



# POPULAR APPROACHES TO HEALTH SCIENCES

**Editors**

**Assoc. Prof. Dr. Sadettin DEMİREL**

**Assist Prof. Kemal Alp NALCI**



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## Chapter 1

### Morphological and Production Traits of Lalahan Sheep, A New Genotype

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## 1. Introduction

Sheep breeding occupies an important place in the livestock sector in Türkiye. Socio-economic conditions, land structure, climatic features and various low-quality pastures increase the importance of sheep breeding with local breeds. Sheep breeding in Türkiye is generally carried out with local breeds under semi-intensive or extensive conditions. Although local sheep breeds have low combined productivity, they have the advantage of making better use of low-quality pastures and flora that cattle cannot benefit from, making better use of roughage, and being resistant to adverse environmental conditions and diseases.

Lamb production represents the primary source of income in sheep breeding. In order to enhance lamb production, it is necessary to have many lambs with a high survival rate and to reach slaughter weight in a short time. Consequently, ewes exhibiting high fertility and milk yield for their offspring, as well as lambs with high survival, fattening, carcass and meat quality performance, are crucial for the production of quality lamb meat (Ünal *et al.*, 2006b).

In animal breeding, yields can be increased by improving both the environment and the genotype. Crossbreeding is one method used to improve genotypes, resulting in new genotypes with high-yielding traits and adaptability to different environmental conditions. Furthermore, it is possible to enhance the productivity of local breeds and improve certain traits. For the production of high-quality lamb meat in developed countries, crossbred or pure genotypes with high fertility and sufficient milk yield are mated with rams from meat breeds to produce large quantities of lamb meat (Ünal *et al.*, 2003; Akçapınar and Özbeyaz, 2022).

Lalahan sheep was obtained under the leadership of the Department of Animal Breeding and Husbandry of the Faculty of Veterinary Medicine of Ankara University, with the significant support of the General Directorate of Agricultural Research and Policies and the General Directorate of Agricultural Enterprises of the Ministry of Agriculture and Forestry. The Lalahan sheep was obtained by backcrossing + combination crossing between the K1Vırcık sheep breed, reared in the Marmara region, and the Akkaraman sheep breed, reared in the Central Anatolian region. The Lalahan sheep (K1Vırcık x Akkaraman B<sub>1</sub>, KAB<sub>1</sub>) is a genotype suitable for steppe conditions and was developed to obtain new genotype for lamb production. Pure breeding of the K1Vırcık breed under Central Anatolian conditions cannot achieve the expected performance. K1Vırcık x Akkaraman crossbreeding studies were carried out at the Ulaş State Farm, Sivas, and the International Centre for Livestock Research and Training (ICLRT), Ankara, between 1995 and 2001. K1Vırcık x Akkaraman F<sub>1</sub>, KAF<sub>1</sub>, crossbreds were obtained from Ulaş State Farm between 1995 and 1997, and K1Vırcık x

Akkaraman B<sub>1</sub>, KAB<sub>1</sub>, crossbreds were obtained from ICLRT between 1997 and 2001. KAB<sub>1</sub> sheep have been bred by selection at the ICLRT since 2001. The F<sub>1</sub> crossbreds were obtained by mating Akkaraman ewes with Kırırcık rams, and B<sub>1</sub> crossbreds were obtained by mating F<sub>1</sub> ewes with Kırırcık rams. At present, Lalahan sheep have been developed by breeding B<sub>1</sub> genotype ewes and rams under selection. Lalahan sheep are approximately 75% Kırırcık breed and 25% Akkaraman breed (Ünal *et al.*, 2004; Ünal *et al.*, 2006b; Erol, 2013; Erol *et al.*, 2017).

The Akkaraman breed is reared in a wide area and is the first quantity in Türkiye. The body is covered with a coarse mixed white fleece. The head is narrow and long, the ears are long and drooping. The tail is fat and the tail vertebrae make an "S" bend at the tip. The meat quality is fair to good and the yield is good. It is well adapted to the steppe climate. Akkaraman lambs grow well. After weaning they can produce 20-22 kg carcasses with three months of intensive fattening. The live weight is 60-80 kg, the lamb production rate is 100%-150%, the twinning rate is 20%-50%, the lactation period is 135-150 days and the lactation milk yield is 60-120 kg. Greasy fleece yield is 1.5–2.0 kg, staple length is 8–12 cm, fleece quality is 36–42 S (D-E), and fleece percentage is 62%–70% (Akçapınar, 2000; Ünal, 2002; Ünal *et al.*, 2002; Güngör and Ünal, 2017).

The Kırırcık breed is bred in the Thrace region, the Southern Marmara region, and in some provinces of the Aegean region. The animal's body is covered with a white fleece. The fleece is of the carpet-wool type, but of better quality to that of the other local breeds. The head is of medium size and the ears are relatively short. Males are distinguished by the presence of white spiral horns, while females are hornless. The distal end of the tail usually extends to the tarsal joint, although in some instances it extends beyond this point. It ranks first among local sheep breeds in terms of meat quality. The meat is tasty and tender due to the homogeneous distribution of fat in the muscle fibres. The average daily weight gain of the lambs after weaning is sufficient during the fattening period. They can produce carcasses of 17-18 kg with two months of intensive feeding. Average daily weight gain during intensive fattening is 263 g, adult live weight is 40–50 kg, lamb production is 100%–120%, twinning rate is 10%–20%, birth weight is 3.7–4.0 kg, lactation period is 150–160 days and lactation milk yield is at the level of 78–106 kg. Greasy fleece yield is 1.5 kg, staple length is 8–12 cm, fleece quality is 44–56 S (B-C), and fleece percentage is 60%–65% (Akçapınar, 2000). The Kırırcık breed has been used in various crossbreeding studies to develop new genotypes suitable for lamb production (Küçük *et al.*, 2002; Aytaç, 2004; Ünal *et al.*, 2004; Ünal *et al.*, 2006a). However, of these studies, only the Kırırcık x

Akkaraman crossbreeding studies have been continued to date (Ünal *et al.*, 2004; Ünal *et al.*, 2006a; Erol *et al.*, 2017; Ünal and Aslan, 2022).

The Lalahan sheep can be reared under the same conditions as the Akkaraman sheep. It is worth noting that consumer demand for Lalahan lamb meat is high. Being a crossbreeding between two local breeds, the Lalahan sheep has excellent adaptability and herd instinct and is easy to manage (Erol, 2013; Erol *et al.*, 2017).

Scientific research on the Lalahan genotype has been ongoing since 1995. Many studies on morphological and production characteristics have been carried out in the process of obtaining the genotype (Akçapınar *et al.*, 2000; Akçapınar *et al.*, 2001; Ünal *et al.*, 2002; Mundan and Özbeyaz, 2003; Ünal *et al.*, 2004; Aytaç, 2004; Ünal *et al.*, 2006b; Ünal *et al.*, 2006c; Ünal *et al.*, 2007; Erol *et al.*, 2017, Aslan and Ünal, 2023). The genotype has been named Lalahan sheep since 2010. A project on fattening, slaughter, carcass, meat quality and expression levels of some genes in Lalahan lambs (Ünal and Arslan, 2022) was recently completed.

## **2. Morphological Characteristics of the Lalahan Sheep**

### **2.1. Phenotypic Characteristics**

The body of the Lalahan sheep is covered with a white fleece. There may be black or brown spots on the head (mouth, around the eyes, face and ears). There is no fleece on the head, abdomen, and legs. The head structure is slightly convex or flat in ewes and convex in rams. In general, males have forward spiral horns, while females are hornless. Rudimentary horns may be found in females. The horns are generally white and brown-black in colour and strip-like pigmentation can also be seen. Compared to the Akkaraman, the head, neck, and ears are smaller, and the legs are shorter. The chest is broad, the waist and rump are flat and broad, with the rump sloping down. While the body is seen as a straight line when viewed from the side, the height of the back is slightly lower than the waist and withers. The tail is thin and lean, ending at the tarsal joint. A small amount of fat may be present at the point of attachment to the body. The nails are well defined. The breed is agile and active in its behaviour (Erol, 2013; Erol *et al.*, 2017; Ünal and Arslan, 2022).

### **2.2. Morphometric Characteristics**

Body measurements are crucial in determining whether lambs exhibit the growth and development characteristics of their breed/genotype during the growth period. They can also be used to determine meat yield in intensive lamb fattening. Additionally, body size is a key factor in selecting breeders. These values are also useful in monitoring the body structure and size of new genotypes



resulting from crossbreeding studies. Leg structure is an important factor for sheep to effectively utilize pasture.

During the process of obtaining the Lalahan genotype, it was observed that the KAF<sub>1</sub> genotype lambs were generally closer to the Akkaraman breed in terms of body measurements. Conversely, the KAB<sub>1</sub> lambs exhibited similarity to the Kıvırcık breed (Akçapınar *et al.*, 2000; Ünal *et al.*, 2001; Mundan and Özbeyaz, 2003; Aytaç, 2004). This is an expected outcome since the Kıvırcık breed constitutes 75% of the genetic structure of KAB<sub>1</sub>s. However, the body measurements of Lalahan genotype lambs are slightly lower than those of crossbreds at various stages during the generation of the genotype (Erol *et al.*, 2017). This is expected due to the limited selection possibilities for the small herd size of the Lalahan genotype in the ICLRT and the decrease in the effect of the initial heterosis.

The body measurements of Lalahan sheep of different ages (1-5) reveal that the values for body length and withers height are similar to each other, with an average of 67.4 cm and 65.9 cm, respectively (Erol *et al.*, 2017). This indicates that the genotype does not have a long structure.

Rangelands play a crucial role in sheep breeding. To ensure the optimal utilization of rangelands, sheep need to have strong, enduring, and relatively long legs. When evaluating leg height, the difference between withers height and body depth, and shank circumference characteristics in the Lalahan genotype, it is observed that leg height, with an average of 34.7 cm, is greater than the mean body depth of 31.2 cm, and the mean anterior shank circumference of 8.2 cm. This suggests that the genotype is well-suited for rangeland grazing, particularly on low-quality rangelands. Observations made during grazing of Lalahan sheep on grassland suggest that grazing the Lalahan genotype with Akkaraman ewes in the rangeland is successful, supporting this conclusion.

### **3. Production Traits of the Lalahan Sheep**

#### **3.1. Fertility Traits**

The relationship between fertility traits and meat yield is significant in sheep breeding, as the latter contributes the most to the income. Table 1 provides a summary of the literature on the fertility traits of Lalahan sheep, as well as the KAF<sub>1</sub> and KAB<sub>1</sub> genotypes that gave rise to the Lalahan genotype.

**Table 1.** Fertility traits in the genotypes

Fertility traits	Genotypes			References
	KAF <sub>1</sub>	KAB <sub>1</sub>	Lalahan Sheep	
Age at the first breeding (months)			16–18	Aytaç, 2004; Ünal <i>et al.</i> , 2006b; Ünal <i>et al.</i> , 2006c; Erol, 2013; Erol <i>et al.</i> , 2017; Şenyüz <i>et al.</i> , 2022
Gestation period (days)	149	150		
Oestrus cycle (days)	17.8	17.3		
Oestrus rate (%)	88–100	92–93	97–100	
Lambing rate (%)	63–84	73–78	89–97	
Twinning rate (%)	19–30		17–41	
Litter size	1.19–1.30		1.14–1.41	
Lamb production (%)	81	73	110–140	

The gestation period and estrous cycle duration of the Lalahan genotype are similar to those of the sheep species. The litter size of 1.14-1.41 and lamb production of around 110%-140% indicate that the Lalahan genotype performs well in the Central Anatolia Region in terms of fertility. In terms of fertility traits, the Lalahan genotype is considered favourable as it is similar to the Akkaraman breed and partially better than the Kivırcık breed from which it originated.

### 3.2. Survival Rates of the Lambs

To ensure continuity of the herd in sheep breeding, it is necessary for survival rates in lambs at weaning to be higher than 95%. Lalahan sheep have optimal values in terms of survival, with survival rates at weaning ranging from 87% to 100% during the obtaining of the genotype and around 95% to 98% in the ICLRT conditions today (Table 2). The high survival rate of the genotype indicates successful adaptation to the conditions of Central Anatolia.

**Table 2.** Survival rates of the genotypes

Survival rate (%)	Genotypes			References
	KAF <sub>1</sub>	KAB <sub>1</sub>	Lalahan Sheep	
Day 30	92–99	97		Akçapınar <i>et al.</i> , 2000; Mundan and Özbeyaz, 2003; Aytaç, 2004; Erol, 2013; Ünal <i>et al.</i> , 2006b
Day 90	87–96	96–100		
Day 180	91–95	92–100	97	

### 3.3. Growth and Body Weight

Birth weight is a crucial criterion for growth, particularly intrauterine growth. The Lalahan genotype's birth weight range of 4-5 kg indicates a favorable value for this trait. When evaluating the live weights of lambs at different growth stages and adult live weights (refer to Table 3), it is evident that the Lalahan genotype

is generally similar to the Kıvrıkcık breed and slightly lower than the Akkaraman breed.

**Table 3.** Growth and body weight of the genotypes

Live weight (kg)	Genotypes			References
	KAF <sub>1</sub>	KAB <sub>1</sub>	Lalahan Sheep	
Birth weight	4.1–4.7	4.1–4.4	3.8–5.0	Akçapınar <i>et al.</i> , 2000; Akçapınar <i>et al.</i> , 2001; Mundan and Özbeyaz, 2003; Ünal <i>et al.</i> , 2004; Aytac, 2004; Ünal <i>et al.</i> , 2006a; Ünal <i>et al.</i> , 2006b; Erol, 2013; Erol <i>et al.</i> , 2017; Şenyüz <i>et al.</i> , 2022
Day 90	20–22	19–21		
Day 180	28–35	27–31	28.2–31.7	
Age 1*		42	46	
Body weight after shearing*	49–57	50–55	50–57	
Adult body weight*	–	–	55–60	

\*Females only

### 3.4. Milk yield and Quality

Lalahan sheep was developed to obtain new genotypes suitable for steppe region conditions for lamb production. Therefore, milk yield and quality of Lalahan ewes are important both in terms of ensuring pure breeding of the genotype and determining its suitability for commercial crossbreeding (Table 4). When examined in this respect, the Lalahan genotype has the necessary milk yield for the ewe line in commercial crossbreeding. In addition, it can be said that the genotype can be benefited partially in terms of milk production with its current form.

**Table 4.** Milk yield and quality traits of the genotypes

Milk Yield and Quality	Genotypes			References
	KAF <sub>1</sub>	KAB <sub>1</sub>	Lalahan Sheep	
Lactation period (days)	113–160	135–175	147–154	Ünal <i>et al.</i> , 2002; Mundan and Özbeyaz, 2003; Erol, 2013; Şenyüz <i>et al.</i> , 2022
Lactation milk yield (kg)	50–74*	43–71	50–60** 57–80***	
Daily average milk yield (g)	182–474*	160–420	383–540***	
Dry matter in milk (%)			14.9	
Fat in milk (%)			4.9	
Protein in milk (%)			5.2	
Lactose in milk (%)			5.4	
ΣTUFU/ΣSFA			0.30	
ω6/ω3			2.59	

\*First lactation, \*\*Hand milking, \*\*\*Machine milking; ΣSFA: Total Saturated Fatty Acids, ΣTUFU: Total Unsaturated Fatty Acids, ω6: Omega 6 fatty acids, ω3: omega3 fatty acids

### 3.5. Fleece Yield and Quality

It can be seen that the fleece quality of KAF<sub>1</sub> sheep, which is the origin of the Lalahan genotype, is similar to that of the Kıvrıcık breed and is of higher quality than that of Akkaraman (Table 5). In this context, it can be said that the fleece of the Lalahan genotype is suitable for carpet-rug production.

**Table 5.** Fleece yield and quality of the genotypes

Fleece Yield and Quality	Genotypes			References
	KAF <sub>1</sub>	KAB <sub>1</sub>	Lalahan Sheep	
Greasy fleece yield (kg)	2.0–2.3	1.9–2.1	1.8–2.5	Akçapınar, 2001; Ünal <i>et al.</i> , 2004; Aytaç, 2004; Erol, 2013
Fibre diameter (µm)	28–32	29–31		
Fibre length (cm)	12			
Stable length (B, Barbe) (cm)	6–7	6–7		
Stable length (H, Hauter) (cm)	3–4	3–4		
Breaking strength (g)	16	15		
Fiber elasticity (%)	30	29		

### 3.6. Meat Yield and Quality

#### 3.6.1. Fattening Performance

The male lambs of Lalahan genotype are generally similar to the Kıvrıcık breed, but have a lower average daily weight gain than the Akkaraman breed. However, they have a better feed conversion ratio than Kıvrıcık, Akkaraman, and various local breeds during intensive fattening (refer to Table 6).

**Table 6.** Fattening performance of the genotypes

Fattening Performance	Genotypes/Slaughter Weight					References
	KAF <sub>1</sub>	KAB <sub>1</sub>	Lalahan Sheep			
	45 kg	45 kg	35 kg	40 kg	45 kg	
Average daily weight gain (g)	271	279	242	243–250	236	Ünal <i>et al.</i> , 2006a; Erol, 2013; Şenyüz <i>et al.</i> , 2019; Ünal and Arslan, 2022; Arslan and Ünal, 2023
Feed conversion ratio	4.8	4.8	3.6	4.0–4.4	4.2–4.4	
Fattening period (days)	92	89	68	93	113	

#### 3.6.2. Slaughter and Carcass Traits

When evaluating the meat, fat, and bone ratios in the carcass of Lalahan male lambs, it can be observed that the genotype has a higher meat ratio, lower fat ratio, and similar bone ratio compared to the Kıvrıcık breed (refer to Table 7).

Additionally, the Lalahan genotype has an advantage in terms of carcass meat, fat, and bone ratios, as it is in better or similar condition than the local breeds.

