completed by the parents of 98 children with CP. Results showed that overall participation in daily activities was significantly associated with quality of life in 3 of 10 domains (Physical well-being, Social support and peers, and Mental states and emotions) in the analysis adjusted for gender, age, and level of impairment. (35) In Ploypetch et al.'s study, which examined the participation restriction and the factors affecting the participation restriction of children with cerebral palsy living in Thailand, the frequency of participation was evaluated with FPQ. It has been reported that the difference in participation frequency between groups with high and low motor function is very high, and better gross motor and communication are strong determinants of participation. (36)

**5. Participation and environment measures for children and youth (PEM-CY)**

PEM-CY Scale is a scale that aims to evaluate the participation in life and environmental factors of children aged 5-17 in home, school and community conditions and is completed by families. A total of 25 separate activity types were defined for three life situations to assess life participation. 10 different life participation activities were determined for home environment, 5 for school and 10 for social life. Specific objectives were set for each activity: Frequency of activity in the last 4 months (with 8 options ranging from never to every day), Level of involvement during the activity (with 5 options ranging from minimum to maximum), The family's change request regarding the child's participation in the activity (with 5 different options if there is/no change request and if there is a change request). To understand the impact of environmental factors on participation in life, there are 12 questions for the home environment, 17 questions for the school environment and 16 questions for social life. (37)

After the scale was created, 576 families from Canada and the United States were included in the study in 2010. The study showed that the PEMCY had moderate to very good internal consistency (alpha=0.59-0.91) and moderate to good test-retest reliability (internal consistency coefficient = 0.58- 0.95) in questions regarding both participation and environmental factors when administered at 1-4 week intervals. (38) PEM-CY has been translated into 22 different languages, including French, German, Korean, Japanese and Arabic. The reliability and validity study of PEM-CY for Turkish children was conducted by Kara et al. in 2019. In the study in which families of 24 children with special needs and 410 children without special needs were accepted, the internal consistency coefficient (alpha = 0.67- 0.80) and test-retest reliability

(internal consistency coefficient; 0.67-0.93) was found to be similar to the original study. (37)

PEM-CY was employed in the study to determine if the functional gains brought on by goal-directed training, adaptive cycling, and functional electrical stimulation-assisted cycling in cerebral palsy children sustained 8 weeks after the intervention was stopped. The results showed that functional improvements persisted 8 weeks after the intervention. (39) Feitosa et al. included PEM-CY among the outcome measures they used in their feasibility study of individualized intense goal training for adolescents with cerebral palsy. (40) PEM-CY was used in the study in which two groups of children with cerebral palsy and those with normal development were compared regarding their home and community participation. Children with CP had lower levels of home, community participation, and environmental support than typically developing children. (41) PEM-CY was used to measure the contribution of physical, personal and environmental characteristics to physical activity in children with cerebral palsy who can move independently. As a result of the study, older age and decreased community participation were associated with high inactivity.

**6. Participation survey/mobility (PARTS/M)**

PARTS/M is a self-report survey instrument consisting of 6 sections and 20 different activities designed to measure the participation of people with movement disorders in basic life activities. (42) Each activity has four aspects of participation: chronological, evaluative, health-related, and supportive. Temporary queries concentrate on the frequency and duration of an activity. The choice, satisfaction, and value of engaging in a specific activity are the three evaluation criteria. When it comes to your health, you should consider whether an activity is restricted because of an ailment, a physical limitation, pain, exhaustion, or another condition. The amount of environmental and/or personal support needed to complete an activity is also sought. For each of the 20 events, the six locations, the four components, and the overall score, participation points can be computed. Internal stability and consistency for PARTS/M range from moderate to high. (42)

Crafword et al. aimed to examine the physical activity level, health, community integration and social participation characteristics in their study with 604 participants with mobility limitations who were diagnosed with cerebral palsy, spinal cord injury, multiple sclerosis, stroke or polio. As a result, positive

health status and higher community participation were found in a group with high physical activity compared to low-active or inactive groups with movement disorders and limitations. (43)

### 7. Questionnaire of young people's participation (QYPP)

Despite the variety of tools for assessing participation in children and the elderly, due to the lack of tools for assessing participation in adolescents, QYPP was developed by Tuffrey et al. Survey questions were created by combining a review of the literature and comments about participation by young people aged 14-21. Relevance and clarity ratings of the survey items were then obtained from 17 experts. The survey was tested on small and large samples respectively. Young people with CP between the ages of 17-21 were used in the survey stages. In the last stage, it was tested in a population of 540 people from the general population. The survey, which initially consisted of 92 items, was later reduced to 45 items. Test-retest reliability for all sections was greater than 0.80. In the final version, the basic subsections consisted of home life, getting along with people, education life, business life, recreation and entertainment, autonomy and preparation for the future. (44) In a study conducted in 2014, the participation of adolescents with or without CP from 8 countries in Europe was evaluated. QYPP was used to assess participation. Individuals were followed between the ages of 13 and 17. The authors stated that the "Children's Assessment of Participation and Enjoyment" questionnaire was mostly used in similar studies. However, they reported that they preferred QYPP because it was shorter and evaluated participation in adolescent-specific situations such as texting, online communication, spending time with friends without adult supervision, and having a romantic relationship. (45) In a study conducted by Javed et al in 2022, QYPP was used to evaluate the participation of adolescents aged 10-19 with CP. (46) In a study published in 2018, QYPP was included in the study to evaluate the participation of young people born extremely prematurely before the 27th week of pregnancy. (47) Finally, a different version of the QYPP was developed in the study protocol developed to evaluate the participation of young adults with CP in 2021. Based on the questions of this survey, 15 questions were created through group discussions and expert interviews. 8 selected questions from the original form were also added to these questions. Then, as a result of the tests, the final version consisting of 22 questions was created. (48) To our knowledge, no Turkish validity and reliability study of this survey has been conducted.

### 8. Self-reported experiences of activity settings (SEAS)

SEAS was developed considering the shortcomings in assessing participation in various populations and settings, with an emphasis on the diversity of surveys that assess participation. King et al. It was created in 2013 by. The survey can be applied in all communities, provided that young people with or without disabilities have at least a 3rd grade level and language comprehension skills. It is designed to be completed by a caregiver or an assistant when appropriate. The survey particularly focused on the concept of "event environment". The questionnaire showed good-excellent psychometric properties. The scale consists of the subdomains "personal development, psychological participation, social belonging, meaningful interactions, and choice and control". The scale has a total of 22 items. Evaluation is made on a 7-point scale from +3: strongly agree to -3: strongly disagree. The survey was developed by conducting experiments on 45 young people between the ages of 14-23, 10 of whom were severely disabled. (49) There is also a pictorial communication symbols version of the survey for young people who need graphic symbol support. (50) SEAS was used by King et al. in 2013 to determine the leisure activity environments and experiences of young people with severe disabilities. (51) In another study, SEAS was included in the study to evaluate the participation of young people who use empowering and alternative communication in social media environments. (52) In the research protocol to determine the effectiveness and sustainability of the life skills program for young people with disabilities, the use of the SEAS survey was preferred to capture the instant experiences of young people. (53) MacIntosh et al. In their 2020 study, the feasibility of a game-based technological intervention that supports home therapy participation was examined. 19 individuals with CP between the ages of 8-18 were included. SEAS was used to assess activity and participation. (54) A study investigated the physical and psychosocial effects of immersion therapy on individuals with different disabilities between the ages of 24-54. In this study, SEAS was preferred to evaluate the activity experiences of the participants. (55)

A study was designed by Aleksandra et al. in 2019 to validate the Polish version of the survey in a population of 153 people aged 10-22. As a result, it was found to meet all validation criteria. (56) A Portuguese adaptation of this questionnaire was made by Peruzzo et al. The research conducted in 2021 was conducted with a total of 22 adolescents with and without physical disabilities. As a result, it was found that its compatibility with the original version was maintained and it was suitable for use in the Brazilian population. (57) No

research has been found in the literature regarding the validity and reliability of this questionnaire in Turkish.

### 9. Assessment of preschool children's participation (APCP)

APCP was designed in 2012 to evaluate the daily activity participation of children aged 2-5 years. Model; It contains 45 illustrations of daily activities in the areas of play, skill development, active physical recreation and social activities. Parents are asked to answer by thinking about the last 4 months. 120 children with CP were used to determine its psychometric properties. As a result of the analysis, it was found that the APCP had moderate to very good internal consistency. Additionally, it is known that the family's participation, which is an important point, will affect the child's participation. At this point, it has been found that APCP can discriminate in terms of participation for children below and above the average regional income range. In addition, it can distinguish between children under and over the age of 4 according to the Gross Motor Function Classification System. (58) In 2013, Chen et al In the study, the validity and clinical features of APCP in children with CP were investigated. In the study in which 82 children with CP participated, evaluations were made at the beginning and 6 months later. The Gross Motor Function Measure and the Functional Independence Measure for Children were used for validity. The survey was found to have fair to excellent validity. Additionally, APCP was found to be sensitive to change over time. (59) In the study conducted in 2015 to determine the potential determinants of the participation of preschool children with CP, participation was evaluated through APCP. 80 children with CP between the ages of 2-6 participated. (60) In 2018, APCP took part in the research to evaluate the participation of children aged 3-6 with mild-moderate mental development disabilities. (61) Also in 2018, APCP was used in a study conducted in Ireland to determine to what extent personal factors and adaptive behaviors affect participation in children aged 2-5 with or without a history of preterm birth. (62) In 2021, APCP took part in a study examining the physical activity and motor performance status of children with and without autism spectrum disorder to evaluate participation. (63) In the study conducted by Bult et al. in 2013, the construct validity and test-retest reliability of the Dutch version of the APCP were evaluated. 126 preschool children participated in the research. It was found that internal consistency was sufficient for 4 sections, and intra-class correlations ranged between 0.63-0.91 in test-retest evaluation. In general, it was noted that the Dutch version showed good, albeit limited, psychometric

properties. (64) In 2017, Kang et al. the psychometric properties of the Chinese version of the APCP were examined by. 94 physically disabled children aged 2-6 years were included. Excellent results have been demonstrated on internal consistency and test-retest measures in terms of total scores. In addition, the results were found to be less satisfactory for some subsections. (65) As far as examined in the literature, no studies on the Turkish version of APCP have been found.

**10. Children participation questionnaire (CPQ)**

The survey was adapted from Rosenberg et al. it was developed by in 2010. A survey was developed by obtaining information from the parents of preschool children aged 4-6 and its psychometric properties were examined. The CPQ has been found to show good internal reliability and homogeneity. It was also noted that this questionnaire was able to discriminate between children with and without disabilities, socio-economic classes and age groups, and as a result, it had good psychometric properties. (66) In 2015, the CPQ-school version of this questionnaire was developed. This version evaluates children aged 4-6 in the areas of daily living activities, instrumental activities of daily living, play, leisure, social participation and education. It has been shown to have good internal reliability. (67) A study conducted in 2023 aimed to investigate the relationship between screen time use and activity participation and physical activity of school-age children. The CPQ-School version was used to evaluate participation in the study, which included typically developing children between the ages of 8-12. (68) In 2013, CPQ was included in the evaluation of a study in which the participation-related situations of children with developmental coordination disorder aged 5-6 were compared with typically developing children. (69) In 2014, in the study of the relationship between executive functions and participation in primary school children, children's participation was evaluated through the CPQ filled out by their parents. (70) In a study conducted by Rosenberg et al. in 2016, which included 98 typically developing children, CPQ was included to evaluate participation in the study, which was designed to examine the effects of children's individual characteristics on the enjoyment they received from participation. (71)

A study conducted in 2019, a study was conducted to evaluate the correlation of the CPQ survey with the perceived meaning of participation in activities of daily living for typically developing children. The CPQ-School version was used in the study evaluating 60 Israeli children aged 6-12. (72)

In a systematic review, scales that can be used to evaluate the hand participation of children between the ages of 2 and 12 were examined. It was concluded that 4 measurement methods, including CPQ, among the 9 measurements in total, were sufficient in terms of validity and reliability. (73) Amini et al. in 2017, they investigated the psychometric properties of CPQ for Iranian children. The study was conducted on 120 children with CP, with an average age of 5.1 years. As a result, good-excellent internal consistency and excellent test-retest results were found. (74) To our knowledge, no Turkish validity and reliability study of this survey has been conducted.

## 11. Conclusion

There are many scales to evaluate participation. However, it has been observed that the questionnaires used especially in individuals with cerebral palsy have a more comprehensive content in evaluating these children.

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# CHAPTER XI

# EXERCISE IN INFERTILITY AND INFERTILITY TREATMENT

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## 1. Introduction

Infertility is defined as the inability of couples to achieve pregnancy despite having had regular sexual intercourse for 12 months without using a family planning method or donor vaccination. (1, 2) According to the World Health Organization (WHO)'s 2023 report, approximately 17.5% of the adult population (one in six people) worldwide have problems with infertility. (3) According to the 2018 Türkiye Demographic and Health Surveys (TDHS), it was reported that 7.6% of married women aged 15-49 years have no children and cannot get pregnant, and 3.9% cannot get pregnant again even though they have a living child. (4) These figures show that infertility is a major health problem worldwide

and that access to affordable, quality fertility treatment for those who need it is urgently needed. (3)

Causes of infertility; They can be divided into female, male and idiopathic (unexplained) causes. Pelvic inflammatory disease (39.38%), tubal inflammation (39.17%) and abortion (36.41%) were the most commonly cited causes of female infertility, while oligospermia (31%), asthenozoospermia (19.39%) and varicocele (19.2%) were the most commonly cited causes of male infertility. (5) Immunological factors, mild tubal disease, endometriosis and advanced age of the woman can be mentioned as unexplained causes of infertility. (6, 7) In addition, psychosocial stressors, diet and other modifiable lifestyle factors also impact fertility in both women and men (8, 9, 10); however, it should be kept in mind that most of these factors are not absolute barriers to pregnancy.

Along these lines, exercise, which is one of the lifestyle changes in this section; The impact of fertility preservation and care and infertility treatment will be discussed.

## 2. INFERTILITY: DEFINITION AND PREVALENCE

Infertility is defined as the inability to become pregnant or the inability to maintain a pregnancy despite having regular sexual intercourse three or four times a week for one year without using contraception. (11) Although the prevalence of infertility varies from society to society, it is increasing worldwide. In a 2016 study, the global prevalence of infertility was reported to be 10% on average. Furthermore, the same study found that Australia has the lowest prevalence of infertility and Africa has the highest prevalence. (12) According to the demographic and health research data conducted by the Institute of Population Studies at Hacettepe University in Türkiye in 1993, 1998, 2003, 2008 and 2013, the prevalence of infertility has been reported higher in the eastern region (10%) of Turkey. (13, 14, 15, 16, 17, 4)

Infertility is divided into primary and secondary. Primary infertility is infertility with no previous live birth or pregnancy in the past. (18) Causes of primary infertility include abnormalities of the female and male genital organs, abnormalities of the sex chromosomes (such as Turner syndrome) and hormonal disorders. (19, 20) The most common secondary infertility in women in the world is the inability to conceive after a previous pregnancy without birth control, breastfeeding or postpartum amenorrhoea. (21, 18) Miscarriages, abortions and deliveries in unsafe environments or inadequate postpartum care are common causes of secondary infertility. (1)

It can be said that primary and secondary infertility rates vary around the world. In a study examining the prevalence of infertility in 190 countries, it was determined that the prevalence of secondary infertility was high in the Central/Eastern Europe and Central Asia region, while the prevalence of primary infertility was high in some countries in the North Africa/Middle East region. (22) In another study conducted in the West Marmara region of Türkiye in 2023, it was found that 61.9% of infertile women were diagnosed with primary infertility. (23)

### *2.1. Etiology of Infertility*

The causes of infertility are not only female, but also contribute to both male and female infertility. In a meta-analysis, it was found that 54.0% of the causes of infertility were due to the female factor, 22.26% were due to the male factor and 21.36% were due to both female and male factors. It was noted that the causes of infertility cannot be explained in about one-tenth of couples diagnosed with infertility. (5)

#### *2.1.1. Etiology of Female Infertility*

Factors causing female infertility include: premature ovarian failure (cessation of ovarian functions before age 40) (24), polycystic ovarian syndrome (endocrine and metabolic disorder causing hyperandrogenism and menstrual irregularities) (25), endometriosis (colonization of endometrial tissue outside the uterine cavity) (26), uterine fibroids (benign tumors) (27), endometrial polyps (localization and overgrowth of endometrial glands and stroma in the uterine cavity). (28) In the systematic review and meta-analysis study that included 42 studies conducted in 2022 among women with genital tuberculosis, it was found that overall infertility was 88%, primary infertility was 66% and secondary infertility was 34%. (29)

#### *2.1.2. Etiology of Male Infertility*

Factors causing male infertility; sperm (sperm production disorders) (30, 31), primary testicular failure (31), hypogonadism, testicular (varicocele, anorchia, testicular dysgenesis and cryptorchidism) (31, 32) and ejaculatory disorders. (31, 33)

#### *2.1.3. Etiology of Female and Male Infertility*

Causes of infertility in both sexes include hypogonadotropic hypogonadism, hyperprolactinemia, ciliary dysfunction, cystic fibrosis, infections, ischemic diseases and lifestyle-related factors (34).

Unexplained infertility is defined as the absence of any pathology in the basic assessment of couples who cannot achieve pregnancy after 12 months of regular unprotected sexual intercourse. To diagnose unexplained infertility, patients should have objective evidence of ovulation, tubal patency, the presence of a normal uterine cavity, adequate ovarian reserve and a normal semen analysis. (35)

Since there is no identifiable barrier to conception in unexplained couples in infertility cause, natural conception remains a possibility. It is difficult to plan specific treatment as there is no clear underlying pathology for unexplained infertility. (36)

### *2.2. Assessment of Infertility*

Assessment of infertility in couples should begin with a detailed history and physical examination. Assessment of female infertility; detailed history (age, height, weight, smoking, alcohol and drug use, inability to conceive, first gestational age, history of abortion, age of menarche, menstrual cycle, pelvic and abdominal pain, history of cancer, frequency of sexual intercourse, sexually transmitted infections et.), physical examination (breast and detailed pelvic examination et.), genetic and hormonal tests (FSH, AMH, LH, androgen).

Male infertility evaluation also includes a detailed history (age, presence of chronic diseases, smoking, alcohol and drug use et.), physical examination (testicular and lumbopelvic area examination et.), semen analysis, genetic and hormonal evaluation tests. It should also be noted that semen analysis is traditionally the first step in the screening of infertile men.

### *2.3. Treatment of Infertility*

An ideal infertility treatment should be individualized, highly effective, with few side effects and inexpensive. (37) However, it is not always easy to determine the appropriate treatment for infertility, as more than one factor is at issue when assessing couples.

The first step in treating infertility is to identify the problem causing the infertility. If the cause of infertility is due to an anatomical (uterine septum, cryptorchidism et.) or physiological (varicocele et.) problem, surgical treatment should be performed. (38, 39) If the infertility is due to disorders of ovulation or sperm production, treatment should focus on ovulation and sperm production. Hormone therapy (FSH, LH) can be used for this. (40, 41) If the cause of infertility has not been determined, assisted reproductive techniques such as

in vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI) should be applied. (42)

In addition to medical, surgical or assisted reproductive techniques, couples turn to complementary and alternative medicine practices (CAM) before and during treatment or after unsuccessful treatments. (43) CAM Applications according to the National Institutes of Health classification; These include naturopathy, traditional medicine, herbal medicine or teas, acupuncture, homoeopathy, mind-body medicine (meditation, yoga, deep breathing, etc.), energy therapy, manipulative and body-based interventions. (44, 45) In reviewing the literature, it is difficult to make clear recommendations on the effectiveness and safety of CAM in treating infertility. However, there are studies showing that CAM can improve sex hormone levels, endometrial thickness, ovulation rate and pregnancy rate in problems that cause infertility, such as premature ovarian failure, tubal obstruction and polycystic ovary syndrome. (46, 47, 48)

## 3. THE RELATIONSHIP OF EXERCISE WITH FERTILITY AND INFERTILITY TREATMENT

The use of physical activity or exercise in the treatment of infertility is increasing. Although physical activity and exercise are generally used interchangeably, WHO defines physical activity as "any physical movement produced by skeletal muscle that uses energy". (49) The concept of exercise is seen as a type of planned, repeated and structured physical activity. (50) It does not matter whether physical activity or exercise is used as a concept. However, it is believed that determining the type, intensity, frequency and duration of physical activity can help clarify the relationship between exercise and infertility.

Exercise, which affects fertility in men and women regardless of gender, can increase the chance of fertility by maintaining body weight and hormone levels in women (51), while high levels of physical activity can prevent ovulation and lead to a decrease in fertility. (52) The American University of Obstetrics and Gynecology (ACOG) recommends that women planning to conceive should engage in moderate physical activity for at least 150 minutes per week. (53) In the systematic review of Hakimi and Cameron (2017); It has been determined that participation of women in excessively heavy exercise for more than 60 minutes a day increases the risk of anovulation, and participation in vigorous exercise for 30-60 minutes a day decreases the risk of anovulatory infertility. (54) The results of two different systematic reviews conducted in 2022 and 2023 have also shown us that exercise is a protective factor against infertility and that fertility

is negatively affected in individuals participating in vigorous physical activity. (55, 56) Although there is no clear consensus, it is emphasized that exercise can affect fertility in men by suppressing gonadotropins and serum testosterone and altering sperm characteristics such as concentration, motility and morphology. (57, 58) In a meta-analysis conducted by Perez et al. in 2019, it was found that moderate physical activity can have a positive effect on male fertility, while high exercise intensity can also have a negative effect on male fertility. (57)

### *3.1. Exercise in Infertility Treatment*

#### *3.1.1. Yoga in Infertility Treatment*

Infertility; it is a stressful crisis that affects couples psychologically, emotionally, and economically. (59, 60) In this lengthy, painful, and economically costly process, the failure of medical treatment can cause even more stress for couples. This situation may discourage couples from starting a new treatment process and refer them to more affordable, easily accessible complementary treatments.

Yoga, a type of exercise and one of the complementary treatments preferred by infertile people, especially women, is one of the ancient mind-body practices that originated in the Indian subcontinent. Moreover, it is a type of meditation that enables individuals to be physically, mentally, and emotionally healthy. (61, 62) Yoga; It includes asanas (postures), pranayama (breathing techniques), meditation (mindfulness), and relaxation techniques (yoga nidra, instant relaxation technique, quick relaxation technique, deep relaxation technique). (63) These types of yoga exercises not only provide physical flexibility and increase muscle strength, but also improve blood circulation and oxygen supply to the reproductive organs. (64) In addition, yoga improves reproductive function by balancing neural hormones. (65)

Yoga has been suggested as a relaxation method to cope with the difficulties of infertility treatment. (66) This is because women with infertility problems usually feel better and stronger after doing yoga. They tend to feel better about their body image and begin to respect their bodies more. This understanding can lead to women being more sensitive to their body image and noticing physical problems more easily. (67) This situation can have a positive impact on the infertility treatment process.

A randomized controlled trial conducted by Mohseni et al. 2021, it was showed that a 6-week yoga program improved anthropometric measurements (abdominal circumference, hip circumference, and hirsutism score) in women

diagnosed with polycystic ovary syndrome who were being treated for infertility (65). In addition, studies have highlighted that body-based interventions, including mindfulness-based interventions and yoga, are also effective in reducing psychological problems in women undergoing infertility treatment. (68, 69) However, when examining the literature, it was found that there is no study showing that infertility treatment is successful in reducing stress and there is a need for studies in this area.

### *3.1.2. Aerobic Exercise in Infertility Treatment*

Aerobic exercise is defined as any form of physical activity that increases heart rate and respiration to meet the oxygen demand of muscles during a given effort. (70, 71) As defined by the Physical Activity Guidelines for Americans, aerobic exercise is an endurance or cardio activity in which large muscles move rhythmically over an extended period of time. (72) Walking, cycling, running, or swimming can be cited as examples of aerobic exercise. (73)

When the literature is examined, there are only a limited number of studies investigating the effectiveness of aerobic exercise in the treatment of infertility. In these studies, aerobic exercise has been found to affect fertility outcomes by altering one or all of the processes of ovulation, fertilization and implantation. Gaskins et al. (2014) showed that the sperm density of infertile men who cycled more than 1.5 hours a week was lower than those who did not cycle. The same study found that time spent in physical activities such as walking, running, swimming, tennis, and squash was not related to sperm concentration. (74)

In another study of 273 women receiving IVF treatment conducted by Gaskins et al. (2016), it was found that women who engaged in 1.5 hours or more of aerobic physical activity per week were more likely to have a live birth compared with inactive women. (75)

In a randomized controlled trial by Hajizadeh Maleki and Tartibian (2017), 210 infertile men who had gone to an infertility clinic for treatment underwent 24 weeks of moderate-intensity aerobic exercise and sperm quality was compared to sperm parameters of 209 infertile men who had not exercised. Improvements in semen parameters and sperm DNA integrity were observed in men who performed aerobic exercise. (76)

### *3.1.3. Resistance Training in Infertility Treatment*

Resistance training is one of the training methods that increase muscle strength, muscle endurance, motor performance, balance and coordination.

(77) This exercise is recommended by national health organizations such as the American College of Sports Medicine and the American Heart Association for adolescents, healthy adults, the elderly, and populations with various diseases (such as cardiovascular disease, neuromuscular disease). (78, 79) Resistance training reduces blood lipids and back pain, lowers hypertension, increases basal metabolic rate and muscle strength, improves insulin sensitivity (80), attenuates seminal markers of inflammation and oxidative stress, may improve body composition, semen quality parameters, and sperm DNA integrity. (81) Due to these positive effects, it can be said that resistance exercises have positive effects on fertility.

A 2018 randomized controlled trial of 430 infertile men found that 24 weeks of resistance training had a positive effect on sperm parameters, sperm DNA integrity, and pregnancy rates. (81) In a systematic review and network meta-analysis evaluating the efficacy of exercise training on seminal fluid inflammatory markers, all available options for improving semen quality parameters of combined aerobic and resistance training (combined aerobic and resistance training, moderate-intensity continuous training, resistance training, high-intensity continuous training, and high-intensity interval training) were determined as the best intervention among the available options (82) Similar results were obtained in another study in which aerobic and resistance training were used in combination in 556 infertile women. (83)

The literature search did not find any study that examined the effects of aerobic, resistance, or combined exercise training in infertile individuals. However, in a study that examined the efficacy of 24-week aerobic, resistance, and combined exercise training on seminal parameters in healthy individuals, resistance training was found to have a synergistic effect and was more beneficial than the other interventions used. (84) This finding suggests that resistance training may be superior to other infertility treatment options and can be used in the treatment of infertility.

