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CHAPTER I

Hearing Loss Types in Hereditary Syndrome Diseases

Derya KOCA[1]
Özkan ŞİMŞEK[2]

Introduction

Hearing occurs when the mechanical vibrations generated by the sounds received from the external environment enter the external auditory canal and stimulate the inner ear and the corresponding electrical potential formed is transmitted to the auditory cortex via the auditory nerve (Serttaş, 2018). The human ear cannot hear all the sounds that exist in nature. The hearing threshold (decibel) is the lowest sound level that humans can hear. The hearing frequency is the rate of vibration of sound waves that humans can hear and is

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usually measured in Hertz (Hz). The human ear is capable of perceiving sound levels in the frequency range of 20-20,000 Hz and 0-120 dB (Güler, 1997).

Hearing loss can occur in people due to genetic or non-genetic factors. People with hearing loss may have difficulty accessing information and therefore be at a disadvantage in learning processes. Hearing loss can be detected early through hearing screening in newborns and adults. Case study research has found that hearing loss has also been observed in people with inherited syndromes such as Alport, Brankio-auto-renal, CHARGE, Usher, Stickler and Down (Ahmed et al., 2001; Acke et al., 2012; Mathur and Yang, 2015). The hearing loss in these patients may be due to one or more different types (conductive, sensorineural and mixed types). In this study, the types of hearing loss that occur in people with hereditary syndromic diseases are presented in detail.

Physiology of the Hearing Mechanism

The outer ear (the part between the pinna and the eardrum), the middle ear (the part between the eardrum and the oval window), the inner ear, the acoustic nerve (vestibulocochlear nerve) and the auditory areas in the brain (subcortical and cortical areas) together form the auditory system.

This system can be divided into two parts with regard to the physiological mechanism: the peripheral and the central hearing system. The peripheral hearing system includes the structures between the pinna and the cochlea, and the central hearing system includes the section between the acoustic nerve and the auditory areas in the brain (Kırbıyık, 2014; Serttaş, 2018; Topal, 2018).

Peripheral Hearing System

The peripheral auditory system is a system that includes outer ear anatomical structures, the middle ear and the inner ear, which are located in the ear and form the beginning of the hearing process. The outer ear collects the sound waves. The sound travels via the external acoustic canal and causes the eardrum to vibrate. The vibrations of

the eardrum are amplified by the malleus, incus and stapes bones in the middle ear and is then transmitted to the oval window. The sound vibrations in the oval window cause fluid movement in the cochlea in the inner ear. This movement in the cochlea is converted into nerve impulses and transmitted to the brain. The peripheral auditory system plays a key role in the perception of sound and the onset of hearing. Problems in the peripheral auditory system due to genetic and non-genetic factors can lead to hearing loss by causing conduction disturbances in this system (Belgin, 2004; Baş, 2021).

Central Hearing System

The central hearing system refers to the parts of the central nerve system that are involved in the process of hearing. These structures are the cochlear nucleus, the superior olivary complex and the lateral lemniscus in the pons, the inferior colliculus in the midbrain and the medial geniculate nucleus caudal to the thalamus. The auditory subcortex and cortex contain structures such as the internal capsule, the insula, the Heschl gyrus, the planum temporale and the superior temporal gyrus (Baş, 2021). The sound waves that are transmitted from the inner ear to the auditory nerve are converted into mechanical vibrations and transmitted to the brain via these structures. The auditory information is interpreted by the auditory cortex in the brain. The auditory cortex in the brain processes the sound information and makes sense of it. Characteristics of sounds such as frequency, intensity, rhythm and source are evaluated by the auditory cortex. Problems with the auditory nerve or conduction disorders along the central auditory pathway can lead to hearing loss in humans.

Hearing Loss

Hearing loss is the partially or completely loss of hearing due to damage to the outer ear, the middle ear, the inner ear or the auditory pathways in the ear. The cause of hearing loss can be attributed to genetic, environmental, structural or pathological (as a result of disease) factors (Aslan et al., 2013; Serttaş, 2018). Since

this disorder can be caused by many different reasons, there are different classifications of hearing loss. In this study, hearing loss is analysed under two main categories: syndromic and non-syndromic.

Syndromic hearing loss is observed in addition to genetic anomalies. The most important hereditary syndromic diseases in which these hearing losses occur are Alport, Brankio-oto-renal (BOR), CHARGE, Usher, Stickler and Down syndrome (Ahmed et al., 2001; Acke et al., 2012; Mathur and Yang, 2015).

Non-syndromal hearing loss is defined as hearing loss that occurs in the absence of other associated symptoms or medical conditions. Non-syndromal hearing loss is usually not inherited and occurs as a result of damage to the ear. Ageing, noise, infectious diseases, trauma, injuries, medications and toxins are the main factors that can cause this damage (Ocak, 2007; Mustafaoğlu, 2021).

Hearing Loss Types

There are three different kinds of hearing loss: conductive, sensorineural, and mixed hearing loss.

Conductive hearing loss

Conductive hearing loss is a type of hearing loss that occurs when the intensity of sound decreases and conduction is impaired as it travels through the external auditory canal, eardrum and middle ear bones (Birkent, 2012). This hearing loss is usually caused by mechanical or physical obstacles and prevents the sound is transmitted to the inner ear. The conductive type of hearing loss usually occurs due to problems (such as infection, trauma, dirt accumulation) in the external or middle ear (Aslan et al., 2013). These types of hearing loss can often be treated through medical or surgical means.

Conductive type hearing loss is diagnosed with a hearing test and an audiogram. To diagnose a conductive type of hearing loss on the audiogram, the hearing thresholds for bone conduction should be

pronounced between -10 dB and +20 dB and the air conduction hearing thresholds should be above the normal hearing threshold of +20 decibels (Figure 1).

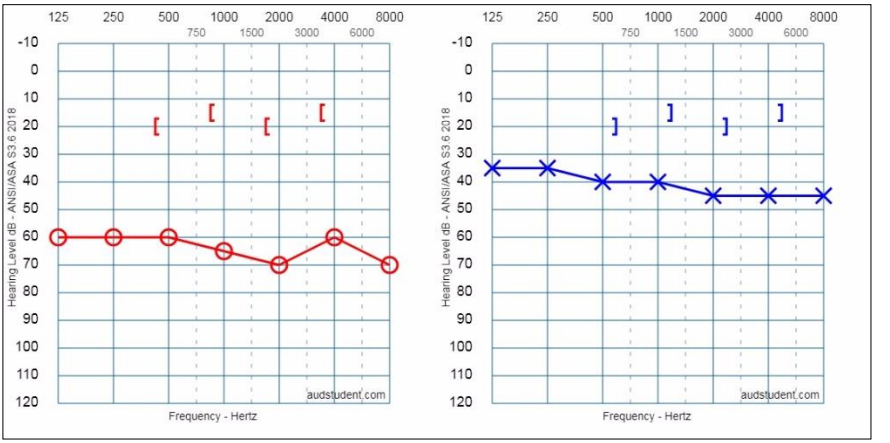

Figure 1. *Example of an audiogram for conductive hearing loss.*

Sensorineural Hearing Loss

Sensorineural hearing loss is a condition resulting from damage to the nerve pathway from the inner ear to the brain, the auditory nerve or the sensory cells in the cochlea (Çetin, 2016). It usually cannot be treated with medical or surgical methods and is the most common form of permanent hearing loss (Birkent, 2012).

Sensorineural hearing loss can be diagnosed through a hearing test and audiogram analysis. To diagnose sensorineural hearing loss on the audiogram, the marked air and bone conduction hearing thresholds must be above 20 decibels. However, there should be no more than 10 decibels difference between the air and bone conduction hearing thresholds (Figure 2).

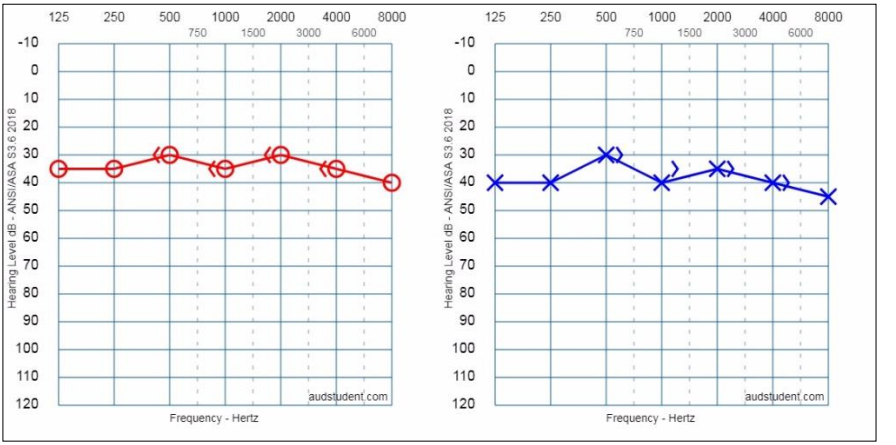

Figure 2. *Example of an audiogram for sensorineural hearing loss.*

Mixed Type Hearing Loss

Mixed type hearing loss is a combination of both conductive and sensorineural hearing loss (Birkent, 2012). This means that both the sound conduction system of the auditory pathway (outer ear, middle ear) and the acoustic nerve or sensory cells in the cochlea are affected. In this case, there may be problems with both the correct transmission of sound and auditory perception (Yaşar, 2021).