**Table 7.** Slaughter and carcass traits of the genotypes

Slaughter and Carcass Traits	Genotypes/Slaughter Weight					References
	KAF <sub>1</sub>	KAB <sub>1</sub>	Lalahan Sheep			
	45 kg	45 kg	35 kg	40 kg	45 kg	
Hot dressing percentage (%)	50.0	49.3	46.2	45.5	47.1	Ünal <i>et al.</i> , 2006a; Ünal and Arslan, 2022
Cold dressing percentage (%)	48.9	48.2	45.3	44.7	46.1	
Meat ratio in carcass (%)	56.0	56	61.8	61.0	57.5	
Bone ratio in carcass (%)	23.4	23.9	18.5	18.6	18.0	
Fat ratio in carcass (%)	20.6	20.3	13.6	14.1	19.5	
MLD area (cm <sup>2</sup> )	14.2	13.0	14.3	16.2	17.7	

MLD: *Musculus longissimus dorsi*

### 3.6.3. Meat Quality

Upon evaluation of the carcass meat quality characteristics of Lalahan male lambs, it is determined that the genotype is similar to the Kivırcık breed, from which it originated (Table 8).

## 4. Conclusion

Lalahan sheep genotype was developed in order to obtain new genotype suitable for lamb meat production in steppe regions. Its genetic structure comprises 75% Kivırcık and 25% Akkaraman genotypes.

Morphologically, the Lalahan genotype is covered with white fleece. Rams have spiral forward horns, while ewes are polled. Compared to the Akkaraman breed, Lalahan genotype has smaller heads, necks, and ears, shorter legs, and thin, lean tails. Morphometric features make them suitable for rangeland grazing. Lalahan genotype is quite similar to the Kivırcık breed in terms of morphology.

**Table 8.** Meat quality traits in MLD Muscle

Meat quality traits	Lalahan Sheep/ Slaughter Weight			Reference
	35 kg	40 kg	45 kg	
pH (24 <sup>th</sup> hour)	5.38	5.50	5.45	Ünal and Arslan, 2022
Color (24 <sup>th</sup> hour)	L* 40.55 a* 16.73 b* 8.98	L* 40.60 a* 17.04 b* 8.80	L* 41.17 a* 18.47 b* 8.67	
Water holding capacity (24 <sup>th</sup> hour) (%)	11.53	12.50	12.93	
Cooking loss (%)	27.72	28.55	26.48	
ΣTUFAs/ ΣSFA (MLD)	1.02	0.97	0.84	
ω6/ω3 (MLD)	10.55	9.17	7.87	

ΣSFA: Total Saturated Fatty Acids, ΣTUFAs: Total Unsaturated Fatty Acids, ω6: Omega 6 fatty acids, ω3: omega3 fatty acids, MLD: *Musculus longissimus dorsi*

The Lalahan genotype exhibits high adaptability to steppe climatic conditions, displays a strong herd instinct, and is easy to manage. It performs well in the Central Anatolia Region, exhibiting higher fertility and survival rates compared to the K1vırcık breed. However, it has slightly lower growth and body weight than the Akkaraman breed.

The Lalahan genotype has sufficient milk yield for the ewe line in commercial crossbreeding. Furthermore, the fleece of this breed is appropriate for producing carpets and rugs. Concerning male lambs, Lalahan lambs have a comparable average daily weight gain to the K1vırcık breed, but lower than the Akkaraman breed in intensive fattening. However, it has a better feed conversion ratio than both the K1vırcık and Akkaraman breeds, as well as various local breeds. Although the carcass composition is comparable or superior to that of local breeds, the meat quality characteristics are similar to those of the K1vırcık breed.

The Lalahan sheep has significant potential for lamb meat production in the Central Anatolian region. It is predicted that breeding this genotype will become more widespread in the future. In order to improve the genotype, it is strongly recommended to conduct further selection studies and research on various production traits.

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## **Chapter 2**

### **Understanding The Epidemiology Of Noncommunicable Diseases**

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## **Abstract**

Non-communicable diseases (NCDs) are diseases which last for a long time and progress slowly. The most common types of NCDs are cancers, cardiovascular diseases, diabetes and chronic respiratory diseases. The number of deaths caused by NCDs are higher than the sum of all other causes of death. Risk factors of non-communicable diseases are divided into two main groups: modifiable and metabolic risk factors. Modifiable risk factors include tobacco use, physical inactivity, unhealthy diet and the harmful use of alcohol. Metabolic risk factors are hypertension, being overweight/obesity, hyperglycemia and hyperlipidemia. Multi-sectoral protection and control methods for risk factors in society are as important as the studies to be carried out for the treatment of diseases. Promotion of health, protection of health, primary prevention, secondary prevention and tertiary prevention are the basic principles in protecting against non-communicable diseases.

***Keywords:** Non-communicable diseases, epidemiology, chronic diseases, prevention.*

## **Özet**

Bulaşıcı olmayan hastalıklar (BOH), uzun süre devam eden ve yavaş ilerleyen hastalıklardır. En yaygın BOH'lar kanser, kardiyovasküler hastalıklar, diyabet ve kronik solunum yolu hastalıklarıdır. BOH'lardan kaynaklanan ölümlerin sayısı diğer tüm ölüm nedenlerinin toplamından daha fazladır. Bulaşıcı olmayan hastalıkların risk faktörleri değiştirilebilir ve metabolik risk faktörleri olmak üzere iki ana gruba ayrılmaktadır. Değiştirilebilir risk faktörleri arasında tütün kullanımı, fiziksel hareketsizlik, sağlıklı beslenme ve alkolün zararlı kullanımı yer alır. Metabolik risk faktörleri hipertansiyon, fazla kiloluluk/obezite, hiperglisemi ve hiperlipidemidir. Hastalıkların tedavisine yönelik yapılacak çalışmalar kadar toplumdaki risk faktörlerine yönelik çok sektörlü koruma ve kontrol yöntemleri de önemlidir. Bulaşıcı olmayan hastalıklardan korunmada sağlığın geliştirilmesi, sağlığın korunması, birincil korunma, ikincil korunma ve üçüncül korunma temel ilkelerdir.

***Anahtar Kelimeler:** Bulaşıcı olmayan hastalıklar, epidemiyoloji, kronik hastalıklar, korunma.*

## **Introduction**

Non-communicable diseases, which are also called chronic diseases, are diseases that have a chronic character, have a long and slow course, have many risk factors, negatively impact the individual's quality of life, require progressed aptitude in treatment, have complexities that can be lethal or lead to handicap, are exorbitant to screen and treat, and get no opportunity of cure. Non-communicable diseases epidemiology deals with chronic, degenerative and “non-infectious” diseases (Güven Tezcan, 2017 & Bilir & Erbaydar, 2015).

Seven out of ten leading causes of death worldwide in 2019 were non-communicable diseases. These seven causes account for 44% of all deaths and 80% of the top 10 causes. Non-communicable diseases (NCDs), including cardiovascular diseases, diabetes, cancer and chronic respiratory disease, are collectively responsible for 74% of all deaths in the world. The NCD epidemic threatens to disrupt health systems and has negative effects on individuals', families', and communities' health. The financial expenses related with non-transmittable illnesses are important to prevent and control in the development of the 21st century. (WHO, 2024).

The effects of non-communicable diseases on human health are clear, but these effects are only one aspect. NCDs also impose large economic costs beyond direct healthcare costs. NCDs prevent individuals from fully participating in the labor market and reduce productivity at the macroeconomic level due to the effects they have on themselves, their caregivers, and the state (Kontsevaya et al., 2018).

Controlling NCDs involves detecting, diagnosing and treating these diseases and ensuring that people with them have access to preventive care. The most effective NCD interventions can be delivered through primary care approaches that improve early diagnosis and appropriate treatment (WHO, 2024).

### **1. Protection Levels**

The aim of controlling chronic diseases is to reduce the incidence of disease, delay the development of disability, reduce the severity of disease as much as possible, and prolong life. The first goal in chronic disease control programs is to stop seeing chronic and degenerative diseases as a natural process of aging (Bilir & Erbaydar, 2015).

Primary prevention aims to prevent the disease from occurring and to reduce risk factors and disease incidence. Secondary prevention aims to prevent the emergence of undesirable effects by detecting asymptomatic people. Early diagnosis and screening programs such as cervical or breast cancer screening programs are widely used for this purpose. Tertiary prevention strives to increase

the patient's quality of life by minimizing sequelae in people with the disease (Beaglehole et al., 2006, Bilir & Erbaydar, 2015).

## **2. Risk Factors**

NCDs share five major risk factors. These can be listed as physical inactivity, the harmful use of alcohol, tobacco use, unhealthy diet and air pollution (WHO, 2024). An important feature of NCDs is nutrition at an early age, physical exercise, sexual life preferences, smoking/alcohol/addictive drug use, etc (Bilir & Erbaydar, 2015).

- Modifiable behavioral risk factors: Tobacco use, physical inactivity, unhealthy diet, the harmful use alcohol.
- Metabolic risk factors: high blood pressure, overweight/obesity, hyperglycemia, hyperlipidemia.

A high level of one of the metabolic factors significantly increases the risk of cardiovascular events, and the risk increases even more in individuals with more than one metabolic risk factor.

The most important risk factor worldwide for mortality is high blood pressure (19% of global deaths are attributed to it), followed by high blood sugar and overweight and obesity (WHO, 2024).

- Environmental risk factors: Many environmental risk factors contribute to NCDs. Air pollution is the leading cause, causing 6.7 million deaths worldwide. About 5.7 million deaths are related to non-communicable diseases, including stroke, ischemic heart disease, lung cancer and chronic obstructive pulmonary disease. (Kontsevaya et al., 2018; WHO, 2024)

### **2.1. Tobacco Use**

NCDs attributable to smoking include different cancers, ischemic heart disease (IHD), stroke and other CVD and circulatory diseases, chronic obstructive pulmonary disease, diabetes, peptic ulcer, cataracts, macular degeneration and rheumatoid arthritis (Kontsevaya et al., 2018). Tobacco causes more than 8 million deaths every year (WHO, 2024).

The proportion of people aged 15 and over who use tobacco daily had increased from 28.0% in 2019 to 28.3% in 2022. This proportion was calculated at 15.5% for women and 41.3% for men in 2022. The proportion of non-smokers (those who quit smoking and do not smoke cigarettes) decreased from 68.7% in 2019 to 68.0% in 2022 (TUIK, 2022).

Based on the results of STEPS study in Turkey, 43.6% of men, 19.7% of women and 31% of people in total, 6 of them currently use tobacco products (Üner et al, 2018).

## **2.2. The Harmful Use Of Alcohol**

NCDs attributable to alcohol include different cancers, diabetes, pancreatitis, cirrhosis, epilepsy, and IHD, stroke, and other diseases of the heart and blood vessels (Kontsevaya et al., 2018).

The percentage of people above the age of 15 who consumed alcohol decreased from 14.9% in 2019 to 12.1% in 2022. This rate was calculated to be 18.4% for men and 5.9% for women in 2022. The percentage of people who abstain from alcohol consumption (those who have used alcohol before and have never used it) was 85.1% in 2019, and increased to 87.9% in 2022 (TUIK, 2022).

Over half of the 3 million yearly deaths caused by alcohol consumption are a result of non-communicable diseases, such as cancer (WHO, 2024).

## **2.3. Physical Inactivity**

Non-communicable diseases caused by lack of physical activity include heart disease, diabetes, breast and colon cancers (Lee et al., 2012).

4 in 10 adults were physically inactive according to the World Health Organization (WHO) recommendation (individuals who engage in less than 150 minutes of moderate-power or comparable physical activity every week). In the STEPS study conducted in 2017, 33.1% of men and women It was found that 53.9% did not meet WHO's physical activity recommendations (Üner et al, 2018). Lack of physical activity is responsible for 830,000 deaths annually. (WHO, 2024).

## **2.4. Unhealthy Diet**

Attributable NCDs to unhealthy diet include gastric cancer and increased risk of ischemic heart disease, stroke, and other cardiovascular and circulatory diseases due to hypertension (Kontsevaya et al., 2018).

WHO recommends no more than 5 grams of salt (equivalent to around 2 grams of sodium) per day per person to prevent cardiovascular diseases. Every year, 1.8 million deaths are linked to consuming excessive salt/sodium (WHO, 2024).

87.8% of men, 87.9% of women and 87.8% of people in total consumed less than 5 portions of fruit and/or vegetables per day. Average daily salt consumption was 9.9 grams, with men consuming 11 g and women consuming 8.7 g. 62.8% of men, 66% of women and 64.4% of people in total are overweight (BMI  $\geq$  25 kg/m<sup>2</sup>). 21.6% of men, 35.9% of women and 28.8% of people in total are obese (BMI  $\geq$  30 kg/m<sup>2</sup>) (Ünal et al, 2018). Salt/sodium consumption is high in Turkey and the main source of salt is baked bread (Erdem et al., 2017).

In Turkey, the prevalence of obesity in 2011 was 36% and central obesity was 53% (Satman et al., 2013).

### **3. The Main Types Of Non Communicable Diseases**

#### **3.1. Cardiovascular Diseases**

Ischaemic heart disease, which represents 16% of worldwide passings, is the main source of death around the world. Between 2000 and 2019, this disease saw the biggest spike in fatalities, surging by over 2 million to reach 8.9 million deaths (WHO, 2020).

Cardiovascular diseases (CVDs) encompass a range of heart and blood vessel disorders, such as coronary heart disease, cerebrovascular disease, rheumatic heart disease, and other ailments (WHO, 2021). Cardiovascular diseases impact the heart and blood vessels and lead to more deaths worldwide than any other illness. 1 out of every 3 deaths accounts for 17.9 million individuals annually. By addressing and treating risk factors, it could have been possible to prevent or delay 86% of deaths caused by cardiovascular disease (WHO, 2022).

Hypertension is linked to heart diseases, stroke, kidney disease, premature death and disability, and has a major impact on health and economy. Yet, high blood pressure can be avoided and managed (Zhou, Perel, et al., 2021).

Hypertension is a significant driving gamble component of CVDs CVDs and premature deaths across the globe. A research was carried out across 90 countries, it has shown that 31.1% (1.39 billion) of adults had hypertension (Mills et al., 2016).

The prevalence of hypertension has decreased over the past two decades in high-income countries, there have been significant increases in low- and middle-income countries. Prevalence of HT among adults; The rate is greater in low-income countries compared to high-income countries (Mills et al., 2016; Zhou, Carrillo-Larco, et al., 2021).

The prevalence of HT continues to increase globally due to population aging, unhealthy diet (excessive sodium and inadequate potassium consumption) and sedentary lifestyle (Zhou, Carrillo-Larco, et al., 2021).

Hypertension is among the top 10 causes of death in Turkey that can be prevented (Bora Başara et al., 2024). In the PatenT2 study conducted in 2012 on the prevalence, awareness, treatment and control of hypertension in adults in Turkey, the general prevalence of hypertension standardized according to age and gender was found to be 30.3% and was found to be higher in women than in men. According to the PatenT (2003) study, in the PatenT2 study, remarkable improvements were observed in hypertension awareness, treatment and control rates over a 10-year period (Sengul et al., 2016).

In 2013, the general age-changed and sex-changed pervasiveness of hypertension in Turkey was 31.8%, and it was higher in women than in men (Satman et al., 2013).

### **3.2. Diabetes**

Diabetes can result from inadequate insulin production by the pancreas (type 1) or poor utilization of insulin produced by the body (type 2). Type 2 diabetes accounts for over 95% of diabetes cases worldwide. (WHO, 2022).

Diabetes is one of the most important public health problems in the world due to its high and increasing prevalence, high morbidity, and impact on individuals, health systems and national economies. It is estimated that 537 million adults (20-79 years old) in the world are living with diabetes and this number will increase to 643 million in 2030 and 783 million in 2045. 3 in 4 adults with diabetes live in low- and middle-income countries. 1 in 3 adults with diabetes is undiagnosed. The prevalence of diabetes increases with age and is more common in women than men (International Diabetes Federation, 2021).

According to a study conducted in Turkey in 2017, 10.6% of men, 11.5% of women and 11.1% of people in total had high blood sugar (Ünal et al, 2018). In 12 years (1998-2010), the prevalence of diabetes in Turkey rose by 90%, from 7.2% to 13.7%, as reported by the Turkish Diabetes Epidemiology (TURDEP-2) study (Satman et al., 2013). While the prevalence of diabetes was reported as 12.7% in the CREDIT (Chronic Renal Disease In Turkey) study conducted in Turkey, the PURE (The Prospective Urban Rural Epidemiology) study conducted in 2018 showed that diabetes prevalence rose from 13.7% in 2008 to 21% in 2015 (Süleymanlar et al, 2011 & Oğuz et al, 2018). The rise in diabetic individuals each day has a detrimental impact on both the sustainability of health systems and the well-being and lifespan of individuals (Coşansu, 2015).

### **3.3. Cancer**

Cancer is a condition where abnormal cells multiply quickly and spread uncontrollably to other areas of the body, resulting in 1 in 6 deaths and affecting 9.3 million individuals annually. Preventing or reducing health risks could have avoided or delayed 44% of cancer fatalities (WHO, 2022).

Cancer is responsible for roughly 10 million deaths globally in 2020, making it a prominent reason for nearly one out of every six deaths. Approximately one-third of cancer-related deaths can be attributed to tobacco smoking, high BMI, drinking alcohol, poor diet, and lack of exercise. In addition, air pollution is an important risk factor for lung cancer. Numerous types of cancer have the potential to be cured if identified in their early stages and managed successfully (WHO, 2022).

In Turkey, the 5 most common cancer types in men are lung, prostate, colorectal, bladder and stomach cancer, respectively, while the 5 most common



cancer types in women are breast, lung, colorectal, uterine corpus and lung cancer, respectively (Bora et al., 2024).

The top 5 cancers with the highest age-standardized incidence rates in the world are breast, prostate, lung, colorectal and cervical cancers, respectively. The cancers with the highest age-standardized incidence rate in men are lung, prostate, colorectal, stomach and liver cancers, while the cancers with the highest age-standardized incidence rate in women are breast, colorectal, lung, cervix and thyroid cancers (Ferlay J, et al., 2024).