### *3.1.4. High Intensity Interval Training in Infertility Treatment*

Although it is commonly believed that exercise positively affects fertility by inducing weight loss (54, 85), the main reason for the increase in fertility rate is thought to be the improvement in insulin sensitivity. (86) One such exercise, high-intensity interval training, is a new generation exercise method that increases aerobic and anaerobic capacity and regulates cardiovascular and metabolic functions. (87) High-intensity interval training requires less time

and provides greater fat loss than other types of training. Because of these characteristics, it is attracting considerable attention. (88, 89)

Although high-intensity interval training is used as a complementary method for many diseases, there is one study that demonstrates the effectiveness of high-intensity interval training in the treatment of infertility. (90, 91, 92) A study was found in the literature to demonstrate the effectiveness of high-intensity interval training in the treatment of infertility. Hajizadeh Maleki and Tartibian studied the effectiveness of a high-intensity training program over 24 weeks in 433 individuals. As a result of the study, it was found that this type of training can be recommended as an additional lifestyle approach in the treatment of male infertility or in combination with other treatments. (93)

## 4. Conclusion

Consequently, we can say that exercise is the key to increasing infertility treatment success rates in infertility, which is an important public health problem in our age. This is because exercise increases blood flow to all organs, oxygenation and nutrition of tissues, reduces stress and regulates the endocrine system. Thus, it may be important in maintaining reproductive capacity by improving fertility parameters. However, when the literature is examined, it is seen that the use of exercise (except yoga) is limited, especially in female infertility and treatment, and randomized controlled studies are needed on this subject. It is believed that it is important to adopt a multidisciplinary approach to preserve fertility and increase success rates in the treatment of infertility. For this reason, healthcare professionals should be informed about the importance of the impact of exercise on reproductive functions, in the evaluation of infertility couples with a holistic approach, we should work as a team and infertility treatment should be supported with CAM.

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CHAPTER XII

# CLINICAL APPLICATIONS OF ELECTROCONVULSIVE THERAPY

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## 1. Introduction

Electroconvulsive therapy (ECT) can be roughly defined as stimulating the brain with an electrical current. Cerebral convulsions are created with the application. The American Psychiatric Association (APA) has approved the use of ECT in the diagnosis of major depression, bipolar disorder, resistant schizophrenia and schizoaffective disorder. (1) Table 1 shows psychiatric diseases for which ECT use is appropriate.

Table 1. Psychiatric Diseases For Which ECT Use Is Approved

| |
|---|
| Major depression |
| Bipolar disorder |
| Resistant schizophrenia |
| Schizoaffective disorder |

In a study investigating the distribution of ECT application according to diagnoses, it was found that: “Major Depressive Disorder 72%, Bipolar Disorder 11%, Schizoaffective Disorder 2%, Schizophrenia 1% and other psychiatric disorders 14%”. (2)

In this article, the clinical application areas of ECT will be emphasized and specific information on clinical practice will be given to those working in the field.

## 2. Clinical Applications of Electroconvulsive Therapy

Patient selection is very important in ECT application. Accurate identification of patient groups that can respond well to ECT application greatly increases the success of treatment.

### *2.1. Depression*

Depression is one of the primary uses of ECT. ECT is currently considered the most effective treatment for refractory MDD. (3) Although the first ECT applications were made to patients with schizophrenia, it turned out that ECT was more effective in depression over time. (4) Table 2 shows the clinical symptoms associated with depression that can respond well to ECT, which is very important in patient selection for ECT. (5,6)

**Table 2.** Depression-Related Clinical Symptoms That May Respond Well To Electroconvulsive Therapy Application

| |
|---|
| Suicide thoughts and attempts |
| Catotonia |
| Psychomotor retardation |
| Delusions and hallucinations of depressive content |
| Ppseudodementia |
| Patients with nutritional problems |
| Diagnosis of depression with psychotic features |
| Patients with major depression who do not respond to antidepressant medication |

The first 4 months after ECT is the period when the risk of relapse is highest. For this reason, antidepressant drug treatment or preventive ECT treatment should be started after ECT. (7,9)

### *2.2. Schizophrenia*

The first patients treated with ECT were patients with schizophrenia. (4) This therapy was the most frequently used one for acute psychosis until 1952, when it was entirely displaced by pharmacological treatment. (10) Regardless, its use has recently gained considerable interest among physicians due to its usefulness in refractory schizophrenia. (11) Table 3 shows the clinical manifestations associated with schizophrenia that may respond well to the application of Electroconvulsive therapy. (12,13)

**Table 3.** Clinical Symptoms Associated with Schizophrenia That May Respond Well to Electroconvulsive Therapy Application

| |
|---|
| Patients who do not respond to drug therapy |
| Patients who cannot continue treatment due to drug side effects |
| Patients with predominant affective symptoms |
| Catatonia |
| Patients with predominant motor behavior changes |
| Patients who develop drug-induced acute psychotic disorder |

Acute onset of clinical symptoms, presence of depressive symptoms, short-term attacks, absence of previous schizoid and paranoid personality traits have been associated with a positive response to ECT treatment. (14,15)

ECT is particularly effective on positive psychotic symptoms. ECT and antipsychotic drugs can be used together. (16)

ECT may also be preferred in postpartum psychosis patients who do not respond to four weeks of drug therapy. (7)

### *2.3. Bipolar Disorder*

The value of ECT in the treatment of BD has a variable amount of clinical evidence in the context of its efficacy in mania, bipolar depression, and mixed states. Different treatment guidelines for BD propose the use of ECT as a first-line treatment only in very serious cases or patients resistant to pharmacotherapy. (17,18)

#### *2.3.1. Bipolar Depression*

Although ECT has been more widely used in the treatment of unipolar depression, its use in bipolar depression has expanded in recent years. (19) It has been reported that clinical improvement is more effectively achieved with ECT than with pharmacotherapy in bipolar depression. (19) In a meta-analysis that included 19 studies, Bahji et al. reported a response rate of 77.1% and a remission rate of 52.3% in patients with bipolar depression treated with ECT. Furthermore, response rates and the speed of the response were higher in individuals with bipolar depression compared with those with unipolar depression. (19)

#### *2.3.2. Bipolar Mania*

The literature researching the use of ECT in mania is very limited; however, response rates higher than 80% have been reported in acute mania and

patients resistant to pharmacological treatment. (20) Due to the efficacy of ECT in the treatment of manic and depressive episodes, its recent use has extended to bipolar disorder mixed states. (21) Table 4 shows the clinical symptoms associated with mania that may respond well to electroconvulsive therapy. (9)

**Table 4.** Mania-Related Clinical Symptoms That May Respond Well to Electroconvulsive Therapy Application

| |
|---|
| Patients who are resistant to drug therapy (Patients who cannot respond to antipsychotics and mood stabilizers) |
| Severe excitation |
| Pregnancy |
| History of neuroleptic malignant syndrome (NMS) |

Among the clinical symptoms of the patient, “anger, irritability and suspiciousness” was associated with a good response to ECT. Although some researchers have stated that ECT will be done every day in mania, it is generally recommended to do ECT every other day. (2)

### *2.4. Other Psychiatric Diseases Where ECT Is Rarely Used*

Although ECT is used in clinical practice in the diagnosis of depression, bipolar disorder, schizophrenia and schizoaffective disorder, it can also be used rarely in other psychiatric diseases. Table 5 shows other psychiatric disorders in which ECT is rarely used. (22)

**Table 5.** Psychiatric Diseases In Which Electroconvulsive Therapy Is Rarely Used

| |
|---|
| Atypical psychosis |
| Obsessive compulsive disorder |
| Anorexia Nervosa |

## 3. Organic Disorders Using Electroconvulsive Therapy Application

“Catatonia” is a non-specific syndrome. Itcan be seen in psychiatric diseases such as mood disorders schizophrenia, while it can also be seen in organic diseases such as cognitive disorders, systemic lupus erythematosus (SLE). Catatonia, which has a multiple etiology, can be improved with a few sessions of ECT. ECT is effective in both psychiatric and organic catatonia. Intoxications, neurological disorders and systemic diseases are the most common causes of organic catatonia. (23,24) Table 6 shows organic disorders in which ECT is used.

**Table 6.** Organic Disorders Using Electroconvulsive Therapy Application

| |
|---|
| Catatonic conditions |
| Delirium |
| Parkinson's disease |
| Epilepsy |
| Drug-induced movement disorders |

## 4. Electroconvulsive Therapy and Drug Interactions

The concomitant use of lithium with ECT is not recommended. If ECT will be applied to a patient using lithium, the patient's blood lithium levels should be lowered before ECT. TCAs should also be avoided because of their strong anticholinergic effects. BDZs and anticonvulsants should also be avoided because they increase the seizure threshold and make it difficult to develop convulsive therapeutic seizures. For a patient who needs sedation, a low-dose antipsychotic may be preferred instead of BDZ. Haloperidol may be preferred in the use of antipsychotics together with ECT. (25,26). Table 7 shows the drugs frequently used in psychiatry clinical practice that may affect ECT applications.

**Table 7.** Psychiatric Drugs That May Affect Electroconvulsive Therapy Application

| |
|---|
| Lithium |
| Tricyclic Antidepressants (TCA) |
| Benzodiazepines (BZD) |
| Selective Serotonin Reuptake Inhibitors (SSRI) |
| Anticonvulsants |
| Antipsychotics |

## 5. Electroconvulsive Therapy Applications

With the application of ECT, convulsive seizures are tried to be created by means of electric current. Even if the current is very strong, ECT is considered ineffective if the convulsion has not occurred. Current intensity exceeding the seizure threshold, lasting at least 20-25 seconds, causing generalized convulsions should be applied. It is very important therapeutically that the convulsion is generalized and covers the whole brain. If the seizure threshold is not sufficiently exceeded, the desired therapeutic effect cannot be achieved. (27,28)

In the room where ECT is applied, the necessary drugs and equipment for emergency intervention, oxygen and intubation equipment must be available. (29)

In the treatment of psychiatric diseases, 6-12 sessions of ECT are generally recommended. The response to the first two ECT applications is a strong predictor of the post-treatment response. ECT sessions can be applied 2 or 3 times a week. Generally, application every other day is preferred. However, it can be applied once a week in elderly patients. (2)

ECT is continued until significant improvement is observed in the patient. If a postictal or interictal delirium picture occurs, ECT is terminated. (7)

Seizures exceeding 180 seconds are considered prolonged seizures. Seizures lasting less than 20-25 seconds are not desirable in therapeutic practice, and prolonged seizures are also undesirable. Prolonged seizures and late onset seizures can lead to cardiogenic arrhythmias. (7,16)

If there are problems with drug use in the continuation of the treatment in a psychiatric patient who has recovered with ECT, prophylactic ECT may also be preferred. Preventive ECT application should last at least 16-20 weeks. It starts with ECT application once a week, and over time, ECT application intervals are arranged to be every two weeks, every three weeks and once a month. Positive results have been reported with preventive ECT, especially in patients with major depression and bipolar disorder. (2)

## 6. Conclusion

Although ECT is a very effective method, it is under-applied and many patients who can benefit from it miss the chance of treatment. Selection of suitable patients who can respond well to ECT application and ECT applications to be performed correctly will make a significant contribution to the therapeutic processes of patients.

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# CHAPTER XIII

# ELECTROCONVULSIVE THERAPY

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## 1. Introduction

Electroconvulsive therapy (ECT) can be roughly defined as stimulating the brain with an electrical current. Cerebral convulsions are created with the application. In its historical development, clinicians thought that schizophrenia and epilepsy cannot coexist. (1,2)

Cerletti and Bini designed a specific device for the application in 1938, and the application became safer with the use of short-acting anesthetics, barbiturates and muscle relaxants such as curare, succinylcholine as premedication. It has been determined that the application, which was used in the treatment of schizophrenia, was most effective in depression over time. (3-5).

ECT can be considered as the first choice in patients who cannot be given medication, who do not benefit from drugs, who need to be treated quickly, and who have had successful treatment results with ECT before, such as pregnant women. (6) Table 1 shows the situations in which ECT can be considered as the first choice.

**Table 1.** Situations In Which ECT May Be Considered As The First Option

| |
|---|
| Patients who cannot be given medication |
| Patients who do not benefit from drugs |
| Patients who need to be treated quickly |
| Patients with positive results with ECT before |

The American Psychiatric Association (APA) has approved the use of ECT in the diagnosis of major depression, bipolar disorder, resistant schizophrenia

and schizoaffective disorder. (7) Table 2 shows the psychiatric diseases for which ECT use is appropriate.

**Table 2.** Psychiatric Diseases For Which ECT Use Is Approved

| |
|---|
| Major depression |
| Bipolar disorder |
| Resistant schizophrenia |
| Schizoaffective disorder |

In a study investigating the distribution of ECT application according to diagnoses, it was found that: "Major Depressive Disorder 72%, Bipolar Disorder 11%, Schizoaffective Disorder 2%, Schizophrenia 1% and other psychiatric disorders 14%". (4)

ECT is under-applied and many patients who can benefit from it miss the chance of treatment. Negative attitudes and behaviors related to ECT can also be seen in mental health workers who will perform ECT. In this article, it is aimed to inform especially those working in the field of mental health about ECT.

## 2. Mechanism of Action of ECT

The mechanism of action of ECT and how it provides recovery are not fully known. Studies have shown that ECT increases cholinergic potency. Anticholinergic drugs also reverse the effect of ECT on mood and physiological functions. (4) When these data are evaluated, it can be said that the mechanism of action of ECT may also be related to the autonomic nervous system. It has been determined that as the number of ECT increases in ECT applications, the seizure threshold increases and the duration of convulsions shortens. From this point of view, it can be thought that ECT also has an anticonvulsive effect. Some researchers have claimed that the effect of ECT is based on this anticonvulsant effect. Convulsions induced by ECT change the neuroendocrine balances in the brain stem and hypothalamo-pituitary axis and cause peptide release from the hypothalamus and pituitary to the cerebrospinal fluid (CSF). Some researchers have stated that healing occurs through these peptides. (8)

## 3. Applied Electric Current (Stimulus)

The voltage and duration (intensity) of the electric current given to the patient to create a convulsion together constitute the "dose". Electric current

should be applied in the dose and duration that will create the appropriate convulsion in the patient. With the ECT device, the electric current can be adjusted to be continuous or intermittent. (9)

While the wave type in the continuous electric current is the traditional "sine wave", the wave type in the intermittent electric current is of two types as "short pulse" and "ultra short pulse". In the "short pulse current", an electric current of 5-40 joules is applied, which moderately exceeds the seizure threshold. (10) Considering that an electric current of 200-400 joules is applied with the cardiac defibrillator used in emergency situations, it will be seen that a very low voltage is applied. Short-pulsed current is especially preferred when unilateral ECT is to be applied. In the studies carried out, the effectiveness of the "ultra short pulse current" was found to be questionable. (11,12)

The electric current applied with the ECT device is transmitted to the patient through the electrodes. The ECT device can be applied both unilaterally and bilaterally. If a unilateral application is to be performed, it is recommended to apply it to the non-dominant hemisphere. (9) Unilateral application is especially preferred in patients who need the least memory impairment and who will undergo ECT on an outpatient basis. Bilateral application, on the other hand, is preferred especially in cases where the clinical picture is severe and in elderly and male patients with a high seizure threshold. (4)

### 4. Therapeutic Convulsive Seizure

With the application of ECT, convulsive seizures are tried to be created by means of electric current. Even if the current is very strong, ECT is considered ineffective if the convulsion has not occurred. Current intensity exceeding the seizure threshold, lasting at least 20-25 seconds, causing generalized convulsions should be applied. It is very important therapeutically that the convulsion is generalized and covers the whole brain. If the seizure threshold is not sufficiently exceeded, the desired therapeutic effect cannot be achieved. (10,13)

While the therapeutic effect of ECT is provided by generalized convulsions, the side effects are due to the applied electrical current. For this reason, the lowest level of electrical current that will cause convulsions in the patient is accepted as the best way to get a response from ECT. There is no established fixed dose to induce seizures suitable for psychiatric patients. There are several factors that affect this dose. Many factors such as the device to which ECT

is applied, whether the application will be made bilaterally or unilaterally, the patient's age, gender, and physical characteristics affect the dose of electric current to be applied. (14) Table 3 shows the parameters affecting the electric current dose to be applied.

**Table 3.** Parameters Affecting The ECT Dose To Be Administered

| |
|---|
| The ECT application itself |
| How the application will be performed (One-way, two-way) |
| Patient's age |
| Patient's gender |
| Physical characteristics of the patient |
| Drugs used by the patient |

In ECT application, the value 50-200% above the seizure threshold is considered as a moderate suprathreshold dose (1.5-3 times the seizure threshold dose) and recommended (Seizure threshold dose: It is the electrical intensity required to create a generalized convulsion lasting at least 20-25 seconds). The seizure threshold can vary up to 40 times between patients. (4) The drugs used by the patient may also affect the occurrence of convulsive seizures positively and negatively. (15-19) Table 4 shows how drugs affect convulsive formation.

**Table 4.** The Relationship Between Drugs And Convulsions

| Negative Affecting Drugs | Positive Affecting Drugs |
|---|---|
| B-Blocker | Theophylline |
| Benzodiazepine | Caffeine |
| Pentothal | |
| Methohexital | |

Superficial anesthesia with low doses should be preferred because barbiturate and anesthetic agents used in anesthesia such as methohexital and pentothal make seizure formation difficult. Since ECT itself is a potent anticonvulsant, it increases the seizure threshold by 25-200% during treatment. Therefore, in practice, the dose administered after both ECT sessions should be increased by 25%. (12-14)

If the seizure threshold is too high, this threshold must be lowered for current to be effective. (4) Table 5 shows the applications that can be done to lower the seizure threshold.

**Table 5.** Medical Applications To Lower The Seizure Threshold

| |
|---|
| Discontinuation of drugs that raise the seizure threshold |
| Hyperventilation |
| Proper hydration |
| Reducing the dose of anesthetic drugs |
| 500-2000 miligrams intravenous administration of caffeine 5-10 minutes before ECT. |
| 500-800 miligrams intravenous administration of Pentylenetetrazole 60-90 seconds before ECT. |

If the convulsion still has not occurred 40 seconds after the electric current is applied, the electrode connections should be checked, the contact with the skin should be reviewed, and the intensity of the previous current should be increased by 25-100% and tried again. In one session, current can be given 4 times until convulsion occurs. (20)

In the room where ECT is applied, the necessary drugs and equipment for emergency intervention, oxygen and intubation equipment must be available. (9)

## 5. Conclusion

Although ECT is a very effective method, it is under-applied and many patients who can benefit from it miss the chance of treatment. ECT applications to be performed with appropriate patient selection, especially for major depression, bipolar disorder, schizoaffective disorder and schizophrenia, will contribute significantly to the therapeutic processes of patients.

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CHAPTER XIV

# OBSTRUCTIVE SLEEP APNEA SYNDROME: DIAGNOSIS

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## 1. Introduction

Obstructive Sleep Apnea Syndrome (OSAS) is a syndrome caused by recurrent episodes of cessation (apnea) or reduction (hypopnea) of airflow during sleep due to upper airway airflow interruption, often accompanied by low saturation and increased respiratory effort.

Additionally, OSAS has several systemic consequences. Although recurrent apneas and arousals cause numerous cardiovascular, metabolic, pulmonary, neurological, and endocrine diseases, clinical symptoms significantly affect patients' daily lives, work performance, and quality of life in multiple ways (1).

## 2. Diagnostic Procedures

Polysomnography (PSG) is an imaging technique which has been accepted as the gold standard for diagnosing OSAS recently. PSG records various physical parameters, including cardiorespiratory and neurophysiological measures, simultaneously and continuously during sleep. Accurate diagnosis is the crucial first step towards treating OSAS and other respiratory disorders that affect sleep (2).

### *2.1. Clinical Diagnosis*

The primary symptoms observed in OSAS are snoring, witnessed apnea, and excessive daytime sleepiness. While cardiopulmonary and neuropsychiatric symptoms are commonly seen, symptoms related to numerous other systems can also be observed. These may include headache, insomnia, decreased cognitive ability, forgetfulness, depression, changes in personality, difficulty adapting, anxiety, chest pain, tachycardia, nocturia, dry mouth, night sweats, decreased libido, impotence, and gastroesophageal reflux (3).

*Snoring:* The symptom of snoring is particularly noteworthy. Snoring is a common symptom caused by a partial obstruction in the upper respiratory tract, which narrows due to the effect of airflow during sleep. It is important to obtain information from relatives, even if patients are unaware of it. Complete obstruction in the upper airways can result in apnea followed by arousal.

*Witnessed Apnea:* Because the upper airways become blocked and breathing pauses completely during obstructive apnea, chest and abdominal movements persist while snoring ceases. This is followed by inspiration accompanied by loud snoring. Patients report feeling suffocated if they awaken during an apnea episode, which is typically noticed by their partners called witnessed apnea (3,4).

*Excessive Daytime Sleepiness (EDS):* EDS manifests as increased sleepiness during the day due to frequent awakenings caused by repeated episodes of breathlessness during sleep. It is necessary to scrutinise this nonspecific symptom thoroughly since it may be attributed to numerous disease presentations. This symptom is prominently observed in OSAS as a neurocognitive impairment affecting motor and cognitive aptitudes during the day. The risk of severe work and traffic accidents increases due to forgetfulness, reflex behaviours and reduced attention. It is necessary to scrutinise this nonspecific symptom thoroughly since it may be attributed to numerous disease presentations. Objective tests (3,4) are preferred for evaluating this symptom accurately.

The Multiple Sleep Latency Test (MSLT) is accepted as the standard index of physiological sleepiness and is an objective test developed for evaluating EDS. MSLT determines the state of sleepiness that occurs without environmental stimulus factors, and it can be applied to evaluate treatment response and diagnose diseases characterised by EDS, such as narcolepsy (5). On the other hand, of all the available tests, the Epworth Sleepiness Scale (ESS) is the most commonly used and practical. The ESS has the disadvantage of objective

limitation due to self-assessment and the possibility of misunderstanding sleep episodes. Consequently, it is crucial to question the partner as well. Of all the available tests, the Epworth Sleepiness Scale (ESS) is the most commonly used and practical. The ESS has major advantages, including its simplicity, speed, low cost, and frequent reproducibility. It comprises 8 questions (6).

**Table 1.** Epworth Sleepiness Scale Scoring System

| | **Score** |
|---|---|
| *Sitting and reading* | |
| *Watching TV* | |
| *Sitting in a public place* | |
| *Sitting in a car a passenger* | |
| *Lying down to rest* | |
| *Sitting and talking to someone* | |
| *Sitting quietly after lunch without alcohol* | |
| *In a car, while stopped for a few minutes in traffic* | |
| **Total Score** | |

The patient is asked to answer with one of the following options to the questions "... do you have sighing, drowsiness during ...?".

0. none
1. mild
2. moderate
3. severe

10 points and above in total scores are considered significant.

### *2.2. Physical Inspection*

Although there are no specific physical examination findings that are diagnostic for OSAS, findings can support the diagnosis, such as short neck and small and retracted mandible. The most appropriate approach is a multidisciplinary one that involves otolaryngology, dentistry, neurology, pulmonology, psychiatry, and cardiology for the diagnosis, as well as the management.

An upper respiratory tract examination can be prioritised to identify possible risk factors, and a dental examination should also be performed to examine oropharyngeal obstructive reasons. Nasal assessment is crucial in cases of OSAS for identifying potential nasal obstructions and potential barriers to using Positive Airway Pressure (PAP) therapy through a nasal mask for

treatment. The examination can explore the presence of nasal septal deviations or turbinate hypertrophy, which might affect breathing in the posterior oropharynx in conjunction with the Mallampati or Friedman scores or retrognathia. The hypertrophy of the tonsils, dental malocclusions, elongation of the palate or macroglossia possibly causes oropharyngeal constriction. It is also essential to assess the size and position of the tongue along with the structure and relationship of the upper and lower jaw (1,7). The results of central obesity (measurement of waist and neck circumference) are also critical.

Taking all these factors into account, it cannot be said that the diagnosis of OSAS can be ruled out solely based on medical history or physical examination. However, it is now possible to conduct pre-test evaluations for OSAS due to the discussed features. The following tests can identify patients at high risk for OSAS:

- Sleep Apnea Clinical Score,
- Elbow Sign Questionnaire,
- STOP-Bang,
- Cricomental Distance
- Berlin Questionnaire,
- OSA50,
- American Society of Anaesthesiologists Checklist (1).

### *2.3. Radiologic Diagnosis*

Radiological methods can support the diagnosis of OSAS but cannot be used as the sole diagnostic tool. Technical term abbreviations such as OSAS will be explained upon first use.

Various imaging modalities, including cephalometry, cineradiography, computed tomography, magnetic resonance, fluoroscopy, and videofluoroscopy, can evaluate bone and soft tissue structures relevant to OSAS. Certain distance and area measurements are used to detect craniofacial pathologies, and they can inform the selection of treatment modalities such as intraoral appliance (IA) treatment. Additionally, post-treatment measurements can be used to assess the efficacy of treatment (4).

### *2.4. Endoscopic Diagnosis*

The upper airway is assessed dynamically using nasopharyngoscopy, a diagnostic method that identifies obstruction levels. However, due to its interventional nature, this method has certain drawbacks.

Conversely, sleep endoscopy (drug-induced sleep endoscopy (DISE)) evaluates the upper airway during sleep and may detect snoring and apnea. Although the criteria for this method have not been completely defined yet, it could be suggested to assess cases that are resistant to therapy and before particular surgical approaches (8).

### *2.5. Polysomnographic Diagnosis*

Polysomnography (PSG) is considered the gold standard in diagnosing obstructive sleep apnea syndrome (OSAS) and in subsequent titration tests. The test encompasses audio and video recordings and monitoring respiratory, neurophysiological, cardiological, and other physical parameters recorded during sleep (9).

To ensure test accuracy, the patient's medications must be reviewed, and those that may affect sleep patterns should be discontinued. The patient should be informed, particularly on the day of recording, not to consume caffeine or alcohol. The procedure will be recorded via camera, and detailed information regarding electrodes and connections will be provided. The captured data is analysed objectively, and the patient's sleep disturbance is evaluated. Scoring and recording should be conducted following the present guidelines disseminated by the American Academy of Sleep Medicine (AASM).

The parameters that should be recorded during a PSG application in accordance with the standards are as follows:

- Electrooculography (EOG),
- Electromyography (EMG; submental, tibial),
- Electroencephalography (EEG),
- Electrocardiography (ECG)

In addition, thoracoabdominal movements, oronasal airflow, saturation, tracheal microphone, and body position are also included. The average recording time should be 6 to 8 hours.

According to the AASM report (9), the indications for PSG are listed below.

1. Respiratory disorders in sleep
- In the diagnosis of Sleep Breathing Disorders (USB)
- Titrating the CPAP or BPAP device
- Before and after the planned surgical procedure for the treatment of USB
- CPAP treatment response and follow-up

2. Narcolepsy
3. If USB symptoms accompany other pulmonary diseases (COPD, etc.)
4. Restless legs syndrome and periodic limb movement disorder
5. Parasomnia and sleep-related epilepsies
6. Depression with insomnia
7. Circadian rhythm disorders

Respiratory events defined as pathological in PSG were apnea, hypopnoea, respiratory effort-related arousal (RERA), hypoventilation and Cheyne Stokes respiration.