Mixed-type hearing loss can be detected by a hearing test and an audiogram analysis. To diagnose mixed type of hearing loss on the audiogram, the marked air and bone conduction hearing thresholds should be higher than 20 decibels. Furthermore, it is necessary to have a difference of over 10 decibels between the air and bone conduction hearing thresholds (Figure 3).

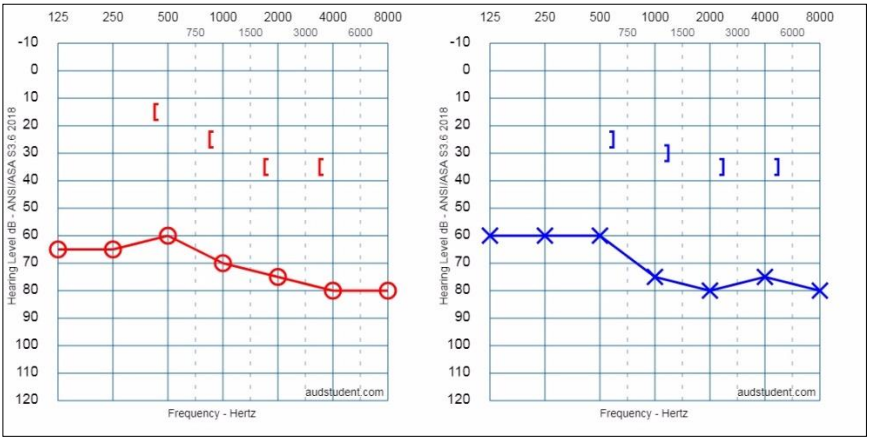

Figure 3. *Example of an audiogram for mixed type hearing loss.*

Hereditary Syndrome Diseases and Hearing Loss

Syndrome refers to the totality of findings that seem to have nothing to do with each other, but manifest as a whole when they come together (Ocak, 2007). This condition can be hereditary, but can also occur due to later causes.

For a condition to be called a syndrome, a number of findings must be observed by definition. These findings are divided into primary and secondary findings. In most syndromic diseases, not all of these findings occur together. Therefore, a certain number of major (craniofacial disorders, cardiac disorders, etc.) and minor findings (monkey line in the hand, hypoplasic face, etc.) must be present in the individual and these must be medically recognised in order for the syndrome to be named. Hearing loss is also a common symptom in people with the syndrome. Syndromal hearing loss is a condition that usually causes hearing loss from birth or gradually. This hearing loss is usually inherited and is influenced by many different genetic factors (Ocak, 2007). Depending on where it affects, one or more types of conductive, sensorineural and combined hearing loss have been identified in inherited syndromic diseases (Figure 4).

HEREDITARY SYNDROME	HEARING LOSS TYPE
Alport Syndrome	Sensorineural Hearing Loss
Brankio-oto-renal Syndrome	Conductive, Sensorineural or Mixed Type Hearing Loss
CHARGE Syndrome	Sensorineural Hearing Loss
Usher Syndrome	Sensorineural Hearing Loss
Stickler Syndrome	Conductive or Sensorineural Hearing Loss
Down Syndrome	Conductive Hearing Loss

Figure 4. *Hearing loss types in hereditary syndromes.*

Alport Syndrome

Alport syndrome is a genetic disorder characterised by a defect in the alpha5 chain of type IV collagen, which is located on the X chromosome. Its characteristic feature is the progressive degeneration of the basement membranes of the eye, kidney and ear. The reason why these organs are affected is the disruption of the synthesis of type IV collagen (Wester et al., 1995; Mahajan, 2003; Rheault, 2012). Type IV collagen chains are important structural components of the cornea, lens capsule, retina, kidney, cochlea and glomerular basement membrane ((Wester et al., 1995; Pajari et al., 1999). The incidence of Alport syndrome in the population is 1 in 5,000-10,000 people. Alport syndrome usually occurs in people aged 20-30 years. As it manifests itself in men with kidney failure, the prognosis is worse than in women.

Patients with Alport syndrome usually have normal hearing at birth. The hearing loss progresses slowly. Some studies have shown that this hearing loss originates in the cochlea and is a sensorineural hearing loss affecting high frequencies (2-8 kHz). Individuals with Alport syndrome experience varying degrees of hearing loss, which is consistently linked to renal involvement (Rheault, 2012).

Brankio-oto-renal Syndrome

Brancho-oto-renal syndrome is an hereditary disorder caused by a defect in the EYA1 gene in chromosomal region 8q13 (Kalatsiz et al., 1998). This syndrome is characterised by simple and protruding external ears, Mondini malformations of the inner ear and malformations of the kidneys (Kumar et al., 2000; Kochhar et al., 2007). The ears of individuals with this condition are small and protruding (Stratakis et al., 1998; Ant et al., 2012).

The proportions of hearing loss types that occur in people with this syndrome are 20% sensorineural, 30% conductive, and 50% mixed hearing loss. The type of hearing loss can manifest itself in different ways in a person's ears. One ear may have a conductive hearing loss, the other a sensorineural type hearing loss. The severity of hearing loss can range from mild to profound (Misra and Nolph, 1998; Ocak, 2007).

CHARGE Syndrome

CHARGE syndrome is a inherited disorder that is mainly triggered by mutations in the CHD7 gene. People with CHARGE syndrome have severe disorders such as hypogonadism, hypothyroidism, parathyroid and growth hormone deficiency, absence of the thymus gland, lymphocyte dysfunction, coloboma and cranial nerve dysfunction (Blake and Prasad, 2006; Arndt et al, 2010; Demerath et al, 2013; Hsu et al, 2014; Uzun et al, 2016; Vesseur et al, 2016).

In people with CHARGE syndrome, the ears are small, fleshy and shovel-shaped. Mondini deformity, one of the malformations of the inner ear, is observed in people with this disease. This deformity is associated with congenital hearing loss. It is characterised by hypoplasia of the apical part of the cochlea and enlargement of the vestibular aqueduct and vestibule (Wright et al., 1986; Guyot et al., 1987). Therefore, people with this syndrome often experience mild to severe sensorineural type of hearing loss.

Usher Syndrome

Usher syndrome has been observed as a result of mutations in a total of six different genes (USH1B, USH1C, USH1D, USH1F, USH2A and USH3) in 10 different gene regions. This is the most common form of autosomal recessive syndrome of syndromic hearing loss to be inherited (Smith et al., 1994; Verpy et al., 2000; Alagramam et al., 2001; Bork et al., 2001; Nance, 2003).

Usher syndrome is defined by progressive deterioration of vision and sensorineural type hearing loss, which can range from mild to severe (Mathur and Yang, 2015). Three different types of Usher syndrome exist: Type 1, Type 2, and Type 3. These types are identified by the degree of hearing loss, the existence or lack of balance problems, and the age at which symptoms are observed (Castiglione and Moeller, 2022). In type 1, congenital bilateral severe sensorineural hearing loss and balance problems due to vestibular dysfunction and progressive vision loss are observed. In type 2, bilateral mild to profound sensorineural hearing loss is observed at birth (Reisser et al., 2002). Vestibular dysfunction is not observed in this type. In type 3, progressive hearing loss with later onset and various balance disorders are observed. Balance disorders are observed in about 50% of people with type 3 Usher syndrome is a condition where individuals are born with or develop hearing loss. It is estimated that over 10% of people with congenital bilateral sensorineural hearing loss have Usher syndrome (Joensuu et al., 2001; Geng et al., 2017).

Stickler Syndrome

Stickler syndrome is an inherited disorder characterised by distinctive facial features, eye problems, hearing loss and joint damage (Keats and Corey, 1999). It probably occurs in one in 10,000 births. People with this disorder have various symptoms such as hypoplasia of the central part of the face, cleft lip, joint hypermobility, myopia and retinal detachment (Robin et al., 1993).

Hearing loss in individuals with Stickler syndrome may result from inner ear changes or middle ear abnormalities (Szymko-Bennett et al., 2001). Depending on the cause, conductive type or progressive sensorineural type of hearing loss is observed. Researchers have identified several types of Stickler syndrome that differ in genetic causes and symptom patterns. When comparing these types in relation to hearing impairment, the likelihood of severe hearing loss is higher in type II and type III than in type I. It is very rare in types IV, V and VI (Acke et al., 2012).

Down Syndrome

Down syndrome is a genetic disorder in which an extra chromosome is present in the 21st chromosome pair. Down syndrome occurs in 1 in 800 to 1,000 births. Studies show that this rate increases with increasing maternal age (Antonarakis et al., 2022).

Down syndrome is characterised by structural and functional changes in the body. Babies with this syndrome have a smaller head and a shorter neck compared to normal babies. They have a flattened nose and discrete, slanted eyes. Their hands are large, the fingers are short and chubby. There is often a single line on the palm, the simian line (Antonarakis et al., 2022).