### **3.4. Chronic Respiratory Diseases**

Chronic respiratory diseases are an important, diverse and often preventable group of diseases that increase morbidity and mortality. Chronic respiratory diseases can be largely prevented with good primary health care and self-care education. These diseases can be listed as asthma, chronic obstructive pulmonary disease (COPD), restrictive respiratory diseases, and occupational respiratory diseases (Thulchinsky & Varavikova, 2019).

Risk factors for chronic respiratory diseases include tobacco smoke, air pollution, occupational chemicals and dust, and lower respiratory tract infections common in childhood (WHO, 2024).

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease causing restricted airflow and breathing problems. Smoking and air pollution are the most common causes of COPD. People with COPD are at higher risk of other health problems. Chronic obstructive pulmonary disease is the third leading cause of death worldwide, causing 3.23 million deaths in 2019 (WHO, 2019). Chronic obstructive pulmonary disease affects about 300 million people worldwide (Ruvuna L, Sood A, 2020). COPD ranks fourth among the top 10 causes of death for all age groups and genders in Turkey (WHO, 2024).

Asthma is a prominent noncommunicable disease (NCD) that impacts individuals of all ages, being the most prevalent chronic illness in children. In 2019, approximately 262 million people were impacted by asthma, resulting in 455,000 deaths (WHO, 2024).

### **Conclusion**

Most deaths around the world are caused by non-communicable diseases. Reasons such as increased life expectancy in society and technological developments increase the incidence of non-communicable diseases.

The most important non-communicable diseases can be listed as cardiovascular diseases, diabetes, cancer and chronic respiratory diseases.

Understanding the risk factors of non-communicable diseases is important in prevention.

Cardiovascular diseases impact the heart and blood vessels and result in more global deaths than any other illness. Hypertension is a disease that affects most of the population in low- and middle-income countries as well as in high-income countries. The fact that hypertension is a leading risk factor for cardiovascular diseases but is preventable increases its importance.

Diabetes is a serious issue for public health whose prevalence is increasing in the world and in our country and is predicted to continue to increase. Diabetes reduces the quality of life due to the complications it causes and also causes significant morbidity and mortality.

The burden of cancer in the world and in Turkey is high and increasing. Approximately one-third of cancer deaths are associated with tobacco use, alcohol consumption, low fruit and vegetable consumption, high body mass index(BMI) and absence of physical activity.

Chronic respiratory diseases are among the important causes of morbidity and mortality in the world and in Turkey. The majority of these diseases are COPD and asthma. COPD is among the top 10 causes of death both in the world and in Turkey.

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## **Chapter 3**

### **Data Mining in Health Sciences**

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## **Data Mining in Health Sciences**

Computers and digital technology are increasingly gaining ground in every aspect of our lives, leading to the generation and storage of large amounts of data. As the amount of data stored in databases increases, it becomes important to keep this data organized and accessible.

Organization of databases ensures effective management of data. Storing data in an organized manner enables quick access and search. Additionally, databases can maintain data integrity, ensure data security, and manage data access privileges.

There are various methods used to organize data. Here are some:

1. **Relational Databases:** It is a type of database where data is stored in tables and relationships are determined. SQL databases can be given as an example.
2. **NoSQL Databases:** It is a type of database that is unstructured, does not require a specific schema and is generally used to process large data sets.
3. **Document-Based Databases:** It is a type of database where data is stored in the form of documents such as JSON or XML. MongoDB is an example of this type of database.
4. **Graph Databases:** It is a type of database in which data is stored in a graph structure and relationships are modeled using graph theory. It is especially used in visualizing relational data.
5. **Key-value Stores:** It is a simple type of database where each data is associated with and accessed by a key. Memory-based databases such as Redis and memcached are examples of this category.

These methods are preferred depending on the nature of the data and usage scenarios. For example, relational databases are ideal for storing structured data and supporting complex queries, but for large data sets, NoSQL databases may be better suited.

It is true that most of the data is in unstructured format. This type of data is generally non-formal data such as texts, music or video files that cannot be directly understood by computers and do not have a specific data structure.

Text mining is a method used to extract meaningful information from such unstructured text data. This process involves discovering previously unknown patterns, relationships, or trends from ambiguous and disorganized text data. It emerged from the combination of fields such as text mining, natural language processing (NLP) and information retrieval.

Text mining is also called text data mining or knowledge discovery from text databases. These terms are used to describe the process of extracting information from text data and the purpose of this process.

It has developed as a result of research in text mining, information retrieval systems and natural language processing. Information retrieval studies, which began in the 1960s, focused on accessing texts and understanding natural language. By the 1990s, topics such as text mining and text analytics rapidly gained importance and expanded as research areas.

This process includes various applications such as extracting information from texts, categorizing texts, and structuralizing unstructured text data. These fields enable more effective use of unstructured text data that is converted into a format that can be understood and processed by computers.

It is indeed a great challenge that most of the data in medicine exists in complex and unstructured format. When physicians manage patients' treatment processes or conduct research, they use data in free text format from a variety of sources, such as patient reports, clinical studies, research reports, hospital records and web pages.

However, the difficulties in analyzing this data and accessing the desired information require serious time and effort when done with traditional methods and human power. In this process, manually scanning, classifying and analyzing information can take a long time and cause errors.

Therefore, the use of technologies such as artificial intelligence and machine learning in the field of medicine is gaining importance. Techniques such as natural language processing (NLP) can automatically analyze, make sense of, and structure complex text data. In this way, physicians and researchers can manage patients' treatment processes more effectively and access the necessary data for scientific studies more quickly.

Artificial intelligence-supported medical information systems can be useful in many areas such as making diagnostic decisions, recommending treatment options and conducting research by analyzing patient data. These systems can improve the quality of healthcare and improve patient care by providing physicians and researchers with access to more accurate, reliable and timely information.

Text Mining is a critical process that transforms texts into structured and meaningful data by revealing unknown information by identifying patterns within the text. This process consists of a series of steps and is usually carried out as follows:

1. Pre-Processing: Text data is subjected to pre-processing such as sentence and word analysis. At this stage, unnecessary or meaningless words are removed from the texts, and grammatical elements such as punctuation marks and stop words are addressed.



2. Categorization: Texts are classified according to certain categories or topics. This step is important to better understand the content of the texts and analyze them more effectively.
3. Analysis and Evaluation: Large volumes of text data are analyzed using traditional data mining methods. Methods such as clustering, artificial neural networks, decision trees, regression analysis help extract meaningful patterns and relationships from text data. The results obtained are then evaluated and interpreted.

Text mining facilitates access to information from a wide range of data, such as thousands of documents in different languages, web page contents, publications and summaries. Researchers can obtain valuable information by analyzing text data from a variety of sources, such as medical reports, web pages, articles, and billing information.

This process is especially important when large volumes of text data need to be analyzed quickly and valuable information must be accessed quickly. Text mining methods help researchers and experts process such masses of data effectively and obtain meaningful results.

Text mining is the process of extracting qualified information hidden within the data in the font, which is usually not in a specific format, and formatting the irregular data. This process involves extracting meaningful information from text data in large data stacks and making this information usable.

Text mining consists of three main components: information retrieval, information processing and information integration. Information retrieval involves accessing relevant text documents and scanning and collecting the information in these documents. During the information processing phase, meaningful information is obtained by extracting patterns and relationships in the accessed documents. Information integration ensures that the information obtained is brought together, analyzed and made usable.

Text mining can also be defined as an architecture that combines the stages of accessing information from text collections, extracting information from individual texts, knowledge discovery from databases, knowledge management in organizations, and visualization of data and knowledge.

Besides these definitions, text mining often includes techniques from fields such as natural language processing, machine learning, statistical analysis and computer science. These techniques can be used in various applications such as analyzing, classifying, summarizing, and sentiment analysis of text data.

As a result, text mining can be defined as a multidisciplinary field that includes a set of techniques and methods used to extract meaningful information from text data within large data stacks and make this information usable.

There are many different definitions for data mining. The American Marketing Association (AMA) defines data mining as "The process of analyzing data to find new and potentially useful information. This process involves the use of mathematical tools to uncover hard-to-find patterns." He defined it as: Gartner defines data mining as "The process of discovering meaningful correlations, patterns and trends by sifting through large amounts of data stored in data warehouses. Data mining uses mathematical and statistical techniques as well as pattern recognition technologies." defines it as.

These definitions clearly state the three basic elements of the data mining process:

1. Large amounts of data: For example, data that a mobile phone company has kept about its more than 34 million subscribers over the past three years, including demographic characteristics, billing details and usage habits.
2. Potentially useful information: For example, the ability to pre-identify customers who are currently inclined to switch to another company and prevent these customers from switching, using characteristics of customers who have switched to another phone company in the past.
3. Mathematical and statistical techniques: For example, using a statistical method such as "logistic regression" to predict the lost customer mentioned in the example above.

The CRISP-DM model was developed in 1996 as an industry standard model for data mining. This model summarizes a data mining project as a six-stage cycle. These six stages are:

1. Problem Statement: A data mining project begins with the recognition of a business problem. Business experts, data mining experts, and domain experts come together to define business goals and requirements. At this stage, the project objective is transformed into a data mining problem.
2. Data Discovery: Domain experts collect, describe and examine data. Data quality issues are identified. Data mining tools are not yet used, but traditional data analysis tools, such as descriptive statistics, are used to explore the data.
3. Data Preparation: Domain experts create the data model for the modeling process. It cleans the data, adapts it to the required format and can create new calculated variables. During the data preparation phase, data may be modified multiple times.
4. Modeling: Data mining experts apply different mathematical models because there can be more than one method to solve the same problem.

The modeling phase and evaluation phase are combined and can be repeated multiple times.

5. Evaluation: The model is evaluated by data mining experts. If the model does not meet expectations, one goes back to the modeling phase and the parameters can be readjusted.
6. Distribution: The best model is selected and the results are presented to the user. At this stage, project results are used within the business or presented to customers.

The CRISP-DM model provides a framework for organizing the management and implementation of data mining projects.

During the evaluation phase, data mining experts examine the model in detail. If the model does not meet expectations, they can go back to the modeling phase and rebuild the model by changing the parameters until they achieve the best values. Finally, once satisfied with the model, the following questions should be answered: Does the model achieve business objectives? Have all business issues been evaluated?

At the end of the evaluation phase, data mining experts decide how to use the obtained results. They can use the results internally or present them to customers.

During the implementation phase, data mining experts transfer the results to other applications. These applications can take various forms, such as internally available databases or spreadsheet applications. In this way, it is ensured that the findings obtained are used effectively within the business. During the implementation phase, data mining experts make the results they obtain available within the business. These results are often presented in the form of databases or spreadsheet applications that company employees can easily access and use. In this way, different departments or teams within the business can analyze, interpret and use the obtained data in decision-making processes. The ease of use of these applications ensures that the results are effectively adopted and used throughout the business.

### **Knowledge Discovery from Data Sets: Data Mining**

It is a common acceptance that the available information forms the basis of a research, discussion or reasoning. Data can be defined as the initial information required to reach a conclusion or the quantities, events, records and sets of numbers used to reach this conclusion. Nowadays, there are many data sets in daily life and various information can be obtained by using these data. The amount of data we have as humanity has now reached the level of zettabytes

and even yottabytes. Even such large amounts of information doubles every 20 months.

In the past, accessing data took time, while analyzes and decisions were completed quickly. However, today, access to data has become easier and faster, but data-based analyzes have become more complex and difficult. Therefore, it became necessary to transfer the analysis, conclusion and decision-making processes to computers. With this need, algorithms based on mathematical and statistical calculations were developed and the concept of "Data Mining" was born. Data Mining, used in many sectors such as marketing, e-commerce, banking, insurance, telecommunications and health, has increased the quality of life of humanity and provided faster access to information. In these sectors, data mining has played an important role and has greatly benefited humanity. Developing data mining has reduced the workload and enabled access to more information in a shorter time. In this way, living standards have increased and professional groups have had the opportunity to work more effectively.

Data mining, in short, is the acquisition of previously unknown, valid and applicable information from data stacks through a dynamic process. This method, which is frequently used especially in the field of engineering, has also gained great importance in the field of medicine in recent years. With the growing growth of data in the healthcare industry, data mining and statistical analysis methods play a critical role in uncovering valuable information. This information makes significant contributions to computer-aided diagnosis processes and doctors' ability to make correct decisions, thus providing great support to the development of healthcare practices.

### **History of Data Mining**

Data mining is one of the techniques that mathematicians began studying in the 1950s. During this period, fundamental studies were carried out in areas such as artificial intelligence and machine learning. In the 1960s, statisticians also conducted research on methods such as regression analysis, maximum likelihood estimation, and neural networks, which formed the first steps of data mining. In the 1970s, 1980s and 1990s, with the development of new programming languages and computer techniques, algorithms such as genetic algorithms, clustering methods and decision trees also emerged. In the 1990s, concepts such as knowledge discovery and data warehousing databases emerged and data mining became increasingly common. As a result, data mining has become a widely used technique today, making significant contributions to health, commerce, finance and many other fields.

The term data mining has become known as "knowledge discovery" in data-driven research fields since the 1990s. During this period, although studies were initially generally limited to data in databases, over time this scope expanded beyond databases. Examining this past research provides important clues about the future of data mining.

The first use of data mining techniques in health information systems began with expert systems in the 1970s. However, the widespread use of expert systems in the field of medicine has been limited due to the rapid change of data and differences between experts. Later, especially in the 1990s, techniques such as neural networks began to be used to investigate issues such as patients' future health status and cost predictions.

Today, data mining is successfully applied in many fields. The rapid development of technology has allowed the emergence of new methods. With the development of various techniques such as decision trees, artificial neural networks, statistical methods, algorithms and variance analysis, access to information has become easier.

### **Legal Aspects of Data Mining**

Today, the use of computers in the medical field is an important development in modern medicine. Computers are frequently used in areas such as diagnosis, treatment planning, laboratory analysis and hospital management. However, it is acknowledged that in some cases traditional methods can be misleading and computers can provide more accurate information. At this point, it is important that computers use patient information correctly and prevent unauthorized persons from accessing this information.

Responsibilities arising from the use of computers generally belong to the physicians in the clinic. Physicians and healthcare personnel must protect patient information uploaded to computer systems and comply with medical confidentiality principles. Additionally, accurate processing and storage of medical data is critical to preventing misdiagnoses and treatment errors.

Protecting the confidentiality of personal data is also of great importance. Therefore, a unique identification number is assigned to each patient on hospital computers and the security of this information is ensured. Data uploaded to and received from computer systems must be processed with respect for the patient's interests and privacy rights. Otherwise, the patient's right to privacy would be violated.

The World Medical Association announcement is based on a concluding decision adopted at the 27th World Medical Association General Assembly (October 1973, Munich-Germany) and developed at the 35th World Medical

Association General Assembly (October 1983, Venice-Italy). According to the announcement, which states that there is a moral relationship between the doctor and the patient, this relationship must always be kept alive and the patient must not be harmed during medical procedures. In order to comply with the principle of doing no harm, the following ethical issues must be taken into consideration: Accurate information about the patients must be loaded into the computer. Only the physician should be able to access patient information from the computer. Information about the patient should not be given to any person or institution and the principle of medical confidentiality should be observed. It is important to make legal regulations on this issue. The benefit of society should be considered superior to the benefit of the individual, and concrete and individual issues should be reported to the relevant authorities. Especially if certain diseases threaten public health, it is mandatory to disclose these diseases. In this way, the spread of the disease to others is prevented and society is protected.

## **Elements of Data Mining**

### **Database**

Database refers to a collection of data organized in accordance with its intended use. More specifically, a database is a logically and physically structured collection of data where related data is kept together. This data is usually stored in digital format and made accessible when needed. Databases usually contain large amounts of data and are used for information storage purposes.

### **Data warehouse**

Data warehouses are special data storage systems created by the integration of various databases. These structures are known as special databases that provide the data source from which the Data Mining process is carried out. Data warehouses, where data from different sources and in different formats are generally stored, aim to combine all this data under a single integrated structure. In this way, it becomes possible to perform a holistic analysis by bringing together data from different sources.

### **Data Sources**

Data sources are the main sources that form the basis of research, discussions and judgments. These resources include various data types such as books, articles, data files, relational databases, data warehouses, advanced databases, films, electronic resources, journals, reference resources,

dictionaries, encyclopedias, almanacs, statistical resources, atlases, biographical resources and chronologies.

### **Application Areas of Data Mining**

Data mining can be applied in almost every field where data is intensively produced and databases are created. Some application areas are:

- Database analysis and decision support systems
- the market research
- Risk analysis
- Similarity analysis between documents, e.g. news sets and emails
- Customer credit risk analysis
- Using corporate resources in the most effective way
- Future predictions with past and current structure analysis
- Scientific and engineering fields
- Health sector
- trade sector
- shopping industry
- Banking and finance sector
- Education sector
- Internet (web) use
- Document usage
- insurance
- Marketing

### **Techniques and Methods Used in Data Mining**

Many of the techniques used in data mining are based on statistical methods. Here are some basic statistical techniques and their uses in data mining:

**Classification:** This technique is used to separate data into specific classes. For example, it can be used for a classification problem such as determining whether an email is spam. Algorithms used include techniques such as decision trees, support vector machines (SVM), and k-NN (nearest neighbor).

**Regression:** This technique is used to model the relationship of a dependent variable (outcome) with one or more independent variables (predictors). For example, regression can be used to model the factors that determine the price of a home.

**Clustering:** This technique is used to divide data into groups with similar characteristics. For example, it can be used to identify customers with similar

shopping behavior in a customer data set. Algorithms used include k-means and hierarchical clustering.

**Dimensionality Reduction:** It is used to reduce the complexity in large-scale data sets. It is especially useful in high-dimensional data sets. For example, principal component analysis (PCA) is a frequently used technique for dimensionality reduction.

**Hypothesis Testing and Analysis of Variance:** These techniques are used to determine the significance of differences in data sets. For example, hypothesis testing can be used to test the effectiveness of an advertising campaign.