One complete sleep cycle comprises Non-REM (Rapid Eye Movement) and REM stages and lasts for 90 to 120 minutes. Typically, individuals experience 4-6 cycles per night. Non-REM 1 stage constitutes 2-5%, Non-REM 2 takes up 45-55%, Non-REM 3 accounts for 20-25%, and REM comprises 20-25% of the total sleep duration (9).

Sleep scoring involves classifying each 30-second recording as an "epoch" and then staging each epoch accordingly. Following the determination of sleep stages in PSG scoring, respiratory events are scored.

OSAS is categorised based on its apnea-hypopnoea index (AHI) value. AHI is calculated by counting the total number of apneas and hypopnoeas during one hour of sleep.

- AHI<5/hours Basic Snoring
- 5-15/hours Mild OSAS
- 15-30/hours Moderate OSAS
- >30/hours Severe OSAS

According to the diagnostic criteria of ICSD-3 for OSAS, the presence of one of the following A, B or C criteria is required for diagnosis (9):

A. Presence of at least one of the following;

1. Daytime sleepiness, nonrestorative sleep, fatigue, or insomnia complaints.

2. Waking up with a feeling of breathlessness or choking.

3. Routine snoring during sleep, breathing pauses, or both reported by the patient's partner/relative.

4. Presence of hypertension, cognitive dysfunction, mood disorder, congestive heart failure, coronary artery disease, type 2 diabetes, atrial fibrillation, or stroke.

B. Demonstration of the following by PSG or Out of Centre Sleep Testing (OCST):

1. 5 or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopnoeas or RERA) in one hour of sleep.

C. Demonstration of the following by PSG or OCST:

1. 15 or more predominantly obstructive respiratory events (obstructive and mixed apneas, hypopnoeas or RERA) in one hour of sleep.

## 3. Conclusion

The diagnosis of Obstructive Sleep Apnea Syndrome (OSAS) is based on medical history, physical examination, and specific diagnostic tests. The gold standard diagnostic method of OSAS is known as polysomnography (PSG). This test records respiratory movements, oxygen levels, heart rate and other physiological parameters during sleep (10).

Another important diagnostic method is the home sleep test (HSAT). This test works similarly to polysomnography but has fewer sensors and is a version that can be easily applied in patients' homes. HSAT is generally a preferred test for patients with suspected OSAS but for whom PSG is difficult to perform in a hospital setting (11).

Another diagnostic aid for OSAS is a clinical evaluation based on symptoms such as snoring, respiratory pauses and excessive daytime sleepiness reported by the patients' spouses or sleeping partners. However, the presence of these symptoms is not sufficient to definitively diagnose OSAS; an objective sleep test is required (12).

For patients at risk of moderate to severe OSAS, anatomical assessment of the upper airway may be performed in addition to PSG or HSAT. This assessment is used to identify narrowed or obstructed regions and to select the appropriate treatment method (13).

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CHAPTER XV

# IDENTIFICATION OF DIABETES RISK FACTORS AND DEVELOPMENT OF A DIAGNOSTIC MODEL BY MULTIVARIATE ADAPTIVE REGRESSION

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## 1. Introduction

Diabetes has expanded as a global health concern, and its effects can have a significant impact on people's lives. The number of births, blood sugar levels, blood pressure, skin thickness, insulin production and effect, body mass index (BMI), and family history of diabetes are all important factors, even if there are many others that contribute to the development of diabetes. (1-3). However, the link between diabetes and these variables is complicated. For instance, obesity and high glucose levels can raise the risk of type 2 diabetes, and insulin action and synthesis are crucial for the onset of this condition. The risk of diabetes can also be determined by a person's family history at the same time. If there have been past diabetes cases in the family, the person may be predisposed to the condition (4).

Age plays a significant role in determining diabetes risk. Older people may be at risk for type 2 diabetes as the pancreas' ability to produce insulin may decline with age. In addition, lifestyle factors, particularly inactivity and poor eating patterns, may raise the risk of diabetes (5–6). For the prevention and control of diabetes, it is crucial to monitor and comprehend these aspects. The risk of diabetes can be decreased by living a healthy lifestyle, engaging in regular exercise, eating a balanced diet, and scheduling routine medical exams. Additionally crucial are regular doctor visits and taking into account

genetic factors like family history. (7).In his study, Bottalico (2007) notes that the incidence of prediabetic risk factors is rising. These factors include dietary practices and way of life, which when combined with a genetic predisposition, raise the risk of type 2 diabetes and GDM. (8).

Witzel et al. (2015) clarified the reason for diabetic neuropathies, assessed the patient's risk profile, and eventually helped create a genetic-metabolic model that will aid in the person's preventive and specific treatment. (9).The causes of the increased effects of insulin resistance were studied by Gencer et al. in 2023. He looked into how adding HT to PCOS affected ovarian volume and how that affected ovarian volume change. They concluded that insulin resistance should be looked at in all individuals with polycystic ovary syndrome and increased ovarian volume. (10).Derraik et al. looked at how age, gender, body mass index (BMI), and anatomical area affected skin thickness in diabetic children and adults. He discovered that factors such as age, puberty, gender, BMI, and anatomical area had an impact on skin thickness. (11).

According to Huntley and Walter's study, people with diabetes frequently have thick skin on the palms and fingers, and those who have the condition are more likely to have diabetic retinal microvascular disease. They discovered that the general prevalence of thick skin on diabetics' extremities appeared to be unrelated to thick skin syndromes linked to illness consequences. (12). 89 patients with insulin-dependent diabetes and 25 healthy control participants were evaluated by Hanna et al., and they discovered clinical evidence of skin thickening (diabetic thick skin) in 22% of the insulin-dependent diabetes patients and 4% of the control subjects. (13).As a result, a variety of variables, including parity, blood sugar levels, blood pressure, skin thickness, insulin production and action, body mass index (BMI), and family history, can influence the development of diabetes. Given that these variables have the potential to either increase or lower the chance of developing diabetes, it is crucial for people to lead healthy lifestyles and receive frequent medical checkups in order to both avoid and effectively manage the disease. In order to create a diagnostic model and identify aspects that are crucial in the diagnosis and management of diabetes, this study employs the Multivariate Adaptive Regression Splines (MARS) approach.

Demographic data and several biometric parameters of diabetic individuals are included in the data set. Pregnancies, blood sugar levels, blood pressure, skin thickness, insulin, BMI (body mass index), family history of diabetes, and age are just a few of the variables that are measured.

The complicated correlations between these variables were discovered using the MARS technique, which also helped to pinpoint diabetes risk factors. The study's findings demonstrate the significance of characteristics including BMI, insulin levels, and glucose levels in predicting the likelihood of developing diabetes. Age and family history are other factors that have been discovered to have an effect. These characteristics were identified using the MARS approach to create a regression model, which provides sensitivity in the diagnosis of diabetes. This study demonstrates how the MARS technique may be used to identify critical diabetes risk variables and create a diagnostic tool to aid in the better management of the condition. These results might significantly improve our knowledge of and ability to treat diabetes.

## 2. Some Factors Affecting The Risk Of Diabetes

A difficult topic that encompasses many variables is the association between diabetes and variables like glucose, body mass index (BMI), age, blood pressure, insulin, pregnancy, and skin thickness. These elements play a significant role in the development of diabetes and the risk of developing it. Here are some key ideas to keep in mind as you think about how these factors relate to diabetes:

Glucose (Levels of Blood Sugar): High blood sugar levels and diabetes are frequently linked. High blood glucose levels are a symptom of type 2 diabetes, which is defined by circumstances where your body cannot use insulin efficiently or cannot generate enough of it.

Body mass index, or BMI, is a measurement of a person's weight and body fat. Diabetes, especially Type 2 diabetes, may be more likely in those with high BMI. Insulin resistance can rise as a result of excess body fat. Age has an impact on the chance of developing diabetes. In general, type 2 diabetes is more prevalent in middle age and later.

History of diabetes A person's risk of diabetes might be influenced by function and family history. Due to their genetic propensity, people with a family history of diabetes may be at a higher risk.

Blood pressure is a problem that must be handled in conjunction with diabetes since it can raise the risk of both diabetes and high blood pressure (hypertension).

The pancreas does not create enough insulin in Type 1 diabetes, an autoimmune condition. As a result, one of the main Type 1 diabetes therapy

options is insulin. Insulin resistance is linked to type 2 diabetes; even when enough insulin is produced, cells cannot efficiently use it.

The development of diabetes and the risk of diabetes are both significantly influenced by pregnancy. Obstetric Diabetes Gestational diabetes is a condition that some pregnant women may get. This illness typically starts during pregnancy and is characterized by higher-than-normal blood sugar levels.

Skin Thickness: Although the connection between skin thickness and diabetes is less well understood, some evidence points to a possible association between subcutaneous fat deposits, insulin resistance, and Type 2 diabetes. Numerous variables, such as a person's lifestyle, genetic predisposition, environmental influences, and other medical disorders, may have an impact on how these variables relate to diabetes. To analyze and reduce the risk of diabetes, it is crucial to have frequent health examinations, lead a healthy lifestyle, and receive the proper treatment. For managing diabetes risk, a customized health plan and doctor's advice are crucial. (14).

### 3. Multivariate Adaptive Regression Analysis

Regression analysis method known as Multivariate Adaptive Regression Splines (MARS) also goes by the name of Multivariate Adaptive Regression Analysis. (15). This strategy, a modeling one that is employed in the fields of data mining and statistical analysis, is particularly useful for figuring out intricate connections between the dependent variable and independent variables. MARS is a tool for modeling complex, skewed, or nonlinear relationships and is used to address regression problems. In the body of research in the topic of health, this methodology has been used in several studies. (16-19). With the use of this technique, a better regression model can be produced by measuring the impact of the data set's variables. MARS is essentially a two-stage process. Basic functions are first created, and they are used in the first step to attempt to describe the relationships between the independent variables and the dependent variable. These basis functions can precisely depict nonlinear effects and variable interactions. The second stage is the creation of the regression model, which establishes the connections between fundamental operations and independent variables. The basis functions and variables used in this model are appropriate for describing the data.

MARS works exceptionally well when predictive model development and data mining are involved. It is the best technique for outlining the links and structures in intricate data sets. Additionally, it is effective where other

conventional regression analyses fall short because of its capacity to recognize nonlinear effects.

The user-friendly interfaces of MARS, which is included in data mining software packages, give data analysts and statisticians freedom while performing regression analysis. For researchers looking to model complex interactions and produce more precise predictions, this technique is a crucial tool (20–22).

## 4. Material and Methods

In this study, the classification performance of 8 independent variables in defining diabetes was examined, and the MARS model was used to determine and rank the most significant factors causing diabetes. Both the feature selection and classification phases used the MARS model. The National Institute of Diabetes and Digestive and Kidney Diseases is where this data set was first acquired (23). The dataset's goal is to use particular diagnostic metrics included in the dataset to diagnostically forecast whether a patient has diabetes. Pregnancies, blood sugar levels, blood pressure, skin thickness, insulin, BMI (body mass index), family history of diabetes, and age factors are among the parameters that are taken. R Studio 4.3.1 is running. The application was used to choose features and classify them.

## 5. Results

In this section, both feature selection and classification success of diabetes with MARS will be analyzed. As a result of feature selection with MARS;

**Table 1:** MARS Model Performance and Variable Selection Results

| |
|---|
| 7 out of 8 predictors and 17 out of 31 terms were chosen. |
| Termination criterion: At 31 terms, RSq changed by less than 0.001. |
| Importance: Diabetes, Glucose, BMI, and Age Function of the Pedigree, Blood Pressure, Insulin, Pregnancy, and Unused Skin ThicknessTerms at each level of interaction are as follows: 1 7 9 |
| RSS 105.2999 GCV 0.1496974 GRSq = 0.342795, RSq = 0.3964404, and CVRSq = 0.267935 |

Table 1 shows that although the model has 31 terms overall, only 17 were chosen for their performance. There were also 8 predictors (independent variables), and it was determined that 7 of these words were significant. When the RSq change is smaller than 0.001, it is the condition under which the model

terminates. The performance of the model was not greatly enhanced by the addition of extra terms. It matters how the predictors are ranked in importance. From most significant to least important predictions, this ranking is made. For instance, the three predictors with the highest significance are glucose, BMI, and age. “Number of terms at each degree of interaction: 1 7 9” Here is a list of how many terms in each degree there are in the model. The 7th and 9th order components may indicate more intricate relationships while the first order terms represent single predictors. This is based on some model performance information;

GCV (Generalized Cross-Validation): It is the cross-validation error corrected according to the complexity of the model. A lower GCV value is considered a better model.

RSS (Residual Sum of Squares): It is the error measure that shows how well the model fits the real data. Lower RSS means better fit.

GRSq (Generalized R-Squared): Measures the model’s ability to explain variance. A higher GRSq indicates a better model.RSq (R-Squared): The classic R-squared measure that indicates how well the model fits the data. The closer it is to 1, the better the model is.

CVRSq (Cross-Validation R-Squared): It is the R-square value of the model on the cross-validation data. It is used to evaluate the generalization ability of the model.These statistics are used to evaluate the performance and suitability of the model. The model achieving a higher GRSq and RSq with a lower GCV and RSS is generally considered a better model.

**Table 2:** MARS Modeli Çapraz Doğrulama Sonuçları

$fold1
26 out of 63 terms and 8 out of 8 predictors were chosen.
Termination criterion: At 63 terms, RSq changed by less than 0.001.
Glucose, BMI, Age, Pregnancy, Diabetes Family Function, Insulin, Skin Thickness, and Blood Pressure are important.
Each degree of interaction has the following number of terms: 1 7 18 GCV 0.1463177 RSS 86.44087 GRSq 0.3585263 RSq 0.4483758
$fold2
20 out of 35 terms and 7 out of 8 predictors were chosen.
Termination criterion: At 35 terms, RSq changed by less than 0.001.
Glucose, BMI, Age, Pregnancy, Diabetes Family Function, Insulin, Blood Pressure, and Skin Thickness—unused
Term count for each interaction level: 1 5 14 GCV 0.1453772 RSS 89.58114 GRSq 0.361356 RSq 0.4296662
$fold3
Selected 18 of 34 terms, and 7 of 8 predictors
Termination condition: RSq changed by less than 0.001 at 34 terms
Importance: Glucose, BMI, Age, Pregnancy, Diabetes Pedigree Function, Insulin, Blood Pressure, Skin Thickness -unused
Number of terms at each degree of interaction: 1 5 12
GCV 0.1447535 RSS 90.2929 GRSq 0.3640962 RSq 0.4251347
$fold4
Selected 17 of 60 terms, and 7 of 8 predictors
Termination condition: RSq changed by less than 0.001 at 60 terms
Importance: Glucose, BMI, Age, Pregnancy, Diabetes Pedigree Function, Insulin, Blood Pressure, Skin Thickness -unused
Number of terms at each degree of interaction: 1 4 12
GCV 0.152221 RSS 95.37803 GRSq 0.3317434 RSq 0.3922893
$fold5
Selected 16 of 29 terms, and 7 of 8 predictors
Termination condition: RSq changed by less than 0.001 at 29 terms
Importance: Glucose, BMI, Age, Pregnancy, Diabetes Pedigree Function, Insulin, Blood Pressure, Skin Thickness -unused
Number of terms at each degree of interaction: 1 5 10
GCV 0.1514463 RSS 95.31923 GRSq 0.3355936 RSq 0.3921923
$fold6
Selected 20 of 33 terms, and 7 of 8 predictors
Termination condition: RSq changed by less than 0.001 at 33 terms
Importance: Glucose, BMI, Age, Pregnancy, Diabetes Pedigree Function, Insulin, Blood Pressure, Skin Thickness -unused
Number of terms at each degree of interaction: 1 7 12
GCV 0.1541697 RSS 95.15272 GRSq 0.3222716 RSq 0.3946606
$fold7
Selected 16 of 29 terms, and 6 of 8 predictors
Termination condition: RSq changed by less than 0.001 at 29 terms
Importance: Glucose, BMI, Age, Pregnancy, Diabetes Pedigree Function, Insulin, Blood Pressure, Skin Thickness -unused
Number of terms at each degree of interaction: 1 5 10
GCV 0.1481387 RSS 93.08961 GRSq 0.3505429 RSq 0.4059468
$fold8
Selected 14 of 33 terms, and 7 of 8 predictors
Termination condition: RSq changed by less than 0.001 at 33 terms
Importance: Glucose, BMI, Age, Pregnancy, Diabetes Pedigree Function, Insulin, Blood Pressure, Skin Thickness -unused
Number of terms at each degree of interaction: 1 5 8
GCV 0.1495767 RSS 95.8862 GRSq 0.3420163 RSq 0.3904626
$fold9
Selected 16 of 29 terms, and 7 of 8 predictors
Termination condition: RSq changed by less than 0.001 at 29 terms
Importance: Glucose, BMI, Age, Pregnancy, Diabetes Pedigree Function, Insulin, Blood Pressure, Skin Thickness -unused
Number of terms at each degree of interaction: 1 5 10
GCV 0.1497032 RSS 93.77391 GRSq 0.34581 RSq 0.4017766
$fold10
Selected 18 of 29 terms, and 7 of 8 predictors
Termination condition: RSq changed by less than 0.001 at 29 terms
Importance: Glucose, BMI, Age, Pregnancy, Diabetes Pedigree Function, Insulin, Blood Pressure, Skin Thickness -unused
Number of terms at each degree of interaction: 1 6 11
GCV 0.1500122 RSS 94.02204 GRSq 0.3409293 RSq 0.403925

In Table 2, the nfold parameter is a parameter used when creating a MARS (Multivariate Adaptive Regression Splines) model that determines how many folds of cross-validation will be performed during cross-validation. Cross-validation is an important technique for evaluating the performance of a model and detecting overfitting. Nfold provides a cross-validation procedure in which the data set is divided into pieces and each piece is used sequentially as test

data. This is used to better evaluate the overall performance of the model. The nfold parameter is an integer and usually takes a value between 5 and 10. This determines how many equal parts the data set will be divided into. For example, using nfold = 10 will divide the data set into 10 equal parts.Each piece is used as test data in turn, while the remaining 9 pieces are used as training data. This process is repeated 10 times, each time a different piece is selected as test data. Performance measurements (for example, R-squared or mean square error) obtained as a result of each cross-validation iteration are usually averaged.The overall performance of the model is calculated. Cross-validation is important to detect the overfitting problem of the model and to better estimate its overall performance. It also helps evaluate the stability and generalization ability of the model as it is tested on different cross-sections of data. As a result, the nfold parameter is an important cross-validation control parameter used to more reliably evaluate the performance of the model and detect overfitting. According to this model, for example, in $fold7, pregnancies and skin thickness variables appear to be unimportant.

**Table 3:** MARS Model Coefficients and Importance Ranking: Effects of Variables and Terms

| | Coefficents |
|---|---|
| (Intercept) | 0.26317350 |
| h(73- Glucose) | 0.00518019 |
| h(Glucose -73) | 0.00730012 |
| h(21.1-BMI) | 0.07559818 |
| h(BMI-21.1) | 0.00827170 |
| h(1.251- Diabetes Pedigree Function) | -0.21416011 |
| h(Diabetes Pedigree Function -1.251) | -1.55319713 |
| h(46-Age) | -0.01026104 |
| h(Pregnancy-6) * h(Insulin-56) | 0.00029545 |
| h(Glucose -73) * h(31.6-BMI) | -0.00032169 |
| h(44- Blood pressure) * h(46-Age) | 0.00028477 |
| h(Insulin-66) * h(46-Age) | -0.00002948 |
| h(21.1-BMI) * h(46-Age) | -0.00315766 |
| h(35.1-BMI) * h(Age-46) | -0.00179088 |
| h(BMI-35.1) * h(Age-46) | -0.00615896 |
| h(0.153- Diabetes Pedigree Function) * h(Age-46) | 2.06241252 |
| h(Diabetes Pedigree Function -1.101) * h(46-Age) | 0.06419094 |

The coefficients in Table 3 indicate the contribution and effect of each term of the model. h(73-Glucose) and h(Glucose -73): Related to glucose (possibly a predictor). The first term refers to situations where Glucose is less than 73, while the second term refers to situations where Glucose is greater than 73. These terms represent the relationship between Glucose and the target variable (Diabetes). h(21.1-BMI) and h(BMI-21.1): They are related to BMI and similarly refer to cases where BMI is less than or greater than 21.1. h(1.251-Diabetes Pedigree Function) and h(Diabetes Pedigree Function -1.251): They are related to the Diabetes Pedigree Function and similarly refer to cases where the Diabetes Pedigree Function is less than or greater than 1.251.

h(46-Age) and h(Age-46): It is related to Age and similarly refers to situations where Age is less than or greater than 46.h(Pregnancy-6) * h(Insulin-56), h( Glucose-73) * h(31.6-BMI), h(44-Blood pressure) * h(46-Age), h(Insulin-66) * h(46-Age), h(21.1-BMI) * h( 46-Age), h(35.1-BMI) * h(Age-46), h(BMI-35.1) * h(Age-46) and h(0.153- Diabetes Pedigree Function) * h(Age-46): This The terms represent the interactions of the satisfiers. Shows how interactions between two predictors affect h(Diabetes Pedigree Function -1.101) * h(46-Age): Represents a specific interaction between the Diabetes Pedigree Function and Age. Each term represents the relationship between relevant predictors and contributes to the model's predictions. The coefficients of these terms indicate the significance and impact of the respective predictors. For example, positive coefficients indicate that the target variable increases as the relevant predictor increases, while negative coefficients indicate that it decreases. Interaction terms specify how the relevant predictors perform together.

**Table 4:** MARS Model Subset Selection and Performance Analysis

| Parameters | nsubsets | gcv | rss |
|---|---|---|---|
| Glucose | 16 | 100.0 | 100.0 |
| BMI | 15 | 56.1 | 63.0 |
| Age | 14 | 45.1 | 54.0 |
| Diabetes Pedigree Function | 12 | 32.9 | 43.9 |
| Blood pressure | 8 | 26.8 | 35.6 |
| Insulin | 7 | 21.9 | 31.4 |
| Pregnancy | 5 | 17.8 | 26.0 |

Table 4 shows some statistics obtained when the MARS model has different variable subset sizes. nsubsets: indicates how many different subsets are calculated when used for a different subset of each variable. So each row

represents a different subset of variables. These statistics in the table can be used to compare the performance of the MARS model with different subsets of variables. In particular, gcv values show how it varies with the complexity of the model and can help select the best subset. A lower GCV value indicates that a less complex model may be preferred. When the variables affecting diabetes are examined, the most important variable is glucose and the least important variable is pregnancy. Skin thickness could not be included in the model.

**Table 5:** MARS Classification Model Performance and Complexity Results

Each interaction level has the following number of terms: 1 31 71 GCV 0.1204952 RSS 49.73079 GRSq 0.4709999 RSq 0.7149758 CVRSq -3.861988

Standard deviations across folds are shown in the cross-validation sd's below.

Cross verification Nvars 88.50 sd 2.59

| CVRSq | sd | ClassRate | sd | MaxErr | sd |
|---|---|---|---|---|---|
| -3.86 | 9.79 | 0.723 | 0.047 | -22.4 | 7.39 |

When the performance of MARS on the question "Can diabetes be explained with 8 different independent variables" was examined, a classification rate of 72.3% was observed. When the number of terms in MARS is examined according to the degree of interaction, 1 term in the model contains 1st degree interaction, 31 terms contain 31st degree interaction and 71 terms contain 71st degree interaction. This shows the complexity of the model. The Overall Cross Validation Error (GCV) value is 0.1204952. This is a value that measures the complexity of the model and it is preferable to be low. A lower GCV indicates a better fit of the model. The model has acceptable GCV value. The Sum of Squares (RSS) value of residuals is 49.73079. This is a value that measures the fit of the model and it is preferable to be low. A lower RSS indicates a better fit of the model to the data. The overall R Square (GRSq) value is 0.4709999. This indicates how well the model fits the data. A high GRSq value indicates a good fit of the model.R Square (RSq): RSq value is 0.7149758. This indicates how much of the variance of the dependent variable the model explains. A high RSq value indicates that the model explains the data well.Cross Validation R Square (CVRSq): The CVRSq value is -3.861988. Cross-Validation Results: Cross-validation results include standard deviations for nterms and nvars. These values indicate how variable the cross-validation results are. Lower standard deviations indicate more stable cross-validation results.

## 6. Discussion and Conclusion

The MARS model contains 31 terms in total, but only 17 terms were selected to give the best performance. Additionally, there were 8 predictors (independent variables) and 7 of these terms were found to be significant. In the study of Lai et al., fasting blood sugar, body mass index, high-density lipoprotein and triglycerides were the most important determinants of diabetes (24). The order of importance of the predictors in this study is as follows: Glucose, BMI, Age, Diabetes Pedigree Function, Blood Pressure, Insulin, Pregnancy variables. In their study, Huntley and Walter (25) found that the general occurrence of thick skin on the extremities of people with diabetes was apparently independent of thick skin syndromes associated with disease complications. In our study, skin thickness is not included in the model as a useless variable. The relationship of skin thickness to diabetes is less known, but some research suggests that subcutaneous fat stores may be linked to insulin resistance and Type 2 diabetes. (11) (13). The MARS model performed quite well when used for classification. The GCV value is 0.1204952, which measures the complexity of the model and a low value is preferred. The RSq value is 0.7149758, indicating that the model explains most of the variance of the dependent variable, and a high value is preferred. The results show that the MARS model is effective in feature selection and performs well for classification. However, it should be taken into consideration that the generalization ability of the model may be poor based on cross-validation results. More data or improving the model's settings can improve the model's cross-validation performance. The effect of skin thickness on diabetes prediction may be lower compared to other predictors. Therefore, it may be understandable that the model evaluates this variable as useless. However, this may not always be the case and different results may be obtained with different data sets or analyzes in further studies.