Hearing loss is observed in 50 to 70 percent of people with Down syndrome (Shott et al., 2001). Patients with this syndrome commonly experience conductive hearing impairment, while sensorineural type of hearing loss is rare (Kreicher et al., 2018).

Conclusion

Studies have shown that people with Alport, BOR, CHARGE, Usher, Stickler, and Down syndrome, which are inherited syndromic conditions, have hearing loss among many other symptoms. In these studies, one or more types of conductive, sensorineural and combined hearing loss have been identified in inherited syndromic diseases.

Because hearing loss is common in hereditary syndromic diseases, it is important to perform early hearing evaluations in people with these diseases and to determine the types of hearing loss with a routine follow-up programme. The crucial influence of hearing on speech development, psychosocial development, communication and learning is well recognised. For this reason, it is important to carry out regular hearing health checks in order to intervene at an early stage in people with hereditary syndromes for possible associated hearing loss. This is because the earlier hearing loss occurs in a child's life, the more significant the impact on their development is likely to be. So the earlier the problem is detected, the more successful the prevention of these effects will be. Early detection of hearing loss therefore helps to ensure that these people do not lag behind their peers in terms of speech, language, learning ability and psychosocial development.

REFERENCES

Acke FRE, Dhooge IJM, Malfait F, Leenheer MR (2012). Hearing impairment in Stickler syndrome: a systematic review. *Orphanet J Rare Dis.,* 7, 84.

Ahmed ZM, Riazuddin S, Bernstein SL, Ahmed Z, Khan S, Griffith AJ, Morell RJ, Friedman TB, Riazuddin S, Wilcox ER (2001). Mutations of the protocadherin gene PCDH15 cause Usher syndrome type 1F. *Am J Hum Genet*., 69, 25-34.

Alagramam KN, Yuan H, Kuehn MH, Murcia CL, Wayne S, Srisailpathy CR, Lowry RB, Knaus R, Van Laer L, Bernier FP, Schwartz S, Lee C, Morton CC, Mullins RF, Ramesh A, Van Camp G, Hagemen GS, Woychik RP, Smith RJ (2001). Mutations in the novel protocadherin PCDH15 cause Usher syndrome type 1F. *Hum Mol Genet*., 10, 1709-1718.

Ant A, Karamert, R, & Bayazıt, Y (2012). *İşitme Kayıplarının Genetik Yönü ve Türkiye deki Görünümü.* Türkiye Klinikleri Tıp Bilimleri Dergisi, 5, 2.

Antonarakis SE, Skotko BG, Rafii MS, Strydom A, Pape SE, Bianchi DW, Sherman SL, Reeves RH (2020). Down syndrome. *Nat Rev Dis Primers.,* 6, 9.

Arndt S, Laszig R, Beck R, Schild C, Maier W, Birkenhäger R, Kroeger S, Wesarg T, Aschendorff A (2010). Spectrum of hearing disorders and their management in children with CHARGE syndrome. *Otol Neurotol.,* 31, 67-73.

Aslan F, Sevinç Ş, Özkan B (2013). *İşitme Engelli Öğrenciler İçin Öğretmen Kılavuz Kitabı*. T.C. MEB Özel Eğitim ve Rehberlik Hizmetleri Genel Müdürlüğü, s:5

Baş B (2021). *Farklı işitsel implant kullanan çocuklarda duyusal işlemleme ve dil becerilerinin değerlendirilmesi*. Doktora Tezi, Sağlık Bilimleri Enstitüsü Hacettepe Üniversitesi, Ankara.

Belgin E (2004). *Çalışma Yaşamında Gürültü ve İşitmenin Korunması* (İşitme Fizyolojisi). 1. Baskı, Ankara. Türk Tabipleri Birliği Yayınları, s:7.

Birkent ÖF (2012). *Mikst tip işitme kayıplı yetişkinlerde saf ses odyometri eşikleri ile klik ve tonal işitsel beyinsapı cevap odyometri eşiklerinin karşılaştırılması* Yüksek Lisans Tezi, Kulak Burun Ve Boğaz Hastalıkları Anabilim Dalı, Sağlık Bilimleri Enstitüsü, Fırat Üniversitesi, Elazığ.

Blake KD, Prasad C (2006). CHARGE syndrome. *Orphanet J Rare Dis.*, 1, 34.

Bolz H, von Brederlow B, Ramirez A, Bryda EC, Kutsche K, Nothwang HG, Seeliger M, del C-Salcedo Cabrera M, Vila MC, Molina OP, Gal A, Kubisch C (2001). Mutation of CDH23, encoding a new member of the cadherin gene family, causes Usher syndrome type 1D. *Nat Genet*., 27, 108-112.

Bork JM, Peters LM, Riazuddin S, Bernstein SL, Ahmed ZM, Ness SL, Polomeno R, Ramesh A, Schloss M, Srisailpathy CR, Wayne S, Bellman S, Desmukh D, Ahmed Z, Khan SN, Kaloustian VM, Li XC, Lalwani A, Riazuddin S, Bitner-Glindzicz M, Nance WE, Liu XZ, Wistow G, Smith RJ, Griffith AJ, Wilcox ER, Friedman TB, Morell RJ (2001). Usher syndrome 1D and nonsyndromic autosomal recessive deafness DFNB12 are caused by allelic mutations of the novel cadherin-like gene CDH23. *Am J Hum Genet*., 68, 26-37.

Castiglione A, Möller C (2022). Usher Syndrome. *Audiol Res.*, 12, 42-65.

Çetin SY (2016). *Konjenital Sensörinöral İşitme Engelli Çocuklarda Tai Chi'nin İşitme Engelli Çocuklarda Denge Ve Fonksiyonel Ambulasyon Üzerine Etkisi*. Doktora Tezi, Sağlık Bilimleri Enstitüsü, Pamukkale Üniversitesi, Denizli.

Demerath T, Krüger M, Meckel S (2013). CHARGE-Syndrome: Pictorial Review of Cranial Malformations – Das CHARGE-Syndrom. *Rofo.*, 185, 683-688.

Geng R, Omar A, Gopal, SR, Chen DHC, Stepanyan R, Basch ML, Dinculescu A, Furness DN, Saperstein D, Hauswirth W, Lustig LR, Alagramam KN (2017). Modeling and Preventing Progressive Hearing Loss in Usher Syndrome III. *Sci Rep.*, 7, 13480.

Guyot JP, Gacek R, Di Raddo P (1987). The temporal bone anomaly in CHARGE association. *Arch Otolaryngol Head Neck Surg.*, 113, 321-324.

Güler Ç (1997). *Ergonomiye giriş*. Çevre Sağlığı Temel Kaynak Dizisi, 45, 9-12.

Hsu P, Ma A, Wilson M, Williams G, Curotta J, Munns CF, Mehr S (2014). A review of CHARGE syndrome. *J Paediatr Child Health.*, 50, 504-511.

Joensuu T, Hamalainen R, Yuan B, Johnson C, Tegelberg S, Gasparini P, Zelante L, Pirvola U, Pakarinen L, Lehesjoki AE, la Chapelle Ad, Sankila EM (2001). Mutations in a novel gene with transmembrane domains underlie usher syndrome type 3. *Am J Hum Genet*., 69, 673-84.

Keats BJB, Corey DP (1999). The Usher syndromes. *Am J Med Genet.*, 89, 158-166.

Kırbıyık K (2014). *Tek taraflı kronik otitis medialı hastalarda orta kulak hacmi ölçümü ve hasta kulakla sağlam kulağın karşılaştırılması*. Uzmanlık Tezi, Kulak Burun Boğaz Anabilim Dalı, Cerrahpaşa Tıp Fakültesi, İstanbul Üniversitesi, İstanbul.

Kochhar A, Fischer SM, Kimberling WJ, Smith RJH (2007). Branchio-oto-renal syndrome. *Am J Med Genet.*, 143A, 1671-1678.

Kreicher KL, Weir FW, Nguyen SA, Meyer TA (2018). Characteristics and progression of hearing loss in children with down syndrome. *J Pediatr.*, 193, 27-33.

Kumar S, Deffenbacher K, Marres HA, Cremers CW, Kimberling WJ (2000). Genomewide search and genetic localization of a second gene associated with autosomal dominant branchio-oto-renal syndrome: clinical and genetic implications. *Am J Hum Genet*., 66, 1715-1720.

Mahajan SK, Sud S, Sood BR (2003), Alport Syndrome. *JIACM.*, 4, 337-339.

Mathur P, Yang J (2015). Usher syndrome: hearing loss, retinal degeneration and associated abnormalities. *Biochim Biophys Acta.*, 1852, 406-420.

Misra M, Nolph, KD (1998). Renal failure and deafness: branchio-oto-renal syndrome. *Am. J. Kidney Dis.*, 32, 334-337.

Mustafaoğlu R (2021). *Vestibüler sistem bozuklukları; Unilateral ve Bilateral Vestibüler Hipofonksiyon*. Kara B, editör. Vestibüler Rehabilitasyon, Değerlendirme ve Tedavi Yaklaşımları. 1. Baskı. Ankara: Türkiye Klinikleri, s:17-22.