**Association:** This technique is used to determine relationships between variables in the data set. For example, it can be used to identify items purchased together at a grocery store.

In addition to these statistical techniques, machine learning techniques are also frequently used in data mining. These include techniques such as support vector machines (SVM), decision trees, random forests, deep learning. These techniques are used to model complex relationships and make predictions in large data sets.

Although memory-based or sample-based methods were proposed in the statistical literature in the 1950s, they could not be used at that time due to computational and memory requirements. However, today, as the prices of computers decrease and their capacities increase, especially with the spread of multiprocessor systems, these methods have become available. The best example of such methods is the k-nearest neighbor algorithm.

Artificial neural networks gained popularity after the 1980s. These networks represent functions distributed over a network of simple processing units. Learning algorithms used in artificial neural networks calculate connection weights between data. Artificial neural networks do not assume a parametric model about the data like statistical methods, so their application area is broader and does not require as much processing and memory as memory-based methods.

Once decision trees are learned in statistical methods or artificial neural networks, the resulting functions may be difficult for humans to understand. However, after decision trees are created, rules can be written by descending from the tree root to the leaf. Rule extraction in this way ensures the validity of the result of the data mining study. The rules can be shown to a person who is an expert in their application to check whether the result is meaningful or not. Even before using another technique, a preliminary study with the decision tree is recommended and provides information about important variables and approximate rules.



## **Data Mining in Medicine**

Today, in information systems in the field of medicine and health, many data, from demographic information of patients to disease and treatment conditions, from examinations to information regarding billing and administrative affairs, are stored and accessed digitally. Since health and medicine are one of the most important scientific research fields of our age, information systems in this field are also big data sources for research.

In the last three decades, there have been major advances in health information systems around the world. Although health informatics is a new field, rapid innovations have been made, especially in information modeling and diagnostic tools. The first use of data mining techniques in health information systems began in the 1970s and continued with expert systems developed in later years.

Although expert systems offer powerful tools in the field of medicine, they have not become widespread due to the rapid change of data in this field and differences of opinion among experts. However, in the 1990s, neural networks began to be used to investigate issues such as future health status of patients and cost predictions.

Health and medicine are the research fields that need the most information today. In recent years, there have been significant developments in the information systems used in hospitals and health centers, especially thanks to innovations in health data models, standards and coding systems. These developments have enabled more and more diverse data to be stored and have revealed the need for information discovery.

Data Mining makes great contributions to both medicine and improving service quality by revealing valuable information from large databases in the field of health and medicine. Today, databases developed within the scope of international joint projects and storing biological data, access to these databases and data mining systems have become an important part of clinical research.

### **Text Mining in Medicine**

The use of text mining techniques in the medical field has increased significantly in the last few years. Medical data is often available in free text format, which can lead to critical patient information being missed and making information difficult to access. While Electronic Health Records and Health Information Management are identified as one of the important goals in the medical field, the fact that clinical documentation is in free text format may limit the success of these systems. This situation has increased the need for text mining techniques in medicine. Data such as clinical studies, research reports,

hospital records, doctor's notes, procedures, and invoices are the primary sources of data in medicine and are often available in free text format.

Text mining plays an important role, especially in medical research. In this field, it is used for purposes such as finding causal links between symptoms and diseases, relationships between drugs and chemicals, analyzing patient records, identifying gene-gene and protein-protein relationships, improving diagnosis and treatments, improving service quality and controlling costs. For example, Shatgay's study searched biomedical publications to discover functional relationships between genes in DNA microarray experiments and attempted to find relationships based on abstracts of articles. In Swanson's study, text mining techniques were used to find relationships and connections between diseases and their symptoms. Using medical research pages, articles and news, patterns of relationships between symptoms, drugs, diseases and chemicals were looked at. In this type of studies, the causes of a particular problem or disease are determined and studies are carried out on treatment or prevention methods. Tools such as Swanson's ARROWSMITH play an important role in the field of text mining and provide valuable sources of information in medical research. Researchers such as Lindsey and Gordon have expanded on Swanson's approach and attempted to find common words and phrases using word frequency statistics. However, it is stated that these approaches still need human filters at some points.

With the increase in data-based scientific studies in medicine, the information obtained by analyzing data plays an important role in decision-making processes. However, the vast majority of scientific knowledge is stored in publications and other unstructured formats. Approximately 90% of data worldwide is in unstructured format, making access and use of information difficult. This situation leads to the development of new technologies due to the increasing importance of information and difficulties in accessing it.

Text mining offers researchers new solutions in reviewing literature and accessing information available in free format in businesses. This technique increases efficiency by significantly reducing the time spent. Since most data in medicine is semi-structured or unstructured, text mining is an important tool to assist physicians in both clinical research and decision-making processes. These systems make it easier to access the desired information from text masses and improve the quality of patient care.

Especially in our country, the field of text mining has not yet received sufficient attention, which requires more attention to be given to this field and more intensive studies to be carried out. In this way, the importance of text

mining in the field of health can be spread to a wider audience, its use can increase and the efficiency in health services can be increased.

### **Medical Informatics**

Although medical informatics is generally thought of as the use of computer technologies in the field of medicine, it actually refers to the intersection of the disciplines of medicine and computer science. This discipline includes all processes from producing, collecting, evaluating, analyzing, storing, processing, presenting and archiving patient information.

According to J.H Van Bommel, medical informatics or medical informatics lies in this set of intersections between computer science and various medical disciplines. According to this definition, medical informatics covers information management processes in the field of medicine and refers to the application of computer science to healthcare. In this context, medical informatics plays an important role at every stage of patient data and ensures effective management of this data.

Medical informatics aims to use today's computer and communication technology at the highest level in interaction with various branches of science in order to use information in the field of medicine effectively and efficiently, disseminate this information, analyze it and manage it in a way that enables new structures. This discipline lies at the intersection of information technologies and health sciences and has played an important role in theoretical and applied education as well as in medical research and development.

Medical informatics techniques greatly increase the data collection, processing and evaluation capabilities of health centers, enabling accurate, detailed and reliable results to be achieved on a global scale. Thanks to these techniques, healthcare professionals can manage patient information more effectively, medical research can be conducted more quickly and efficiently, and the quality and accessibility of healthcare services can be increased.

The British Medical Informatics Association defines medical informatics as "the tools, skills and awareness that will enable the sharing and use of information necessary for the expansion of healthcare services." According to this definition, medical informatics centers data and information management in health services and makes the best use of computer and communication technologies in this process.

Additionally, medical informatics lies at the intersection of different disciplines such as health, informatics, psychology, epidemiology and engineering. This field is a branch of science that researches and teaches how information systems can be applied to healthcare. Therefore, the discipline of

medical informatics focuses on the design, development and implementation of information systems necessary for the effective delivery of healthcare services.

Medical informatics covers a variety of topics. These include data and information management, coding systems, data processing, database management systems, telecommunication systems, medical classification systems, patient registration systems, electronic patient records, biosignal analysis, medical imaging systems, image processing and analysis methods, clinical information systems, society. There are topics such as medical information systems, nursing information systems, decision support systems, health information systems and hospital information systems. Each of these issues is important to improve the quality of healthcare and ensure its effective management.

Medical informatics focuses on understanding the information and communication technologies used in the field of medicine, contributing to the development of existing technologies, creating methods and principles that will enable this contribution, and evaluating the achieved developments from the perspective of institutions and individuals.

In this context, the field of medical informatics conducts research to understand how technologies used in medical practice work and determines how these technologies can be improved. In addition, it creates the necessary methods and principles for the effective use of existing technologies and monitors new developments in this field.

Medical informatics also evaluates the advantages and disadvantages of using these technologies for healthcare institutions and individuals.

This assessment helps develop strategies to improve the quality of healthcare and achieve better outcomes.

#### Data Mining Use and Applications in Medicine and Health Services

The health sector is one of the areas where information changes most rapidly in terms of content and structure. In order to provide health services in the fastest, most accurate, highest quality and responsive manner, health professionals need to access the most accurate and up-to-date information and use this information by making use of decision support systems. Data Mining is used to reveal hidden, valuable and usable information from large amounts of data and to provide strategic decision support; It is a method that creates decision-making models based on the analysis of data. Therefore, the use of Data Mining as a decision support tool in the provision of health services, management of health institutions at all levels and establishment of health policies will help health professionals make the most appropriate decisions.

In our country, the Ministry of Health, through its evaluations, has determined that there are no national or international standards in the collection, storage and analysis of data that is vital for making policies in the field of health, and that there is a serious confusion, especially in data collection, and within the scope of the "Health Transformation Program", "Effective in the Decision Process" It initiated studies under the title "Access to Information: Health Information System". The National Health Data Dictionary, Minimum Data Sets, Health Coding Reference Server, Electronic Health Record (EHR) database and Decision Support System components where health data are collected constitute the scope of these studies (15). It is inevitable for the Ministry of Health to resort to Data Mining solutions, where collected data are converted into indicators for analysis purposes and will create models that guide decision-making. However, applying the right Data Mining solution here is very important to achieve correct results (20,24).

### **Application Areas of Data Mining in Medicine**

Data accumulated in health institutions vary over time and geographical regions. These data sets may contain inconsistent, incomplete, contradictory and extreme data. Much of the research in the field of medicine relies on Data Mining techniques that enable this data to be analyzed and meaningful conclusions drawn. These techniques generally include various methods such as classification, clustering and association rules. Health and treatment data stored in electronic media offers a wide area where Data Mining techniques can be applied. Some of these areas are: Determining the factors affecting diseases. Early diagnosis of diseases and choosing the right treatment methods. Increasing the quality of health services and creating health policies for the future. Promoting preventive medicine and reducing health expenditures. Detecting epidemic diseases and taking precautions. Detecting fraud in healthcare expenses and reducing costs. Developing the right drugs by using health databases during the drug development process. Increasing the quality of health services. Using Data Mining techniques in these areas can provide significant innovations and improvements in the healthcare sector.

### **Application Examples and Achievements in The World**

In order for healthcare institutions to provide high quality service and survive in the competitive environment, it is of great importance to establish informed decision-making processes in the treatment, marketing, planning and management stages. One of the studies carried out in this direction aims to

improve the quality, accessibility and budget of child health programs in a large district in England.

This study was initiated to increase the effectiveness of child health programs and to ensure that health services are more inclusive and accessible. In this process, through analysis and evaluation of existing data, the strengths and weaknesses of the programs were identified and improvement opportunities were revealed. In addition, strategic plans were developed to ensure more effective use of the budget of the programs and the correct distribution of resources.

This study demonstrates how informed decision-making processes are an effective tool in improving healthcare. Data analysis and evaluation is an important step for institutions to improve service quality and provide better service to patients. Therefore, by focusing on informed decision-making processes, healthcare institutions can be successful in the competitive environment and continuously improve their service quality.

Boehringer Ingelheim Italy is one of the leading pharmaceutical companies worldwide and is headquartered in Germany. The company specializes in the production and marketing of medicines for human and animal health and has more than 140 subsidiaries. Boehringer Ingelheim Italy used data mining methods to classify its customer base of pharmacies in order to diversify its business activities and develop more targeted and effective sales strategies.

Texas Health Services, founded in 1997, is one of the largest healthcare organizations in the state. There are 13 hospitals, many clinics, treatment and intensive care centers. Providing services in rural and urban areas, the institution provides basic and first aid services to a wide range of people. This organization used data mining methods to improve data quality and reduce data mining costs. The results obtained are as follows:

- Data quality has been improved and data mining costs have been reduced by 50%.
- Multiple patient population results were evaluated.
- A fast and interactive data analysis environment is provided for quality comparisons.

These studies demonstrate the effectiveness and efficiency of data mining techniques in healthcare. These methods allow healthcare organizations to provide better service and use their resources more efficiently.

San Francisco Heart Institute is a major healthcare institution where hundreds of heart patients from all over the world receive treatment. The results obtained as a result of the data mining studies are as follows:

- By analyzing the treatment processes, the demographic and structural characteristics of the patients, and their responses to the treatment, the duration of hospital stay of the patients was shortened.
- By performing patient mortality analysis, patients with high risk of death were identified. The risk of death has been reduced by developing special solutions for these risk groups.
- By performing revenue analysis, more efficient contract types were developed and implemented.

In a study conducted by A. Kusiak and his team, data mining methods were used to determine whether the tumor in the lung was benign or not. As a result of the analysis performed on invasive test data collected from different clinics, it was observed that the diagnosis could be made with 100% accuracy.

In a study conducted on a database prepared by the Korean Medical Insurance Corporation, data on high blood pressure were examined. It has been determined that living conditions (diet, salt intake, alcohol, tobacco, etc.) are not effective in prediction, and the age factor plays an important role. This study was an important step in identifying risk factors for high blood pressure and developing treatment strategies.

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## **Chapter 4**

### **Myasthenia Gravis**

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## **Introduction**

Myasthenia gravis (MG) is an autoimmune disease of the neuromuscular junction that affects postsynaptic cholinergic receptors (1, 2). It is the most common autoimmune disorder of the neuromuscular junction (3). Autoantibodies formed against the acetylcholine receptor (AChR) on the postsynaptic membrane are the mechanism responsible for generalized myasthenia gravis (GMG) in approximately 85% of patients. A minority of patients have autoantibodies against muscle-specific kinase receptor (MuSK) or lipoprotein-receptor-related protein-4 (LRP-4). It causes variable weakness in the ocular, facial, bulbar, extremity and respiratory muscles (4, 5). Ocular symptoms are usually the first to appear in 50% of patients, and most patients progress from ocular to GMG within 3 years (1, 2). It affects all striated muscles (2). In rare cases, it may occur as bulbar palsy. Ocular symptoms are typical findings such as ptosis and diplopia (6). Ptosis is initially unilateral but later becomes bilateral (7). Bulbar symptoms include dysarthria, dysphagia and dysphonia. MG can be divided clinically into two forms; the form with pure ocular symptoms and the GMG form with mild, moderate and severe symptoms (2, 6, 7). Only ocular findings are not expected in an anti-MuSK patient (8). It is a serious disease with predominantly bulbar involvement (9).

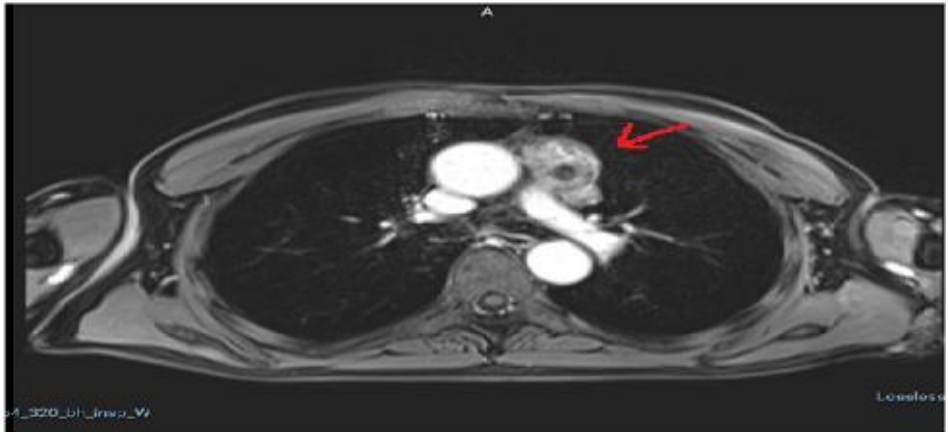
It is less likely to generalize when symptoms remain confined to the ocular muscles for 2 years. Approaching MG as a disease with subgroups with different clinical, serological and genetic features is important for planning treatment (2). Weakness is more evident in proximal muscles than in distal muscles. It is symmetrical except for the eyes (10). It becomes more symptomatic in the evening (7). Ocular MG is not life-threatening but can cause significant disability when diplopia is persistent (11). Conduction across the neuromuscular junction cannot produce sufficient muscle activation, resulting in fatigue-inducing weakness (4).

## **Laboratory Examination**

The AChR+MG patient has complement-mediated IgG1 and IgG3 antibodies (1). However, approximately 15% of patients do not have these antibodies and are considered seronegative (9). MuSK antibodies are mainly IgG4 (4). In approximately 10% of patients with GMG, no antibodies are detected by standard tests. Many of these patients had low concentration or low affinity AChR antibodies when tested with more sensitive methods (10). Autoantibodies against LRP-4 are believed to be pathogenic by impairing MuSK activation (4). It is associated with pure ocular forms (8).

## **Thymus Gland**

Thymus dysfunction is considered an important cause of the immune mechanism in AChR+ MG (4). It plays a role in this disease, but its exact pathogenesis is still unclear. Thymic hyperplasia is observed in 60% of patients and thymoma is observed in 10% (6, 7). The presence of thymoma is associated with poor prognosis (2). Thymoma-associated MG mainly presents with late onset and severe symptoms (1). Thymectomy is recommended and should be performed as early as possible for all adult patients who are diagnosed with AChR+ or seronegative GMG in the absence of thymoma, whose disease onset is <50 years of age, who do not respond to initial immunosuppressive treatments, who cannot tolerate immunosuppressive treatments, who have side effects and recurrence after immunosuppressive treatments (3, 11). If there is thymoma, thymectomy is mandatory. Thymectomy is not recommended in MuSK+ MG (2). Early thymectomy is recommended in AChR+ GMG patients (4). The thymus gland of newly diagnosed MG patients should be examined with computed tomography (CT) or magnetic resonance imaging (MRI). In MG patients with thymoma, thymectomy improves MG symptoms in most patients and some achieve complete remission. Before thymectomy, the patient's clinical condition must be stable (10). There is uncertainty about performing thymectomy in MG patients without AChR or MuSK antibodies but with LRP-4 antibodies. Thymectomy is not recommended as first-line treatment for ocular myasthenia but should be performed when drug therapy has not been successful and there is a risk of GMG (11).