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CHAPTER XVI

# STATISTICAL ANALYSIS AND MODELING OF THE COVID-19 PANDEMIC ON WEEKLY DEATH COUNTRIES IN OECD COUNTRIES IN 2021 AND 2022

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## 1. Introduction

Around the world, the medical and health industries have undergone tremendous transformation as a result of the COVID-19 epidemic. It has had a significant impact on a number of areas, including social life, the economy, and health care. (1-2). In this process, making decisions about science and health policies has relied heavily on tracking the progression of COVID-19 and comprehending its implications. This study's primary goal is to assess the death patterns for the years 2021 and 2022 and to analyze in detail the weekly number of deaths in OECD nations as a result of the COVID-19 epidemic during those years. Understanding the spread of the pandemic, the effectiveness of vaccines, and the dangers to healthcare systems and civilizations can only be accomplished by carefully examining COVID-19 death data. In this investigation, the estimated weekly death tolls were calculated by statistical modeling and compared to several statistical distributions. The Anderson-Darling goodness of fit test was also used to assess the adequacy of the model. Bertozzi et al.(3), in his work, he demonstrated the utility of simple models for understanding the epidemic and provided an accessible framework for generating policy-relevant insights into the course of the epidemic. He discusses in his paper how he used statistical modeling to anticipate fatality figures and react to the pandemic. Masum et al. applied a mathematical epidemic model (MEM), statistical model,

and recurrent neural network (RNN) variables to predict cumulative confirmed cases. (4). It provides a method specifically used to calculate the daily and overall number of cases in Turkey.In order to analyze the COVID-19 epidemic's effects in India, Gautam and Sharma (2020) (5) put out a mathematical model that aims to simulate the dynamics of the total population infected and mortality. Wu et al. (6) proposed a mathematical model that predicts the dynamics of COVID-19 across India. It has given a complete scenario to illustrate the estimated pandemic lifecycle along with real data or history to date and revealed the predicted turning point and end phase of SARS-CoV-2. Ullah et al (7) evaluated a mathematical model for COVID-19 that included non-pharmaceutical interventions, taking into account Pakistan's actual infected cases to obtain parameter estimates and model fit. Borchering et al. Modeled Future COVID-19 Cases, Hospitalizations and Deaths, Vaccination Rates and Non-drug Intervention Scenarios. (8). In addition, Gencer and Gencer (2021) (9) made regression modeling for the years 2019 and 2020 regarding the COVID-19 pandemic. This study's objective is to predict the weekly Covid-19 death rates for the OECD nations in 2021 and 2022 using statistical distributions and to look at the death patterns over those years. By statistically modeling the weekly mortality rates for 2021 and 2022, the current state of affairs was exposed, forecasts were generated, and OECD nations were compared across years. Covid-19 death rates were modeled using well-known statistical distributions. One of the goodness-of-fit tests, the Anderson Darling (AD) test, was used to demonstrate the models' fit. Covid-19 death statistics have been seen to be represented using the Weibull, Log-logistic, Type 1 Half Logistic, Type 1 Generalized Half Logistic, and Gamma distributions.As a result, this study underlines the value of statistical modeling in order to analyze the COVID-19 pandemic's effects on healthcare services using statistical distributions and to create pandemic management plans.

## 2. Material and Methods

The information utilized in this analysis came from the OECD.Stat website, which provides data and metadata for health care quality indicators for OECD nations and a few non-member economies (OECD, 2023).(10). Programs from Matlab and R Studio were used in the study's analyses. The COVID-19 weekly death figures were modelled using well-known statistical distributions. What are these distributions?

The Weibull distribution is a statistical distribution that may be used to analyze discrete or continuous data and is frequently connected to the length

of time between events. Particularly in disciplines like reliability engineering, health sciences, and industrial engineering, the Weibull distribution is extensively employed. While the time it takes for a certain event to occur is modeled using this distribution, the distribution may be increasing or decreasing during this time.The flexibility provided by the Weibull distribution's parameters (its shape parameter and scale parameter) is its key characteristic. The Weibull distribution might behave differently depending on the values of these factors. Depending on the features of your dataset and your research goals, the Weibull distribution can be used to describe an ascending or descending process. The behavior of this distribution depends on the shape parameter value, hence it is important to thoroughly examine the data before choosing a model. The Weibull distribution is frequently used in data analysis and forecasting because it might be an appropriate model for real data. (11-12).The log-logistic distribution is a type of continuous probability distribution used in data modeling and statistical analysis. It is applied to models of illness lifetimes or durations. For instance, this distribution might be used to determine how well a treatment plan works or to forecast how long the illness will last. (13). Dennis Lindley, a British statistician, first introduced the continuous probability distribution known as the Lindley distribution in 1958. Particularly when modeling positive discrete data, such as time intervals or the intervals between anticipated events, this distribution is used. Health information such as lengths between recurrences of an illness, treatment outcomes, or healing times are examined using the Lindley distribution. (14).

Half Logistics Distribution was first described by Balakrishnan in 1985 (15) and is a subset of the logistic distribution family.The Type I Generalized Half Logistic Distribution, also known as the Generalized Type I Half Logistic Distribution, was generalized by Olapade (2014). (16). Positive real numbers are modeled using the gamma distribution, a continuous probability distribution. It is frequently applied in a variety of contexts, including duration, life expectancy, processing times, and anticipated number of random events. Gamma distribution is utilized in a variety of applications, including analysis of patient reaction times to therapy in the health sciences and modeling of processing times and anticipated service times. Situations call for its application. (17).

### 3. Model Compatibility and Goodness Of Fit Tests

In this section, the Anderson Darling goodness of fit test, which will be used to measure the fit of the distributions used in the study, is introduced.

### *3.1. Anderson Darling Goodness of Fit Test*

A statistical technique called the Anderson-Darling Goodness-of-Fit technique is used to determine how well a collection of data fits a specific probability distribution. (18). This test, which may be applied to both discrete and continuous probability distributions, evaluates how closely the sample distribution of data resembles a theoretical distribution. (19).

$$A^2 = -\frac{2}{n}\sum_{i=1}^{n}\left[\begin{array}{l}\left(i-\frac{1}{2}\right)\log\left\{F_0\left(x_{(i)}\right)\right\} \\ +\left(n-i+\frac{1}{2}\right)\log\left\{1-F_0\left(x_{(i)}\right)\right\}\end{array}\right]-n \quad (1)$$

## 4. Discussion

In Table 1, the weekly number of deaths from COVID-19 in OECD countries is modeled separately for 2021 and 2022.

**Table 1:** Distributions Modeling Weekly COVID-19 Deaths in OECD Countries for 2021 and 2022

| Countries | 2021 | 2022 |
|---|---|---|
| Chile | Weibull | Log-logistic |
| Colombia | Weibull | Log-logistic |
| Costa Rica | Weibull | Tip 1 Half Logistic |
| Greece | Weibull | Gamma |
| Italy | Weibull | Log-logistic |
| Türkiye | Weibull | Tip 1 Half Logistic |
| Iceland | Lindley | Weibull |
| New Zeland | Lindley | Tip 1 Half Logistic |
| Australia | Tip 1 Half Logistic | Weibull |
| Austria | Tip 1 Half Logistic | Log-logistic |
| Belgium | Tip 1 Half Logistic | Log-logistic |
| Estonia | Tip 1 Half Logistic | Log-logistic |
| Finland | Tip 1 Half Logistic | Gamma |
| Japan | Tip 1 Half Logistic | Weibull |
| Latvia | Tip 1 Half Logistic | Log-logistic |
| Lithuania | Tip 1 Half Logistic | Tip 1Gen.Half Logistic |
| Luxembourg | Tip 1 Half Logistic | Tip 1 Half Logistic |
| Slovenia | Tip 1 Half Logistic | Log-logistic |
| Israel | Tip 1Gen.Half Logistic | Log-logistic |
| Holland | Tip 1Gen.Half Logistic | Gamma |

| | | |
|---|---|---|
| Norway | Tip 1Gen.Half Logistic | Weibull |
| Switzerland | Tip 1Gen.Half Logistic | Log-logistic |
| Canada | Log-logistic | Tip 1 Half Logistic |
| Denmark | **Log-logistic** | **Log-logistic** |
| Ireland | Log-logistic | Gamma |
| Korea | **Log-logistic** | **Log-logistic** |
| Mexican | **Log-logistic** | **Log-logistic** |
| Portugal | Log-logistic | Gamma |
| Spain | **Log-logistic** | **Log-logistic** |
| Sweden | **Log-logistic** | **Log-logistic** |
| United Kingdom | Log-logistic | Weibull |
| Czech Republic | Gamma | Tip 1Gen.Half Logistic |
| France | Gamma | Log-logistic |
| Germany | **Gamma** | **Gamma** |
| Hungary | Gamma | Log-logistic |
| Poland | Gamma | Log-logistic |
| Slovakia | Gamma | Log-logistic |
| Unit. States of America | Gamma | Log-logistic |

In all nations with the exception of Denmark, Korea, Mexico, Spain, Sweden, and Germany, it has been noted that the distributions simulating the weekly number of deaths from COVID-19 have changed (Figure 1). In general, it has been determined that the number of weekly deaths would rise in 2022.

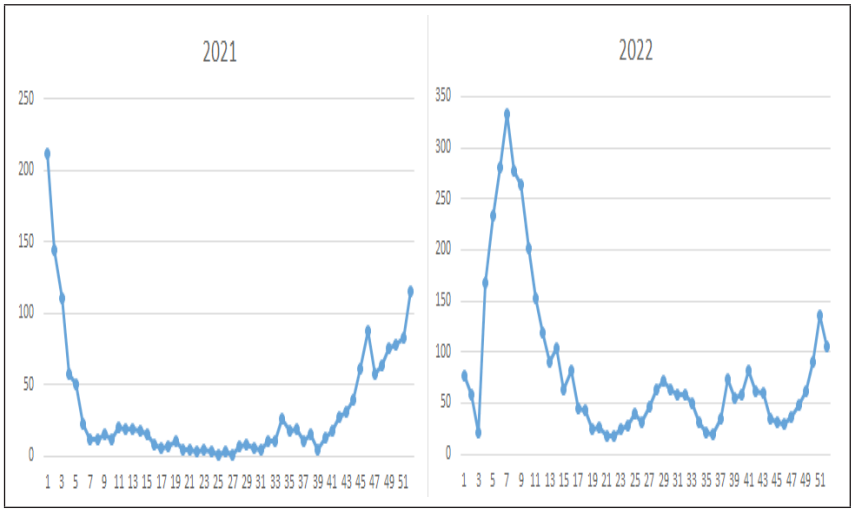


**Figure 1.** Weekly Covid-19 Death Numbers For Denmark in 2021 and 2022

For instance, while the weekly death toll for Italy in 2021 complied with the Weibull distribution (Figure 2), it complied with the log-logistic distribution in 2022 (Figure 3), indicating that different types of distributions are more suitable for the statistical modeling of the death toll for both years. Weibull distribution modeling for 2021 reveals that the weekly death rate fits this distribution more closely, that these data represent the distinctive characteristics of the Weibull distribution, and that the distribution makes sense of the data. It may be concluded that the data for this year can be more effectively described or predicted using the Log-Logistic distribution than with the Weibull distribution since it complies with the Log-Logistic Distribution for 2022. These variations show that the distribution of fatalities in the two years varied, and statistical models were modified to account for these variations. The sort of distribution that best explains or forecasts the data is chosen using statistical modeling.

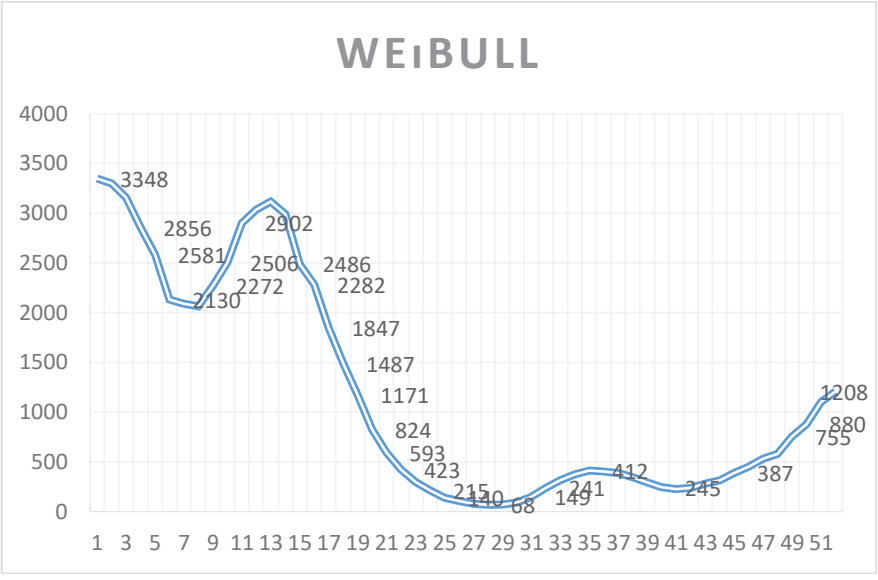


**Figure 2.** Weekly covid-19 death numbers for Italy in 2021

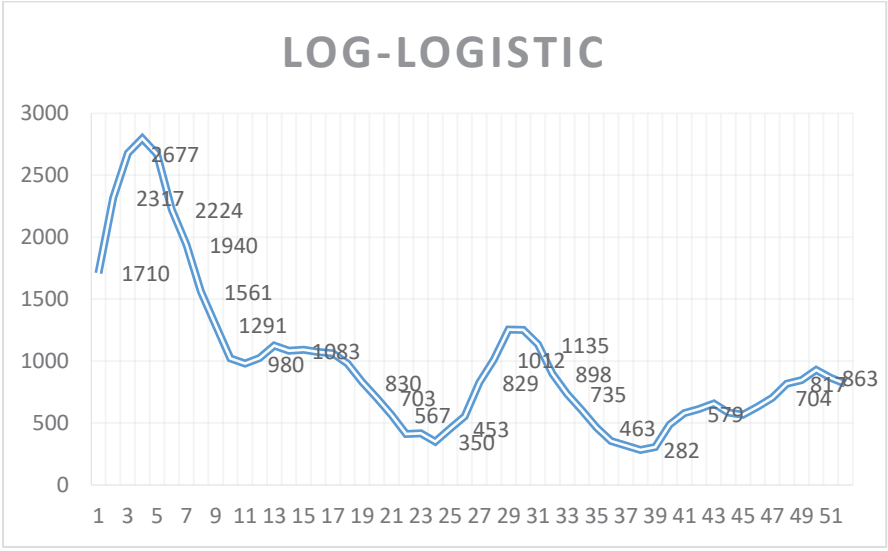


**Figure 3.** Weekly covid-19 deaths for Italy in 2022

When looking at Table 2's distributions of the OECD nations' weekly COVID-19 death rates for 2021, the countries are typically categorized as Weibull, Log-logistic, Type 1 Half Logistic, Type 1 Gen. It is clear that they are modeled using the Gamma and Half Logistic distributions. It is understood that the distributions listed in the table per nation are suitable for modeling weekly COVID-19 death numbers ($p>0.05$) and can be used to assess which theoretical distribution the COVID-19 death data fits with the Anderson-Darling test and to aid in model selection.

**Table 2:** Distributions and Goodness Of Fit Tests Modeling
The Weekly Covid-19 Death Numbers Of OECD Countries For 2021

| Countries | Distributions | AD Statistics | p value |
|---|---|---|---|
| Austria | Tip 1 Half Logistic | 0,8253 | 0,4625 |
| Belgium | Tip 1 Half Logistic | 1,0257 | 0,3437 |
| Canada | Log-logistic | 0,4454 | 0,8021 |
| Chile | Weibull | 1,7538 | 0,1262 |
| Colombia | Weibull | 1,8011 | 0,1187 |
| Costa Rica | Weibull | 0,3618 | 0,8851 |
| Czech Republic | Gamma | 2,047 | 0,0868 |
| Denmark | Log-logistic | 0,37 | 0,8773 |
| France | Gamma | 1,1285 | 0,2961 |
| Germany_ | Gamma | 0,5884 | 0,6582 |
| Greece | Weibull | 0,5417 | 0,7039 |
| Hungary | Gamma | 1,5302 | 0,1695 |
| Ireland | Log-logistic | 0,7586 | 0,5112 |
| Italy | Weibull | 1,5848 | 0,1576 |
| Japan | Tip 1 Half Logistic | 1,1425 | 0,2902 |
| Korea | Log-logistic | 0,7833 | 0,4926 |
| Latvia | Tip 1 Half Logistic | 0,4982 | 0,7479 |
| Lithuania | Tip 1 Half Logistic | 0,4946 | 0,7515 |
| Mexican | Log-logistic | 1,0939 | 0,3112 |
| Holland | Tip 1 Gen. Half Logistic | 0,7639 | 0,5071 |
| Poland_ | Gamma | 2,153 | 0,076 |
| Portugal | Log-logistic | 0,8844 | 0,4234 |
| Slovakia | Gamma | 1,7073 | 0,1341 |
| Spain | Log-logistic | 0,6578 | 0,5943 |
| Sweden | Log-logistic | 0,4189 | 0,8291 |
| Switzerland | Tip 1 Gen. Half Logistic | 0,6986 | 0,5593 |
| Türkiye | Weibull | 0,8349 | 0,4559 |
| Uni. Kingdom | Log-logistic | 0,9962 | 0,3589 |
| Unit. States of America | Gamma | 0,3095 | 0,9306 |

Examining Table 3's distributions for the OECD countries' weekly COVID-19 death rates for 2021 reveals that the nations are often modeled using Weibull, Log-Logistic, and Gamma distributions. The distributions listed

in the table by nation are suitable for modeling weekly COVID-19 mortality numbers ($p>0.05$), according to an evaluation of which theoretical distribution the COVID-19 death data matches with the Anderson-Darling test.

**Table 3:** Distributions and Goodness Of Fit Tests Modeling
The Weekly Covid-19 Death Numbers of OECD Countries For 2022

| Countries | Distributions | AD Statistics | p value |
|---|---|---|---|
| Australia | Weibull | 0,4263 | 0,8216 |
| Austria | Log-logistic | 0,577 | 0,6692 |
| Belgium | Log-logistic | 0,5799 | 0,6664 |
| Chile | Log-logistic | 1,5873 | 0,1571 |
| Colombia | Log-logistic | 0,8627 | 0,4374 |
| Czech Rep. | Tip 1 Gen. Half Logistic | 0,3995 | 0,8486 |
| Denmark | Log-logistic | 0,4546 | 0,7926 |
| Estonia | Gamma | 0,4267 | 0,8212 |
| Finland | Gamma | 0,7084 | 0,5511 |
| France | Log-logistic | 0,5108 | 0,735 |
| Germany | Gamma | 0,3328 | 0,9113 |
| Greece | Gamma | 1,4409 | 0,1913 |
| Hungary | Log-logistic | 0,5133 | 0,7325 |
| Ireland | Gamma | 0,4616 | 0,7854 |
| Israel | Log-logistic | 0,6229 | 0,6258 |
| Italy | Log-logistic | 0,2899 | 0,9453 |
| Japan | Weibull | 0,4708 | 0,776 |
| Korea | Log-logistic | 0,6265 | 0,6225 |
| Latvia | Log-logistic | 1,3223 | 0,2252 |
| Mexican | Log-logistic | 0,8788 | 0,427 |
| Holland | Gamma | 0,9585 | 0,3793 |
| Poland | Log-logistic | 1,5753 | 0,1596 |
| Portugal | Gamma | 1,5288 | 0,1698 |
| Slovakia | Log-logistic | 1,2639 | 0,2443 |
| Slovenia | Log-logistic | 0,4153 | 0,8328 |
| Spain | Log-logistic | 0,6071 | 0,6405 |
| Sweden | Log-logistic | 0,5142 | 0,7316 |
| Switzerland | Log-logistic | 0,6876 | 0,5685 |
| United States of America | Log-logistic | 3,0907 | 0,0248 |

While this study helped us understand the differences and similarities between countries, it also contributed to our better understanding of the effects of the COVID-19 outbreak on death rates. It also constitutes an important resource in terms of establishing health policies and increasing the capacity of health systems. It is to provide a useful roadmap for researchers, health policy makers and health professionals who want to analyze the effects of COVID-19 on health systems and be better prepared for similar situations in the future. It can also help us take steps to improve healthcare and protect communities by better understanding the impacts of epidemics.

## 5. Conclusion

The conclusions drawn through data modeling and analysis provide crucial information for comprehending the pandemic's consequences over the past two years and developing future health policy. This study aims to use statistical distributions to examine the weekly death rates in OECD nations during the COVID-19 pandemic in 2021 and 2022. First of all, death trends during various times of the COVID-19 outbreak were shown by the findings of statistical modeling. Important details concerning the pandemic's peaks and troughs, seasonal variations, and its trajectory were revealed by this investigation. Additionally, the use of several statistical distributions for both years showed regional disparities and the variety of the pandemic's dynamics. These outcomes, which are country-specific, are a reflection of variations in regional health systems and response tactics. In order to prepare for such crises in the future, it is crucial to recognize these distinctions amongst nations. The study's conclusion highlights the value of statistical modeling in examining how the COVID-19 pandemic has affected healthcare services and developing pandemic management measures. The results show that in order to make effective plans, the health sector's existing state should be assessed. We can better prepare for future health catastrophes by using these analyses as a resource for health policymakers, medical experts, and academics.

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CHAPTER XVII

# UNDERSTANDING SHOCK: PATHOPHYSIOLOGY AND CURRENT APPROACH IN THE EMERGENCY DEPARTMENT

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## 1. Introduction

Shock is a condition of circulation failure, which emerges as a result of a circulatory pathology between life and death secondary to an underlying etiology (1). This condition occurs not as a disease but with underlying causes' effects on the whole circulation system. The requirements of the whole body that have to be transported by the circulation system do not reach the tissues, and therefore, this is a process with a high probability of morbidity and mortality resulting from organ, tissue, cell, and cell organelles dysfunction, or the selection of alternative pathways (2). As compensatory mechanisms cover up the first stages of shock, and there is no clear consensus in identification, mortality can be seen to be high in patients with shock both in hospital and after discharge even if the underlying etiology is established, because of insufficient support and treatment. The in-hospital mortality rates have been reported to be 26% for septic shock, 39-48% for cardiogenic shock, and <20% for neurogenic

shock and spinal cord injuries (3, 4). A patient with shock can present with different clinical symptoms depending on age, comorbid diseases, response to compensatory mechanisms, the patient status before this condition, one or more underlying etiologies, and the stage of shock. This prevents the identification of shock with universal clear rules. Although management is obvious and easy in a patient with evident shock appropriate to the universal recommendations, close follow-up of a patient with suspected shock and the initiation of appropriate treatment at stages that may be overlooked or ignored by the clinician will have a valuable effect on survival (5).

As the shock is basically a circulation disorder, the treatment principles are similar if the condition can be recognized. The circulation system is fundamentally formed of the cardiac and vascular systems. Therefore, it is important to know this system and how it works to be able to understand shock. The heart functions as a pump in the circulation system. For vascular structures, circulation can be disrupted by three different mechanisms. These are impaired permeability, blockage, and tears of the vessels (4). A final mechanism can be roughly defined as insufficient fluid carried by the vessel without any vascular pathology (Table 1).

Shock is the response to insufficient circulation in the body, which is provided through various mechanisms. It is the process of using systemic defense mechanisms to avoid death. This response usually occurs with the emergence of a sympathetic activation response supporting the circulation (4). The sympathetic activation response has the effect of increasing blood pressure and heart rate. It starts rapidly, continues until the condition recovers, and is then quickly terminated (4).

**Table 1.**

| **Types of Shock according to the underlying pathology** | |
|---|---|
| The heart cannot sufficiently perform the pump function | Cardiogenic shock |
| Conditions that increase vascular permeability | Distributive shock |
| Conditions related to blockage of the large vessels (thrombus or emboli) | Obstructive shock |
| Conditions that disrupt vascular integrity or decrease the amount of fluid in circulation | Hypovolemic shock |

The sympathetic response can occur through several mechanisms. When the condition does not improve, the body tries to keep circulation in

the central organs to be able to survive, starting from the peripheral tissues until a status is achieved which will provide blood circulation to the vital organs. During this process, irreversible tissue ischemia and organ failure can occur depending on which stage the shock is in. Even if mortality is avoided in shock for which timely intervention is not made, permanent damage can occur in other organ systems, including the kidneys, liver, heart, and ultimately the brain.

## 2. Shock in the Emergency Department

Although shock is the strongest of the human protective mechanisms on the road to death, it must be kept in mind that death is inevitable when this stimulus is not recognized or this mechanism to avoid death is not supported. The human body is a mechanism that tries to continue existing with many different internal and external stimuli or effects. One of the most important functioning mechanisms of this dynamic mechanism is the conduction of oxygen to mitochondria which is related to the transformation of this oxygen to energy by the mitochondria (6). Although there is an undeniable presence of substances used as nutrients in this energy transformation, the most important mechanism for the body, which has nutrient stores, is a form of oxygen transmission to tissues. Shock is the stage at which this transmission is disrupted and that the body tries to tolerate, but may not always be fully successful without an external effect. By very rapidly giving an alarm response to hypoxia, mitochondria respond by starting a lactic acid cycle from non-oxygenated respiration instead of oxygenated respiration and this causes the triggering of a series of chemical processes that can lead to secondary damage (6).

Although shock is a condition that requires correction, it must be kept in mind that this is not a disease but the development of a response to a pathology in the cardiac-vascular system, and if the body cannot treat itself on this path to death, seeing it as a process that starts by sacrificing some organs to maintain life will provide a better understanding of the shock-death relationship and better planning of the treatment steps.

With respect to factors specific to the Emergency Department (ED), there is a benefit in stating that almost all the pathways to death are connected to circulation problems. All the pathologies that cause vascular blockages, tears, and permeability problems, and cause pump dysfunction of the heart are common causes of death in the ED. Therefore, recognizing shock in the ED and

knowing the stages, types, and treatments, means that the clinician can focus with all strength on survival (Table 2).

### 3. The Pathophysiology of Shock

Understanding the pathophysiology of shock goes beyond understanding that circulation failure is formed from a series of effects and responses due to failure of local and substrate presentation (4). For circulation to become ineffective, there are four main different mechanisms (7). The primary of these is that the heart cannot undertake the pump function. Each etiology that can disrupt the contractility of the heart will be a cause of increasing the initial burden by blood not being sent to the peripheries and pooling within the ventricles. In the continuing processes, obstructive conditions, which will be classified later, become involved which block the vascular structure and prevent blood from going to the peripheries even if the pump function can perform adequately (8). Another pathophysiology is an increase in vascular permeability so that the blood cannot be kept within the vessel for infective, anaphylactic, neurogenic, or other reasons.

**Table 2**

| Diseases frequently seen in the Emergency Department that can be a Cause of Shock | |
|---|---|
| • Acute myocardial infarctus<br>• Cardiomyopathies<br>• Heart valve diseases<br>• Cardiac arrhythmias<br>• Cardiac tamponade<br>• Pulmonary emboli<br>• Pericarditis<br>• Hemorrhage<br>• Trauma<br>• Ileus<br>• Severe burns<br>• Severe vomiting | • Anaphylaxis<br>• Surgical operations<br>• Chronic diseases<br>• Hyperinsulinemia conditions<br>• Central nervous system pathologies<br>• Dissections<br>• Aneurysm ruptures<br>• Oral intake disorders<br>• Intoxication<br>• Conditions disrupting water retention in the kidneys<br>• Infections<br>• Severe diarrhea |

The vessel creates a response, either secreted in the body or with stimulation of the vessel by an external stimulus, by increasing permeability,

and this response causes severe fluid extra-vascular leakage and becomes a barrier to the substrate required to reach all the tissues. Whether or not there is a different underlying reason for this condition, a hypovolemic shock-like status is formed, but the difference is that unlike vascular injury occurring in trauma or from insufficient oral intake, it is related to fluid leakage from all the vessels in the body. Finally, disorders occur due to hypovolemia. Shock associated with trauma or oral intake disorders can be examined in this group. The extra-vascular volume from vessels injured in trauma decreases the volume of the whole system, and even if the pump and vascular system are working, it will result in the volume being sent to the periphery not being sent in an effort to maintain the central organs.