Nance WE (2003). The genetics of deafness. *Ment Retard Dev Disabil Res Rev.*,9, 109-119.

Ocak Z (2007). *Otozomal Resesif Non-Sendromik İşitme Kayıplarında Connexin 26 Gen Çalışmaları*. Uzmanlık Tezi, Tıbbi Genetik Anabilim Dalı, Atatürk Üniversitesi Tıp Fakültesi, Erzurum.

Pajari H, Setala K, Heiskari N (1999). Ocular findings in 34 patients with Alport syndrome: Correlation of the findings to mutations in COL4A5 gene. *Acta Ophthalmol. Scand.*, 77, 214-217.

Reisser CFV, Kimberling WJ, Otterstedde CR (2002). Hearing loss in Usher syndrome type II is nonprogressive. *Ann Otol Rhinol.,* 111, 1108-1111.

Rheault MN (2012). Women and Alport syndrome. *Pediatr Nephrol.,* 27, 41-46.

Robin NH, Moran RT, Ala-Kokko L (1993). *Stickler Syndrome*. In: GeneReviews. University of Washington, Seattle, Seattle (WA), PMID: 20301479.

Serttaş M (2018). *Mikro elektromekanik sistem ile orta kulak kemikciklerinin hareketinin algılanması*. Yüksek Lisans Tezi, Fen Bilimleri Enstitüsü, Yıldız Teknik Üniversitesi, İstanbul.

Shott SR, Joseph A, Heithaus D (2001). Hearing loss in children with Down syndrome. *Int J Pediatr Otorhinolaryngol.*, 61, 199-205.

Smith RJ, Berlin CI, Hejtmancik JF, Keats BJ, Kimberling WJ, Lewis RA, Moller CG, Pelias MZ, Tranebjaerg L (1994). Clinical diagnosis of the Usher syndromes. Usher Syndrome Consortium. *Am J Med Genet.*, 50, 32-38.

Stratakis CA, Lin JP, Rennert OM (1998). Description of a large kindred with autosomal dominant inheritance of branchial arch anomalies, hearing loss, and ear pits, and exclusion of the branchio-oto-renal (BOR) syndrome gene locus (chromosome 8q13.3). *Am J Med Genet.*, 79, 209-214.

Szymko-Bennett YM, Mastroianni MA, Shotland LI, Davis J, Ondrey FG, Balog JZ, Rudy SF, McCullagh L, Levy HP, Liberfarb RM, Francomano CA, Griffith AJ (2001). Auditory Dysfunction in Stickler Syndrome. *Arch Otolaryngol Head Neck Surg.*, 127, 1061-1068.

Topal K (2018). *Olgularla Kulak Enfeksiyonları*. Klinik Tıp Aile Hekimliği, 10, 44-47.

Uzun AK, Demirel N, Baş AY, Çakır BÇ, Akman AÖ (2016). A Case of CHARGE Syndrome in the Neonatal Period. *Turkish J Pediatr Dis.*, 1, 60-62.

Verpy E, Leibovici M, Zwaenepoel I, Liu XZ, Gal A, Salem N, Mansour A, Blanchard S, Kobayashi I, Keats BJ, Slim R, Petit C (2000). A defect in harmonin, a PDZ domain-containing protein

expressed in the inner ear sensory hair cells, underlies Usher syndrome type 1C. *Nat Genet.*, 26, 51-55

Vesseur A, Langereis M, Free R, Snik A, van Ravenswaaij-Arts C, Mylanus E (2016). Influence of hearing loss and cognitive abilities on language development in CHARGE Syndrome. *Am J Med Genet Part A.*, 170A, 2022-2030.

Wester DC, Atkin CL, Gregory MC (1995). Alport syndrome: clinical update. *J Am Acad Audiol.*, 6, 73-79.

Wright CG, Meyerhoff WL, Brown OE, Rutledge JC (1986). Auditory and temporal bone abnormalities in CHARGE association. *Ann Otol Rhinol Laryngol.*, 95, 480-486.

CHAPTER II

Endemıcs, Pandemıcs In Hıstory And Covıd 19 Wıth Its Effects On Physıology And Psychology

Recep ASLAN[1]

Introduction

In 1796, a new era began for human and animal health with the development of the first vaccine for smallpox, in the following years for diseases such as plague and rabies, and subsequently for Bovine Plague in the Bacteriological Centre-i Osmanî. In 1928, with the discovery of the first antibiotic, penicillin, a much safer process for the sustainability of human and animal health began. Post-antibiotic and post-vaccine societies cannot adequately understand the periods before vaccination and antibiotics. Especially before these two discoveries, endemics, and pandemics, which caused deep suffering, loss and death in humans and animals, have been experienced since the early periods of history, deeply affecting health, psychology, and life, leading to the collapse of states, change of rulers and great social

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migrations. Pandemic is a concept that means "affecting all people" consisting of the word "pan" meaning "all" and "demos" meaning "people" in Ancient Greek language. Infection is when agents such as bacteria and viruses enter the body, develop or multiply there. When arthropods such as lice and scabies settle on the body surface, on the skin or subcutaneously, and when intestinal worms settle in the intestine, develop, and reproduce there, the resulting picture is called infestation. If an epidemic disease is caused by a new and different virus and can be transmitted from person to person and very easily, it comes to the agenda of the World Health Organization (WHO) as a global threat. The WHO decides whether an outbreak is a pandemic or not. According to the WHO, an infection that has turned into a disease is a pandemic if it meets the following three conditions. One: The emergence of a previously unexposed epidemic disease. Two: The disease agent is transmitted to humans and causes a dangerous disease. Three: The disease agent can spread easily and continuously. The fact that a disease or condition is widespread and causes the death of many people is not enough to qualify as a pandemic, it must also be contagious. Although some types of cancers, which are a common cause of death, are caused by infectious agents, cancer is not considered a pandemic because it is not an infectious disease (Cohen, 2020).

This study priorities Covid-19, which is the current pandemic that deeply affects life in every dimension. However, it is also important to remember some pandemics for a holistic approach. Covid-19 causes scientific concerns due to the uncertainties it still contains. It aims to contribute to the formation of information and awareness about Covid-19 disease, which has turned into a pandemic with its rapid and borderless spread.

Glossary of Concepts for Pandemics and Endemics

Contamination: The presence of the infectious agent on the body surface, clothing, bedding, toys, surgical instruments and medical supplies, beverages, and food.

Incubation: In case of exposure to a disease agent, the period until the first symptoms of that disease appear.

Latent period: The period that must elapse from exposure to a disease agent until it starts to transmit that agent. This period may be longer or shorter than the incubation period.

Infection: A condition that occurs when an agent such as bacteria or virus enters the human or animal body, develops, and multiplies there.

Infestation: It is a condition in which arthropods such as lice and scabies settle, develop, and reproduce on the body surface or skin. The settlement of intestinal worms in the intestine is also an infestation.

Disease: A condition caused by abnormal structural and functional changes in tissues, cells.

Host: A person or animal that provides a chance for an infectious agent to survive under natural conditions.

Vector: Carrier of an infectious agent from an infected person or animal or its waste to others.

Reservoir: The ambient environment in which the infectious agent lives, reproduces, and from which it is transmitted to the susceptible host, whether human, animal, plant, arthropod, soil, or several of these.

Prevalence: The ratio of the number of cases presents in a community in a time interval to those at risk.

Incidence: The ratio of the number of new cases occurring in a time interval to those at risk.

Epidemic: The observation of a disease or health-related condition in a population more than expected.

Hyperepidemic: The high incidence or prevalence of a disease in all age groups.

Endemic: The widespread presence of a disease agent in a geographical area or population.

Holoendemic: The occurrence of an infectious disease at an early age and more frequently in children.

Pandemic: When an epidemic affects too many people, countries, and continents.

Sporadic: The irregular and occasional occurrence of an infectious disease.

Attack Rate: The proportion of unvaccinated individuals who become ill.

Zoonosis: Infections that can be transmitted from vertebrate animals to humans, such as rabies and plague.

Epizootic: Epidemic of any disease in an animal population.

Endozootic: The endemicity of a disease in animals.

Nosocomial infection: Nosocomial infection is when a patient develops a new disease independent of the original disease in a hospital or health institution.

Opportunistic infection: Infections such as AIDS, systemic fungal infections, which occur because of the disease agents becoming active because of weakened body resistance.

Eradication: The termination of a disease by the disappearance of a disease agent from the earth.

Elimination: The state in which the disease caused by the disease agent is not seen despite the presence of the disease agent.

Some Pandemics From History

There is no doubt that there have been numerous endemics and pandemics in the history of mankind, which spread over large geographies and caused mass deaths and health problems. In addition to epidemics dating back to BC and recorded epidemics

such as the Plague of 664 (668-664 BC) which was effective in the British Isles, the Justinian Plague Epidemic (542-541 BC) in Europe, the Antoninus Plague (429-426 BC) in Athens, the Cyprus Plague (266-250 BC), the Antoninus Plague (180-165 BC) which was effective in Europe, Asia and North Africa, as well as epidemics that caused shocking effects in every century are known. We will return to Covid-19 by mentioning a few cases that have been effective in recent periods.