**Figure-1/Thimoma\***

*\*Erzincan Binali Yıldırım University*

## Electromyography (EMG)

Repetitive nerve stimulation is an important test in diagnosing MG (12). There is usually no decrement in limb muscles with repetitive nerve stimulation. The most ideal muscle for repetitive nerve stimulation is the orbicularis oculi muscle. Repetitive nerve stimulation is sometimes not useful in patients with only ocular symptoms. Single fiber EMG is very sensitive but not specific for MG (2). In MG, a decrease in the compound motor action potential (CMAP) occurs as a result of repetitive nerve stimulation at a rate of 3 Hertz, and a decrease in CMAP amplitude of more than 13% is required for diagnosis (7, 12).

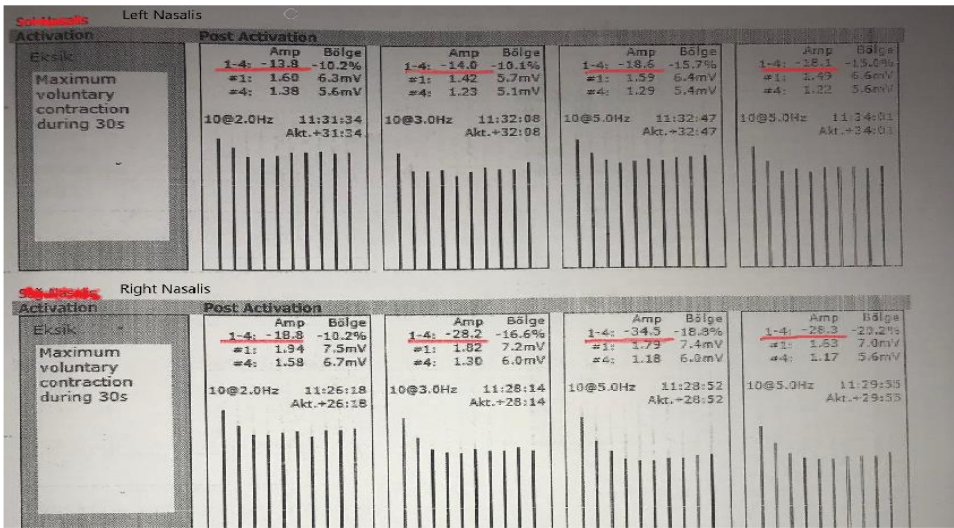


Figure-2/Decrement\*

\*Erzincan Binali Yıldırım University

## Myasthenia Gravis Treatment

The aim of treatment in MG disease is to quickly control the symptoms and achieve remission. There is no single, universally accepted treatment regimen (11). The initial treatment drug for all MG patients is pyridostigmine. The average pyridostigmine dose is 60 mg 2-5 times a day. If patients remain symptomatic under anticholinesterase treatment, immunosuppressive treatments are started. Corticosteroid is started at 15-20 mg per day. It can be increased if necessary up to 0.5-1 mg/kg. Azathioprine is used together with corticosteroids (3). If long-term corticosteroid treatment is required in GMG patients, thymectomy and immunosuppressants should be added. Oral corticosteroids are the first line of immunosuppressive treatment. Initially, it should be started at a low dose (6). In addition, immunosuppressive treatments such as Azathioprine can be given in

addition to or instead of corticosteroids in cases where corticosteroid use is risky (11). Low doses of corticosteroids are usually sufficient. Generally, an average corticosteroid maintenance dose of 6 mg/day with additional azathioprine may be sufficient for remission. Anticholinesterases are not generally helpful for diplopia. In many patients, relapse occurs after discontinuation of corticosteroids. Therefore, it is necessary to apply low doses of corticosteroids for a long time. Corticosteroids are beneficial in all subgroups, but MuSK+ MG patients require high doses, whereas low doses are usually sufficient in OMG (2). Other drugs used together with corticosteroids are mycophenolate mofetil, cyclosporine, tacrolimus, rituximab, methotrexate and cyclophosphamide (9). Intravenous immunoglobulin (IVIG) or plasma exchange (PE) may be added to prevent corticosteroid-induced weakness. Corticosteroids are expected to take effect within 2-4 weeks. Once the patient is stable, the corticosteroid dose should be reduced gradually over months to the lowest effective dose. Immunosuppressives begin to show their effects after about 6 months. Azathioprine (2-3 mg/kg) is usually dosed. Mycophenolate (1-2 grams per day), methotrexate (20 mg/week), and tacrolimus (3 mg per day) are secondary alternatives. Thiopurine methyl transferase enzyme activity should be measured before starting azathioprine. It determines the risk of side effects of azathioprine. Azathioprine should not be given to patients with no or low enzyme activity. In those in remission or with minimal symptoms, tapering of corticosteroids and non-steroidal immunosuppressants should be considered after 1-2 years (10). When the corticosteroid dose drops below 15 mg per day, a dose reduction of 1 mg per month may be attempted to prevent recurrence of symptoms. Symptoms usually recur at doses below 5 mg/day and most patients require long-term low-dose corticosteroids (8, 13). Patients should be given daily calcium, vitamin D, and proton pump inhibitors. Annual bone density testing is recommended. The initial dose of azathioprine is 50 mg per day for one week and then increased by 50 mg/day up to 2-3 mg/kg per day. The dose of azathioprine should be reduced when there is lymphopenia ( $<500/\text{mm}^3$ ) or the WBC count falls below 4000, and the dose should be discontinued if the WBC count is below 1500. Leukopenia and hepatotoxicity are the main toxicities of azathioprine. It is recommended that azathioprine be reduced slowly and discontinued after 1-2 years. Abrupt discontinuation of azathioprine resulted in clinical relapse in more than 50% of patients (13).

### **Refractory Myasthenia Gravis**

Patients who have persistent disabling symptoms or side effects, whose symptoms remain unchanged or worsen after corticosteroids and at least two



other immunosuppressive drugs used at adequate doses for a sufficient period of time, are considered drug-resistant (9).

In resistant cases, PE therapy and IVIG are used when a rapid response is required, such as before surgery, or when the risk of myasthenia crisis is high (6). Approximately 10-15% of patients are drug resistant. The presence of anti-MuSK antibodies and thymoma increases drug resistance. Anti-MuSK patients are treated with corticosteroid as a first-line immunosuppressive agent, rituximab if they do not respond favorably to corticosteroid, and PE as immunomodulatory therapy for crises (9).

### **Rituximab**

Rituximab is a chimeric anti-CD20 monoclonal antibody approved for B-cell lymphoma, rheumatoid arthritis, and vasculitis (5). It has proven to be highly effective in treating anti-MuSK positive patients (9). It is recommended that rituximab be considered as an early treatment option for MuSK+MG patients who respond inadequately to initial immunotherapy. The effectiveness of rituximab for anti-AChR+ GMG is unclear. However, it remains an option if patients fail other immunosuppressive treatments (4). Rituximab has been shown to shorten the duration of remission and the need for additional immunosuppressive treatments in patients with MG. The risk of multifocal leukoencephalopathy with rituximab treatment is low. But you should not forget when using it (14). Rituximab can be used in resistant seronegative patients. Rituximab dosage for MG patients is unclear. In contrast to anti-AChR levels, anti-MuSK antibody levels have been reported to correlate well with patient symptomatology and can predict relapses in the majority of cases (15).

### **Eculizumab**

Eculizumab binds to C5 and inhibits enzymatic cleavage to C5a and C5b. It is a recombinant monoclonal antibody that prevents the formation of the membrane attack complex. Unlike AChR+MG-associated IgG1 or IgG3 antibodies, IgG4 antibodies do not activate the complement cascade. In other words, eculizumab, a complement pathway blocker, is ineffective in patients with anti-MuSK. It can be used in people with AChR+MG-resistant symptoms. During its use, there is an increased risk of infection caused by encapsulated bacteria, especially *Neisseria meningitidis*. Meningococcal vaccination should be administered at least two weeks before the first drug infusion, and revaccination is recommended 2-5 years later. Antibiotic prophylaxis is mandatory if medication is started within two weeks after vaccination (4, 14).

### **Myasthenic Crisis**

Myasthenic crisis is a severe exacerbation of MG with risk of death due to respiratory failure. Myasthenic crisis occurs in approximately 10% of patients with GMG within the first 2 years after diagnosis, and the mortality rate is 5-10%. To prevent increased mucus secretion and obstruction of the airways during the crisis, pyridostigmine should be discontinued and restarted before weaning from mechanical ventilation. During the crisis, PE is given 4-6 times and IVIG is given for 5 days. It is recommended to give PE first to avoid washing out the immunoglobulins. High doses of corticosteroids can be used as additional treatment in intensive care (3-4 mg/kg corticosteroids per day or 500 mg parenteral corticosteroids per day). This treatment is recommended in cases of inadequate recovery in intensive care. Some patients may require additional PE or IVIG treatment 4-5 weeks after the initial treatment and may relapse even after initial improvement. The reason is that the effect of corticosteroids can be noticeable after 6-8 weeks. The effects of IVIG or PE usually last for about 4 weeks. Patients with MuSK-MG respond extremely well to Rituximab. It is recommended that Rituximab be considered in patients who do not respond to high-dose corticosteroids, IVIG or PE during the crisis and if there is resistance to weaning off ventilation (10, 11).

### **Cholinergic Crisis**

Taking 450-600 mg or more of Pridostigmine daily may cause increased muscle weakness and cholinergic crisis. It has side effects such as stomach cramps, nausea, vomiting, diarrhea, muscle cramps, sweating, bronchial secretions, hypotension and bradycardia. Pyridostigmine should not be given in case of gastrointestinal symptoms, urinary obstruction, and should be used with caution in those with bronchial asthma, bradyarrhythmia or a recent history of coronary artery disease (10).

### **Myasthenia Gravis and Pregnancy**

During pregnancy, the risk of worsening MG increases. Thymectomy should be performed before pregnancy as it reduces the risk of MG in the newborn. Pyridostigmine is safe during pregnancy. Low doses of corticosteroids and azathioprine are safe. It can be used during pregnancy and breastfeeding. Daily doses should be as low as possible and under 20 mg of corticosteroids is recommended. Rituximab should be discontinued 3 months before and during pregnancy. Mycophenolate, methotrexate and cyclophosphamide should not be used in women of childbearing age. Vaginal birth is recommended and cesarean birth should only be recommended for obstetric indications. Epidural analgesia is

preferred. The use of magnesium should be avoided in the treatment of preeclampsia and eclampsia. Breastfeeding is not recommended for those using mycophenolate, methotrexate and cyclophosphamide. Rituximab use is recommended 2 weeks after birth, and breastfeeding is recommended 6 hours after infusion. Vaccinations are recommended according to standard schedules (10).

### **Side Effects**

Patients using corticosteroids should be closely monitored for osteoporosis, obesity, diabetes, cataracts, infection risk and mental disorders. In these patients, corticosteroids should be given at the lowest dose for a short period of time until they respond to another immunosuppressant drug. All patients using corticosteroids should be monitored for blood pressure, body weight, bone mineral density, blood sugar levels, sleep and mood problems. It is important to remember the risk of developing progressive multifocal leukoencephalopathy (PML) during rituximab treatment. Using rituximab for a long time does not increase the risk of cancer (10). Side effects of pridostigmine are abdominal cramps, diarrhea, nausea, frequent urination, hypotension, bradycardia, sweating, increased salivation, increased bronchial secretions and other symptoms of cholinergic excess. Sometimes patients with asthma may experience increased sensitivity and increased bronchospasm when using pyridostigmine. It may cause cholinergic crisis in high doses. As a result of long-term use of azathioprine, skin lesions such as actinic keratosis and also skin malignancies such as squamous cell carcinoma may develop (11). Monitoring of liver enzymes (alanine aminotransferase, aspartate aminotransferase and gamma glutamyltransferase) and complete blood count are required monthly while using azathioprine (8).

### **Results**

Anticholinesterases, corticosteroids, and azathioprine and other immunosuppressives are used in the treatment of myasthenia gravis. PE and IVIG are used in myasthenic crisis. If there is thymoma, thymectomy is performed (7). Thymectomy is not recommended if there are MuSK, LRP-4 antibodies (8) There is no definitive treatment yet for MG. However, different treatment options can significantly alleviate MG symptoms and improve patients' quality of life (16).

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## **Chapter 5**

### **Practical Clinical Approach to Ankyloglossia**

**Mustafa Yaşar ÖZDAMAR<sup>1</sup>**

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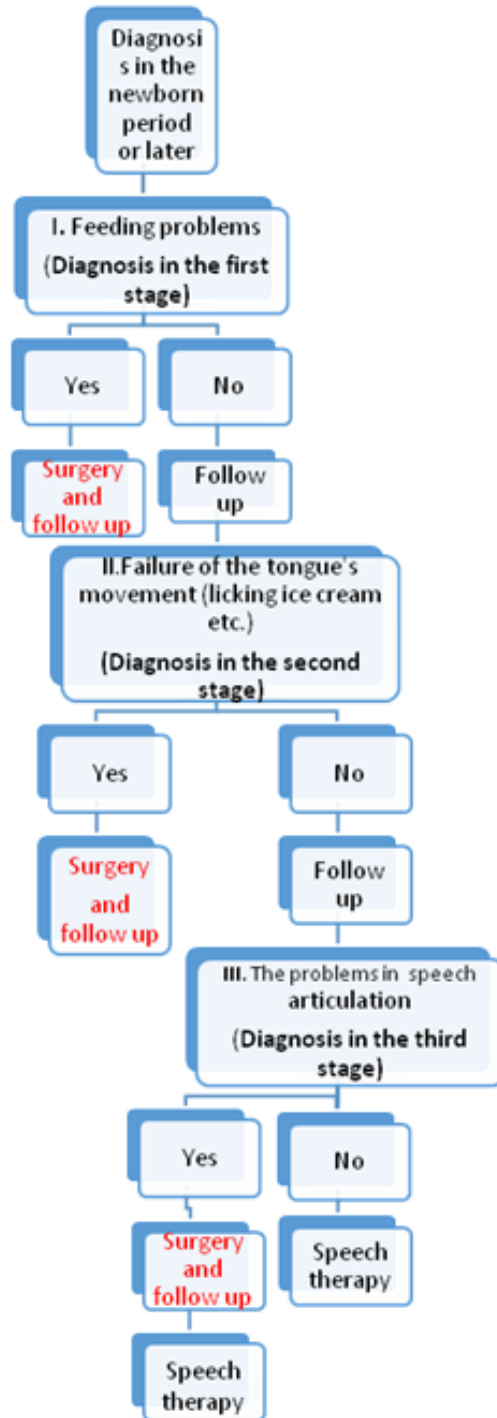
## **Introduction**

Since there is no complete consensus on both diagnosis and treatment, the prevalence of ankyloglossia (AG) has a vast range. AG is also named a tongue tie. Although AG, which has a known prevalence between 0.1- 10.7%, does not have any known life-threatening complications, both practitioners and parents may remain in a dilemma. The wide range in prevalence is also due to differences in the criteria for defining AG. Some authors distinguish between symptomatic and non-symptomatic AG, while others may change the definition based on the function and anatomical abnormality of the tongue. Nevertheless, AG is defined as a congenital remnant between the tongue's ventral surface and the mouth's floor and at the vestibulum of the mandibular midline incisors. This definition has been reported recently as a condition of limited tongue mobility caused by a restrictive lingual frenulum (Suter et al. 2009, Walsh et al. 2017).

Although some practitioners define the membranous short frenulum extending only posteriorly from the ventral surface of the tongue as posterior AG, most authors accept this condition as a normal frenulum. Posterior AG is a definition usually made for breastfeeding difficulties. These authors believe that conditions such as the anatomy of the tongue, maternal milk production, and the mother's experience of difficulty breastfeeding should be investigated rather than the condition of the tongue in babies with posterior AG. Anterior AG is a definition used for the classically known AG (Messner et al. 2020, Suter et al. 2009).

Although the subject of treatment is very controversial, conservative approaches such as follow-up by observation and consultation with professionals when breastfeeding difficulties or speech disorders are considered conservative approaches. In contrast, surgical methods such as frenotomy/frenuloplasty are other treatment options with the joint decision of the parent and the practitioner (Donati-Bourne et al. 2015, Messner et al. 2020).

## Clinical evaluation in AG



**Figure 1:** An AG algorithm that can be applied in clinics



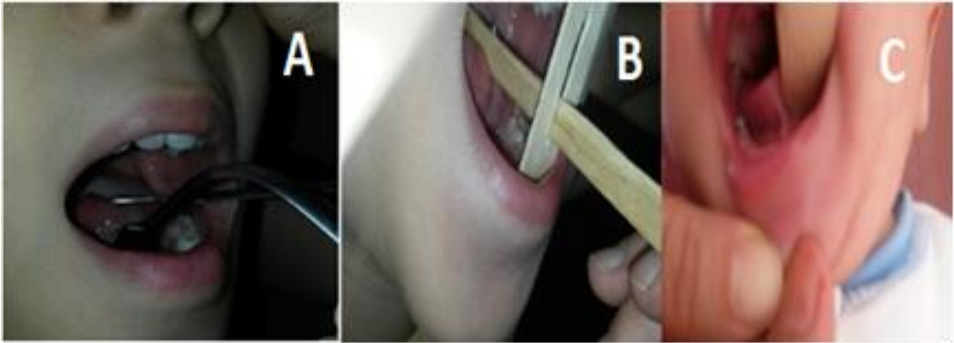
As with many patients and diseases, the examination begins with the history. Situations such as the mother's difficulty in breastfeeding her baby, the baby's recent weight loss, pain in the maternal nipple during breastfeeding, and a decrease in the mother's milk secretion should be questioned (Walsh et al. 2017). In cases where AG is absent or suspected in breastfed or bottle-fed babies, the simplest solution may be for the baby to be suckled by a practitioner using a pacifier. If there is no AG due to the examination, it will be sufficient to investigate the above secondary causes of feeding difficulties and recommend professional help.

A clinical algorithm that can be used in AG patients is given in Figure 1. The most significant factor in the low number of patients we perform surgery on as a result of this algorithm we apply in our clinic is that information about AG is explained to parents with sample cases. Ensuring that the parents are not in doubt or anxiety and monitoring the patient at frequent or specific intervals saves practitioners from dilemmas.