Hypovolemia occurring due to oral intake disorders leads to an increase in blood viscosity and the fragmentation of blood products in the periphery or organs such as the spleen, and ultimately results in hypoxia and failure in the transmissions of substrate products. Although the treatments of all these systems contain fundamental differences, the process acts as a common pathway and the response develops in a similar way (Table 3).

**Table 3**

| **Shock Types and Pathophysiology** | | | |
|---|---|---|---|
| **Type** | **% Frequency** | **Hemodynamic change** | **Etiology** |
| Distributive | 33-50 | SVR and PL decrease, CO mix | Sepsis, neurogenic shock, anaphylaxis |
| Hypovolemic | 31-36 | PL and CO decrease, SVR increase | Bleeding, capillary leakage, GI losses, burns |
| Cardiogenic | 14-29 | PL, AL, SVR increase, CO decrease | MI, arrhythmias, heart failure, valve disease |
| Obstructive | 1 | PL and CO decrease, SVR increase | PE, pericardial tamponade, tension PTX |

**PL:** pre-load; **AL:** after load; **CO:** Cardiac output

The sympathetic system is activated when the carotid baroreceptor contraction reflex is reduced. The activated sympathetic system causes arteriolar vasoconstriction providing redistribution of the blood in the skin,

musculoskeletal system, kidneys, and splanchnic system (9). Arteriolar vasoconstriction immediately increases heart rate and contractility. If circulation does not come to a level that will prevent stimulation of baroreceptors, venous vessel constriction starts to increase venous return. Epinephrine, norepinephrine, corticosteroids, and dopamine expression are started for arteriole and venous contraction. If competence cannot be provided, anti-diuretic hormone expression is started to activate the renin-angiotensin-aldosterone system to protect the volume, and thus sodium and water retention come into effect (10).

The compensatory mechanisms use only a mechanism established to provide central (heart and brain) oxygenation. The blood circulation of all other systems in this mechanism can be ignored when necessary (11). The presentation of less oxygen causes less energy to be produced (adenosine-3-phosphate), disrupting the ion channels, intracellular sodium, and extracellular potassium leakage, causing reduced resting potential. If this is not corrected, homeostasis in the progressing shock process is impaired and this results in cell death. The systemic effects of this lead to hyponatremia, hyperkalemia, hyper-hypoglycemia, and lactic acidosis with lactate dehydrogenase activity through an alternative energy production pathway (Figure 1).

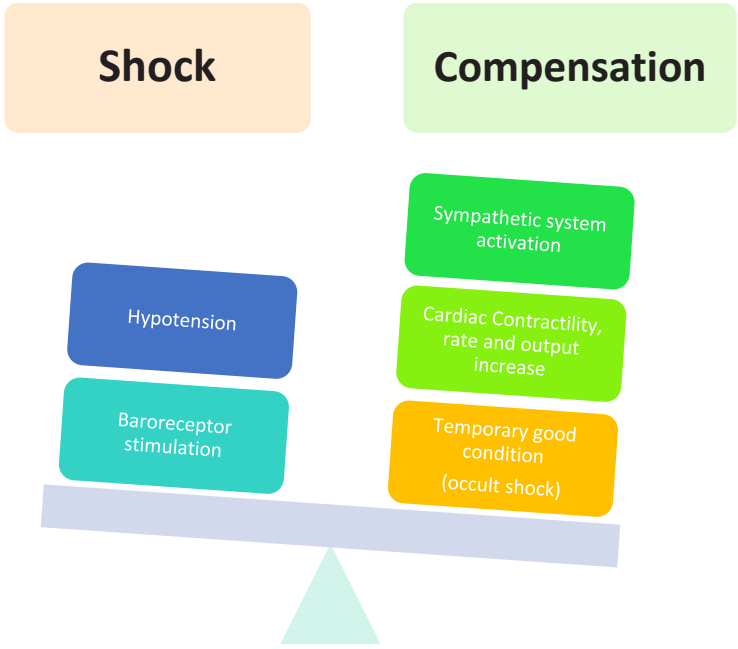


**Figure 1**

Consequently, the body activates other mechanisms to try to correct all these mechanisms that have emerged (Figure 2) and despite already insufficient oxygenation, tachypnea occurs to compensate for lactic acidosis. Decreasing carbon dioxide due to respiratory arrest, increasing hyperkalemia due to myocardial depression, deepening hyponatremia due to clouded consciousness and cell death, and mediators expressed from fragmented cells may be reasons for the increase in permeability. Shock progressing to this point has gone beyond the easy management at previous stages of fluid resuscitation, inotropes, or for other reasons, and will require a focus on more complicated treatments. Therefore, it is critical to recognize shock, to learn pathophysiology when treating a shock patient, to treat the underlying etiology not just with fluid therapy, and not to have the approach of simple hyperkalemia treatment or hyponatremia treatment but to predict from what stage of the condition it will progress to disseminated intravascular coagulation (12). Consideration of electrolyte deficiencies, acidosis, and hypoxia that can occur at every stage in the differential diagnosis is also extremely important with respect to being able to decide whether the condition originates from shock or another condition and to be able to apply the correct treatment.

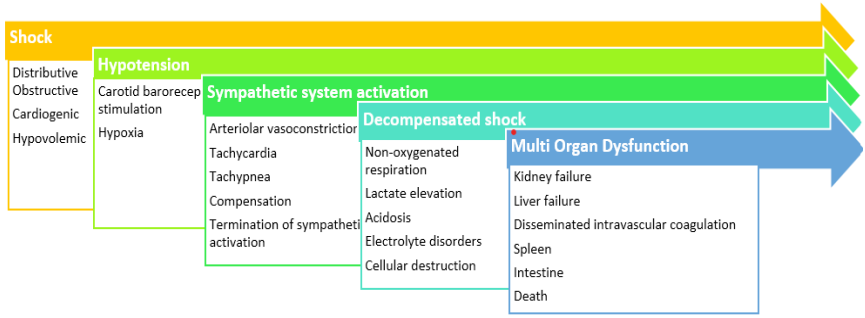


**Figure 2**

## 4. The Diagnosis and Grading of Shock

There are many stages and classifications of shock. Although there are differences between shock types at certain points, as it is fundamentally a circulation problem, the outcomes are similar. This is significant with respect to some values indicating shock which can be examined bedside. Body temperature, heart rate, systolic blood pressure, diastolic blood pressure, pulse pressure, mean arterial pressure, central nervous system findings, skin, and capillary circulation,

some cardiovascular systems, and some respiratory systems can be indicators of shock and the stage while at the patient bedside or of progression to shock (Table 4). All the laboratory findings that can indicate hypoxia, lactic acidosis, and procalcitonin together with infective parameters and hypovolemia on USG imaging bedside can be seen as warnings of shock. However, despite all these data, it may not be possible to understand that a patient in the compensatory stage is in shock (9). The best diagnostic tool for shock is the experience of the clinician to be able to arrive at a decision by evaluating the current status of the patient holistically with a good anamnesis. Although cardiogenic or obstructive shock is easily recognized as the characteristics can be differentiated from others with more definitive limits, the diagnosis and etiology of hypovolemic or distributive shock are not always easy. In a patient at the compensated (occult) stage with no shock findings, no mechanism has yet been established that can predict progression to septic shock, and it is therefore dependent on the experience of the clinician (4).

In a patient with suspected hypovolemia or trauma, it will be useful to evaluate USG volume. Obstructive or cardiogenic shock can be considered in a patient with a shock status and no volume failure. Although a scientific differentiation cannot be made, if shock is separated into two in the first stage, a simple classification is possible as hypovolemic and hypervolemic shock or normovolemic shock. In a patient with hypovolemia on USG, distributive or hypovolemic shock can be considered, and when hypovolemia is not determined on USG, obstructive or cardiogenic shock can be considered. Findings can be determined on USG which will differentiate cardiogenic and obstructive shock, and the absence of trauma or anaphylaxis in a hypovolemic patient can indicate septic shock. If trauma or distributive shock is not considered in a patient with hypovolemia, other hypovolemic causes can be considered.

Shock can be basically classified in two different ways; the first is according to the etiology and the second is according to the pathophysiology. Etiological classifications are more complex and similar treatment approaches are separately recommended. Therefore, it will be easier to understand the approach to shock by gathering the pathophysiology and similar treatment under main headings, and categorizing sub-headings specific to these main headings. Shock is gathered into four main groups according to the pathophysiology. The circulation system is basically formed by the heart, which functions as a pump, the vessels, and the blood circulating within the

vessels. When there is no other barrier to the pump function of the heart, the shock occurring because of dysfunction is said to be cardiogenic shock (13). The most evident examples of pathologies impairing cardiac muscle contractability are acute myocardial infarctions, myocarditis, heart failure, and dysrhythmias (14).

The shock occurring with insufficient blood circulating in the vessels is said to be a hypovolemic shock (15). Hemorrhagic shock occurring secondary to trauma is also dealt with in this group (15). Shock occurring with a barrier to the pump function of the heart by a thrombus or with an effect from outside the vessels and heart is obstructive shock (16).

Although obstructive shock and cardiogenic shock show similarities to each other, there is no primary problem related to heart contractions of the heart in obstructive shock. When the heart cannot perform because of an obstruction in the middle of the pump function, circulation is impaired. Although rare, examples can be given of an obstruction formed by large arterial thrombi such as massive pulmonary emboli or pressure forming on the vascular structure, such as a tension pneumothorax, or cardiac tamponade restricting contractility and relaxation by surrounding the heart (17). Finally, distributive shock is caused by all the etiologies that increase vascular permeability. Septic shock, neurogenic shock, and anaphylaxis are dealt with in this group (18). Within this group, it is especially important that there is no pathology in the pump function of the heart, the volume in the body, or at any stage of the circulatory system, that can be recognized and corrected more easily than others and is seen more frequently.

In the mechanism of cardiogenic shock, as there is no pathology related to the vascular structure or volume and there is a single pathology of the heart in the circulation system, there will be an increase in the afterload (AL) of the heart.

**Table 4**

| Compound Physical Examination Findings in Shock | |
|---|---|
| Fever | Hyperthermia or hypothermia may be present. Endogenous hypothermia (hypometabolic shock) must be differentiated from exogenous environnmental hypothermia. |
| Heart rate | Generally high; but because of hypoglycemia, the use of ß-blockers and pre-existing heart disease, paradoxical bradycardia can be seen in shock conditions. |
| Systolic blood pressure | As cardiac contractility increases in early shock, it can slightly increase and then decrease as shock progresses. |
| Diastolic blood pressure | This is associated with arteriolar vasoconstriction, and may increase in the early stage of shock then may fall when cardiovascular compensation is not successful. |
| Pulse pressure | It increases in the early stage of shock then decreases before systolic pressure starts to fall. |
| Mean arterial blood pressure | Generally <65 mm/hg |
| Neurological findings | Acute delirium secondary to a decrease in cerebral perfusion pressure, agitation, disorientation, confusion, and coma. |
| Capillary filling | There may be pallor, blackening/bruising, cyanosis, sweating, cold, and capillary filling time >2-3 seconds. |
| Cardiovascular system | Decreasing coronary perfusion pressures can cause ischemia, decreased ventricular compliance, increased left ventricle diastolic pressure, and pulmonary oedema. Swelling or flattening in the neck vessels associated with the type of shock. Tachycardia and arrhythmia. |
| Respiratory system | Tachypnea, increased ventilation per minute, dead space, bronchospasm, and hyper or hypocapnea progressing to respiratory failure. |
| Splachnic organs | Ileus, GI bleeding, pancreatitis, and mesenteric ischemia may develop because of low perfusion. |
| Renal | Decreased glomerular filtration rate. Renal blood flow leads to oliguria by redistributing from the renal cortex to the renal medulla. |
| Metabolic | Lactic acidosis, hyperglycemia, hypoglycemia, and hyperkalemia. As shock progresses, metabolic acidosis forms together with respiratory compensation. |

Another reason for the dysfunction of the heart pump is that pre-load (PL) will increase due to left ventricle diastolic end volume pooling. Systemic vascular resistance (SVR) will increase to be able to send blood to the periphery due to normal vascular structure and contractility (19).

Cardiac output (CO) refers to the amount of blood pumped per minute by the ventricles. If tachycardia develops due to the shock response formed to be able to send more oxygenated blood to the periphery, the increased PL and AL may not be sufficient to pull CO back to normal and CO will decrease (20, 21). Although the distributive character of cardiogenic shock is not clear, blood starting to pool due to circulation not being able to fulfill the pump function of the heart will cause the rapid development of an inflammatory response and will emerge as a septic response.

In hypovolemic shock, PL will decrease due to a reduction in the volume returning to the heart as the volume within the vessels is reduced. To increase this reduced PL, SVR will increase as a response, and CO will again remain insufficient.

In obstructive shock, blood cannot be sent to the periphery as it cannot sufficiently overcome the obstruction in front of the heart. This causes reduced venous return, which in turn causes decreased PL, increased SVR as a response, and a decrease in CO. When the obstruction in front of the heart is not removed, an improvement in the shock condition cannot be expected.

There is evident systemic vasodilatation in distributive shock. The extravascular volume leakage due to this causes systemic hypovolemia, which then prevents the formation of SVR as a response to the mechanism leading to vascular permeability. In the first stages, tachycardia and increased cardiac contractility occur as a response to decreased SVR, and with the existing volume in circulation, CO may increase or be kept within normal limits. If the condition is not corrected, greater volume leaking extra-vascularly on every heartbeat causes a decrease in CO with the greatly reduced PL, reduced AL, and the already reduced SVR. When this status occurs, temporary cardiomyopathy can form in patients and this is closely associated with mortality (22).

Although a patient can be said to be in shock when there is an evident shock condition, it is almost impossible to say that a patient is in shock when at the cryptic stage or the sympathetic response has only just started. No laboratory test, vital signs, or imaging method can state that a patient is not in shock. Shock is a condition that should be predicted by combining the examination of the underlying etiology, clinical experience, physical examination, and anamnesis.

***Laboratory:*** No laboratory test is sufficiently sensitive or specific for shock. Tests can be requested according to the underlying etiology or the current shock status. Lactate is associated with hypoxia (increased anaerobic energy production activity) and mortality in all shock types (23). The normal value is expected to be <2.0 mmol/L and increased levels of >4 mmol/L may be associated with mortality (24, 25). At advanced stages of shock, poor kidney and liver function test results can be a warning that the shock has deepened and has entered a critical stage (Table 5).

***Imaging:*** All imaging methods can be used in the differential diagnosis of shock and/or to reveal the etiology. Ultrasonography (USG) can be used to evaluate the volume status in suspicious cases and/or to differentiate underlying conditions in hypovolemic and non-traumatic patients (26). USG can show cardiac contractility, cardiac tamponade, pneumothorax, some septic foci, aortic dissection, and intra-abdominal free fluid in trauma cases. Findings of right-side insufficiency may indirectly reveal signs of massive pulmonary embolism (26).

In shock which is identified early and treatment is started early, survival rates are greatly increased. Despite aggressive treatment for shock which can only be determined at late stages, the patient may not respond to treatment, and therefore patients may be lost. Although there are differences in the cause and early stages of shock, advanced stage shock can be graded and it can be understood at which stage it is from the current condition (Table 6).

***Pre-shock(cryptic or occult) stage:*** This is the stage at which shock has been compensated for by the activation of compensatory mechanisms, and significant organ damage or hypovolemia may not yet be observed. To be able to make a diagnosis at this stage requires the clinician to take a suspicious approach in the true sense. The increase in heart rate at this point, and the mechanisms increasing cardiac contractility and SVR, other than septic shock, protect the body oxygenation. Successful resuscitation of a patient at this stage achieves survival and the prevention of organ damage.

***Shock stage:*** This is the critical stage at which tissue hypoxia starts as a result of compensatory mechanisms remaining insufficient. A decrease in pulse pressure, hypotension, tachypnea, oliguria, and changes in consciousness start to be seen at this stage. Ischaemia in one or more organs can also be seen at this stage. Peripheral circulation deteriorates and an irreversible process at the cellular level starts. Compared to the pre-shock stage, this is the stage at which morbidity significantly increases.

***Multi-organ failure:*** At this stage, several organs progress to ischemia at the same time. Cell death starts in the heart and all other organs. This is

the stage at which coma and death are usually seen. Cell membrane integrity is impaired because of an advanced degree of impaired oxygenation, and the mediators emerging due to cell fragmentation further deepen shock, and the condition enters a vicious circle. This stage is the irreversible stage of shock.

**Table 5**

| The First Diagnostic Examinations for Evaluation of a Patient in Shock | |
|---|---|
| Cultures: blood, urine, suspicious wounds, quantitative expectorant culture | Hemogram |
| Cortisol level | Electrolytes, glucose, calcium, magnesium, phosphorus |
| Pregnancy test | BUN, creatinine |
| Anamnesis, chest-abdomen-pelvis CT as indicated by physical examination | Lactate |
| Clotting studies: prothrombin time, PTT, INR | ECG |
| Arterial blood gas (pH, carbon dioxide and oxygen levels, base deficit) | Full urine analysis |
| Hepatic function panel | PA pulmonary radiograph |

**Table 6**

| Markers | Stage I | Stage II | Stage III | Stage IV |
|---|---|---|---|---|
| Fluid/blood loss (ml) | 0-750 | 750-1500 | 1500-2000 | > 2000 |
| Fluid/blood loss (%) | 0-15 | 15-30 | 30-40 | >40 |
| Pulse/min | <100 | 100-120 | 120-140 | >140 |
| Systolic pressure | Normal | Normal | Decreased | Decreased |
| Pulse pressure | Normal/increased | Decreased | Decreased | Decreased |
| Respiratory count/min | 14-20 | 20-30 | 30-35 | > 35 |
| Urine output (ml/hour) | >30 | 20-30 | 5-15 | Almost none |
| Mental status | Slightly anxious | Anxious | Anxious and lethargic | Lethargic and confused |

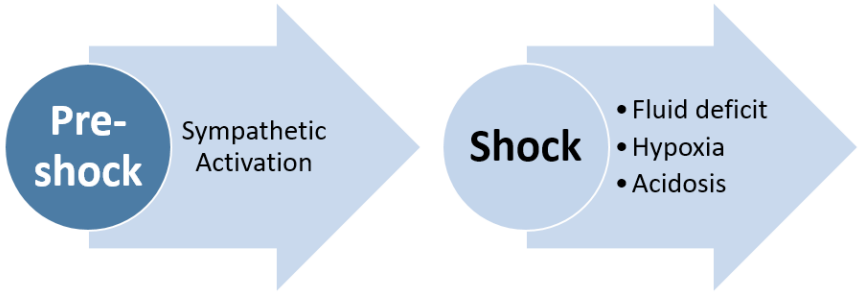


**Figure 3**

### 5. Shock Treatment

Although there are continual advances in shock treatment, there are no very strict rules for treatment (17). However, it has been shown that even in shock status, morbidity and mortality can be significantly reduced with 6 hours of follow-up and treatment applied in the Emergency Department (ED).

Shock treatment in ED is formed of steps A-E; A: airway- protecting the airway, B: breathing-providing respiration, C: circulation- optimizing circulation, D: delivery- optimizing respiration, E: end-terminating resuscitation.

***Airway preservation:*** Although the airway is best preserved with endotracheal intubation, a positive-pressure balloon reduces PL and CO, and the agents used for intubation can depress the myocardium and cause a drop in blood pressure, and this can lead to a worsening of the whole condition because of hemodynamic collapse. To avoid this situation, intubation should be performed when the hemodynamic status has become more stable with the use first of fluid resuscitation and vasoactive agents (9).

***Respiration Control:*** If hypoxia has not been able to be avoided in shock and auxiliary respiratory muscles have been activated together with tachypnea, then respiration should be controlled mechanically (27). The auxiliary respiratory muscles consume a high degree of energy and oxygen, and this causes a deepening of lactic acidosis. By intubating the patient, the respiratory activity becomes mechanical, which means that sedation is provided, sufficient oxygen is provided, and supported, reliable, and rhythmic respiration is achieved, and this brings hypercapnia under control. To be of significant benefit to survival, there must be no hesitation at this stage and respiratory activity should be brought under control in the correct way. Improvement in the condition and the acid-base balance must be followed up with arterial blood gas monitorisation.

At the moment when it is noticed that a patient has entered acute respiratory distress syndrome (ARDS), muscle contractions must be rapidly brought under control with neuromuscular blocking agents to suppress the deficit in energy and oxygen used by the auxiliary respiratory muscles to protect the organs. The pre-intubation ventilation values should be taken as the basis for the mechanical ventilation settings of the patient.

***Circulation optimization- Fluid resuscitation:*** When providing hemodynamic stability, one of the most important steps is fluid resuscitation. Peripheral access for two large cannulas should be opened on the admission of the patient or when the shock is detected. Although the supine position or Trendelenburg position shows no effect on cardiac performance, they should not be applied because of the aspiration risk. Fluid resuscitation is indicated for a patient with improved blood pressure or CO when the legs are passively raised above heart level. With the exception of cardiogenic shock with pulmonary edema, there is a relative or absolute fluid deficit in almost all shock conditions.

Fluid resuscitation is started with 0.9% NaCl. There is no significant superiority of lactate ringer solution, which is a balanced crystalloid, in shock conditions. A total of 500-1000 ml 0.9% NaCl is given rapidly within 5-20 mins to patients with shock. Lactate ringer can be given to patients with a severe fluid deficit to avoid hyperchloric acidosis. In patients with moderate fluid deficit, fluid can be started at 20-30 ml/kg/hour. In patients with gastrointestinal losses, vomiting, and Cl loss with diuretics, 0.9% NaCl should be selected first. The fluid requirement of patients can be followed up with urine output (Table 7).

***Fluid Resuscitation-Vasopressors:*** These should be used when fluid treatment is not sufficient or when the volume load of the patient is normal, and are most effective in these situations. While there is a volume deficit in the body, the use of vasopressors has almost no efficacy.

However, it is known that vasopressors can cause more severe kidney damage in patients with chronic hypertension than in normal conditions. Even if there is a significant perfusion pressure increasing effect of vasopressors on large vessels, it must be kept in mind that there could be ischaemic effects on the gastrointestinal system and the kidneys, and if more than one vasopressor is started, it will be necessary to reduce the drugs when it is understood which is the most effective.

**Table 7:** Resuscitative Fluids

| Resuscitative Fluids | |
|---|---|
| **Crystalloids** | |
| Normal Saline (NS) | Mildly hyperosmolar containing 154 mEq/L sodium and chloride. There is a risk of hyperchloremic metabolic acidosis when given in large amounts because of the relatively high chloride concentration. |
| Ringer Lactate (RL) | Sodium 130 mEq/L, potassium 4 mEq/L, calcium 3 mEq/L, chloride 109 mEq/L, lactate 28 mEq/L. Lactate is accepted as a proton, and carbon dioxide and water then being metabolized by the liver, this leads to carbon dioxide being released in the lungs and water expelled by the kidneys. Compared to NS, RL creates a more advantageous tamponade of acidemia. There is a theoretical risk of renal failure because of the low potassium content (very small amount) or hyperkalemia in patients with renal failure. |
| Plasma-Lyte® | Balanced pH 7.4, sodium 140 mEq/L, chloride 98 mEq/L, potassium 5 mEq/L, magnesium 3 mEq/L, gluconate 23 mEq/L, acetate 27 mEq/L. |
| **Colloids** | |
| Albumin | It is obtained from human plasma at strengths varying from 4%-25%. Several studies have shown no difference in the outcome of using colloids or crystalloids. Colloids are significantly more expensive than crystalloids. In one study there was shown to be an increase in the mortality of trauma patients with head trauma. |
| Hydroxyethyl Starch | This is a synthetic colloid derived from hydrolysed amylopectin. These agents must be avoided in sepsis as there are several harmful effects; kidney failure at recommended doses and reduced long-term survival at high doses, clotting and bleeding complications due to decreased factor VIII and von Willebrand factor levels, and thrombocyte dysfunction. |

## Table 8

| Commonly Used Vasoactive Agents (all vasopressors increase myocardial oxygen demand; most must be titrated to the desired effect) | | | | | | |
|---|---|---|---|---|---|---|
| **Drug** | **Dose** | **Effect** | **Contractility** | **VC** | **VD** | **CO** |
| Dobutamine | 2-20 µg/kg/min | ß1, some ß2 and a1 at high doses | ++++ | + | ++ | Increases |
| Side-effects and comments | Only inotropes in hypovolemic patients cause tachyrhythmia, GI problems, and hypotension, and less peripheral vasoconstriction than dopamine, and less arrhythmia than isoproterenol. | | | | | |
| Dopamine | 0.5-20 µg/kg/min | a, ß and dopaminergic | At a dose of 2.5-5 µg/kg/min ++ | At a dose of 5-20µg / kg/min ++ | At a dose of 0.5-2 µg/kg/min + | Generally increases |
| Side-effects and comments | Tachydysrhythmias; cerebral, mesenteric, coronary, and renal vasodilators at low doses; great overlap with the second line of the Surviving Sepsis Campaign, a/ß/dopaminergic receptors and dose | | | | | |
| Epinefrin | 2-10 µg/min | a and ß | At a dose of 0.5-8 µg/kg/min ++++ | At a dose of >8 µg / kg/min ++++ | +++ | Increases |
| Side-effects and comments | Tachydysrhythmia causes leukocytosis; myocardial oxygen consumption increases, lactate can be increased, there is no real maximuum dose. | | | | | |
| Isoproteranol | 0.01-0.1 µg/kg/min | ß1 and some ß2 s | ++++ | 0 | ++++ | Increases |
| Side-effects and comments | Inotrope; causes tachydysrhythmia, face reddening, and hypotension in hypovolemic patients; myocardial oxygen consumption increases | | | | | |
| Norepinephrine | 0.5-50 µg/min | a1 main effect, some ß1 | ++ | ++++ | 0 | Sightly increases |
| Side-effects and comments | It is useful when venous tonus loss is suppressed; it is the agent first used in most cases | | | | | |
| Fenilefrin | 10-200 µg/dk | Pure a | 0 | ++++ | 0 | Decreases |
| Side-effects and comments | Reflex bradycardia, headache, agitation, excitability, occasionally arrhythmia; it is used in patients in shock with tachycardia or supraventricular arrhythmia; relatively not good for septic shock | | | | | |
| Vasopressin | 0.01-0.04 IU/dk | Direct stimulation V1 receptor in smooth muscle | 0 | ++++ | 0 | 0 |
| Side-effects and comments | Primarily vasoconstriction; it is generally started at the maximum dose and is not titered, typically added to norepinephrine | | | | | |

**VC:** Vasoconstruction; **VD:** Vasodilatation; **CO:** Cardiac output

Vasopressors are time-saving drugs until effective treatment, and when perfusion pressure is increased, positive inotropes that will increase CO should be added to the treatment (Table 8).