Amvas Plague

One of the plagues, which the West calls the "black death", had significant effects is the Amvâs Plague. It is known by this name because the first place it was seen was Amwâs, 33 kilometres from Jerusalem. It emerged in 639 and was effective in a wide geography including Urfa, Damascus, Jordan, and Palestine. In this epidemic, about twenty-five thousand people died, including Companions such as Abu Ubaydah b. al-Jerrah, Muâz b. Jabal, al-Fadl b. al-Abbas, the son of Hazrat Abbas, Shurahbîl b. Hasenel, Suhayl b. Amr, Utba b. Suhayl, Hâris b. Hisham (ra). Hz. Umar (ra) travelled to the region during the days when the disease was effective, Abu Ubaydah b. al-Jarrah met him outside the city and reported that the plague was spreading rapidly. As a result of his meetings, Hz. Umar returned without entering the area where the disease spread. In response to Abu Ubaydah's question, "Are you fleeing from Allah's fate?" he said, "Yes, we are fleeing from Allah's fate to Allah's fate. If you have a herd of camels, and you take them to a valley that is barren on one side and fertile on the other side, and you graze them in the fertile place and the barren place, will you not graze them by Allah's destiny?" Abdurrahman b. Awf said, "I have information for this situation. Rasulullah (saw) said, "If you hear that there is plague in a place, do not enter it. If the plague appears where you are, do not leave it." The approach of Rasulullah and the attitude of Umar Faruk show the stance of Islam against endemics and pandemics. Behind this non-stress and non-panic attitude and strong self-confidence in

Islam, there is a scientific surrender resulting from an advanced mind, a correct faith, and a correct reading of the universal system.

Black Plague

Also known as the Great Plague Epidemic, it is the plague epidemic that started in China and the south-west of Asia and reached Europe in 1347-1351, causing great destruction. It has been suggested that the epidemic was caused by a bacterium called Yersinia pestis, and spread by fleas carried by rats biting humans, and then by human-to-human transmission. In this epidemic, swelling in the groin occurred, but the same symptom was not observed in the plague epidemic in Asia in the 19th century. Since swelling in the groin can also be a symptom of other diseases, it is still debated whether the Black Death was a plague epidemic, and the causes of the epidemic are still being investigated. In the 14th century alone, 200 million people died due to the plague. It is thought that about one third of the European died in this plague epidemic.

Cholera

It is characterized by acute and severe diarrhea due to intestinal infection caused by Vibrio cholerae bacteria. Cholera epidemics were experienced in Japan in 1817, in Moscow in 1826, in Berlin, Paris and London in 1831, in Hamburg in 1892 and in Canada, and these epidemics caused death of thousands of people. The largest cholera epidemic in our country was observed during the Balkan Wars of 1912-1913, and many soldiers were killed due to the disease. The treatment of cholera, which has a very high risk of death and still causes thousands of deaths today, is simple. With oral fluid therapy, also known as oral rehydration therapy, cholera patients can regain their health in a short time. The treatment is based on replacing lost water and electrolytes such as sodium, potassium, chlorine, bicarbonate, and salt and glucose mixtures to provide energy to the patient who cannot eat normally. The mixture is administered IV to severely ill patients who are unable to drink

anything. Tetracycline and tetracycline-like antibiotics are administered to very severe and emergency patients.

Spanish Flu

An influenza pandemic between 1918 and 1920 caused by a deadly subtype of the H1N1 virus. It was the largest known pandemic in history, killing nearly 100 million people (15 per cent of the world's population) in 18 months. The characteristic of the epidemic is that it fatally affected healthy young adults rather than weak, elderly and children. It affected the world in the last days of World War I and was an important factor in the end of the four-year war. Samples taken from some mass graves showed that the disease was caused by the H1N1 virus that causes swine flu. Although the epidemic did not start in Spain, the fact that it was called Spanish flu is attributed to the fact that Spain did not take part in World War I and that the epidemic was not mentioned in other European states due to censorship, and that the Spanish press brought the epidemic to the agenda for the first time.

Hong Kong Flue

Also known as Asian Flu or Chinese Flu, it emerged for the first time in Hong Kong. It is the influenza epidemic that killed approximately one million people in 1968-1969. The type A H3N2 virus that caused the disease was derived from the H2N2 virus by antigenic divergence, which is defined as viruses with more than one subtype coming together to produce a virus center different from the original. The new virus contains the genes of the avian influenza virus H2N2. The probability of death from the disease is higher for people over 65 years of age. Starting on 13 July 1968 in Hong Kong, the outbreak spread to Vietnam, Singapore, the Philippines, northern Australia, Europe, and California after 1968. It became widespread in the USA with the entry of troops returning from the Vietnam War. The epidemic spread to Japan, Africa, and South America in 1969.

Smallpox

It is a febrile, severe, contagious disease that occurs in people of all ages and sexes, leaving scars on the face by shedding purulent blisters; it is also called Variola. The vaccine of the disease was found in Istanbul in the 1700s with the observation of the methods that pioneered the smallpox vaccine. It is more common in children. Variola has two types, major and minor, and the mortality rate is higher in the former than in the latter. The causative agent of smallpox is a virus from the Poxvirus group. The causative agent is found in the wounds and is transmitted through the patient's belongings, by approaching the patient, by flies and by inhalation of infected air. More than 20 million people are reported to have died from this disease. The first known vaccine in history is the smallpox vaccine. Smallpox, which causes large epidemics and leads to the death of many people, became invisible with immunity ranging between 1-20 years, and for this reason, smallpox vaccine was removed from the compulsory vaccination program.

Swine Flu

The disease is caused by a virus belonging to the Orthomyxoviridae family. The disease is defined in medicine with the initials of the words "swine influenza virus" (SIV). The known types of SIV are mostly Influenza virus A, rarely Influenza virus C. A vaccine is available, but SIV is constantly changing its structure so that it can be transmitted from person to person. The most recent outbreak was in 2009. This outbreak was caused by H1N1, a subtype of influenza A virus. Outbreaks in 1976 and 1988 led to desensitization to the virus. In this epidemic, 1 person died from the disease and 25 people died from the side effects of the vaccine, so the 1976 epidemic was described as the "swine flu fiasco". The 1988 outbreak showed similar results, with only one woman and her unborn baby dying. However, the outbreak in 2009 started in Mexico and infected approximately 800,000 people in 191 countries, causing the death of 8238 people due to the H1N1 virus. People who have close and unprotected contact with poultry and pigs can become

infected. When the meat of the sick animal is cooked properly, it does not pose a risk of transmission.

Bird Influenza

It is a fatal animal disease caused by a virus, also known as Avian Influenza, Pestis Avium, Bird Flu, Avian Flu, Chicken Plague. The H5N1 variant of the virus can be fatal for humans. Fever, cough, sore throat, muscle aches and lung pain are observed. It can result in pneumonia, respiratory distress, and death. The body starts to turn blue because there is not enough oxygen entering the cells, which is why it is also called "blue death". It is estimated that the H1N1 pandemic in 1918-1919 caused the death of 40-50 million people. Currently, H3N1 and H1N1 viruses are circulating together in the world, so new pandemics seem to be inevitable. Finally, avian influenza emerged between 2005 and 2008. There is no treatment, H5 and H7 types have been seen mainly in the USA, Australia, and Turkey. Protection is provided by vaccination. Animals infected with the disease must be culled. Due to frequent and permanent antigen changes, influenza virus activity must be monitored continuously, and the composition of influenza vaccines must be updated every year.

Ongoing Pandemics

HIV/AIDS

AIDS is an infectious disease caused by HIV (Human Immunodeficiency Virus), which causes the immune system to collapse. HIV slowly penetrates the immune system, destroys resistance to infections, makes the individual vulnerable to diseases and causes death. It is mostly sexually transmitted. It is a global active pandemic. It is reported that 36.9 million people in the world carry HIV virus. 2.2 million people died in 2005 and 1.8 million people died in 2010 due to AIDS. WHO 2017 data report that there are 36.7 million HIV-infected individuals in the world and 35 million people have lost their lives due to the disease since 1981.

Coronavirus Pandemic (Covid-19)

It started in Wuhan, the capital of China's Hubei region, in December 2019. Upon the occurrence of a pneumonia that developed without an identifiable cause and did not respond to treatment and vaccines, it was understood that the disease, called SARS-CoV-2, was caused by a new coronavirus, and the disease turned into an epidemic. It spread to Europe, North America, Asia-Pacific countries, and the whole world. On 11 March 2020, the pandemic was declared as a "pandemic". It can be transmitted from person to person with high transmission ability. At the end of ten cycles of three people infecting three other people, the disease agent is transmitted to 59 thousand people. The transmission rate of the virus increased in January, and virus cases started to be reported in all countries on a global scale. As of 13 March 2020, the epicenter of the coronavirus outbreak changed to Europe. As of 25 March 2020, 415,876 cases were reported worldwide, while 107,811 recoveries and 18,574 deaths were reported.