Since the lingual frenulum is short and thick, it restricts the tongue's mobility, so the tongue cannot protrude beyond the vermilion border, cannot be moved out of the lips, and is bent in the shape of a heart (Walsh et al. 2017). If this condition is easily detected during the examination, the diagnosis of AG is correct (Figure 2).

AG's second most well-known complication is mechanical complications that cause speech impairment and restrict activities such as licking ice cream and kissing (Figure 1). Speech disorders are not always observed in patients with AG, and the rate of AG in patients with speech disorders is meager. Therefore, this issue is still considered speculative (Lalakea et al. 2003, Suter et al. 2009)

A surgery decision may be made due to the patient's or the mother's follow-up. Frenotomy can be performed in newborns in a few minutes without the need for anesthesia. However, in cases where frenuloplasty is required or if the mucosa opened on the ventral surface of the tongue needs to be sutured, sedation may be necessary (Messner et al. 2020).



**Figure 2.** A 10-year-old girl with normal lingual frenulum (a,b) and a 2-month-old infant with AG.

### **Conclusion**

In cases of feeding disorders, speech difficulties, and mechanical disorders in children with AG, practitioners should consider surgical intervention as the final decision, with patience and reassurance from parents, since even evidence-based studies have not yet provided a definitive conclusion. Although classifications are made according to the function and anatomical structure of the language, they are not mentioned here. Although AG treatment is reported in the literature according to the anatomical or functional classifications of the language, it cannot be said that it is widely used in practical applications. Each patient should be treated individually.

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## Chapter 6

### The Importance of Potential Treatment Aspects of Hydrogeological and Hydromineral Resources in Van Region for Health Tourism

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## **Abstract**

Psoriasis, an autoimmune and chronic inflammatory skin condition affecting 2-3% of the global population, is characterized by erythematous, scaly plaques, with its aetiology remaining partially elusive. This disease significantly impacts patients' quality of life and is associated with various comorbid conditions, including cardiovascular diseases, diabetes, and psoriatic arthritis, yet lacks a definitive, long-term cure. The recurrence of psoriasis and its variable clinical manifestations have led clinicians to seek alternative treatments, with geothermal and hydrotherapies emerging as supplementary options within health tourism alongside conventional treatments. Turkey is known for its abundant thermal and mineral waters, with temperatures ranging from 20°C to 102°C, particularly around the Van province, where tectonic activity has given rise to waters rich in ions such as  $\text{Ca}^{+2}$ ,  $\text{Mg}^{+2}$ , and  $\text{HCO}_3^-$ . These waters are popularly believed to treat skin conditions like psoriasis, eczema, atopic dermatitis, and rosacea. Despite these beliefs, scientific research on the therapeutic benefits of Van's hydrogeological and hydro mineral resources for skin diseases remains limited. This study aims to scientifically assess the efficacy of Van's geothermal and hydrobiological resources in treating psoriasis and explore the region's potential as a health tourism destination for skin disease treatments. The significance of investigating Van's subterranean and surface water resources extends beyond health benefits, potentially positioning the region as a key site for healthy living tourism and developmental growth.

**Keywords:** Psoriasis, Hydromineral Therapy, Thermal Therapy, Health Tourism, Van Lake (Turkey)

## **1. Introduction**

### **'Psoriasis' Beyond the Skin: Definition, Symptoms and Traditional Treatments**

Often perceived as just a skin condition, psoriasis is a complex autoimmune disease with significant implications for an individual's health and well-being. Psoriasis affects millions of people worldwide, with estimates suggesting a prevalence of 2-3% in Western societies (Nițescu et al., 2021). This chronic inflammatory disease crosses geographical boundaries and has a significant impact on healthcare systems because of the associated treatment and management costs. The exact cause of psoriasis remains under investigation, but research suggests a well-organized interaction between genetic predisposition and environmental triggers. While genetic factors determine an individual's susceptibility, environmental factors such as stress, infections, and certain medications can initiate or exacerbate the disease. The immune system plays a central role; activated T cells and the release of inflammatory cytokines lead to the rapid proliferation of skin cells, which is the hallmark of psoriasis (Mattei et al., 2014).

#### **1.1. Clinical Symptoms: Beyond Typical Plaques**

Plaque psoriasis, characterized by raised, red patches with silvery white scales, is the most common form and typically affects the elbows, knees, scalp, and lower back. However, psoriasis occurs in several forms; there are less common variants such as guttate psoriasis, which presents with small, teardrop-shaped lesions, and pustular psoriasis, characterized by white pustules on red skin. In severe cases, erythrodermic psoriasis may include widespread redness, scaling, and pain (Tseng et al., 2021). The chronic inflammation in psoriasis extends its effect beyond the skin. Psoriatic arthritis, a comorbidity affecting 30% of individuals with psoriasis, can cause joint pain, stiffness, and swelling. Individuals with psoriasis have an increased risk of developing cardiovascular diseases such as heart attack and stroke. In addition, the inflammatory condition can contribute to metabolic syndrome, a cluster of conditions such as obesity, type 2 diabetes, and high blood pressure. Furthermore, the psychological burden of psoriasis can exacerbate mental health problems (Verma et al., 2021). Psoriasis significantly affects the quality of life of an individual. The physical discomfort associated with itching, burning and cracked skin can disrupt sleep and daily activities. The visible nature of plaques can lead to social stigmatization, isolation, and reduced self-esteem. This can further affect mental health by contributing to the development of anxiety and depression (Ferrari et al., 2021). Psoriasis is a complex, systemic disease with significant impacts on physical and

mental health. Recognizing its multifaceted nature is crucial for developing comprehensive management strategies. The symptoms of psoriasis can vary greatly in severity, from small, localized patches to full-body coverage. Flare-ups can be unpredictable, which contributes to the psychological and emotional strain experienced by patients (Blackstone et al., 2022). Treatments should not only address the visible symptoms, but should also aim to reduce inflammation, improve quality of life, and manage comorbid conditions. A holistic approach integrating conventional treatments with psychological support is essential to ensuring optimal patient outcomes. The conventional treatment setting for psoriasis is very diverse, encompassing topical treatments, phototherapy, and systemic medications. Topical treatments, such as corticosteroids and vitamin D analogues, aim to reduce inflammation and slow the overproduction of skin cells. Phototherapy involves exposing the skin to ultraviolet light under medical supervision, which can help to alleviate skin cell growth and relieve symptoms (Bochénska et al., 2017). Systemic treatments, including oral medications and injectable biologics, as well as stem cell therapies, are usually reserved for moderate-to-severe cases or when other treatments have failed. These systemic options work by targeting specific pathways in the immune system to reduce inflammation and overproduction of skin cells. Despite the availability of these treatments, psoriasis remains a difficult condition to manage due to its chronic nature, the potential side effects of long-term medication use, and the variability of individual responses to treatment. Furthermore, the psychosocial effects of psoriasis are profound, with patients often experiencing decreased self-esteem, social isolation, and an increased risk of comorbidities such as depression, anxiety and cardiovascular disease (Han, 2014). Consequently, there is a constant search for alternative and complementary therapies that can provide relief and improve the quality of life for individuals living with psoriasis. This section for alternative treatments overlaps with the interests of health tourism, where unique treatment resources, including hydrogeological and hydro-mineral assets in specific regions such as Van, offer new prospects and avenues for treatment outside of traditional medical settings.

## **1.2. The Rise of Health Tourism as a Global Trend**

Medical tourism has emerged as a significant sector within the global travel industry, serving individuals seeking medical treatment, wellness, and recovery in settings outside of conventional healthcare jurisdictions. This multi-dimensional sector not only underlines the quest for advanced medical care and wellness practices but also highlights the growing willingness of individuals to integrate improving their health into their travel experience (Smith & Puczko,

2014). A variety of factors fuel the growth of the sector, including advances in medical technology, the search for cost-effective treatment, the appeal of combining medical care with travel, and the therapeutic importance of natural and cultural resources. In this context, health tourism plays an important role in contributing to the economic development of host regions as well as promoting cross-cultural exchange and understanding of health practices.

A rapidly growing segment of the travel industry, medical tourism involves individuals traveling to destinations to receive medical treatment, wellness services, or preventive care. Under the influence of various factors, health tourism has become a global phenomenon. Increasing disposable income, globalization, and advances in medical technology allow individuals to seek high quality yet affordable healthcare abroad (Kupcewicz & Bentkowska, 2023). In addition, the aging population and the growing desire for preventive and wellness-oriented treatments increase the demand for specialized services offered by health tourism destinations. Several factors contribute to the popularity of medical tourism. Cost savings can be an important motivator, as medical procedures and treatments can be significantly cheaper in certain destinations compared to their home countries. Access to advanced medical technologies or expertise not available locally may also drive individuals to seek healthcare abroad. In addition, some individuals prefer health tourism to combine medical treatment with a holiday experience, allowing them to recover in a new environment. Health tourism covers a wide range of services. Under the name of wellness tourism, preventive and health-promoting services such as spa treatments, detox programs, and stress management programs are offered. Some destinations also specialize in alternative and complementary therapies such as acupuncture, Ayurveda, or traditional Chinese medicine. Developed countries with high quality healthcare infrastructure and advanced technologies attract individuals seeking specialized treatments (Pessot et al., 2021).

### **1.3. Therapeutic Potentials of Hydromineral Resources**

The intersection of hydrogeology and human health constitutes a vital area of study within the environmental, and medical sciences, emphasizing the influence of water-based geological formations and mineral resources on health outcomes (Ozturk & Disli, 2023; Tawfeeq, Disli, & Hamed, 2024). Hydrogeological and hydromineral resources, including groundwater, mineral springs, and therapeutic muds, possess unique compositions that have been utilized for health benefits across various cultures and time periods. Hydrogeological resources offer numerous therapeutic benefits due to their unique physical and chemical properties. Mineral springs, characterized by various mineral contents such



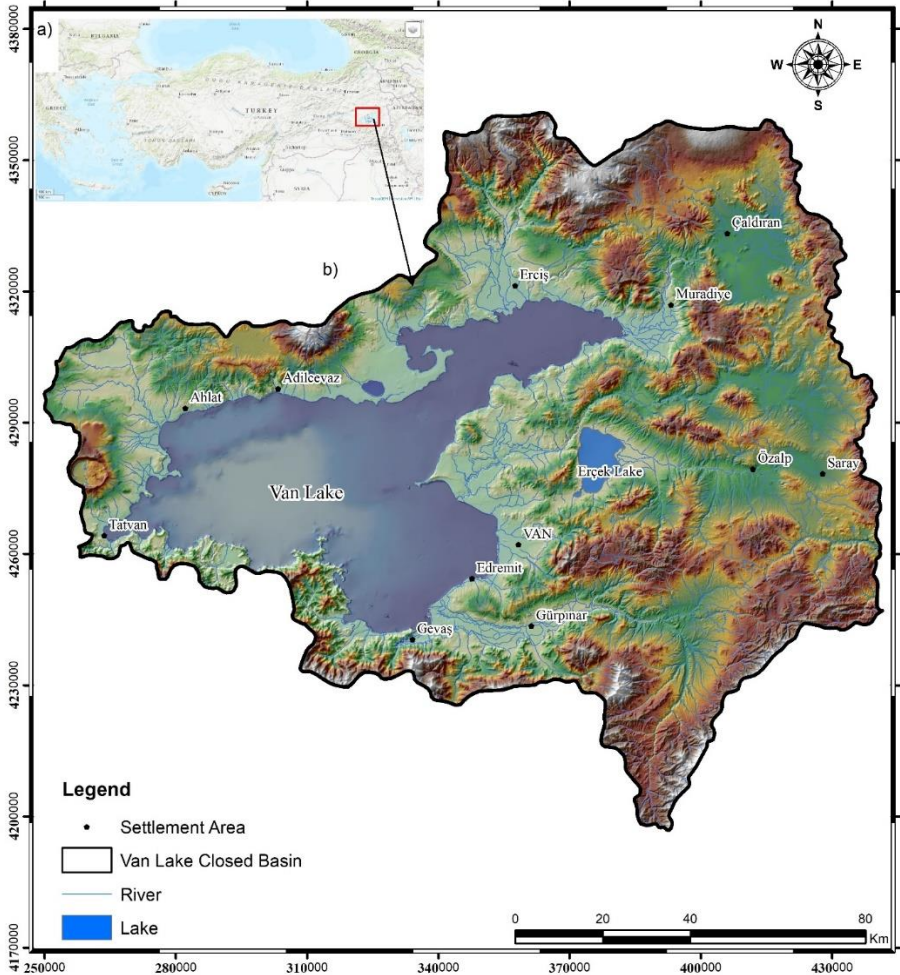
as sulphur, radon, bicarbonate, sodium, and chloride have been associated with improvements in various diseases, including skin diseases, musculoskeletal disorders, and cardiovascular diseases (Egamberdiyevna & Sodiqovich, 2024). The therapeutic efficacy of these waters is attributed to their mineral composition, which can exert direct biological effects on the body, such as anti-inflammatory and keratolytic actions, particularly relevant for the treatment of skin conditions such as psoriasis and eczema. Moreover, especially the thermal and physicochemical properties of these waters play a critical role in terms of their health benefits (Protano et al., 2024). Hot mineral springs facilitate vasodilation, increasing blood circulation and metabolic processes, thereby aiding in the rehabilitation of musculoskeletal disorders and supporting the patient's general state of well-being. Furthermore, the buoyancy provided by the water reduces pressure on joints and muscles, providing a supportive environment for exercise and rehabilitation. Hydromineral waters, another aspect of hydrogeological resources, are used in balneotherapy and pelotherapy because of their therapeutic properties (Malkhazova et al., 2022; Moini Jazani et al., 2023). Water resources rich in minerals and organic compounds are topically applied in the treatment of various skin conditions, rheumatic pains, and inflammatory disorders. The properties of soda waters provide sustained thermal and chemical effects that contribute to their therapeutic effectiveness by ensuring uniform distribution of heat and slow release of minerals (Tirinsi et al., 2024). The importance of hydrogeological and hydro-mineral resources goes beyond direct health benefits to include health tourism and sustainable wellness practices. These natural resources attract individuals seeking alternative or complementary treatments, leading to the development of health tourism in regions with such assets (Protano et al., 2024). The economic and social impacts of this type of tourism are profound and offer opportunities for regional development the preservation of cultural heritage, and improvement of public health. Hydrogeological and hydro-mineral resources represent a valuable natural asset with significant impacts on human health. Their unique therapeutic properties offer alternative and complementary treatment options for a variety of health conditions, awaiting investigation in terms of preclinical research, and emphasize the importance of protecting and studying these resources in the environmental health sciences. As the global community continues to explore sustainable and holistic approaches to health and wellness, these resources are becoming increasingly important and require concerted efforts to conserve, research, and integrate them into public health strategies.

#### **1.4. Health Tourism in Van Region**

The Van Basin, located in the east of Turkey and characterized by its closed basin feature, is emerging as a hub for health tourism due to its abundant hydrogeological and hydromineral resources (Figure 1). Characterized by its unique geological formations, thermal resources, and rich cultural heritage, this region has an intriguing geography in the evolving landscape of health tourism (Reimer et al., 2009). The growing interest in Van's potential as a health tourism destination is multifaceted, based on its therapeutic natural resources, historical significance, and wider economic and environmental sustainability implications. The attractiveness of Van as a health tourism destination is because it is home to extensive hydrogeological and hydro mineral resources, including numerous hot springs and mineral waters. These natural assets are packed with a variety of minerals and thermal properties believed to provide therapeutic benefits to a range of ailments, particularly skin diseases such as psoriasis, rheumatic diseases, and respiratory ailments (Metin et al., 1999). The therapeutic benefits of these waters are not merely anecdotal or based on folk rumours; they are grounded in the mineral composition and scientifically proven thermal properties of Lake Van water and geothermal springs. These natural features make them prime candidates for consideration in balneotherapy and hydrotherapy. Van thermal springs are a natural laboratory for exploring the therapeutic interface between nature and human health and offer an attractive alternative to conventional medical treatments (Alaeddinoglu & Can, 2011). The cultural and historical dimensions of health tourism in Van further enhance its attractiveness.

The history of the region is rich, with a rich tapestry of civilizations that have recognized and used mineral resources for health and wellness purposes. The historical continuity of therapeutic use adds cultural depth to the practice of health tourism in Van, providing visitors with not only physical healing but also a connection to a long-standing tradition of natural health practices. The integration of cultural experiences such as visits to historical sites and interaction with local traditions enriches the health tourism experience, creating a holistic approach to wellness that appeals to a wide demographic. Especially in recent years, it has been noted that health tourism in Van presents significant opportunities for economic development and environmental sustainability. The influx of health tourism provides the region with a vital source of income, contributes to local economies, and fosters job creation in both the health and service sectors. Furthermore, the development of health tourism in Van can further stimulate economic growth by encouraging investment in infrastructure, including accommodation and health facilities (Bilgili et al., 2013). In parallel, the emphasis on sustainable tourism practices means that the development of

health tourism in Van can also contribute to the protection of natural resources and cultural heritage. Sustainable health tourism models focus on minimizing environmental impact, promoting efforts to preserve the natural fabric, and ensuring that the benefits of tourism are shared fairly among local communities. This approach is in line with global priorities for sustainable development and environmental management and positions Van as a model for responsible health tourism development. As a result, the Van region is emerging as a centre of interest in the health tourism sector with its unique combination of therapeutic natural resources, historical depth, and potential for sustainable economic development (Alaeddinoglu & Can, 2011). As the global community is increasingly turning towards natural and holistic approaches to health and wellness, Van's offerings are in line with these preferences and promise not only therapeutic benefits but also cultural enrichment and sustainable development. Therefore, exploring and promoting Van as a healthy tourism destination can contribute to the well-being of individuals while promoting regional development and environmental protection.