***Providing sufficient oxygen:*** Pain, anxiety, cold treatment rooms, hyperadrenergic response, and physiological stress are all conditions that will increase the oxygen availability-consumption deficit of tissues. The oxygen consumption equation represents the balance between the oxygen supply and the oxygen demand of tissues. As far as possible, this balance in a patient in shock should not be kept at minus values. All conditions increasing the underlying oxygen consumption should therefore be brought under control and myocardial suppression should be avoided. Muscle relaxants, painkillers, anxiolytics, warm coverings, sedatives, and when necessary neuromuscular blockage should not be avoided. After obtaining hemodynamic stability, oxygen saturation should be >90%. To keep the hemoglobin level at ≥7 grams/dL in a patient with shock, erythrocyte suspension can be given. Lactate levels are of guidance in the follow-up after resuscitation, and the shock treatment method should be continued until lactate falls to a normal level. Although CO is useful in the follow-up of treatment, devices that can directly monitor CO are not usually found in ED, and the most practical method is follow-up of the treatment with lactate levels until the patient is transferred to the intensive care unit.

## 6. Conclusion

All types of shock are clinical conditions that lead to high mortality and require early and rapid intervention. Shock; It can be defined as the cardiovascular system's failure to meet the metabolic needs of the tissues. Absolute or relative hypovolemia is the main problem in shock cases. Choosing effective treatment, especially fluid replacement, is extremely important for these patients. Since shock is basically a circulatory disorder, the treatment principles are similar if the condition can be recognized. In order to understand shock, it is important to know this system and how it works. For this reason, all clinicians, especially emergency physicians, need to know the pathophysiology of shock and have up-to-date information in patient management.

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CHAPTER XVIII

# A DIFFERENT DIALOG BETWEEN BREAST CANCER CELL AND INSULIN RECEPTOR: FROM BENCH TO BEDSIDE

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## 1. Introduction

Insulin is a peptide hormone secreted by the β cells of the pancreatic islets of Langerhans, weighing 5.8 kDa. It maintains normal blood glucose levels by facilitating cellular glucose uptake, regulating carbohydrate, lipid and protein metabolism, and promoting cell division and growth with its mitogenic effects (1). Insulin secretion from beta cells begins with an increase in blood glucose levels. The effects of glucose on pancreatic cell metabolism, combined with the normal cholinergic effects of the autonomic nervous system, provide insulin secretion from beta cells. Important functions of insulin as an anabolic hormone; transmembrane transport of glucose and amino acids, glycogen formation in liver and skeletal muscles, conversion of glucose to triglycerides, nucleic acid synthesis and protein synthesis (2). The insulin gene is expressed in pancreatic beta islet cells, where insulin is synthesized and stored in granules before being released. The insulin gene is a gene containing 3 exons located on chromosome 11p15.5. Insulin is produced in the precursor form of proinsulin, which consists of a single chain of protein building blocks. The proinsulin chain

is formed by the cutting of two polypeptide chains (A and B), one consisting of 21 amino acids and the other 30 amino acids, linked by disulfide bonds to form insulin (3).

The term insulin resistance began to be used in the case of insulin overdose to correct hyperglycemia in some patients with the introduction of insulin therapy in 1922. Researchers named Himsworth and Carr used the term "insulin insensitivity" for the first time in 1936 to describe this condition, which manifests itself with an insufficient glycemic response to exogenous insulin in obese diabetics (4). Insulin resistance is a complex cellular disorder that affects many organ systems and causes severe metabolic defects. Insulin resistance, which has been showing a significant increase in recent years, is closely associated with obesity and is accepted as a strong precursor for type 2 diabetes (5,6). In a study, the body mass index (BMI) value of primary hypothyroid patients was found to be higher than those of subclinical hypothyroidism patients and the control group (7). Although the pathophysiology of insulin resistance is not clear, some molecular mechanisms are known to be involved (8). These; upregulation of protein tyrosine phosphatase 1B (PTP1B), inflammatory mediators and adipokines, increased free radicals, defects in insulin receptor substrate (IRS-1) phosphorylation, obesity and adipocytes, mitochondrial dysfunction, decreased capacity of insulin-binding receptors, glucose transporter type 4 (GLUT) -4) mutations and endoplasmic reticulum stress (9). Insulin resistance in hepatocytes increases the glucose level in the plasma due to decreased glycogen synthesis. This is accompanied by the inability to take up glucose in skeletal muscle and adipocytes (8,10). Therefore, any problem in insulin signaling is associated with hyperglycemia, as cells cannot take up glucose. Therefore, insulin resistance is expressed as the strongest precursor for type 2 diabetes (10).

## 2. Insulin Receptors

The action of insulin begins with the binding of insulin to its receptor on the surface of the target cell membrane. Insulin is a powerful anabolic hormone that increases the synthesis of DNA, RNA and proteins in the target tissue. The basic functions of insulin have been elucidated at the molecular level in studies conducted to date (2). Insulin receptor is present in many different cells in the human body. In particular, the biological response of fat, liver and muscle cells to insulin occurs when insulin binds to its receptor in these tissues. Insulin receptors bind insulin rapidly, with high specificity, and an affinity that can recognize even at the picomolar level. IR, a tyrosine kinase protein found physiologically in all

mammalian tissues, is a membrane glycoprotein containing two protein subunits encoded by the insulin receptor gene (INSR) and is a member of the growth factor receptor family (11). The INSR gene is a gene with more than 120 kb and 22 exons located in the chromosome 19p13.3-p13.2 region. The 11 exons encoding the α subunit are distributed over an area of more than 90 kb, while the 11 exons encoding the β subunit are located in an area of approximately 30 kb. The 135,000 kda α subunit that binds the insulin molecule is larger and completely extracellular. The smaller 95,000 kDa β subunit and the α subunit are linked by disulfide bonds. The β subunit crosses the cell membrane from one end to the other and reaches the cytoplasm, and has tyrosine kinase activity that initiates specialized signaling pathways in the intracellular part (11,12).

IR is structurally similar to the Type I insulin-like growth factor receptor (IGF-IR) and regulates glucose metabolism in response to insulin stimulation. IR is a heterotetramer protein consisting of two extracellular subunits and two transmembrane subunits linked by disulfide bonds. It consists of 2 α-subunits located outside the cell and 2 β subunits that pass through the cell membrane and extend into the cell. After binding the ligand to the α-subunit, the intrinsic tyrosine kinase activity in the β-subunit is stimulated, resulting in an insulin response (13). The α-subunits present two different binding sites for ligands, a low-affinity site and a high-affinity site. Insulin first binds to the low-affinity region of one α-subunit and then to the high-affinity region of the other α-subunit. A second insulin molecule binds to both sites of the α-subunits, causing the first molecule to dissociate. After binding of ligands to α-subunits, the tyrosine kinase activity of β-subunits is triggered and subsequently, several intracellular proteins involved in cell metabolism, survival and growth are phosphorylated (14).

IR activates phosphotidylinositol-3 kinase (PI3K)/protein kinase B (AKT) and mitogen-activated protein kinase (MAPK) signaling pathways that regulate essential functions such as cell division, cell migration, cell proliferation, differentiation, metabolism and body growth (15). When insulin binds to the α-subunit of the IR in the cell membrane, tyrosine residues in the β subunits of the receptor are phosphorylated. IRS-1 and IRS-2 are activated by phosphorylating the tyrosine kinase. PI3K and guanine triphosphatase are stimulated by phosphate by active IRS-1 and IRS-2. PI3K phosphorylates the membrane lipid phosphatidylinositol 4,5-bisphosphate (PIP2) and converts PIP2 to phosphatidylinositol 3,4,5-triphosphate (PIP3). Phosphotidylinositol-dependent kinase (PDK-1/PDK-2), a serine/threonine kinase, is activated

by stimulation of PIP3. AKT is phosphorylated by PDK-1. Phosphating Akt mediates the upregulation of GLUT4 translocation, glycogen synthesis, protein synthesis, and fatty acid synthesis, as well as the inhibition of apoptosis and hepatic gluconeogenesis. Glucose is taken into the cell by binding GLUT4 to the cell membrane (16,17). AKT supports glycogen production by inhibiting glycogen synthase kinase 3 (GSK3). Forkhead box O1 (FOXO1) is the main target of AKT and affects energy homeostasis in the body. AKT inactivates FOXO1 in the liver by phosphorylation. FOXO1 migrates from the nucleus to the cytosol, suppresses glucose production in the liver and promotes cell survival in the heart (193). In contrast, MAPK phosphatase-3 (MKP-3) dephosphorylates FOXO1 at pSer256 and stimulates the nuclear translocation of FOXO1, thereby activating gluconeogenic genes and increasing hyperglycemia (18).

IR, which is expressed in excess in muscle, adipose tissue and liver, has two isoforms, IR-A (fetal isoform) and IR-B (mature isoform). IR-B differs from IR-A in that it contains a region of 12 amino acids located in exon 11 in the α-subunit (19). IR-B is commonly found in the liver, muscle and adipocytes, which are mainly the tissues where insulin acts. It has been shown that the expression of the fetal form, IR-A, is increased predominantly in embryo and fetal tissues, central nervous system (CNS), hematopoietic cells and cancer cells (19,20). IR-B binds to insulin with high affinity and to IGF-1 and IGF-2 with low affinity. While IR-A binds with insulin and IGF-2 with high affinity, it binds to IGF-1 with approximately ten times lower affinity (21,22). IR-A shows twice the interest in insulin; although its internalization and reuse are faster, it has two times lower tyrosine kinase activity (21). As a result of studies with hematopoietic cell lines, IR-A was found to be mitogenic and anti-apoptotic; It has been shown that IR-B triggers the differentiation signal (23). It has been reported that glucose uptake returns to normal when IR-A is given to “IR knockout” mice (24). Cancer cells respond quite well to circulating insulin. This is especially important in diabetic and obese patients with excess insulin. Studies show that hyperinsulinemia seen in obesity and insulin resistance is associated with breast, prostate, colon and kidney cancers (25-27).

### 3. Breast Cancer Cell and Insulin

Breast cancer is the most common type of cancer among women with a heterogeneous structure at the molecular level (28). Although breast cancer develops sporadically in general, 5-10% of it occurs due to genetic reasons (29). Many risk factors such as oncogenes, tumour suppressor genes, different

signaling pathways, epigenetics and inflammation, immune system deficiency, genomic imbalance, and the Warburg effect play a role in the development of breast cancer (30). Breast cancer is the most commonly diagnosed type of cancer among women worldwide. According to the evaluations of the global cancer observatory (GLOBOCAN) (2020), conducted by the International Agency for Research on Cancer (IARC), it is stated that the number of new cases and deaths of breast cancer has increased compared to previous years. In 2020, 2,261,419 women worldwide were diagnosed with breast cancer for the first time. This number accounts for about a quarter of all cancer cases diagnosed in women worldwide. In 2040, it is estimated that 3,025,471 women worldwide will be diagnosed with breast cancer for the first time. In 2020, 684,996 women worldwide died from breast cancer. It is estimated that 1,037,723 women worldwide will die from breast cancer in 2040 (31). Breast cancer has a very low incidence among men. About 1% of all breast cancer cases are in men. Breast cancer accounts for approximately 0.2% of cancer-related deaths in men (32).

Regulation of cell energy and reprogramming of energy metabolism are hallmarks of cancer. Cancer cells increase glycolysis in the presence of sufficient oxygen (Warburg effect), increasing the need for glucose as an essential nutrient to maintain key cellular functions (33). On the other hand, high glucose use plays an important role in the development of breast cancer by stimulating cell proliferation, cell survival, cell migration and cell metastasis (34). A large number of clinical, experimental and epidemiological data support the view that activation of insulin and insulin-like growth factor signaling pathways is critical for the progression of breast cancer (35). The relationship between insulin resistance and cancer has been noted for many years. The relationship between insulin resistance and breast cancer was shown in 1992 (36).

Many different results have been obtained in studies conducted to date on the effects of insulin levels on breast cancer. Insulin is known to play a critical role in carcinogenesis in various parts of the human body, including breast tissue, and increased blood insulin levels have been demonstrated in patients with cancer. It is thought that insulin shows these effects in two ways (mitogenic, and metabolic), and some studies have been carried out on this. Insulin is most commonly known for its metabolic effects (37,38), but it also has mitogenic effects, such as stimulating cell mitosis and migration and inhibiting apoptosis in mammary epithelial cells that have not transformed into damaged DNA (39). It is known that insulin promotes cell proliferation in normal breast tissue and human breast cancer cell lines (40,41) and increases

breast tumour growth in animal models (42). Studies stating that the effects of insulin on breast cancer recurrence and mortality can be directly explained by its mitogenic effect have shown that insulin stimulates malignant cell proliferation via receptors and IGF and suppresses apoptosis via phosphoinositide-3-kinase/Akt and mitogen-activated protein kinase (43). In a cohort study of 512 women newly diagnosed with breast cancer, conducted by Goodwin et al., it was concluded that the risk of breast cancer recurrence and overall survival was higher in patients with high fasting insulin compared to patients with low fasting insulin (44). In addition, insulin can increase the risk of breast cancer through changes in circulating estrogen levels. This condition is associated with chronic hyperlipidemia, increased ovarian estrogen production, decreased hepatic secretion of sex hormone-binding globulin, and increased free estradiol levels (45). Hyperinsulinemia was found to be an independent risk factor for postmenopausal breast cancer in the "Women's Health Initiative Observational Study" (46). Analysis of data from 64,479 diabetic breast cancer patients showed that insulin users had 52% increased risk of all-cause death and 33% increased risk of breast cancer death compared to non-insulin users. Analysis of a limited number of studies indicated that insulin use was associated with 43% greater risk of relapse compared to non-insulin users (47). In a large cross-sectional study of postmenopausal women in which fasting serum insulin and glucose concentrations were determined; It found that 147 of the 4,286 people had a history of breast cancer and had higher fasting insulin and glucose levels than those without breast cancer (48). In a cohort study by Hemkens et al., it was suggested that basal high insulin levels play a role, mainly as a negative marker in cancer prognosis. This means that individuals with type 2 diabetes treated with insulin have an increased risk of malignancies, including breast cancer (49). High fasting insulin levels have been associated with an increased risk of developing breast cancer and worse outcomes in both premenopausal and postmenopausal women, and this association has been shown to persist after adjustment for adjuvant chemotherapy and hormone therapy (50). It has been stated that hyperinsulinemia is significantly associated with a more advanced stage of cancer and positive nodal status. Thus, hyperinsulinemia is thought to be consistently associated with increased breast cancer risk and mortality. In a study supporting this, it is emphasized that the probability of developing breast cancer and the risk of death increase in diabetic women (51). A positive correlation was found between hyperinsulinemia and breast cancer in postmenopausal healthy women (52), and it was also stated that fasting

insulin concentrations at young ages were directly related to increased breast cancer cases in later life (46).

A limited number of studies that cannot show a clear relationship between insulin and breast cancer are included in the literature. In the study conducted by Kaaks et al. in 2002, measurements of the plasma concentration of insulin were performed in two prospective cohort studies consisting of 513 breast cancer cases and 987 controls. It was found that breast cancer risk did not show a clear relationship with insulin levels, and this result did not support the hypothesis that high plasma insulin levels are associated with increased breast cancer risk (53). In another cohort of 7,894 women aged 45-64 years, the relationship between breast cancer incidence and serum insulin levels was examined, and 187 breast cancer cases were identified after an average of 7.1 years of research. It was found that breast cancer was positively associated with body mass index, but not with serum insulin level. It was also concluded that circulating insulin levels are not predictable for future incidence of breast cancer (54). A published systematic review showed no difference in fasting insulin or postprandial/fasting C-peptide levels between women with and without breast cancer. It has been stated that there is no difference in breast cancer risk between high levels of fasting insulin or fasting/fasting C-peptide levels and their lowest levels (55).

## 4. Breast Cancer Cell and Insulin Receptors

IR-A and IR-B are the ones that provide signal transmission of insulin. IR-A has a higher affinity for insulin-like growth factor-1 (IGF-1) and IGF2. IR-B plays a major role in maintaining glucose homeostasis. Insulin exerts its effects on cell growth and proliferation by binding to IR-B. In addition, insulin increases the hepatic expression of the insulin-like growth factor-1 receptor (IGF-1R) and the hepatic clearance of IGF-binding protein, increasing the level of free and therefore active IGF-1 in the blood. Cell growth is stimulated as a result of IGF-1 binding to IGF-1R. Insulin also acts by binding to the IGF-1 receptor, but its affinity for IR-A is 1,000 times greater than for the IGF-1 receptor. IR-A and IGF-1 are frequently expressed in tumour cells (56). Considered one of the first studies in this field, Papa et al., as a result of their analysis, found that the IR value was more than six times higher in human breast cancer samples compared to normal breast tissues. In addition, IR was shown to be within the normal range in only about 20% of cancer tissues. Overexpression of IR was also found to be associated with tumour size, cancer staging, and estrogen receptor (ER) expression (57). In the following years, both in vitro and

in vivo studies have shown that insulin stimulates proliferation in normal breast tissue cells and breast cancer cells (58). IR-A stimulated by insulin and IGF is highly expressed in breast cancer tissue (59). Preclinical studies have shown that IR induces and accelerates mammary tumour progression in a mouse model of hyperinsulinemia (60). When its relationship with ER is evaluated; IR-A levels of ER+ breast cancers and breast cancers refractory to ER+ hormone (HR ER+) were found to be higher than ER- tumours (61). Moreover, Gradishar et al. published that endocrine-resistant ER+ breast cancers have little expression of IGF-1R and much higher IR levels (62). Although there is little evidence to suggest that IR is regulated by the ER in breast cancer, the regulation of IGF-1R by estradiol has been well characterized in ER+ breast cancer cells (63). While both high IR-A levels and the presence of hyperinsulinemia are associated with more aggressive and hormone-resistant breast cancers; IR-A activation has been associated with a dominant mitogenic effect and poor patient prognosis (64). Increased IR-A expression with decreased IR-B expression detected in human breast cancer showed that it was up-regulated with an increased IR-A:IR-B ratio (65). The IR-A:IR-B ratio was observed to be significantly higher in the luminal B subtype, which is characterized by tamoxifen resistance, and with a more unfavorable prognosis than the luminal A breast cancer histotype, which is characterized by response to hormonal therapy and a relatively good prognosis (66). The expression dysregulation of IR isoforms and the increased IR-A:IR-B ratio supported the possibility that they are associated with more aggressive and prognostically unfavorable breast cancers (67).

IR-A is more associated with mitogenic signaling, while IR-B is more associated with metabolic signaling (64). It is necessary to specifically target the mitogenic IR-A isoform, to leave the metabolic IR-B isoform uninterrupted, to prevent glucose dysregulation. This proposed mechanism drives the development of an IR inhibitor with isoform specificity (68). In this context, the relationship between IR isoforms and breast cancer has led researchers to therapeutic targets. MicroRNAs (miRNAs) is one of them. It has been shown that miR-128 may be an inhibitor of glucose metabolism, mitochondrial respiration and cell proliferation by targeting the inhibition of IR and IRS-1 in patients with triple-negative breast cancer and may be a prognostic marker for treatment (69). In another study, it was emphasized that disruption of IR by shRNA or a blocking peptide inhibited growth in endocrine-resistant breast cancer cells (70). S961, a small peptide IR antagonist developed by Novo Nordisk (71), has been used in the investigation of IR-related diseases such as hyperinsulinemia

and breast cancer (72). Chan et al. showed that S961 inhibits insulin-stimulated growth and cell cycle progression in breast cancer cell lines (70). Knudesn et al., researchers found that S961 showed agonist activity in the low concentration range (73). Despite these data, serious side effects such as hyperglycemia and hyperinsulinemia are observed in the mouse breast cancer model of S961 (72). A clinical drug study involving linsitinib was terminated in phase II in patients with metastatic breast cancer due to serious toxicities such as hyperglycemia. It has been emphasized that the side effect caused by linsitinib is due to the disruption of IR, which plays an important role in the maintenance of glucose homeostasis (74).

## 5. Conclusion

Insulin effect is a known factor in breast cancer. IR is now a factor that needs to be detected in the history of breast cancer. The expression of IR isoforms may be a predictive biomarker for insulin and IGF-targeted therapy. In the presence of hyperinsulinemia, IR expression should be evaluated in several different processes, including breast cancer prognosis, staging, angiogenesis, and resistance to chemotherapeutic agents. The level of IR expression will provide the basis for understanding population-level physiological differences and human genetic variation underlying disease. IR may be a good candidate to be used as a target to suppress cell proliferation and enhance differentiation. Since molecular studies reveal how the process is reflected in the clinic, therapeutic strategies aimed at IR-A and IR-B are important.

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CHAPTER XIX

# SCIENTIFIC FACTS BEHIND THE PLACENTOPHAGY

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## 1. Introduction

The word placenta is derived from the Greek word "plakoenta" meaning a flat, plate-like object. (1) The placenta, a temporary organ in the woman's body throughout pregnancy, begins to form in the second week of pregnancy and completes its formation in the sixth month of pregnancy. (2,3) The placenta is derived from trophoblasts which develop from the blastocyst from which the embryo also develops, and it is highly complex. (4,5)

The human placenta connects the prospective mother and her baby physically, metabolically and immunologically. (6,7) The placenta, which achieves important vital tasks during pregnancy, not only serves as a channel for oxygen, nutrients and waste products between maternal and fetal circulation systems but also produces hormones that maintain the pregnancy and prepare the mother's body for childbirth. (1-3,8-10) There is no significant difference between various species in terms of the biochemical content of the placental tissue. (3) In recent research, it has been demonstrated that the placenta increases its own activity in response to certain hormonal signals, which indicates that

there is a greater interaction between the placenta and maternal tissues more than expected. (4) The placenta is also considered as a source of valuable biological products such as blood products, hormones and stem cells. (2)

As the number of studies conducted on placenta has increased, there have been changes in definitions of the placenta, and today this unique organ is addressed more with its physiological function rather than its structural features as a result of which the concept of placentophagy emerged. (4) The placenta is treated in various ways depending on cultural, social, personal or institutional factors. For example, it may be buried, burned or hung on a tree. (1) These reflect the belief systems of the society. One of these practices is placentophagy. (7,10)

Placentophagy is generally defined as the consumption of postpartum products such as the placenta and amniotic fluid; (2,11-16) however, these definitions for humans and animals differ. In animals, placentophagy refers to the consumption of the placenta, umbilicus, amniotic and chorionic membranes, and amniotic fluid after birth whereas in humans, it refers to the consumption of the placenta in an unaltered or altered form (cooked, dried, etc.) by any person at any time after birth. (3,17,18) There are two forms of placentophagy in humans: maternal and non-maternal placentophagy. While maternal placentophagy is the consumption of the placenta and its appendages by the mother in any form at any time after birth, non-maternal placentophagy is the consumption of the placenta and its appendages by anyone other than the mother. (15,19,20)

## 2. History of Placentophagy

The earliest source for placentophagy is Deuteronomy 28:56-57, the fifth book of the Torah, obtained during the Siege of Jerusalem (587 B.C.). (7,21) The second source on placentophagy is the Great Pharmacopoeia, which emerged in 1596 A.D. In the Great Pharmacopoeia, it is recommended that placental tissue must be mixed with human milk to relieve fatigue. (7) Written sources on placentophagy in traditional Chinese medicine date back to five centuries ago. (7,12,22) In Chinese medicine, the human placenta is called “Zi He Che” and it is used after it is dried and powdered. (11,23) This Chinese medicine product called “he che da zao wan” meaning “placenta great creation pill” is believed to increase breast milk supply and to have various benefits for certain organs such as kidneys, liver and lungs, and it is used for conditions such as infertility, sexual dysfunction, tinnitus, dizziness, weight loss, asthma, epilepsy. (23-25) However, many Chinese medicine products have not been empirically tested for

their effectiveness. As for the tested products, there are some doubts about the reliability of the data obtained from these tests. (11)

Dried placenta is described as a drug that contributes to realization of labor in the Historical German Materia Medica. (26) In the first sources of pharmacy, there is information about the use of placenta and amniotic fluid in the management of postpartum pain. Evidence indicating that placentophagy was practiced in ancient Egypt is available. (14,27) There are also theories that placentophagy was quitted after beliefs in pagan religions were left with the rise of Judeo-Christian religious traditions. It is claimed that in cultures whose people were at risk of famine and had difficulty in accessing meat, they displayed behaviors of placentophagy. (14) In 17th- and 18th-century France, the placenta was inserted into the skin for the renewal of the skin and consumed by mothers to increase their milk production. (2) In the 1960s, a Czechoslovak physician leaked to the media that midwives and obstetricians of Chinese and Thai origin living in northern Vietnam working in a local hospital consumed the fried placentas of young and healthy mothers served with onions. (3) In an autobiography describing life in China during the great famine of the 1960s, it was reported that human placenta was consumed. (24) In various cultures, placentophagy has been considered as a useful contraceptive method. (28) It has also been claimed that dried human placenta is used to treat chronic cough and male sexual dysfunction. (5) Members of the Kurtachi tribe living in the Solomon Islands preserved the placenta in a bowl of lime and ground it into powder for the mother to chew it with areca nuts as a source of calcium. (21)

According to several reports, either individuals or groups consumed raw or cooked placenta during the popular hippie lifestyle of the late 1960s and early 1970s. (11,12) Today, placentophagy is considered as the part of the movement called New Age which aims to return to what is natural, opposes unnecessary medical interventions at birth and supports home birth. Therefore, placentophagy practice has been observed more frequently in postpartum women since the 1980s. (2,11,29-31)

### 3. Ways to Consume Placenta

Placenta is often consumed raw, cooked, roasted, dried or in capsule form. It is also available in tincture, body butter, ointment, or beverages such as tea and smoothie. (13,23-26,31-35) While some women consume their placentas raw immediately after giving birth, others keep them in the freezer to consume later. (36) Placenta can be consumed by mixing it with fruit or fruit juices to

mask its unpleasant taste, or used as a meat substitute in dishes such as lasagna and pasta. (4,37)

Today, placenta is most commonly consumed in capsules. (13,16,18,25,37,38) As the interest in placentophagy has increased, the demand for services in which placenta is turned into a consumable form and the number of people willing to provide this service has increased. (13,17,39-41) While the placenta is encapsulated, it undergoes the following processes: rinsing the placenta in water, cleaning its membranes, cutting it into slices, steaming it, drying it at 46-71°C, grinding and placing it in gelatin capsules at room temperature. (4,7,21,33,38,42,43) It is possible to fill 75-200 capsules with one placenta. It is generally recommended that placenta capsules should be taken 2-4 times a day for the first six months after birth, which equals to an intake of approximately 3000 mg per day. (2,9,42) Those who advocate that placenta should be consumed in capsule form claim that the greatest benefit can be obtained from the placenta when it is consumed in capsule form. (4) A company called Placenta Benefits that works with around 100 partners from the United States, Canada, Australia, New Zealand, United Kingdom, Malaysia, United Arab Emirates and Spain provides the placenta encapsulation service. (4,39,44) The average cost of converting the placenta into capsule form ranges from $200 to $400. Many companies that provide this service also offer a certification program on converting the placenta into capsule form. (4)

All these developments have brought about debates about whether the placenta is a food or not. The U.S. Food and Drug Administration (FDA) (2007) sent a warning letter to a company because the food supplement produced by that company contained human placenta. Apart from this warning letter, the FDA, which argues that food does not have to be approved before it can be commercially sold, has not yet issued any regulation for the process of bringing the placenta into consumable form. In addition, the FDA issued a statement that the placenta does not belong to any of the dietary ingredient categories defined in section 201(ff) of the Federal Food, Drug, and Cosmetic Act. As a result, the FDA does not accept the placenta as a food. (4) The Food Standards Agency, which represents England, Wales and Northern Ireland on food safety in Europe, announced in June 2014 that they would consider human placenta as “new food” within the scope of the European Union Council Regulation. (4,23) After the Food Standards Agency’s decision, consumers of encapsulated placenta and providers of encapsulated placenta service reacted against the decision intensely because as soon as the placenta is considered as food, it is not

processed for personal use and is sold commercially. This causes encapsulated placenta consumers and encapsulated placenta service providers to be at risk of being prosecuted. Ultimately, the Food Standards Agency has not yet made a final decision and placenta is not yet considered a nutrient by any agency. (4)

## 4. Placentophagy in Mammals

It has been observed that in carnivorous, herbivorous and omnivorous mammals, mostly female animals have widely practiced placentophagy. (2,44) More than 4,000 mammalian species consume their placenta and amniotic fluid. (8,13,45-47) Exceptions are Homo sapiens, marine mammals, and camels (19,23,24,37,44,45) because their kidneys have a medullary pyramidal structure. In addition, these creatures do not practice placentophagy because camels consume very salty plants and drink the water of salty ponds, and marine mammals can easily access hypertonic salty substances. It is thought that those who do not have a pyramidal kidney medulla, those who do not have access to hypertonic saline substances after birth, and those who have an urgent need for certain nutrients, especially minerals, especially after birth, practice placentophagy. (45)

Placentophagy is a common and somewhat mysterious feature of mammalian births and maternal behaviors. Marsupials eat both their placenta and amniotic fluid after birth. (11) In particular, rats have a strong desire for placentophagy especially. (30) It has been observed that mother rats respond less nervously to the removal of their offspring from the birth area than they do to the removal of their placenta. (11,30) In studies conducted in rodents (Rattus norvegicus, Peromyscus californicus, Phodopus sungorus etc.), it was determined that they generally practice placentophagy in the first few minutes or a while after birth. (5,30) Rats and monkeys are known to reject non-placental meat at birth. (11) In a study in which the effects of estrogen on placentophagy were investigated by administering a certain level of estrogen to trigger maternal behavior in rats whose reproductive organs were removed, it was observed that placentophagy behavior was inhibited in them. In another study, it was concluded that virgin rats which had experienced at least one stressful event were more likely to practice placentophagy than those which did not experience a stressful event. (48)

Data on placentophagy in non-human primates are limited to observations and no biomarkers have been recorded. According to these observations, practice of placentophagy in primates differs from one primate species to another. For

instance, the rate of practicing placentophagy is 83% in rhesus macaques, 69% in baboons and 25% in chimpanzees, and it is mostly practiced by captive primates. (30) Wild primates silently respond to labor pain, the female giving birth is less conspicuousness due to its limited movement, and some primate species give birth at night time, which prevents witnessing them during birth and observing practice of placentophagy in them. (2,49) In their study (2016), Fujisawa et al. investigated the behaviors of two chimpanzees giving birth and reported that both chimpanzees ate their placentas, and that while one chimpanzee shared the placenta with other chimpanzees, the other did not. (49)

What caused placentophagy, a common practice among mammals, has not been determined yet; (2); however, there are various theories. The cause of placentophagy in mammals is associated with "specific hunger". Specific hunger is a process that makes a certain substance attractive after a nutrient included in it is needed, due to deprivation or physiological change. (11,13) Some herbivorous animals' practicing placentophagy is attributed to the change in feeding preference during parturition. (5) In other words, according to this theory, during parturition, the mother makes a transition in food preference from herbivorousness to carnivorousness. (44,47) Other theories regarding the causes of placentophagy practice in mammals are as follows: protecting the nest area from predators, replenishing the nutrients and hormones in the mother, keeping the nest clean, and eliminating general hunger. (19,23,28,42,46,47,49) However, these theories are not certain.