Covid-19: Characteristics, Spread

Contrary to some claims, Covid-19 is not man-made, therefore it is a naturally mutated virus. The virus is transmitted by droplet spread and contact. One of the two important parameters for the virus to be transmitted by contact and touch is the holding and touching time, and the other is the humidity. Under normal conditions, 10 seconds are required for the virus to pass. However, if one of the contacting surfaces is damp, this time decreases to 5 seconds, and if both surfaces are damp, it decreases to about 3 seconds. In this case, there is no possibility of transmission of the virus by touching a place or opening a door. The current spread of the virus is person-to-person. Being within 1 meter of an infected or infected person for 10 minutes without contact poses a risk of virus transmission. Communicating without contact and maintaining social distance below this time, for example saying hello and asking how you are doing, does not pose a risk of virus transmission. The ability to adhere to the surface, which is present in all coronaviruses, is not the

important and priority point in the transmission of the virus, the important point in transmission is the virus transmission at the level that causes disease. For example, there is information that the virus lives on steel surfaces for 72 hours. However, the number of viruses, which is millions at the beginning, decreases to 1-2 at the end of 72 hours, this number is not sufficient for the virus to make the individual sick. Even if the medium to which the virus adheres is plastic or steel, the number of viruses is halved after 1 hour under the most ideal adhesion conditions, and after 2-2.5 hours, there is no more virus to be transmitted. In this case, there is no risk of virus transmission when a suspicious package or a package from the external environment is not contacted for 2-3 hours. The virus can withstand the sun's rays for about half an hour, so being in open and sunny weather reduces the risk considerably. There are no publications and notifications regarding the transmission of the virus through food and beverages, and there is no possibility of live virus in foods heat-treated at 60 °C and above. Virus-related illness should not be underestimated, especially in young people, even if the symptoms of the disease are very mild, especially in the lungs, if it can descend, it leaves damage to the lower tissues. Although the common perception is that young people are not affected by the disease or can overcome the disease easily, it leaves permanent damage, especially in the lungs, regardless of the age of the body it enters. Therefore, it is not possible to postpone this virus and disease.

Outbreak Management and Individual Measures

One way to manage a virus outbreak is to flatten the epidemic curve. This prevents overloading the health system by delaying and weakening the peak of the epidemic and gives time for the development of a vaccine and treatment. Personal measures such as hand cleaning with non-pharmaceutical chemicals, use of masks, individual quarantine; social measures such as closing schools and cancelling collective activities, reducing the workload in the public sector, and reducing work mobility in all sectors; environmental measures such as cleaning surfaces in social areas are used to slow

down and control the spread of the virus. Therefore, success in the fight against the Covid-19 virus is based on radical measures and uncompromising implementation. In China, the government took very serious measures, including quarantining Wuhan, the capital of Hubei Province, which was the origin point of the Covid-19 pandemic, after the severity of the outbreak was realized. South Korea initiated mass screenings, local quarantines, and surveillance of affected individuals; Singapore provided financial support for patients and suspects to voluntarily quarantine themselves, imposed penalties on those who did not comply with quarantine, Taiwan accelerated mask production and banned drug stockpiling. Our country conducts the process in a cool and scientific manner. A Scientific Committee was rapidly formed, education was suspended in educational institutions at all levels, and a curfew was imposed on people over the age of 65, and mobility, social field activities and the process were managed with high sensitivity. Vaccine development efforts for COVID-19 continue multinational, but there is not yet a developed vaccine and an effective drug. In general, there is no specific treatment for human coronaviruses. Individually, it is recommended to pay attention to hand hygiene, washing hands with soap and water for at least 20 seconds, and using alcohol-based hand sanitizers when soap and water are not available. Covering the mouth and nose during coughing and sneezing, avoiding close contact with people and animals, especially those who show symptoms of coughing, sneezing and high fever, staying away from crowded and social environments, keeping a social distance of 1-2 meters and not exceeding 1-2 minutes; avoiding emotional states such as anxiety, stress and panic, and resting are recommended methods to keep the immune system strong. Due to the possibility of contamination, it is important not to go to shopping malls and health centers unless there is a necessity, and when it is necessary to go, measures such as distance to minimize contact, leaving as soon as possible, using masks and gloves are important. Individual precautions include postponing travelling for all individuals, including the elderly over 65 years of age and those with chronic

diseases; eating healthy and safe foods, avoiding raw milk and poorly cooked animal products in the diet, and washing raw vegetables and fruits thoroughly.

Transmission, Symptoms, Clinical Course

The virus is transmitted from person to person by inhalation and contact with virus-containing droplets in the air and on surfaces. There is evidence that the virus can be transmitted from person to person without showing any symptoms. The proportion of asymptomatic transmission in the spread of the epidemic is not yet fully known. This rate is important because if it is large, it will make it difficult to control the outbreak. Typical symptoms caused by Covid-19, also known as Wuhan coronavirus or Chinese flu, are sudden onset of high fever, cough, and shortness of breath after an incubation period of 2 to 27 days. In some patients, this picture is accompanied by sore throat and runny nose; the disease usually shows a moderate to severe clinical course; severe pneumonia, septic shock, acute respiratory distress syndrome (ARDS) and multiple organ failure are seen as complications of the disease, and this picture usually results in death. Although not the same in all individuals, the symptoms and clinical course of the disease that require immediate referral to a health center are as follows:

Days 1-3; cold and flu-like symptoms appear, mild fever and sore throat are observed, and if immunity is weak, these symptoms may be accompanied by nausea and diarrhea. Day 4; sore throat intensifies, voice becomes hoarse, eating and drinking becomes difficult. Diarrhea begins, accompanied by a mild headache. Day 5; the sore throat intensifies, eating and drinking become very painful, and it becomes difficult to move the body and limbs. Joint pains occur, movements are painful and painful. Day 6; a dry cough starts, there is a sore throat that increases when swallowing and talking, a feeling of severe exhaustion begins, nausea increases. Breathing is sometimes difficult; diarrhea and vomiting intensify. Day 7; the temperature rises to 38 °C, coughing and expectoration intensify, painful body and headaches as well as vomiting intensify. Day 8;

breathing becomes more difficult, the chest feels very heavy, headaches and joint pains increase, the temperature rises above 38 °C. Day 9; symptoms intensify; bruising of the face or lips due to cyanosis, coughing and expectoration, body and headaches, vomiting become very severe. Of course, there are many unknowns about the new type of coronavirus, but findings in the field show that the virus does not make everyone sick, and in very few cases the disease is severe. Although the lungs are commonly involved in patients, not all have fatal outcomes such as pneumonia and cardiac arrest. In some patients where the virus can descend, it is reported that the heart, liver, and kidneys are also involved. The risk of the disease is not the same for everyone and there are risk groups. The first risk group consists of smokers, COPD patients, those with severe organ failure, cancer patients and those receiving chemotherapy and immunosuppressive drugs. The second risk group consists of diabetic patients, cleaning, and healthcare workers, those who live and work in polluted and unhygienic environments, and those who are malnourished and malnourished. It is known that although they have the same genetic structure, identical twins with different lifestyles age at different rates, and the sibling with the wrong lifestyle and habits gets sick more frequently and more easily. In this case, it is revealed that lifestyle causes damage to genes and destruction of cells, tissues, and organs. Lifestyle is not only about diet, exercise, smoking, and alcohol; it also includes mental and spiritual weights and burdens related to beliefs and moods. Depression, which manifests itself with actions such as gossip, lies, slander, objecting to everything, not liking anything, liking only oneself, and deception, and which is the output of false beliefs, creates a favorable ground for Covid-19 as in all diseases.

Some Global Effects of Coronavirus-19

Turkey closed its border gates to its neighbors to passenger entry and exit as part of coronavirus (Covid-19) measures. All international flights were suspended except for five points in four countries. Those returning from Umrah, those wishing to return from

abroad and those studying abroad were quarantined in student dormitories belonging to KYK. As of 17 March, the activities of theatres, cinemas, restaurants, coffee houses, internet cafes and indoor playgrounds, barbers and hairdressers were suspended. As of Monday 16 March, education at all levels, including higher education, was suspended for a long period of time, and it was decided to conduct education remotely. The Covid-19 vaccine developed in the USA was tested on volunteers. WHO declared the situation due to the new type of coronavirus a pandemic. Umrah visits were cancelled and circumambulation in Kaaba was restricted. The USA and many countries raised the alert level or declared a national emergency. In Italy and Spain, the whole country was quarantined. China quarantined 13 cities, including Wuhan. A partial curfew was declared in France as of 17 March 2020. Bulgaria declared a state of emergency in the country until 13 April 2020 to prevent the spread of the virus. Schools, universities, and sports competitions were suspended all over the world. 2020 European Football Championship, 2020 Eurovision Song Contest were postponed to 2021 due to the coronavirus pandemic. Airlines such as THY, British Airways, Finnair, Qatar Airways, United Airlines and Air Canada suspended flights to China and the United States suspended flights to Europe. Starbucks closed more than half of its branches in China. Ikea decided to close its stores in China. Tesla and Apple temporarily closed some of their factories in China. Volkswagen stopped production in its factories for two weeks. Companies such as Airbus, Michelin, Skoda, Brembo, Maserati, Renault Group, Fiat, Lamborghini, and Ferrari suspended production at their factories in Italy, Spain, France, Serbia, Slovakia, and Poland. Toyota suspended production at its production facility in Sakarya for two weeks. With these and other profound effects, Covid-19 is seen as a pandemic that will seriously change and affect human health and psychology, as well as the global economy, societies' views and approaches to events, perceptions of education, economy, profession, and work, and thus lifestyles.