**Figure 1.** Location map and drainage basin hydrology of the Van Lake Basin, (Turkey)

## 2. Lake Van: Jewel of Eastern Anatolia

The Van region in eastern Turkey is famous for its outstanding hydrological features, such as lakes and hot springs, which play an important role in shaping the landscape, ecology, and cultural heritage of the region. With an area of approximately 3,755 km<sup>2</sup>, Lake Van (Figure 1) is the largest soda lake in Turkey and the second largest in the world (Reimer et al., 2009). Lake Van, formed millions of years ago by tectonic processes (Dhont and Chorowicz 2006), hosts various endemic species such as the Pearl Mullet and Van Catfish due to its unique hydro chemical properties stemming from the geological structure of the region. This structure is characterized by high alkalinity and salinity levels (Reimer et al 2009). Furthermore, Lake Van

serves as a vital habitat for migratory birds such as flamingos and pelicans and has been designated as a Ramsar site of international importance for the conservation of wetlands. Also of great cultural significance, the shores of the lake are dotted with ancient ruins, such as the historic Van Castle and Armenian monasteries, attesting to its rich archaeological heritage (Degens et al., 1984). The Van Region is blessed with numerous thermal springs (Pasvanoglu, 2020) recognized for their therapeutic properties and healing benefits. These geothermal springs originate from geological activities associated with the uplift of mountain ranges and the formation of fault lines because of the collision of the Anatolian Plate with the Arabian Plate (Dhont and Chorowicz, 2006). The mineral-rich waters of the thermal springs in Van are valued for their therapeutic effects on various ailments, such as rheumatism, skin disorders and respiratory ailments (Ozler, 2003). Among the most important thermal springs is the Muradiye Thermal Spring (Düzen & Ozler, 2015), which has been revered for its healing power since ancient times and is frequented by visitors seeking health and rejuvenation. Van's unique hydrological and hydrogeological features, such as Lake Van and hot springs, are incredibly valuable natural assets that enhance the ecological diversity, cultural identity, and tourism potential of the region. However, sustainable management and conservation of these hydrogeological resources are crucial to ensuring their preservation for future generations. Efforts to protect water quality, reduce pollution, and promote responsible tourism practices are essential for safeguarding Van's hydrological heritage and maximizing its socio-economic benefits. Through collaborative efforts between stakeholders, policymakers, and local communities, Van can continue to harness the healing power of its waters while maintaining its ecological integrity and cultural authenticity (Degens et al., 1984).

### **2.1. Chemical Properties of Hydromineral Resources for Psoriasis Treatment**

The therapeutic use of mineral and/or thermal waters, particularly in the treatment of psoriasis, represents a field that combines hydrochemistry and dermatology. Psoriasis, a chronic autoimmune condition characterized by the rapid proliferation of skin cells leading to red, scaly plaques, has been the focus of numerous treatment modalities, including the use of mineral waters. The effectiveness of mineral water therapy or balneotherapy in alleviating psoriasis symptoms is significantly influenced by the chemical composition of these waters (Cheleschi et al., 2022).

Sulfur is an essential element present in many therapeutic mineral waters, renowned for its keratolytic and antibacterial properties. In psoriasis, sulphur aids in reducing scaling by dissolving keratin, resulting in a smoother skin texture. Furthermore, its anti-inflammatory effect helps alleviate the redness and itching associated with psoriasis plaques. Sulphur baths have been documented to enhance

skin integrity and alleviate the severity of psoriasis symptoms (Benevento-Italy, 2015; Tsourelis-Nikita et al., 2002; Wątor, 2024). Selenium, a trace element found in some mineral waters, plays a very important role in skin health thanks to its antioxidant properties (Genchi et al. 2023). It contributes to the protection of skin cells from oxidative stress, which can exacerbate psoriasis flare-ups. Selenium's involvement in the modulation of immune responses makes it a valuable element in the management of autoimmune conditions such as psoriasis, potentially reducing the frequency and intensity of attacks (Çetin & Karagözoğlu, 2022; Degens et al., 1984). Magnesium in mineral waters may have therapeutic benefits for psoriasis patients thanks to its role in skin hydration and barrier function. It helps maintain skin moisture, reducing dryness and flaking associated with psoriasis plaques. Furthermore, magnesium's anti-inflammatory properties may help soothe irritated skin, providing relief from the discomfort of psoriasis (Ozler, 2003; Palmisano et al., 2024; Pessot et al., 2021).

Calcium is another important element found in mineral waters (Disli, 2018; Disli and Gulyuz, 2020) and contributes to the regulation of skin growth and differentiation. For psoriasis patients, calcium can help normalize the rapid skin cell turnover rate, which is the hallmark of the disease. By promoting healthier skin regeneration, calcium-enriched mineral waters can reduce the thickness and scaling of psoriasis plaques (Çetin & Karagözoğlu, 2022; Reimer et al., 2009). Bicarbonate ions in mineral waters play a role in maintaining skin pH balance, which is crucial for skin barrier function and overall skin health. For individuals with psoriasis, the use of bicarbonate-rich mineral waters can help soothe inflamed skin and enhance the skin's natural protective mechanisms (Alaeddinoglu & Can, 2011; Albertini et al., 2007).

The chemical composition of mineral waters, characterized by elements such as sulfur, selenium, magnesium, calcium and bicarbonate, underpins their therapeutic potential in the treatment of psoriasis. Through mechanisms such as keratolysis, anti-oxidation, anti-inflammation, hydration and pH regulation, these essential components offer a versatile approach to alleviate psoriasis symptoms. Although the integration of balneotherapy into psoriasis treatment regimens is promising, further experimental research is required to fully elucidate the efficacy and mechanisms of mineral water therapy. This convergence of hydro chemistry and dermatology not only expands the therapeutic field for psoriasis but also emphasises the importance of natural resources in advancing medical treatments (Wątor, 2024; Whiting et al., 2024; Yadav et al., 2024).

## **2.2. Water Sources Properties Related to Health Tourism**

Located in the eastern part of Turkey, the Van region is characterized by its rich and complex hydrogeological landscape, which plays an important role in shaping its potential as a destination for health tourism. This landscape is underpinned by a variety of geological and hydrological features, including volcanic formations, mineral-rich hot springs and significant water bodies, which contribute to the therapeutic appeal of the region. This section of Van's hydrogeological landscape reveals the intrinsic link between the region's natural resources and their applicability in health and wellness tourism, particularly in the treatment of dermatological conditions such as psoriasis (Metin et al., 1999; Ozler, 2003). The geological framework of Van is heavily influenced by its volcanic past, with the presence of Mount Nemrut, an extinct volcano, and widespread volcanic rock formations. These volcanic activities have contributed to the formation of numerous hot springs and thermal waters throughout the region. The heat and mineralization of these waters are the direct result of geothermal energy and mineral deposits associated with volcanic activities. Beyond the hot springs, Van is home to Lake Van, the world's largest soda lake, which contributes to the unique hydrological characteristics of the region. The alkaline waters of the lake, with their high pH levels, offer unique conditions that some studies suggest may have health benefits, including skin-healing properties (Ozguven & Demir Yetis, 2020). The presence of this large body of water also contributes to the natural beauty of the region and enhances the overall attractiveness of Van as a health tourism destination by combining therapeutic experiences with natural beauty. The hydrogeological features of Van are important not only for their physical and chemical properties but also for their integration into the cultural and historical narrative of the region. The therapeutic use of these natural resources' dates back to ancient civilizations and historical records show that various cultures have valued and used hot springs and mineral waters for thousands of years. This historical continuity enriches the health tourism experience in Van, offering visitors not only physical healing but also a deep connection with the cultural heritage and historical depth of the region.

The Van region, renowned for its rich hydrogeological resources, has long been a focal point for people seeking natural solutions to various health problems, including psoriasis. Although scientific research in this area is limited, the collection of experiences and observations among the people provides valuable insights into the potential benefits of these natural resources. Local accounts from the Van region often emphasize the therapeutic properties of the mineral-rich waters. Residents and visitors describe improvements in psoriasis symptoms after bathing in these natural springs. For example, individuals reported a reduction in skin redness, scaling, and itching after regular bathing in some hot springs known for their high sulphur content.

These first-hand accounts underline the perceived effectiveness of Van's hydrogeological resources in managing psoriasis symptoms and underpin the region's growing reputation as a destination for health tourism.

The lack of preclinical and clinical studies specific to the Van region has created a need for preliminary research to explore the therapeutic potential of its hydrogeological resources. The use of Van's hydrogeological resources for health purposes is deeply embedded in the cultural and historical fabric of the region. Historical texts and oral traditions describe the use of these springs for skin conditions and other ailments dating back hundreds of years. This deep-rooted tradition not only adds cultural significance to the therapeutic use of these waters, but also contributes to the anecdotal evidence supporting their efficacy in the treatment of psoriasis. The therapeutic application of Van's hydrogeological resources in the treatment of psoriasis, although supported by anecdotal evidence and preliminary case studies, underlines the need for more extensive research in this area (Bilgili et al., 2013; Tekbaş, 2015). The unique combination of Van's mineral waters and hot springs offers an attractive natural remedy for psoriasis symptoms and deserves further research to fully understand their therapeutic potential. As interest in natural and holistic therapies continues to grow, the hydrogeological resources of the Van region may provide valuable information on alternative approaches to the management of chronic skin conditions.

### **3. Therapeutic Aspects of Hydromineral Resources for Psoriasis**

The therapeutic use of hydrotherapy and mineral waters in the treatment of psoriasis, a chronic autoimmune skin disease, is receiving increasing scientific interest. This interest is based on the traditional use of balneotherapy (bathing in mineral or thermal waters) and hydrotherapy (treatment with water) for skin conditions in various cultures. Recent research has begun to elucidate the mechanisms by which these treatments can alleviate psoriasis symptoms and improve patients' quality of life. Hydrotherapy and mineral water treatments for psoriasis are hypothesised to exert their therapeutic effects through several mechanisms. These include moisturising the skin, removing scales, reducing inflammation, improving skin barrier function, and modulating the immune system (Bilgili et al., 2013; Egamberdiyevna & Sodiqovich, 2024; Protano et al., 2024; Tekbaş, 2015; Waçor, 2024). Mineral waters rich in sulphur, magnesium, and selenium are particularly noted for their anti-inflammatory and antioxidative properties, which are beneficial in the management of psoriasis symptoms.

In a study by Matz et al (2003), patients treated with Dead Sea balneotherapy reported significant improvement in psoriasis symptoms. This treatment involves bathing in mineral-rich waters known for their high concentrations of magnesium



and other minerals and showed significant reductions in disease severity scores (Matz et al., 2003). Another study published by Kulisch et al (2016) evaluated the effects of hydrotherapy on patients with psoriasis. The study revealed that regular thermal spring water baths led to improvement in psoriasis area and severity index (PASI) scores, underlining the potential of thermal mineral waters in psoriasis management (Kulisch, 2016). Hercogova et al (2003) investigated the use of balneotherapy in the treatment of psoriasis. In their study results, they emphasised the beneficial effects of balneotherapy in improving psoriasis symptoms and attributed these effects to the high mineral content of the waters used in the treatment (Hercogova et al., 2002). Furthermore, Proksch et al (2005) investigated the skin barrier repair properties of saltwater bathing and found significant improvements in skin condition and hydration, which are crucial for managing psoriasis symptoms. Beyond experimental studies, numerous case reports and anecdotal evidence support the use of hydrotherapy and mineral waters for the relief of psoriasis symptoms. Patients treated in areas with natural thermal or mineral springs often report reductions in itching, scaling, and inflammation associated with psoriasis (Proksch et al., 2005). The scientific evidence for the use of hydrotherapy and mineral waters in the treatment of psoriasis underlines the potential of these natural resources as complementary therapies. While their mechanisms of action include hydration, anti-inflammatory effects, immune modulation, and skin barrier improvement, more rigorous, controlled clinical trials are required to fully understand the extent and conditions of their therapeutic benefits. Nevertheless, the available studies provide a convincing rationale for the integration of hydrotherapy and mineral water treatments into holistic psoriasis management strategies and highlight the need for further research in this promising area of dermatological care (Cheleschi et al., 2022; Matz et al., 2003; Protano et al., 2024).

### **3.1. Mechanisms of Action: How Mineral Water Might Alleviate Psoriasis Symptoms**

The therapeutic application of mineral water in the treatment of psoriasis, an autoimmune skin disease characterized by hyperproliferation of keratinocytes leading to erythematous plaques and scaling, is an area of increasing scientific interest. This interest stems from the potential of mineral water to offer a complementary approach to conventional treatments by utilising its unique mineral composition. The mechanisms by which mineral water exerts its effects on psoriasis symptoms are multifaceted, including dermatological, immunological, and psychological pathways (Manara et al., 2023). One of the main mechanisms by which mineral water benefits psoriasis patients is increased hydration of the stratum corneum, the outermost layer of the skin. Proper hydration can reduce the presence

of scales and plaques characteristic of psoriasis and improve skin texture and elasticity. Certain minerals, such as sulphur present in some mineral waters, have keratolytic properties, helping to break down the thick layers of dead skin cells and thus reducing scaling and smoothing the skin surface (Kulisch, 2016). Mineral water varieties, especially those enriched with elements such as selenium, magnesium, and zinc, can exert significant anti-inflammatory effects. These elements modulate the inflammatory pathways involved in psoriasis, reducing cytokine production and inhibiting the inflammatory response. The reduction in inflammation not only helps to reduce erythema (redness) associated with psoriasis plaques, but also contributes to the relief of itching and discomfort.

Psoriasis is basically an autoimmune condition and T-cell-mediated immune responses play a crucial role in its pathogenesis (Agbuga et al. 2024). Some minerals in therapeutic waters may have immunomodulatory effects, helping to normalize the activity of the immune system. For example, selenium has been reported to have the ability to modulate immune responses and potentially reduce the hyperactive immune response seen in psoriasis. Mineral waters can assist in the detoxification process, helping to remove toxins from the skin that can exacerbate psoriasis symptoms. Furthermore, minerals such as magnesium play a critical role in maintaining skin barrier function (Chakraborty, 2023; Costantino et al., 2023; Elkhawaga et al., 2023; Kulisch, 2016; Kupcewicz & Bentkowska, 2023). A healthy skin barrier is essential in the management of psoriasis as it reduces trans epidermal water loss, maintains hydration and provides protection against environmental irritants and pathogens. On the other hand, the psychological benefits of bathing in mineral water in the treatment of psoriasis should not be underestimated. Stress is a well-known trigger for psoriasis flare-ups. The relaxing effect of bathing in warm, mineral-rich water can reduce stress and anxiety levels, leading to a reduction in the severity and frequency of psoriasis attacks. This reduction is complemented by the physical benefits of mineral water and offers a holistic approach to managing the condition. These properties emphasize the potential of mineral water as a complementary treatment modality for psoriasis. However, while preliminary studies provide promising indications of the benefits of mineral water for psoriasis patients, more rigorous scientific research is needed to fully understand the extent of these benefits and optimize treatment protocols (Carbajo et al., 2024; Egamberdiyevna & Sodiqovich, 2024; Maria et al., 2024; Palmisano et al., 2024; Protano et al., 2024).

#### **4. Integration of Van's Natural Resources into the Health Tourism**

The potential to develop psoriasis-specific treatment packages represents a significant opportunity in the field of health tourism. By harnessing the unique properties of hydrogeological and hydromineral resources and integrating them with

comprehensive care approaches, these packages could offer a new and holistic way to manage psoriasis. This requires careful planning for effective and solution-oriented feedback, interdisciplinary collaboration and a commitment to patient-centered care with the ultimate goal of improving the quality of life of individuals living with psoriasis. It offers a comprehensive strategy to manage psoriasis by integrating physical, psychological and nutritional aspects of psoriasis management. The health tourism enhances the overall treatment experience by combining health benefits with the enjoyment of visiting a new area, thereby reducing stress levels. It enables structured access to natural and alternative therapies that may not be readily available in conventional healthcare settings. This approach not only enhances the treatment experience, but also contributes to the preservation and promotion of local culture, providing significant economic and health benefits (Teixeira & Gomes, 2021). Integrating Van's cultural and historical attractions into health tourism involves the creation of packages that combine treatments with visits to archaeological sites, historical landmarks and cultural events. This approach allows tourists to interact with the rich heritage of the region, including ancient civilizations, architectural wonders and traditional practices, enhancing their overall experience. Such integration encourages a deeper understanding and appreciation of local culture, contributing to a more satisfying and restorative health tourism experience. The successful implementation of this integrated approach to health tourism in Van requires co-operation between health professionals, tour operators, cultural institutions and local authorities. The development of themed treatment packages that include guided tours, cultural workshops and traditional experiences alongside medical treatments can offer tourists a unique and enriching experience (Smith & Puczkó, 2014).

Marketing strategies should emphasize the unique combination of health and cultural tourism available in Van, targeting both local and international markets. In addition, infrastructure development should ensure that health and cultural tourism services are accessible, of high quality and sustainable, and that the natural and cultural resources of the region are preserved for future generations. Integrating health tourism with Van's cultural and historical attractions is promising to enhance the treatment experience while contributing to the economic and social vitality of the region. This approach not only offers comprehensive health benefits by addressing the physical, mental and emotional aspects of healthy living, but also promotes cultural exchange and understanding (Dai et al., 2023). As the global demand for holistic health experiences increases, Van's unique blend of hydrogeological, cultural and historical resources makes it stand out as a leading destination for integrated health and cultural tourism. Health tourism offers a promising avenue for economic diversification and expansion in the Van Region. Van can emerge as a major

destination for health tourism by capitalizing on its natural thermal springs, which are renowned for their therapeutic properties. The establishment of state-of-the-art health centers, spa facilities and rehabilitation facilities can appeal to both domestic patients seeking holistic treatment and international visitors seeking medical procedures at competitive prices (Al Sawah et al., 2017). Furthermore, partnerships with healthcare providers and promotional campaigns targeting health-conscious travellers can strengthen the region's position in the global medical tourism market, stimulating economic growth and job creation.