One of the impressive results of studies conducted with various mammalian species is that consumption of human placenta by rats does not cause any hormonal effects, which indicates that proven effects of placentophagy on animals may be species-specific and should not be generalized to include humans. (4,17,21,41)

Positive Effects of Placentophagy in Mammals: Some benefits of placenta for mammalians are as follows: nest hygiene, replenishment of nutrients and hormones, avoidance of predators. (11,50) Living things that practice placentophagy are not supposed to be conscious of these benefits. What is important is that these benefits have evolutionary significance. (11,17) The first contact between the mother and the offspring outside the womb is established as the mother practice placentophagy by licking the newborn. As a result, this "forced" closeness and contact between the mother and newborn promotes the development of attachment and the initiation of full maternal behavior. (11,13,17) It has been experimentally proven that newborn mice, lambs and dogs covered with amniotic fluid and placenta after birth are more readily

accepted by adult females than are the ones not covered with amniotic fluid and placenta. Maternal behavior occurs in both groups, but this behavior occurs earlier against newborns covered with placenta and amniotic fluid. (11) Some bi-parental and monogamous male animals lick prenatal amniotic fluid before birth, through which they help birth mechanically. They consume the placenta and its membranes by licking them to clean the pups after birth. Thus, they help the pup's breathing by cleaning its nostrils. (5) Another claimed benefit of the placenta in mammals is the prevention of false pregnancy. False pregnancy is the triggering of pregnancy-related hormonal and physiological changes in the absence of fertilization. The claim that placentophagy prevents false pregnancy is probably due to the fact that most puerperal mammals conceive during postpartum estrus. (11)

Mice that eat their placenta are known to have higher serum prolactin levels and lower progesterone levels than those that do not eat their placenta. In several studies, it has been reported that lactation is triggered after placentophagy in wet-nursing mammals. (21,42,46) As is reported in several studies, administration of placentophagy in rodents produces an analgesic effect, raising the pain threshold without impairing the ability to care for the offspring. The substance that provides this effect is the Placental Opioid-Enhancing Factor (POEF) existing in the placenta. (8,11,24) At this point, it is important to emphasize that the POEF produces an analgesic effect internally. It has also been suggested that the POEF is a product of the enzymatic or hydrochloric acid action of the gastrointestinal tract. The analgesic effect occurring after placentophagy in animals differs from one species to another. While analgesic effect occurs immediately in cows and male rats, and lasts for 60 minutes, in female rats, this period is limited to approximately 30 minutes. (5) It is alleged that the POEF can be easily inactivated at temperatures above 40°C. It has also been reported that placentophagy is effective in regaining normative intestinal activity in rats. (4,17,21,41) Despite these findings, if the benefits of placentophagy in mammals definitively are to be confirmed, a greater number of studies should be conducted. (39,46)

In studies conducted on placentophagy, it is pointed out that humans practice it with the claim of balancing postpartum mood, accelerating recovery and increasing milk production and that in animals, it has various physiological and behavioral benefits. There is a theory on why the effects of placentophagy are different in humans and animals. According to this theory, hypotheses attributed to placentophagy in ancient animal studies were transferred to humans before they were proven and well researched. For instance, in 1954, placentophagy was

claimed to be involved in postpartum recovery and milk production in animals. However, this hypothesis has not been investigated thoroughly because animals rarely have problems producing milk, and those who make this claim believe that placentophagy should have a more productive process. Later, it was thought that this effect might occur in humans as well. (17)

The most important step in the hypothetical experiment to be conducted to determine the benefits of placentophagy in mammals would be to prevent the mother from receiving the placenta and amniotic fluid during labor and to investigate the resulting changes in physiology and behavior. It should be kept in mind that in such a study, it will be difficult to collect the data without interfering with the birth, without allowing the consumption of amniotic fluid, without causing stress on the mother and without interfering with the postpartum behaviors. (11,17) Due to these difficulties, the data collected will be considered distrustful, which will reduce the reliability of the study. (11)

Adverse Effects of Placentophagy in Mammals: Consumption of own or donor placenta in dairy cows may cause transmission of Neospora caninum agent, which is a possible horizontal transmission and spread route in the herd. Consumption of placenta exposed to intense contamination of Brucella bacteria by cattle leads to the spread of the disease to the herd. (5)

### 5. Placentophagy in Humans

Although placentophagy is common among mammals, it is not common in humans. (23,41) In other words, placentophagy in humans is not a physiological behavior as it is in most other mammalian species. (13) While most mammals on Earth consume their placentas, there is insufficient evidence for any social culture that accepts placentophagy as part of their tradition. (14,17,30,37,39,51)

Postpartum women are not as intensely interested in the postpartum placenta as other mammals are. Mothers often react to the idea of placentophagy disgustedly. While it is not yet known whether this response to placentophagy in humans is biologically or culturally programmed, it is certain that humans do not have this specific pattern of hunger unique to the placenta as non-human mammals do. (11) It should not be forgotten that there is a taboo about the consumption of the placenta in humans because in modern Western society, placentophagy is contrary to the beliefs of the majority of individuals. (4) On the other hand, some women consider placentophagy as a spiritual event and consume their placenta to celebrate the end of pregnancy. (16)

Placentophagy is common among non-human primates, which suggests that placentophagy is a practice that disappeared with evolution in humans. (27) According to anthropological theories, it is possible that the practice of placentophagy in early humans was routine, but this practice may have disappeared with the use of fire by Homo erectus about two million years ago. (21,27,46) This theory is possibly based on the view that societies considered the placenta as a toxin and burned it with the thought that it might harm the mother or affect the newborn. (4) However, although there are reports that there is anthropological evidence about the practice of placentophagy in present and past human cultures, and that there are traditional cultures and different ethnicities where placentophagy is practiced, it has been demonstrated that the practice of placentophagy in humans is little if any. (11,29,42,45) The Kol tribe in India practice placentophagy to regulate reproductive function. (3,42) The culture known as Chicano or Mexican American has been reported to have one of the few populations practicing maternal placentophagy; however, this view is still uncertain. (19,47) More resources are available on non-maternal placentophagy. In Espiritu Santo, the father eats a pudding made from cooked placenta and blood, the child is made to drink tea made from placenta due to the belief that it keeps the child away from evil spirits, and in Sino-Vietnamese medicine, patients with tuberculosis consume the placenta to recover from the illness, all of which are examples of non-maternal placentophagy. These examples demonstrate that maternal consumption of the placenta immediately after birth, characteristic of placentophagy in mammals, is not always applicable to humans. (19)

There are two main theories cited as the reason why humans do not routinely practice placentophagy. The first theory is that humans have evolved into social beings that have to rely on others for survival. The second theory is that in the past, societies perceived placentophagy as a harmful practice and stayed away from it. (13) Another reason associated with the low prevalence of placentophagy in humans is the hypothesis that humans are considered the only animals that can adequately feed themselves. According to this, women do not need the placenta for postpartum nutritional benefits because there are so many options that they can consume for nutritional benefits. (47) In most cultures, placentophagy is considered as a taboo because they perceive this practice as cannibalism. Another consequence of the fact that placentophagy is perceived as taboo in various societies is that it is hidden or only known by midwives. (11,14,21,42)

The first human case of placentophagy in the literature was reported in 1979 in the United States. (52,53) Although it is not scientifically proven, in Turkey, it is thought that it may be practiced under the influence of popular culture. (54)

With the widespread use of the Internet and social media, the practice of placentophagy has become more common. (11,24,32) It is more common, particularly in North America, Australia, and Europe. (18,23) In popular magazines such as TIME, USA Today, MSNBC, The Huffington Post, and New York, there has been publication on placentophagy. (39) Although many companies today are particularly keen to prepare the placenta in capsule form for consumption, because they claim that it has certain physical and psychosocial benefits, there is little empirical evidence to support or refute their claims that placentophagy provides objectively demonstrable benefits. (4,19,37) For more than 30 years, under the brand name of MFIII, "PE Advanced Formula", supplements derived from sheep placenta in capsule form have been produced. (3) In 2006, the Placenta Benefits website (http://PlacentaBenefits.info) was established to provide women with information about placentophagy and the effects of placenta on postpartum recovery. (39)

Although the interest in placentophagy is increasing day by day, studies on the effects of placentophagy in humans are very few, old, and unclear. (15,24,33,40,55) The Society of Obstetricians and Gynecologists of Canada does not recommend this practice because there are no scientifically confirmed studies on human placentophagy and the current studies are methodologically unscientific. (5)

Positive Effects of Placentophagy in Humans: Claimed benefits of placentophagy are largely mentioned in online resources such as anecdotal personal social media. (56) Those who advocate the practice of placentophagy claim that this practice prevents postpartum depression, reduces postpartum hemorrhage, increases energy, accelerates postpartum uterine involution, increases iron stores, improves general mood, improves mother-infant bonding, and breastfeeding due to the availability of important micronutrients in the placenta. (4,12,23,32,34,36,52,55,57-60) Placenta contains some nutrients and hormones excreted at birth; therefore, it is claimed that these alleged benefits result from regaining these nutrients and hormones in the placenta by consuming them. (37,39) According to the theory, the sudden postpartum loss of the placenta is associated with a dramatic shift in hormone production in the body and the best way to compensate this loss is to consume the lost placenta. (17) A single

placenta which weighs an average of 450 grams contains 234 calories, 4 g fat, 899 mg cholesterol, 513 g sodium, and 48 g protein. Trace elements of iron, selenium, copper, magnesium, phosphorus, potassium, zinc, calcium, essential and non-essential amino acids such as alanine, aspartic acid, arginine, histidine, leucine, lysine phenylalanine, proline, tyrosine, tryptophan and valine, vitamins such as A, C, D, B1, B2, B5, B6, B7, B9, B12, cytokines and growth factors are also present in the content of the placenta. (24,39,42,47) In addition, placental tissue includes oxytocin, estrogen, progesterone, human placental lactogen, adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH), gonadotropin-releasing hormone (GnRH), and relaxin and inhibin hormones. (5,42) Every person has a different metabolism. Therefore, hormone concentrations measured in the placenta differ from one person to another. Factors that can affect individual hormone concentrations in the placenta are as follows: the way the person consumes someone else's placenta, duration of pregnancy and related endocrine activity of the placenta, mode of delivery, stress, interventions during delivery, and drug use. Therefore, the net content of the components in the placenta is not always certain. (5,42,43) What should be researched on placentophagy is to determine the precise nutritional and hormonal content of placental tissue, as well as the effects of various preparation methods on this composition because it is unclear whether the biological components in the tissue remain active after the placenta is prepared for consumption. (39) In their study (2018), Johnson et al. investigated the concentrations of hormones, metals and bacteria in the placental tissue undergoing dehydration and steaming processes, and concluded that after it is processed, hormone concentration and bacterial contamination decreased in placenta and that the toxic metal concentrations were below the toxic threshold. (61) In Young et al.'s study (2018), while the mothers in the intervention group consumed their own placenta in capsule form, the mothers in the control group consumed placebo capsules with beef or vegetarian ingredients but without placenta. Then they analyzed the salivary hormones of the mothers in both groups and determined that although the concentration of all 15 hormones detected in the placenta capsules was higher in the intervention group, there was no statistically significant difference between the two groups. (57) In another study, (2016) when Young et al. analyzed 28 capsules of placenta in order to examine the micronutrients in the encapsulated placenta, they determined that encapsulated placenta comprised iron, selenium, copper and zinc and concluded that encapsulated placenta could be a good source in terms of these micronutrients. (12) In conclusion, the bioavailability and possible

physiological effects of hormones and micronutrients in the placenta are still unclear. (61)

Data on whether the placenta could be a biological source of iron are conflicting. It is claimed that increasing mothers' iron stores through placentophagy results in more energy and ultimately less postpartum depression because fatigue and low level iron are risk factors for postpartum depression. (24) Some supporters of placentophagy practice claim that consumption of this tissue will meet all the iron needs of the mother after birth because the placenta is a vascularized and iron-containing tissue. (32,34,44) In her study (2015) which included the iron group receiving iron supplement, the placebo group receiving beef or vegetarian supplement, and the experimental group receiving placenta capsules, Gryder investigated the effect of placentophagy on postnatal maternal iron levels of these three groups and concluded that the postnatal iron levels of the mothers in the experimental group were statistically neither lower nor higher than were those of the mothers in the placebo and iron groups. (44) In another study, the researchers compared iron levels of the women who consumed their own placenta in capsule form for three weeks after delivery with those of the women who consumed beef in capsule form, and determined that there was no statistical difference between the two groups in terms their iron concentrations. (58)

Advocates of placentophagy claim that hormones such as estrogen and progesterone existing in the placenta relieve postpartum depression symptoms and increase milk production. (56) For instance, measurable amounts of B vitamins (riboflavin, thiamine, and pyridoxine) and beta-endorphins have been identified in human placental tissue, and the claim that placentophagy improves mood is based on these. However, it is not known whether the concentrations of B vitamins and beta-endorphins existing in the placental tissue are sufficient to have a beneficial effect on postpartum women. According to their own perception, some women who consume only their placenta reported that they benefited. (23,24,27) In their research (2018), Benyshek et al. used a data set based on medical records containing pregnancy, birth and postpartum information of 23,242 women to investigate the placentophagy practice and newborn outcomes related to the practice. After their research, they concluded that of the participants, 30.8% practiced placentophagy, 85.3% who consumed their placenta preferred the capsule form, and 73.1% stated that the reason why they consumed placenta was postpartum depression and that the women who gave birth at home were more likely to practice placentophagy than were those

who gave birth at a birth center. According to the results of their study, those who practiced placentophagy were more likely to report anxiety or depression in the antenatal period compared to those who did not practice it. They also reported that placentophagy practice was not associated with any adverse neonatal outcomes. (29) In their retrospective cohort study (2019), Morris et al. investigated the effect of postpartum placentophagy on mood, lactation, energy level, and plasma vitamin B12 levels in women with mood disorders and determined that there was no statistically significant difference between the women who practiced placentophagy and the women who did not in terms of depression symptoms, energy and plasma vitamin B12 levels, and the use of postpartum pharmaceutical lactation supplements. (55) In their study (2018) conducted to investigate the effect of encapsulated placenta consumption on postpartum mothers' mood, fatigue and mother-infant attachment, Young et al. (2018) determined no statistically significant difference between the control and intervention groups in terms of their mood, and attachment and fatigue levels. However, there was a decrease in the depression symptoms and fatigue levels of the women in the intervention group at the end of the study, but the decrease was not statistically significant. (37) In her placebo-controlled study (2016), Young investigated whether the consumption of placenta in capsule form had an effect on postpartum recovery and maternal hormone levels and determined a statistically significant difference between the control and experimental groups in terms of their postpartum depression and fatigue scores but not in terms of infant weight, attachment level and postpartum hormone levels. She also determined that there was no statistically significant relationship between the two groups in terms of their postpartum hormone and attachment levels, and depressive symptoms. (30) Since allopregnanolone, a progesterone metabolite, is used for postpartum depression, and progesterone is detected in the placenta, it is theoretically possible that placentophagy can affect the mother's mood. However, it is controversial whether steroid hormones become bioavailable because they are poorly absorbed when taken orally. (42) In 1917, Hammett and McNeile published their research, the first scientific study on placentophagy in humans, and reported an increase in protein and lactose content in the milk of women who consumed their dried and powdered placenta in capsule form in the first few days after birth. (4,5,62) Their study is one of the oldest articles published on placentophagy. (4) In the literature, the number of studies conducted in the 1900s in which it was argued that placentophagy was beneficial, as in the study mentioned in the previous statement, is limited. (23,37) The methodologies

used in these nearly one-hundred-year-old studies do not meet today's scientific study standards because they included small sample groups and had poor control measures. (13) For instance, in a study conducted in 1954, it was reported that milk production increased in women after placentophagy. However, because the study had no control group, and because the timing and measurements of milk production were uncertain, it is not possible to make conclusions. (17) After their study conducted to investigate the effect of encapsulated placenta consumption on postpartum plasma prolactin levels and newborn weight gain, Young et al. (2019) concluded that there was no statistically significant difference between the experimental group that consumed encapsulated placenta and the placebo group that did not consume encapsulated placenta in terms of the plasma prolactin levels and newborn weight gain. (59)

Most research conducted on placentophagy practice in humans contains anecdotal statements about women's beliefs, experiences and this practice. (37,59) While some of these statements were in favor of placentophagy, some of them were severely negative. (10) In their study conducted on how women utilized their placenta after delivery, Mobian et al. (2022) concluded that two-thirds of the participants consumed their placenta, that some women fed their children a placenta to prevent teething pain, and that very few of them stated that placentophagy could be dangerous. (51) In their study (2020), Botelle and Wllott stated that the most reported motivation for practicing placentophagy was postpartum depression, and that positive experiences were reported more than negative experiences. (18) In another study, 66% of the patients and 89% of the health professionals had heard of placentophagy before, women who had a previous postpartum mental health disorder were more willing to practice placentophagy, and 40% of the health professionals and 70% of the patients were undecided as to whether placentophagy had any benefit. (10) In Selander et al.'s study (2013) conducted to investigate the experiences and motivations of women who practiced placentophagy, of the participants, 90% consumed their placenta only once, and 80% preferred the capsule form when they first practiced placentophagy. While the most common reason to practice placentophagy was to improve mood (34%), the most common reason for choosing the capsule form was that it was less disgusting (27%). Of the women who consumed their placenta, 40% stated that their postpartum mood improved, 69% did not experience any negative effects after placentophagy. Of the reported negative effects, the most frequently experienced one was burping (7%). (39) In a study conducted with women and men to investigate, the participants' knowledge

and attitudes towards placentophagy, while 66% of the participants had heard of the term placentophagy, 3.3% practiced it. The difference between the male and female participants in terms of willing to practice placentophagy was not statistically significant. Of the participants, those who were willing to practice placentophagy stated that if it was suggested by the midwife they would practice it to prevent postpartum depression, and to provide energy. (14)

POEF has not been tested in humans tested whether it has an analgesic effect as it has in mammals. (11) Placentophagy is also claimed to provide immunological benefits by reducing maternal antibodies produced in response to the fetus or any pregnancy product. (24) However, these alleged benefits of placentophagy are currently only hypothetical and there is not adequate scientific evidence to support those benefits. (4)

Adverse Effects of Placentophagy in Humans: Lack of scientific evidence for the benefits of placentophagy is also valid for its harms. (23,52) Theoretically, placentophagy has some risks: pathogens likely to exist in placental tissue, environmental toxins and the prothrombotic and endocrine activity of estrogen. (23) Placentophagy can expose the mother or people in contact with the placenta to pathogens that may be present in the tissue, (23) which raises concerns that the placenta can be a source of infection for HIV, Hepatitis B, Hepatitis, C etc. (32,63) That the placenta expelled from the body is colonized with maternal genitourinary flora also poses a risk for infection after placentophagy. (16) Centers for Disease Control and Prevention Oregon Health Authority (2018) reported a case of a newborn whose treatment was started 5 days after birth for postpartum early-onset group B Streptococcus (GBS) sepsis. According to the family history, the mother consumed the placenta in capsule form three times a day. In tests performed later, no GBS was detected in breast milk; however, the sample taken from the placenta capsules was positive for GBS. (4,42,64) In case of oral intake, the stomach is thought to act as a barrier against bacteria, including streptococci. Therefore, maternal exposure to infection through placentophagy is controversial. In this case, it is also argued that prenatal transmission of bacteria may be due to colonization of the mother's gastrointestinal tract with GBS and close postnatal contact between mother and child after birth. (42) The Centers for Disease Control and Prevention regarding this case hypothesized that the placenta in capsule form may not have been heated at sufficient temperature and for sufficient time to reduce the number of GBS bacteria. (4) Performing the right heat treatment is of great importance especially for the destruction of viruses such as HIV

and Zika Hepatitis. For example, the hepatitis A virus must be exposed to heat four minutes at 70°C to ensure its inactivation. This duration must be at least 30 minutes for the inactivation of the rotavirus. (4,5) It is known that HIV is heat sensitive at 56-62°C. (4) Today, the optimum temperature and duration of cooking or drying of the placenta to eradicate GBS, HIV, and Hepatitis B and C are uncertain. Therefore, it is unclear whether most encapsulated placenta manufacturers follow any preparation standard to avoid viral persistence. (4,16) The lack of standards for the preparation of the human placenta for consumption, the potential for exposure to infection during the processing and preparation of the placenta for consumption bring about the violation of two possible ethical principles: honesty and non-harm. Recognizing that there is little evidence of the benefits of placenta consumption in humans is associated with the principle of honesty and companies should be honest with their consumers on this issue. The no harm principle includes prevention of contamination during the placenta preparation process. (13)

Although it has long been accepted that the placenta is sterile in the uterus, recent research has revealed that there is a similarity between the microbiological composition of the oral cavity and the placenta. (42) It is emphasized that placentophagy can spread the infection in women with acute chorioamnionitis, which will have harmful effects on the mother and newborn .(4) If a woman develops an intrauterine infection during labor, she may be exposed to the pathogen more after she practices placentophagy. (23)

The placenta is a significant source of estrogen during pregnancy. If placentophagy significantly increases the estrogen level, in women who are already at risk of thromboembolic events, this risk may increase even more during pregnancy and postpartum period. However, the evidence for this theory is inadequate. (23,52) Young et al. (2016) conducted a study to determine whether free steroid hormones and melatonin in the placenta could remain functional during the encapsulation process of the placenta. At the end of their study in which they analyzed 28 processed placenta samples, detectable concentrations occurred in 16 of the 17 hormones analyzed. (56) In a published case report, it was stated that the mother of an exclusively breastfed three-month-old baby who had vaginal bleeding and excessive breast development consumed the encapsulated placenta, and that the abnormalities in the baby improved after the mother stopped consuming encapsulated placenta. (38) It was thought that these symptoms were caused by the mother's practicing placentophagy, which exposed the baby to exogenous estrogen. (5)

Exposure to toxic substances accumulating in the placenta is another concern associated with placentophagy. According to this view, toxic components of alcohol or controlled substances (cadmium, lead, etc.) can accumulate and harm the mother and newborn. (4,20,43) It is known that the placenta acts as a barrier to prevent the passage of some harmful substances to the developing fetus during pregnancy as a result of which some toxic substances accumulate in it during pregnancy. When some toxic substances retained by the placenta reach a high enough amount, they not only cause symptoms such as nausea and vomiting but also lead to some negative effects on the endocrine system. Theoretically, maternal ingestion of these substances through placentophagy may adversely affect the health of both the mother and the breastfed newborn who is exposed to contaminated breast, (12,53) which suggests that consumption of more than one capsule placenta may increase the risk of cumulative doses. Symptoms such as headache, nausea, and vomiting suffered by women who practice placentophagy are thought to be associated with the accumulation of toxic substances. (4,13,46) In a study in which the heavy metal content of the human placenta was investigated, no detectable levels of arsenic, cadmium, lead and mercury were detected in the placenta sample taken. (36) In their study conducted to determine the chemical components of the encapsulated placenta (2021), Kasuku et al. detected arsenic, cadmium, lead and selenium in addition to iron, copper and zinc at the highest rates. The levels of all these seven detected elements were within the minimum allowable risk range in terms of toxicity. Another result of the study was that in the babies of the mothers who consumed encapsulated placenta, there was an increase in weight gain and the number of breastfeeding in the 8 weeks postpartum. (33)

It is also claimed that placentophagy may increase the number of placental cells in the uterus after delivery, which may lead to choriocarcinoma. (20) Another serious risk factor for placentophagy is that the placenta is a tissue which has its own bacterial microbiota (Proteobacteria, Tenericutes, etc.). Therefore, it is at risk of being easily contaminated. Another possible harm of placentophagy is the risk of triggering alloimmunization, which may harm subsequent pregnancies. The fetus has an antigenic mixture that includes paternal antigens not rejected by the maternal immune system. Associated with this is the risk that consumption of the placenta may trigger alloimmunization, especially in Rh incompatibility pregnancies. It is claimed that this is because paternal alloantigens in the placenta are recognized by T cells. However, this is purely theoretical and there is no data to support this claim. (5,20) The number of well-designed studies conducted on the harmful effects of placentophagy is

limited. Therefore, it should be kept in mind that these harmful effects, thought to be caused by placentophagy, are nothing more than anecdotes. (4,43)

Contraindications of Placentophagy: Presence of a viral or bacterial infection in the mother and/or newborn or receiving general anesthesia is contraindicated if the mother practices placentophagy. Since smoking during pregnancy will increase the cadmium rate in the placenta, it is another contraindication for placentophagy. Placentophagy is also not recommended in the presence of mastitis or breast obstruction although the possibility of its stimulating effect on milk production has not yet been proven. (5,42)

### 6. Legal Aspect of Placentophagy

For placentophagy, the placenta should be removed from the hospital. At this point, pathological examination of the placenta comes to the fore. Most placentas are normal and do not require pathological examination. The placenta is the only body tissue that is not routinely sent for pathological examination and is allowed to remove from the hospital. (4,28) However, most hospitals have internal guidelines for pathological examination of the placenta only if certain abnormalities are present. As soon as the placenta is removed from the hospital, it loses its integrity and becomes unsuitable for pathological examination. In the United States, most states do not have clear regulations and safety guidelines on placentophagy and placenta removal from the hospital, which indicates that the current health policy at the state level allows the removal of the placenta from the hospital, thus placentophagy. (4)

### 7. Midwives' Placentophagy-Related Responsibilities

1. Is it the responsibility of midwives and other health professionals to provide placentophagy services?

2. Should women's questions on placentophagy be responded or should they be allowed to obtain a placenta for placentophagy? If yes, how?