How Does Covid-19 Affect Physiology and Psychology?

Epidemics are phenomena with unpredictable effects and consequences. Epidemics, which are fatal factors for human and animal masses, have deeply affected individual and social life and caused significant changes. The Novel Coronavirus Disease (Covid-19), which has the distinction of being a global milestone today, has shown a global and rapid spread, except for some limited regions, since the first case notification due to the 2019-nCoV virus, and has started to affect and change life in basic indicators and details. There is a need for constantly renewed data and information on this serious situation. Individuals and societies need information, ideas, and predictions about changing emotions, thoughts, and lifestyles. It is important and necessary to predict how the emotions, thoughts and behaviors of people and society will be in the post-pandemic period. For this reason, it is a responsibility to scientifically examine the basic elements affecting the physiological mechanism, mood, and behaviors in the individual for the epidemic days and the post-epidemic period. Change based on the pandemic also includes the way of thinking and living. All of life, including economic, administrative, political, military institutions and systems, work, transport and consumption, communication are evolving due to changing perceptions. Those whose psychology is damaged by the pandemic and those who are negatively affected by the pandemic constitute a widespread mass. However, the consciousnesses that show strong and sustainable protection behavior during the pandemic and become open to new perceptions and lifestyles by establishing a high fear-hope balance live this new situation without complaint.

Social isolation and quarantine practices that started with the declaration of Covid-19 as a pandemic have encouraged the continuation of interpersonal relations through online platforms and telecommunications, and many businesses and education have managed the process with this method. Reports that this situation leads to depression, stress and anxiety and interpersonal violence cases have increased in those who need other individuals to survive

and spend time together for a long time. Due to the mutually reinforcing structure of psychology and physiology, the analysis of these situations is important for individual and public health. Managing epidemic psychology should be based on keeping the emotional state of individuals in a strong and correct belief before the spread of false information and a motivation that coincides with universal general truths. We are at a point where the number of people who lost their lives due to Covid-19 has reached 500 thousand and the number of cases has reached 10 million. The physiological and psychological effects of the virus are being investigated by universities and scientists, and articles are being published. Since Covid-19 is a new medical condition, we are faced with many unknowns. It is observed that the virus can adhere to cells in almost all tissues, cause permanent damage to the heart, blood vessels, kidneys and brain, and this situation becomes more complicated with its psychological effects. Despite hundreds of studies and millions of cases, many things about the virus are still unknown. The study aims to get to know the phenomenon a little closer by addressing the interaction of Covid-19 with physiology and psychology and to support the creation of a perception and physiology ready for new norms.

Coronaviruses and Covid-19

Coronaviruses (CoV) are a family of viruses that are widespread but usually self-limiting, resulting in mild infections. We also know that the same viruses can cause very serious infections such as Middle East Respiratory Syndrome (MERS) and severe acute respiratory syndrome (SARS). CoV has subtypes such as HCoV-229E, HCoV-OC43, HCoV-NL63, HKU1-CoV, which are found in humans and can be easily transmitted from person to person, as well as subtypes such as SARS-CoV, MERS- CoV, which are found in animals and cause severe disease by passing to humans. When pneumonia cases of unknown etiology emerged in Wuhan in December 2019, it was understood in the first months of 2020 that this was a new coronavirus case that had not been detected in humans

before, the disease picture was named Covid-19, and the virus causing the disease was named SARS-CoV-2 due to its similarity to SARS CoV.

How Does the Virus Affect Physiology?

When the human body is exposed to a foreign pathogen causing disease, it starts to produce proteins known as antibodies, which can survive in the blood and tissues. In the case of a viral infection, these proteins attach to the virus and prevent it from replicating itself, thus preventing the infection from occurring and spreading. The effect of Covid-19 on physiology caused by the new type of coronavirus, which has a high ability to spread and infect, has a very wide and variable spectrum. While the virus does not cause disease in many organisms, it has been found that patients produce antibodies and recover. In symptomatic cases, it has been shown that many physiological systems and tissues are affected by the virus. 1-2% of Covid-19 cases, in which one or more of the symptoms such as sore throat and chest, shortness of breath, fever, cough, weakness, general pain in muscles and body, headache, loss of sense of taste and smell, nasal congestion or discharge, nausea, vomiting and diarrhea can be persistently seen, experience serious cardiovascular problems and high cardiac enzyme picture, cell infiltration in the heart and cardiac inflammation; Since the organ prioritized by the virus is the lungs, 20-25% of patients develop chest stenosis and cough as a result of hyperactivity in the bronchi. Open and closed disease symptoms such as burning in the lungs and dry cough occur even after two months in those who test positive for Covid-19; light grey spots called "ground glass opacities" frequently appear in the lungs of patients on CT scans; this scar tissue in the lung does not allow physiological respiration, and such tissue changes cause permanent damage. It has been reported that patients with Covid-19 may experience very high coagulation (blood clot) formation within the scope of inflammatory response to infection, and the clot may cause serious and permanent complications such as pulmonary thrombosis, pulmonary embolism, which is a fatal

condition that can cut off circulation to a part of the lungs, stroke, and heart attack. Renal failure has also been observed as a common symptom in many Covid-19 patients, and it has been reported that permanent damage may lead to a lifelong dialysis-dependent life. Some critical illnesses are known to put extra stress on the heart and cardiovascular system, especially at low oxygen levels. In Covid-19 cases, it has been observed that viral particles can cause inflammation in the heart muscle and cardiac tissue damage. It is thought that Covid-19 also affects the central nervous system, the long-term consequences of which may appear as neurological diseases and psychiatric cases. In new coronavirus cases, it has been suggested that plasma leakage from the vessels can occur, which can trigger a serious immune problem known as "Kawasaki" due to fluid accumulation in the lungs and other vital organs. Researchers believe that Covid-19 has the potential to cause male infertility in men. Studies showing decreased testosterone levels in men with Covid-19 make the relationship between male infertility and Covid-19 worth investigating. Another frequently reported picture in Covid-19 cases is cytokine storm. Cytokine storm, which is a picture in which the immune system starts to produce undesirable effects, appears as the most important factor leading to devastating lung inflammation and death in Covid-19 patients, especially in young people. Cells called cytokines are also involved in the immune system's response to trauma and infections. In the picture of cytokine storm, cytokines react excessively to defend the organism against foreign proteins and to reach the tissue where these agents are present, compete for defense, and cause damage while playing a role in the healing of the body. When the attack of these defense cells on the area affected by the virus is severe and persistent, an inflammation that kills the tissues begins. Excessive signaling of cytokines leads to chronicization of inflammation, which in turn leads to respiratory failure due to filling of alveoli in Covid-19 patients, and uncontrolled and untreated inflammation pictures result in death in most patients. The fact that the new type of coronavirus targets all vital organs such as the lungs, heart, brain and even kidneys and can directly damage

them shows that the physiological mechanism is under a great risk in these patients; especially the involvement of nerve cells opens the door to virus-related neurological diseases and psychological problems (Tarhan, 2020).

Covid-19 and Perception

There are many unknown aspects of the epidemic that directly affect physiology and mood. Due to the characteristics of the factors that cause epidemics, they either disrupt physiological functioning and psychology themselves or destabilize them with secondary infections and complications. For this reason, it is considered natural for epidemic conditions to affect mood. The individual's beliefs, eating habits, lifestyle, communication, and relationships are also important and determinant in this process. For this reason, changing transmission and recovery findings, emotional states, secondary disease pictures and complications can be observed in Covid-19 cases. These results make the psychology in patients directly related to their beliefs and lifestyle and place them in the position of a distinguishing indicator (Tarhan 2020). Epidemics such as Covid-19, which has caused deaths for thousands of years and is generally referred to as plague, cause disorders in mental organization and mechanisms as well as tissue structures. For this reason, epidemic conditions have caused social disturbances and wars even though they are not related at all. Due to Covid-19, xenophobia (xenophobia) has increased in almost all societies, and in some countries, civil unrest has progressed beyond expectations.

Effect of The Pandemic on Psychology

It is known that epidemics cause traumatic effects and increase the level of anxiety and stress. In patients, factors such as loss of function due to the disease, pain and suffering generally affect psychology negatively. In healthy individuals under the risk of epidemic, on the other hand, conditions such as the danger of the person himself/herself, his/her family and close environment getting the disease, the possibility of losing his/her job, freedoms and some

opportunities, and the inability to continue his/her routine life affect the psychology and turn into behavioral disorders. The way a disease is perceived affects the reaction to that disease; behaviors during an epidemic also play a role in the speed of the spread of the epidemic and the loss of life. For this reason, knowing the psychology and behaviors during the pandemic and managing them correctly is a priority in terms of effective fight against the pandemic. Covid-19-induced mood changes are observed in a wide range from psychological cases to psychiatric cases. The occurrence of serious disorders such as psychosis, mania, depression, fatigue, catatonia (physical and mental introversion) and Guillain-Barre syndrome, and the fact that these conditions are seen in patients of all age groups, but especially in patients aged 20-50 years, make the interaction of Covid-19 and psychology an important issue. Persistent chronic fatigue and depression attacks, behavioral disorders have been reported in individuals with Covid-19, while mood disorders, rarely psychosis and less frequently dementia have been reported in 1/3 of non-sick individuals. In the global picture, indicators such as increasing family violence and divorces, intolerance, increased hatred, and the rise of self-centered approaches make the relationship between Covid-19 and psychology a file that needs to be wondered and solved (Manav, 2011; Wang, 2020).