## **5. Conclusion & Future Perspectives**

The rich hydrogeological resources of the Van Region, especially its natural hot springs, have enormous therapeutic potential for the treatment of psoriasis and the development of health tourism. Moreover, these resources can offer a holistic approach to wellness, attracting health-conscious people seeking alternative treatments among the tranquil landscapes of the region. In this chapter, we have highlighted the synergies between Van's natural wealth and the burgeoning health tourism sector, and the importance of sustainably utilising these resources for economic growth and healthcare innovation. Future studies should focus on elucidating the mechanisms underlying the therapeutic effects of the mineral-rich waters of the region on psoriatic skin lesions, developing optimal treatment protocols, and evaluating long-term efficacy and safety. Furthermore, interdisciplinary research integrating medical, environmental and socio-economic perspectives can provide comprehensive information on the holistic impact of health tourism on the Van Region, informing evidence-based policy decisions and sustainable development strategies. In conclusion, by capitalising on its natural assets, advancing scientific research and implementing prudent policy measures, Van Region can position itself as a leading destination for psoriasis treatment and health tourism, thereby promoting economic prosperity, improving public health and preserving its cultural heritage for future generations.

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## Chapter 7

### Acute Lung Injury Due To Sepsis And Treatment Methods

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## INTRODUCTION

Sepsis, also referred to as systemic inflammatory response syndrome (SIRS), is a life-threatening condition resulting from an excessive immune response to an infection, such as bacterial infections, or other factors that trigger immune responses in the host <sup>1</sup>. In sepsis, an excess of free oxygen radicals disrupts the body's natural balance of scavenging mechanisms. This oxidative stress contributes to microvascular dysfunction and organ damage. Acute organ dysfunction in sepsis primarily impacts the cardiovascular and respiratory systems, with the lungs being especially vulnerable as a key organ involved <sup>2</sup>. Sepsis is a serious medical concern; approximately 30% of sepsis cases lead to multiple organ dysfunction syndrome (MODS), which affects 10 out of every 1000 hospitalized patients. These conditions are thought to play a major role in the development, and progression of sepsis. In individuals diagnosed with sepsis, mortality occurs in 20%, and this rate increases to 60-80% in those progressing to septic shock. The COVID-19 pandemic has further exacerbated these statistics; it has resulted in the deaths of over 6.8 million people globally, with 1.1 million deaths in the United States alone. This pandemic has underscored our vulnerability to new pathogens and sepsis. Given the complex nature of sepsis pathogenesis, immune cells, particularly monocytes, macrophages, and neutrophils, are widely acknowledged to play a central role. Significant accumulation of neutrophils in lung tissue can enhance inflammatory processes, leading to increased production of various inflammatory cytokines, such as tumor necrosis factor (TNF), and interleukins (ILs) <sup>4</sup>. Nuclear factor kappa B (NF- $\kappa$ B) is a key nuclear transcription factor that regulates the expression of various genes, including those coding for adhesion molecules, proinflammatory cytokines, and other mediators associated with septic shock and severe sepsis. Additionally, research indicates that oxidative stress might significantly contribute to organ damage and mortality resulting from sepsis <sup>5</sup>. In a study, it has been reported that high oxidative stress in tissues, as well as in plasma, induced by cecal ligation and puncture (CLP) in sepsis, is attributed to the release of free radicals, which is considered a significant mechanism. To enhance the understanding of underlying mechanisms in clinical sepsis and develop more effective treatments, various models including polymicrobial sepsis induction with CLP are used <sup>6</sup>. The cecal ligation and puncture (CLP) model, widely used as a model for polymicrobial septic shock, is considered one of the most preferred animal models for sepsis research. Other models involve high-dose lipopolysaccharide (LPS) administration and mesenteric ischemia-reperfusion, which are also employed to study sepsis and related conditions <sup>7</sup>. Given the high mortality rate associated with sepsis, timely diagnosis and intervention are crucial. Even though sepsis is

associated with high rates of illness and death, there are ongoing challenges in promptly diagnosing sepsis and its associated complications. Therefore, there is a critical need for biomarkers that can rapidly and accurately identify the onset of sepsis and predict treatment responses <sup>8</sup>.

## **1. Acute Lung Injury**

ALI (Acute Lung Injury) is a condition characterized by disruption of the alveolar capillary barrier and impaired gas exchange in the lungs, accompanied by intense neutrophil infiltration and activation in the respiratory tract <sup>9</sup>. Acute Lung Injury (ALI), frequently marked by elevated levels of extravascular lung water and pulmonary edema, involves damage to the alveolar epithelium. This damage results in a higher permeability of the alveolar-capillary barrier <sup>10</sup>. ALI, or its more severe form known as Acute Respiratory Distress Syndrome (ARDS), is a sudden inflammatory lung condition that causes high rates of morbidity and mortality each year <sup>11</sup>. The clinical course of ALI/ARDS is variable: Some patients recover within 1-2 weeks, while others experience a prolonged course requiring mechanical ventilation for an extended period. Death from primary respiratory failure is relatively rare, but the risk of prolonged critical illness and mechanical ventilation increases the risk of subsequent infections or multiple organ failure, leading to higher mortality. In the United States alone, there are approximately 190,600 cases of ALI/ARDS annually, with a mortality rate of around 40%, equivalent to 75,000 deaths per year. Most deaths can be attributed to sepsis or MODS rather than primary respiratory failure <sup>12</sup>. Ongoing significant morbidity, including pulmonary, neuromuscular, cognitive, and psychiatric sequelae, is observed in 50% to 70% of survivors of ALI/ARDS, imposing a considerable burden on society <sup>13</sup>.

### **1.1. Causes of Acute Lung Injury**

ALI and ARDS can occur due to critical illness stemming from a variety of causes. These include direct injury to the lungs, such as pneumonia, aspiration, toxic inhalation, near-drowning, or lung contusion. Furthermore, indirect causes such as sepsis, burns, pancreatitis, gynecological disorders (placental abruption, amniotic fluid embolism, eclampsia), or massive blood transfusion can also contribute to acute lung injury <sup>14</sup>. ALI and ARDS can be divided into two histopathological stages. The first stage, known as the exudative phase, occurs within 1 to 3 days. This phase is marked by necrosis of most type I pneumocytes, widespread microvascular injury, and the influx of inflammatory cells and protein-rich fluid into the interstitium. These processes lead to extensive damage to the alveoli. The fibroproliferative phase (3 to 7 days) represents a lung repair

process characterized by type II pneumocyte hyperplasia and fibroblast proliferation. In ALI/ARDS, there are intricate autocrine and paracrine interactions involving cytokines and other proinflammatory mediators. These interactions play a key role in initiating and intensifying the inflammatory response, contributing to the pathophysiology of ALI/ARDS <sup>15</sup>. In ALI/ARDS, the core alterations involve heightened permeability of the alveolar-capillary barrier, significant buildup and activation of leukocytes and platelets, inflammation driven by neutrophils, and the stimulation of coagulation processes <sup>16</sup>. In ALI/ARDS, cellular responses involve the presentation of endothelial adhesion molecules and the alignment and migration of polymorphonuclear cells. Humoral responses include both cell-related and cell-independent factors such as cytokines, lipid mediators, proteases, oxidants, growth factors, nitric oxide (NO), neuropeptides, and the transcription factor NF- $\kappa$ B <sup>17</sup>. Alveolar macrophages (AMs), the primary immune cells in lung tissue, play a critical role in ALI pathogenesis by releasing excessive inflammatory cytokines, leading to neutrophil infiltration and lung tissue damage. While the exact mechanism by which alveolar epithelial cells (AECs) initially trigger inflammation remains unclear, AECs are structural cells with a large surface area that form a barrier, serving as the first line of defense against pathogens in the alveoli. Alveolar epithelium not only sustains injury in this process but also drives the progression of lung diseases <sup>18</sup>. Damage to epithelial integrity and harm to type II alveolar cells can interfere with proper fluid transport, which can hinder the clearance of fluid from the alveolar space <sup>19</sup>.

## **1.2. Acute Lung Injury due to Sepsis**

Sepsis is a severe health condition characterized by life-threatening organ dysfunction resulting from an abnormal host response to infection. It is a major global health concern with substantial mortality rates around the world <sup>20</sup>. Sepsis can cause irreversible damage to the lungs by triggering pulmonary inflammation, which in turn leads to the development and progression of ALI and ARDS <sup>21</sup>. Previous studies have demonstrated that sepsis is responsible for over 210,000 cases of ALI/ARDS annually in the United States alone, resulting in more than 74,500 deaths <sup>22</sup>. Sepsis-associated ALI/ARDS has a higher mortality rate compared to ALI caused by other factors <sup>23</sup>. Sepsis-associated ALI and ARDS can result from direct lung injury, such as pulmonary epithelial damage, or from indirect damage involving endothelial cells <sup>24</sup>.

### 1.3. Physiology of Acute Lung Injury Due to Sepsis

ALI/ARDS, triggering conditions such as systemic syndromes (sepsis or shock) or systemic symptoms leading to systemic sepsis or inflammatory response syndrome, such as lung injury or lung infection<sup>25</sup>. Sepsis is a significant contributor to the development of ALI, characterized by excessive inflammatory response production in lung tissue, alterations in alveolar structures, increased endothelial and alveolar permeability, and decreased alveolar fluid clearance, severely impairing lung function<sup>26</sup>. Many studies have explored the progression from ALI/ARDS to multiple organ failure, which involves the activation of inflammation, release of chemotactic factors and proinflammatory cytokines such as interleukin-1, TNF- $\alpha$  and IL-6 resulting in endothelial changes, release of counter-inflammatory cytokines with immunosuppressive effects, modulation of neutrophil margination and systemic activation of monocytes, and microcirculatory damage leading to tissue necrosis<sup>27</sup>. The passage discusses findings from these studies: "In patients with pneumonia-associated sepsis-related ALI/ARDS, pulmonary epithelial damage during ALI/ARDS can be demonstrated by elevated levels of surfactant protein-D. Also, in these patients, levels of IL-6, IL-8 and von Willebrand factor (vWF), which are markers of endothelial damage, are low. Pulmonary epithelial damage observed during ALI directly related to sepsis is more severe compared to sepsis not mediated by indirect pneumonia<sup>28</sup>. Additionally, macrophage inflammatory protein-1 $\alpha$  and CCL-3 mediates neutrophil infiltration, pulmonary vascular leakage, and early mortality, contributing to sepsis-induced ALI<sup>29</sup>. During sepsis-induced acute lung injury (ALI), the pulmonary epithelial barrier is damaged by the production of proinflammatory molecules, including cytokines, reactive oxygen species (ROS), and reactive nitrogen species (RNS), as well as by hypoxia. Damage to the pulmonary epithelium compromises barrier function, resulting in the leakage of fluid and proteins into the alveolar space. Injuries to both type I and II alveolar epithelial cells (AECs) during sepsis can be evaluated using plasma and pulmonary lavage fluid. This assessment relies on the presence of various biomarkers that provide insight into the condition and severity of the lung damage<sup>30</sup>. During sepsis, pulmonary epithelial damage and increased permeability involve changes in actin organization. Pulmonary epithelial cells (PEC) in septic lungs exhibit increased  $\alpha$ v $\beta$ 3 integrin, but the inhibition of this integrin during sepsis-associated ALI needs to be investigated as it may increase endothelial permeability and thus exacerbate sepsis-associated ALI<sup>31</sup>. During the subsequent (fibroproliferative or proliferative) stages of ALI during sepsis, damaged epithelial cells may undergo epithelial-mesenchymal transition (EMT) into fibroblast-like cells, a process requiring mitochondrial ROS and hypoxia-induced

factor-1 $\alpha$  <sup>32</sup>. During sepsis, elevated levels of C5a, <sup>33</sup> one of the most potent inflammatory peptides produced, can lead to severe ALI by binding to either C5aR1 or C5aR, resulting in increased neutrophil infiltration and a cytokine/chemokine storm in the septic lung. Therefore, neutrophils migrating to the lungs during sepsis-associated ALI exhibit more damaging effects on the lungs compared to bacterial pneumonia <sup>34</sup>. During sepsis, neutrophil infiltration into the lung alveoli occurs in response to alveolar macrophage (AM) activation via the pulmonary transendothelium route. ALI, activation of NADPH (nicotinamide adenine dinucleotide phosphate) oxidase in the pulmonary endothelium leads to the production of superoxide anions. These reactive oxygen species are generated in response to alveolar macrophage (AM) activation and play a pivotal role in facilitating transendothelial neutrophil migration, contributing to the inflammatory response and progression of lung injury <sup>35</sup>. In severe sepsis-induced ALI, neutrophils show resistance to undergoing apoptotic cell death. This resilience enables them to remain active, playing a substantial role in the progression and severity of the condition. Additionally, due to their prolonged retention in the capillary beds, these infiltrating neutrophils block pulmonary microcirculation, exacerbating sepsis-induced ALI further by inducing dead space <sup>36</sup>. In sepsis-associated ALI/ARDS, the progression of ALI/ARDS and the resolution of inflammation take place concurrently. The first phase of resolution focuses on reestablishing the integrity of the alveolar-capillary barrier and involves the movement of alveolar type II epithelial cells to occupy the space left by damaged alveolar type I epithelial cells. This migration occurs after the expansion of tissue-based progenitor cells <sup>24</sup>. The unregulated inflammatory response leading to severe acute lung injury (ALI) can impede the resolution process, resulting in irreversible damage in sepsis induced by gram-negative bacteria. This damage is marked by the accumulation of apoptosis-resistant neutrophils in the lungs and elevated levels of proinflammatory cytokines such as IL-1 $\alpha$  and TNF- $\alpha$  in bronchoalveolar lavage fluid (BALF) <sup>21</sup>. Therefore, due to the severe damage to pulmonary epithelial cells (PEC) during sepsis-induced ALI, the injury is more harmful and irreversible compared to ALI observed only during bacterial pneumonia without sepsis <sup>37</sup>. Recently, it has been shown that extravascular lung water formation, closely associated with pulmonary edema, is an independent determinant of intensive care unit mortality in patients with septic shock. Therefore, gaining insight into the mechanisms of water transport across biological membranes and mitigating pulmonary edema during severe sepsis and septic shock could potentially halt the progression of lung injury <sup>10</sup>.

#### **1.4. Experimental Models of Acute Lung Injury**

To study the mechanisms of lung injury, various animal models of experimental lung injury have been utilized. These models often involve inducing known ARDS risk factors in animals, such as sepsis, lipid embolism from bone fracture, acid aspiration, ischemia-reperfusion of pulmonary or other vascular beds, and other clinical risk factors. None of these models perfectly simulate human lung injury, but they provide invaluable insights. Despite their limitations, animal models of ALI/ARDS are crucial for understanding the pathophysiology of lung injury and for testing new therapeutic approaches within complex biological systems. Various model strategies have been developed to replicate aspects of human acute lung injury in animals <sup>7</sup>. Bacterial products such as bacteria or LPS can be administered intratracheally or intranasally to induce lung injury, while aspiration can be induced by delivering an acid or gastric particles, such as hydrochloric acid, into the airways. Models involving the depletion of surfactant by serial lavages with 0.9% sodium chloride, exposure to high inspiratory fractions of oxygen, induction of ischemia/reperfusion by clamping the hilum, or exposure to mechanical stretch by using high tidal volumes during mechanical ventilation are examples of models where the lung is directly damaged by a harmful stimulus. Indirect models of lung injury involve mechanisms that cause lung damage indirectly, such as models based on inducing sepsis. For instance, models like CLP, intravenous administration of bacteria or LPS, and mesenteric ischemia/reperfusion fall into this category. Additionally, the oleic acid model, which simulates the release of oleic acid from bone marrow in patients with multiple bone fractures, is also part of this category <sup>38</sup>.

#### **1.5. Treatment of Acute Lung Injury Due to Sepsis**

While numerous new mechanisms are being investigated to improve our understanding of the pathophysiology of sepsis, there is currently no universally accepted and effective treatment protocol. General treatment approaches include high-flow nasal cannula and non-invasive ventilation, prone positioning, neuromuscular blockade, supportive measures, extracorporeal membrane oxygenation (ECMO), and anti-inflammatory treatments <sup>39</sup>. Recent studies suggest that early short-term use of neuromuscular blocking agents may be beneficial in patients with sepsis-induced acute lung injury if indicated <sup>40</sup>. Steroids are important and effective therapeutic agents in anti-inflammatory treatment. However, the role of corticosteroids in sepsis-induced acute lung injury is not well-defined <sup>41</sup>. While there is no agreement on a particular steroid, corticosteroids can mitigate the excessive inflammatory response observed in sepsis and address relative adrenal insufficiency caused by adrenal suppression



or resistance to glucocorticoid action in tissues. Nevertheless, the evidence on whether corticosteroid administration for sepsis leads to improved clinical outcomes or survival is unclear. Therefore, they are not advised for sepsis or severe sepsis when fluid resuscitation and vasopressors suffice to maintain hemodynamic stability<sup>42</sup>. In a small retrospective study by Marik and colleagues, the potential therapeutic role of vitamin C in septic patients was suggested. The study found that intravenous administration of this vitamin in combination with thiamine and hydrocortisone (HAT therapy) reduced both mortality and organ failure in patients with sepsis and septic shock<sup>43</sup>. One study has shown that the administration of crystalloids contributes to a reduction in overall mortality and decreases the likelihood of adverse renal events. Additionally, it has been associated with lower incidences of new renal replacement therapy and permanent renal dysfunction<sup>44</sup>. Antimicrobial therapy, along with fluid resuscitation, is the cornerstone of treatment for septic patients. While avoiding significant delays in initiating treatment, appropriate routine microbiological cultures should be obtained before antibiotic administration<sup>45</sup>. Reports indicate that statins reduce inflammation. However, in a recent multicenter study, it has been reported that statins did not provide any benefit in terms of mortality in cases of sepsis-induced ALI<sup>46</sup>.

## **Conclusion**

At present, there is no treatment specifically designed for sepsis, and research in this area has shown great promise in animal studies but has not been successfully translated into clinical practice. Therapies such as immune checkpoint inhibitors, growth factors, and cytokines are often studied at the preclinical stage without incorporating standard care practices like antimicrobial therapy and other supportive measures. Therefore, addressing the mechanisms underlying sepsis should be a primary focus of future research endeavors.

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