While the midwives' and other health professionals' responsibilities regarding placentophagy are discussed, answers to these two questions should be sought by taking ethical issues into account.

Because claims that placentophagy has clinical benefits lack reliable evidence, healthcare professionals have no professional responsibility to let women access placenta for placentophagy or to recommend the practice of placentophagy. (4) When midwives and other health professionals are faced with a woman who expressed her desire for placentophagy, they should provide

counseling services to the woman by informing that there is lack of evidence about the benefits and harms of this practice, and by expressing their concerns about the harm that may come from the clinical point of view. They should not forget that providing such counseling is their professional responsibility. (4,17,29,41) In order to prevent cross-contamination during the preparation of the placenta for consumption, the importance of hand hygiene, separation of the placenta from other food sources, attention to the hygiene of cutting boards, kitchen utensils and counters should be emphasized. (16) In addition, it should be questioned whether the mother has a history of placentophagy in cases such as GBS infection in the mother or newborn after delivery. (4)

Further research should be conducted to confirm the health benefits and risks of placentophagy. (10,53) Midwives who are supposed to use, research and discuss evidence-based practices beneficial to women's and infant health and to encourage them to make conscious choice should follow the developments, and results of new research related to placentophagy. (24) Midwives should also have cultural awareness and should raise the women's awareness of placentophagy they care for and prevent risky situations when necessary. (32) Midwives should be knowledgeable enough to answer questions about placentophagy asked by the women they care for, answer their questions willingly, informatively and respectfully, and pay attention to the women's decisions of placentophagy. (9,17,29) In addition, various healthcare organizations should develop clear clinical guidelines to approach human placentophagy scientifically and professionally. (24)

## 8. Conclusion

Placentophagy is a practice that has become increasingly popular worldwide in recent years. Animal studies have enabled us to learn about placentophagy practice in mammals. However, we are still short of evidence for human placentophagy. Absence or lack of evidence about the practice of placentophagy does not mean that it is not useful or reliable in theory. Therefore, well designed, controlled clinical studies should be conducted and question marks about placentophagy should be eliminated.

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CHAPTER XX

# OBSTRUCTIVE SLEEP APNEA SYNDROME: CONSERVATIVE TREATMENTS

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## 1. Introduction

To effectively address Obstructive Sleep Apnea Syndrome (OSAS), it is necessary to establish a diagnosis and precisely define the severity of the condition. Developing a clearly defined treatment protocol requires collaboration from various fields and a consensus that can be framed in this manner (1). Because the management of OSAS is reliant on patient adherence to treatment, it's essential to have the ability to tailor accepted protocols to individual needs. The treatment regimen comprises modifying the patient's living conditions through behavioral changes and differentiating between conservative and/or surgical treatment options (2).

## 2. Professional Organizations and Recommendations for OSAS Management

The American College of Physicians (ACP) guidelines recommend that laboratory sleep studies should be preferred for diagnosis, and if this is not possible, the home sleep apnea test (HSAT) should be used as an alternative. Other factors, such as patient preference and the high costs associated with sleep lab tests, have further bolstered the HSAT's role in diagnostics (1-3).

## 3. The Role of Patients and Their Education in OSAS Management

Patient compliance and motivation are crucial in treating individuals with severe Apnea Hypopnea Index (AHI) scores (4,5). This is primarily because eliminating personal and environmental factors, such as obesity, which plays a significant role in the etiology of OSAS, and the use of alcohol, smoking, sedative drugs, or substances, are directly related to patient compliance. Introducing regular exercise and proper nutrition significantly reduce patients' symptoms and AHI score. Patient education and compliance play a crucial role in ensuring successful treatment outcomes (3,6).

### *3.1. Who Should Be Treated?*

- All patients diagnosed with obstructive sleep apnea syndrome (OSAS) who experience excessive daytime sleepiness should receive treatment.
- Individuals who experience daytime sleepiness leading to traffic or work accidents should be treated promptly and definitively.
- Moreover, those who suffer from systemic health problems due to OSAS should also receive treatment.
- Treatment protocols should initiate with conservative approaches and then move towards invasive treatments to ensure that patients can endure the challenges of the treatment and reap the benefits of it.
- When developing the appropriate treatment plan for an individual, it is crucial to include their sleep partner, if applicable, in the process (1-3,5,7).

## 4. Behavioral Changes, Modification of Habits and Elimination of Comorbid Conditions

### *4.1. Weight Loss and Physical Exercise*

Obesity is a significant risk factor for OSAS. Weight loss helps reduce airway obstruction by decreasing the tendency of the posterior airway to collapse (8).

Studies have shown that individuals with OSAS who adopt weight loss methods and develop behavioral awareness experience reduced severity and symptoms of OSAS (9-11).

Simultaneously initiating weight loss interventions in patients receiving continuous positive airway pressure (CPAP) and/or undergoing surgical treatment protocols enhances compliance with both treatments and consolidates the advantages achieved (4, 5, 12).

### *4.2. Changes in Sleep Position*

For most patients, the force of gravity causes the tongue to fall backwards and obstruct the upper airway when lying on their back. It is suggested by current knowledge that up to half of patients with mild to moderate obstructive sleep apnea syndrome (OSAS) experience this position-related OSAS. Thus, changing the sleeping position is advisable for patients with any severity of OSAS. The methods to encourage patients to sleep on their side rather than their back are outdated, involving techniques like attaching a tennis ball to the back or using a block in the pillow as an aid. Short-term data indicate that changes in sleeping position can decrease the severity of OSAS in patients (13,14).

### *4.3. Cessation of Smoking, Alcohol and Sedative Use*

Simple measures such as reducing alcohol or sedative intake and quitting smoking can significantly decrease disease severity and enhance individuals' quality of life, particularly those who habitually use these substances (15,16).

Alcohol and sedatives reduce the tone of the genioglossus muscle, the most crucial dilator muscle in the upper airway, leading to a narrowed airway and increased occurrence and severity of apnea. Meanwhile, smoking induces inflammation in the mucous membrane of the upper respiratory tract, which complicates respiratory control during sleep (16).

### *4.4. Treatment of Comorbid Conditions*

Diseases like hypothyroidism, congestive heart failure, and myasthenia graves can worsen OSAS severity. Thus, treating cardio-pulmonary, endocrine, and neurologic conditions has a positive impact on OSAS treatment (4,12,17).

## 5. Conservative Treatment Methods of Obstructive Sleep Apnea Syndrome

OSAS, a condition marked by recurring obstruction of the upper airway, can cause several health issues, including cardiovascular and metabolic disorders as well as daytime sleepiness. Hence, developing effective treatment strategies is crucial for alleviating the associated health problems and enhancing patients' quality of life. Conservative approaches for managing OSAS encompass pharmacotherapy, Continuous Positive Airway Pressure (CPAP) therapy, and Intraoral Appliances (IA).

### *5.1. Pharmacotherapy*

Physical factors primarily influence the cause of OSAS. The primary issue is an airway obstruction during sleep. The main objective of treatment should, therefore, focus on preventing this airway obstruction. With this in mind, the role of pharmacotherapy in OSAS treatment is a matter of debate. As such, drug treatment should be considered an additional method in managing OSAS (18).

- Acetazolamide inhibits the carbonic anhydrase enzyme, leading to the induction of metabolic acidosis and subsequently increasing respiratory stimulation. Its metabolic side effects limit its long-term use.
- Tricyclic antidepressants, specifically protriptyline, have shown limited efficacy in the cure of OSAS in certain patients. Nevertheless, protriptyline enhances the number of hypopneas while reducing the total number of apneas. It also results in anticholinergic side effects such as dry mouth, constipation, impotence, and ataxia.
- Serotonin reuptake inhibitors enhance genioglossus activity during wakefulness. a decrease of the Apnea-Hypopnea Index (AHI) score. Nevertheless, it is believed that the number of non-REM apneas and daytime symptoms do not decrease (6,18).

### *5.2. Continuous Positive Airway Pressure (CPAP) Therapy*

Continuous positive airway pressure (CPAP) has been generally considered the primary treatment option for individuals with moderate to severe OSAS. It is recognized as the gold standard by certain medical specialities. Technical term abbreviations, such as OSAS, are explained upon first use. CPAP was first introduced in 1982 and is based on the principle of providing a constant, positive airflow pressure (7-12 cm H2O) during sleep through an oronasal mask which extends along the nasal passage. However, achieving satisfactory results requires patient compliance and regular long-term usage (5, 16, 19).

The determination and adjustment of CPAP therapy typically rely on polysomnographic analysis. A prescription for CPAP therapy is then formulated, specifying the pressure setting as well as the type of mask and other necessary supplies. The therapy must be consistently applied, and the patient's comfort level is of utmost importance when selecting a mask. Masks partially covering the face are generally favored to enhance patient comfort and compliance. The treatment benefits are greater when the patient consistently and frequently uses the device and mask. For patients undergoing their initial CPAP therapy, it is

important to evaluate their device and mask usage and identify any influencing factors. Patient motivation should be taken into account when planning interventions. Early follow-up meetings prove effective in controlling and improving patient compliance (5,16,19).

### *5.3. Intraoral Appliances (IA)*

Intraoral appliances are intended to increase the volume of the upper airway, specifically in a lateral direction, and to alter the position of the tongue, which is typically located in a posterior position, to a more anterior position. The treatment of obstructive sleep apnea syndrome (OSAS) often involves the use of three types of oral appliances (20).

- Mandibular advancing appliances (MIA)
- Soft palate elimination appliances
- Tongue-retaining appliances

While these devices may not be as efficient as CPAP at increasing the AHI and bringing it closer to the normal range, they are a preferred treatment for patients with mild to moderate OSAS. In addition, they are considered an alternative option for patients with a severe OSAS score who cannot tolerate CPAP. Patients tend to tolerate these devices better than CPAP. However, it is worth noting that these devices only provide temporary symptomatic relief and do not bring about any permanent changes to the airway or related tissues (5,20).

The use of these appliances is contingent upon the suitability of the dental structure and health. Furthermore, there are disadvantages and side effects associated with these devices, particularly CBD, which is the most commonly preferred oral appliance (21).

1. Temporomandibular joint-related side effects:
- Temporary morning pain in the jaw
- Persistent temporo-mandibular joint pain and noise
- Myofascial tenderness

2. Side effects related to intraoral tissues
- Soft tissue and gingival irritation
- Excessive salivation or
- Dry mouth

3. Occlusal changes
- Change in occlusion

- Changes in tooth position and/or mobility
- Decreased overjet/overbite
- Interproximal spaces in teeth or restorations
- Tooth fractures or damage to teeth

Additionally, a noteworthy potential side effect of using oral appliances for sleep apnea treatment is increased apnea pressure due to the insertion of a large mass in the mouth. While this effect may not always worsen the patient's condition, it can significantly reduce the expected treatment benefit. Sleep tests should not be used to confirm the efficacy of using these appliances (22).

**Table 1.** Comparison of Differences Between CPAP and IA

| Type | CPAP | IA |
|---|---|---|
| **Mechanism of Action** | Keeps the upper airway open with air pressure | Expands the upper airway by pulling the lower jaw (mandible) forward |
| **Effect** | Generally higher | Generally lower than CPAP |
| **Area of Use** | First choice for moderate to severe OSA | Recommended for mild to moderate OSA |
| **Portability** | Generally larger and less portable | Small, portable and less conspicuous |
| **Compatibility** | Generally lower | Generally higher (more acceptable) |
| **Tooth Structure Requirement** | N/A | Adequate tooth structure is required |
| **Side Effects** | Mask incompatibility, airway dryness, nasal congestion | Temporomandibular joint problems may occur |
| **The Professional to Follow** | Sleep expert | Collaboration with the dentist may be required |
| **Usage Scenario** | Usually at home | When traveling or at home |
| **Insurance Coverage** | Usually covered | Insurance usually covers only one treatment |

## 6. Conclusion

Pharmacotherapies, CPAP treatment, and IA are critical conservative treatments for patients with OSAS. Among these modalities, CPAP is the most effective in addressing OSAS (23). By continuously keeping the airway open, the CPAP device prevents apnea and hypopnea events and improves overall

sleep quality and patient health (24). However, the effectiveness of CPAP therapy relies on patient compliance with the device, and its suitability may not be guaranteed for all patients due to adherence issues (25).

Pharmacotherapy is mainly recommended for mild cases of OSAS and patients with prominent symptoms (26). Pharmacotherapeutic agents are often used in combination with other treatment modalities but can also serve as monotherapy (27). Drug therapy can alleviate symptoms, although it is unlikely to meaningfully decrease the frequency or severity of obstructive events (28).

Intraoral appliances (IA) represent another vital conservative treatment modality for OSAS. For patients with mild to moderate OSAS (29), AIAs can be highly effective. These devices reduce airway obstruction by advancing the lower jaw forward (30). However, oral appliances for obstructive sleep apnea syndrome (OSAS) are often inadequate in severe cases and carry potential side effects (31).

Consequently, CPAP is considered the most efficacious approach within conservative treatments for OSAS. Nevertheless, the selection of the treatment modality should prioritize the individual necessities of each patient along with their compliance with treatment. Pharmacological treatments and alternative interventions may have some efficacy for specific patients but typically exhibit a more restricted efficacy profile compared to CPAP therapy (32).

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CHAPTER XXI

# CHALLENGES IN IMMEDIATE IMPLANT POSITIONING IN THE ANTERIOR MAXILLA

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## 1. Introduction

Many clinicians nowadays prefer immediate dental implant treatment due to its numerous advantages. The traditional timing for the dental implant placement is 3-6 months after extraction. (1) The advantages of this treatment are clear: fewer surgeries, shorter treatment time, better implant orientation, preserved bone in the extraction area, and improved soft tissue aesthetics. (2-8) In the immediate implant placement, which Schulte and Heimke (9) first introduced, the implant is embedded in the socket in the same session immediately after extraction. This advantage, which makes it possible to shorten the duration of treatment, increases the acceptability of the treatment for the patient. (10) Studies indicate that the survival rates for dental implants placed immediately range from 92% to 100%. (11) In addition, placing an implant in the socket after extraction can prevent the alveolar bone from resorption to a certain extent. (3, 6, 12) However, immediate implant placement may not maintain the whole alveolar bone, especially the buccal bone crest causing bony dehiscence and soft tissue recession, which can impact the final aesthetic outcome. (13-17) According to a clinical study, the expected crestal resorption after immediate implant placement is about 1 mm. (18) However, in the horizontal aspect, bone loss is expected to be more. According to Boticelli et al. (19), despite immediate implant placement, the extent of postoperative horizontal bone loss can be up to 56%. The results of another study indicate that immediate implant treatment does not prevent bone loss. (13)

For long-term success, it is essential to have sufficient healthy hard and soft tissue around the implant. Having a minimum 2 mm thick bone vestibular to the implant and placing the implant 1 mm subcrestally supports the preservation of bone and soft tissue dimensions. It is important at this point that we use a smaller diameter implant than we are used to. This is also necessary to maintain the height of the papilla. (10) According to the study of Gakonyo et al. (20) in 2018, using a wider diameter implant poses a risk in terms of dehiscence or fenestration in the buccal bone during the placement of the implant. This will cause grey reflections from the gingiva in the maxilla anterior region and serious aesthetic failure in individuals with high smile lines. However, recession may occur after implant placement, causing aesthetic issues, particularly in patients with a thin gingiva biotype. (15, 21-23) To avoid all these complications, implant placement should be done carefully. However, there are many challenges in the anterior maxilla region due to root position and bone angulation when it comes to placing an implant immediately. In an ideal world, it is best to prefer a prosthetically driven positioning to ensure the screw entry remains invisible in the palatal area. Only 14% of single-tooth implants can have a palatal screw channel due to socket anatomy and bone curvature. (24-26)

In the anterior maxilla, the alveolar bone is generally proclined and concave, and the vestibular cortical plate is thin. Inadequate bone thickness is more likely to cause aesthetic complications due to resorption than in the posterior regions. When a prosthetically driven implant positioning is not possible, bone-driven positioning is preferred to avoid tissue-related complications. (20)

Planning is necessary before an implant treatment in the anterior maxilla. This planning should consider factors such as the implant's angle, the type of prosthesis to be used (screwed or cemented), the abutment (angled or straight), the positions of the adjacent and opposing teeth, and the interocclusal space. (24)

This paper aims to summarize the challenges in immediate implant placement in the anterior maxilla.

## 2. Sagittal Root Position and Initial Drilling

For predictable results, the implant should be embedded in the native bone at least 2mm away from the buccal bone and 1mm above the crest. (10) However, root position in the sagittal plane and alveolar bone angulation will affect the drilling process and 3D position of the implant. (24, 27)

Kan et al. (28) proposed a classification for the sagittal root position (SRP). The system aimed to improve interdisciplinary communication and provide additional data for treatment planning.

According to this classification, there are 4 classes, which represent root positions against the alveolar bone.

Class I is the most common observation in many studies. (25, 29, 30) It appears that implants intended for immediate placement in the anterior maxilla will typically require the shoulder to be angled towards vestibular to get primary stability apical to the socket. The Class IV SRP is the second most common type, where 2/3 of the root engages both cortical plates. (25) After a tooth with class IV SRP is extracted, typically only apical bone remains. Lateral incisors are more commonly observed to have class IV among the anterior teeth. (25) It is likely connected to the limited amount of bone volume that is typically found in this area, which can also be a contraindication for an immediate implant placement. (24, 31)

Gluckman et al. (24) classified radial root position and cortical plate dimensions. This classification, which also considers the facial bone thickness and bucco-palatally inclination of root, is modified from Kan's classification. (28)

In Class I tooth is centrally positioned. In these cases, the preparation for the osteotomy may begin at the deepest point of the socket, which plays a significant role in achieving primary stability. In terms of cement-retained options, this situation may be considered ideal. For a screw-retained alternative, angulation may provide a residual gap for the graft, which is supported by a thick buccal cortical wall. In subtype IB, subtype with a thinner cortical plate, anticipating the possibility of facial bone resorption is crucial, and grafting must be considered. (24)

Class II represents the majority, accounting for 76.5% of cases, and is characterized by either a thick or thin bone crest, according to Gluckman et al. (24). In subtype IIB, as in subtype IB, precautions should be taken against resorption. In subtype IIA thick palatal bone plays a significant role in ensuring primary stability for immediate implant placement. That makes this subtype ideal for a screw-retained option. (24)

In Class III tooth is proclined. A delayed approach could be better in consideration of the thinner buccal cortical plate. Although if immediate implant placement is preferred, a palatally positioned osteotomy is advantageous for contributing the primary stability. (24)

Class IV has a thin facial plate, and a delayed approach is preferred. In immediate implantat placement should be drilled even more palatally.

In Class V, there is no bone present in the facial, palatal, or apical areas that can offer primary stability. Therefore, class V root position has been defined as a contraindication to IIP. (24)

**3. Socket Anatomy**

Another challenge is the anatomy of the extraction socket. In 2007 Elian et al. (18) classified extraction sockets based on bone and soft tissue anatomy.

According to the authors (18) an immediate implant placement in Type I sockets is the most predictable treatment. This is most accurate if the gingiva phenotype is thick and flat. (32)

The diagnosis of Type II sockets can often be difficult. These sockets can be misleading, as an inexperienced clinician may mistake them for a Type I socket. Improper handling of Type II sockets can cause soft tissue recession postoperatively, especially if implant placement is immediate. (18)

Type III sockets are complicated to handle and need staged approach involving augmentation to reconstruct lost tissue. Therefore, it is preferable to wait to place an implant until after the tissues have been enhanced. (18)

**4. Prosthetically Driven Ideal Positioning vs. Bone Driven Ideal Positioning**

If it is possible, a prosthetically-driven implant positioning is the choice for an easy aesthetic outcome. In prosthetically-driven positioning implant will be placed parallel to the root axis but slightly palatal to achieve a palatinal screw channel. Unfortunately, there are other important factors play crucial roles in the positioning of the implant. Those factors are:

- Root position,
- Labial concavity angle (LCA),
- Adjacent teeth and anatomical structures,
- Achieving the primary stability. (20)

For long term success surrounding healthy and enough tissue around the implant is essential. If it is not possible to achieve a secure distance from surrounding bone and anatomical structures and achieve a primary stability with a prosthetically-driven positioning, then a bone-driven approach is necessary. (25)

The ideal bone-driven position for implant placement is to use the shortest implant possible. Although, the implant should be anchored with at least 4 mm apical, while keeping a distance of 2 mm from adjacent structures. (25)

Botermans and colleagues (25) found that the risk of perforation was approximately 80% for prosthetically-driven position and 5% for bone-driven position. The ideal angle for safe implantation is 17.7 ± 7.2 degrees, between two positions. This ensures enough bone anchorage and prosthetic alignment. (25)

**5. Securing the Distance from Anatomical Structures and Implant Diameter**

All adjacent anatomical structures must be considered before any implant placement, if immediate, early, or late. As per literature, a minimum distance of 2 mm ensures safety. (33)

Botermans et al. (25) found that half of the implants in the central incisor area had nasopalatine canal perforation depending on diameter. According to this study, placing 4.3 mm implants in the bone while maintaining a 2 mm safety margin is not feasible. Nasopalatine canal perforation still occurs in 43.7% of cases with diameters lower than 4.3mm. Some authors recommend curetting the contents of the nasopalatine canal before implant placement, as it does not pose a problem postoperatively. (34, 35) After a few months, the region innervated by branches of the major palatal nerve will experience progress. (36) However, the bleeding status of the nasopalatine artery must be taken into account, under which conditions placing the implant in the planned position poses an additional challenge. (37) Canalis sinousus is also an issue that should be taken into consideration. (25)

Implants with larger diameters cause a perforation risk that is twice as high as implants with narrower diameters. (25) Using narrower implant diameters reduces the risk of perforation and helps to maintain a 2mm safety margin. However, narrow implants can cause larger gaps between the implant and socket wall. Fibrous tissue instead of bone formation can jeopardize success in this area. (38) At this point, the principle of “treating the patient, not the disease” should be taken into consideration, and choosing the best possible implant diameter for the case should be prioritized. (25)

In addition, selecting larger implant diameters can reduce the space between the vestibular cortical bone and the implant. (39) According to studies, placing a wider implant is associated with vertical bone loss. (13, 40, 41)

Placing the implant in contact with buccal bone leads to double the expected 1 mm vertical bone loss. (41) In addition, lingual/palatal bone loss is generally minimal. It is thought that a better bone thickness in this region plays a role here. (39)

A study conducted by Caneva et al. (41) found that if the implant embedded in the middle of the socket, there was a 2 mm vertical bone loss after 3 months of healing. However, when the implant embedded 1 mm subcrestal against the lingual socket, the bone loss was reduced to 1.4 mm. In a human clinical study (15), average midfacial recession was shown to be approximately 1mm eighteen months postoperative. Based on the data, it was found that implants positioned closer to the outer surface of the jaw experienced an average resorption of 1.8 mm. On the other hand, those positioned more towards the center of the jaw had a lower average resorption rate of 0.6 mm. (15) In conclusion, avoiding contact between the implant body and the buccal cortex is crucial and this can only be achieved by placing the implant neck palatally/lingually and choosing smaller diameter implants. (39)

### 6. Labial Concavity Angle

The size, inclination, and root position affect the dimensions of the alveolar bone's labial aspect. The risk of perforation during immediate implant placement increases due to susceptibility to resorption in the vestibular cortex. (42)

A Larger LCA means a flatter buccal plate, and a narrower LCA points out a deeper concavity of the buccal plate, which is related to a higher risk of perforation during immediate implant placement. (25)

According to Botermans et al. (25), a 1-degree increase in LCA results in a 2.3% decrease in the probability of perforation. A Larger LCA means a flatter buccal plate, and a narrower LCA points out a deeper concavity of the buccal plate, which is related to a higher risk of perforation during the drilling process. (25)

### 7. Primary Stability

One of the most important factors to ensure primary stability is the anchorage in the bone, which, according to the literature, should be at least 4 mm apically. (43, 44) Considering this, the immediately placed implant may need to be longer than standards. (25)

### 8. Conclusion

Implant placement in the anterior maxilla requires consideration of anatomical characteristics, surgical techniques, and prosthodontic design. As

with every treatment, an evidence-based evaluating of the cases is the first condition for the predictability of the treatment outcome. Different anatomical structures in different individuals require a personalized approach to treatment. Therefore, the importance of meticulous planning before the procedure is indisputable. In the maxillary region, immediate implant treatment should be decided by taking into consideration the patient's smile line, gingiva phenotype, alveolar bone and labial contour angle, sagittal root position, buccal cortical bone thickness, soft and hard tissue dimensions and the patient's expectations should be managed accordingly.

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