A Common Risk in The Pandemic: Health Anxiety

Anxiety is defined as a state of uneasiness that arises as a reflection of scientific or imagined fear of a danger. Health anxiety, on the other hand, is a psychological state that emerges with the thought of a strong and great threat to health and triggers physical and emotional anxiety symptoms. In this condition, the person strongly accepts that he/she has a serious disease, and that this disease will cause bad results even though he/she does not have any disease. Control perception is important in the fight against health anxiety. The perception of control is defined as the ability to change situations considered important and to adapt to new conditions;

people who believe that they can easily influence their environment are considered to have a high perception of control. Perception of control is important not only in psychology but also in maintaining physiology and homeostasis. However, care should be taken to ensure that this feeling does not lead to psychological trauma. Nowadays, when the novel coronavirus pandemic is the main agenda, it is normal to be more distant towards people with the suspicion that they may be the source of disease, but it is not right to hate them and to react against them at a level that may turn into violence. Health anxiety and fear of death underlie the fact that epidemics intensify intra-group relations and make relations with strangers distant. As a positive effect, this situation makes it widespread to react to those who do not obey the rules and to find irresponsible and imprudent socialization wrong. In fact, it is thought that street addiction and attraction to the outside is a genetic habit dating back to primitive times, inherited from the period when cave people were obliged to go outside because all their needs other than shelter were outside the cave. In this case, unless there is an obligation, seeing the outside, the street, the external environment, and spaces more attractive than home becomes situations that are difficult to define in another way. It is accepted as a source of anxiety and stress that the pandemic creates a death anxiety, especially when those in the risk group think about the possibility of dying themselves when they see the number of deaths and experience this feeling. However, this is not the case for those who see thinking about death and its aftermath as a rehabilitation and education recommended by verses and hadiths; contemplation of death keeps them strong in taking precautions, protection, and the joy of living, and moves relationships and motivation to a more accurate, more scientific position. For this reason, death anxiety makes the fact that "one day we will surely die" either an opportunity to make life meaningful for individuals or it makes life meaningless. In fact, the inevitability of death does not make life meaningless. Because in the genes of human beings there is always a desire and goal to move to the next stage. The next step, life in the hereafter, means life in a new

dimension, in new "norms of livable life". Foreseeing the continuation of life in new conditions and new norms of livable life can be a gain for the individual and an opportunity for the evolution of realization in these days when death is thought of more frequently and intensely due to Covid-19. At the very least, it may allow those who are not cold to religion to understand the facts, universal general truths, the meaning implied by Allah and the mathematics in the system of creation (Dündar, 2015, 2016, 2023). Since the possible negative effects of Covid-19 on psychology and relationships are often emphasized, the positive effects of the pandemic can be covered up. Just as it can pave the way to see with reason, foresight, and science rather than limited to the eye, the psychology of the pandemic also contains opportunities that can make cooperation for solving many problems, helping those in need, peace, and the protection of human dignity more possible. Many correct behaviors such as individuals being able to allocate more and better-quality time to themselves and their families, realizing that the home is the most valuable living space and at the same time an area of freedom and security, and making more cautious, more hygienic, and more systematic living a lifestyle will become widespread (Demircan, 2020; Li, 2020).

Covid-19: Nano Herald of The New Era

The global pandemic has affected every single person regardless of criteria such as borders, age, gender, belonging, race and status, and thoughts, approaches and lifestyles have started to change. For this reason, "post pandemic" is accepted as a multidisciplinary concept. Societies are affected by the epidemic in a way that varies according to the measures taken, the power to combat the epidemic, beliefs, social habits, and the level of awareness. Our country is among the successful countries in terms of being affected by the epidemic. In this success, scientific approach, NGOs, central and local administrations draw attention with a harmonious process management. The World Health Organization has reported that Turkey is the country that manages

the epidemic process most successfully in nursing homes and reported that health policies and practices in this regard are successful (https://www.who.int/en/).

Thoughts, perspectives, and lifestyles are directly affected by beliefs. Perspectives and lifestyles change gradually. However, life can also change rapidly under the influence of factors such as religious teachings, revolutions, epidemics, and migrations. The Covid-19 pandemic has had a profound impact on all societies, and the "post pandemic" process, in which this impact will be long-lasting, has been monitored. This process has a dynamism that will irreversibly change thoughts, lifestyles, governance approaches, and all concepts of life. This situation makes it necessary to compare the conditions before and after the pandemic. The article aims to raise awareness of the changes in the Covid-19 and post-pandemic process (Wang, 2020; Tükek, 2020).

Environment and Breath Safety in Pandemic Practice

"Respiratory and transmission" sensitivity, which is also felt in open areas with the pandemic, becomes more pronounced in closed and unventilated environments and indoors where ventilation is fast. Being disturbed and startled by loudspeakers, sneezers and coughers may be a defense reflex that develops due to data showing that the virus can remain in the air for hours. The high virulence, easy acquisition of the disease, the fact that the unknowns of the disease process are still very high, and the atypical epidemic profile in which the disease symptoms are constantly updated make it important to keep some data in mind. It is thought that the risk of transmission of the virus from surfaces is weak, and that outdoor communication that does not exceed 10 minutes is within the scope of low-risk activities. Areas such as offices, public transport vehicles, hospitals, schools, places of worship, shopping malls, crowded marketplaces, streets and streets, cinema or theatre halls, wards are environments with a very high risk of transmission. Virus load is important for the virus to cause disease. It is reported that the virus load predicted for transmission is approximately 1000 virus particles, and that the

disease develops if approximately one thousand vesicles are taken into the body. It has been reported that virus carriers leave about 20 vesicles per minute with normal physiological breathing, this figure is 200 vesicles/minute during conversation, and 200 million vesicles in coughing and sneezing (Alper, 2020) It is easier to acquire the virus load required for the disease in communications, close distances, and poorly ventilated environments where proper masks are not used. Communication with a person carrying the virus for 45 minutes at 2 meters is a high risk, while face-to-face communication with this person, even if masked, reduces this time to 4 minutes. Passing a person carrying the virus on foot, running or cycling is considered a low risk for the disease. Although staying in well-ventilated places where the distance is maintained is low risk, the risk increases in direct proportion to the length of stay in the environment. All indoor areas are high risk areas despite hygiene, mask, and distance. Public areas such as gyms, Turkish baths and saunas are also considered high-risk areas. Restaurants are medium-risk areas even under the conditions of sitting outdoors while keeping distance, not touching surfaces too much and paying attention to hygiene; if they are indoors, the high-risk area status applies. Workplaces and schools are very high-risk areas even if social distancing is observed. Parties, weddings, business meetings, conferences, workshops, gyms, hairdressers, concerts, cinemas are very high-risk areas (Özdelikara, 2018).

Post Pandemy

A process in which individuals who are addicted to strict hygiene, who like to stay with themselves, who are distant from socializing, who live cautiously by anticipating the risks in the air they breathe and in their immediate surroundings will increase is becoming normalized. Behavioral patterns that prefer to use stairs instead of elevators in order to maintain social distance, that see their private space as 1.5-2 meters under all circumstances and therefore stay away from public transport, that meet their needs from virtual markets, that provide sightseeing with virtual reality (VR) glasses,

and that try to meet their information needs such as education and consultancy through e-learning are gradually increasing. Simultaneously, perspectives that do not want to stay at home and in closed environments, dislike barriers such as masks and social distancing, see protection and security behaviors as a constraint on freedom, find living with a high level of cleanliness and basic hygiene behaviors exaggerated are also seeking a ground for legitimacy and organize protests and demonstrations by forming crowds (Aydemir, 2013; Bandelov, 2015). All these can be seen as preliminary signs that define the post-pandemic period in which two different lifestyles have begun to diverge more clearly from each other. In addition to the platform formed by those who do not have a scientific fear of the new and possible risks from the phenomenon that develops by protecting their old routines, a new platform of thought and life is formed where sensitivities change, and foresight is effective. The fear experienced by those who have turned the natural, environmentalist, scientific approach into a lifestyle that focuses more on what they eat, what they wear, what they breathe, how they communicate, what they think and how they live make them stronger and smarter. For example, those who are concerned about the coughing and sneezing of someone next to them, who think that barriers such as masks may not be sufficient, who cannot use public transport, who do not go to the cinema, who eat their meals at home, who prefer distant communication even with family members, and those who do this on a stress and anxiety platform, and those in the database who live the same life peacefully, lovingly and willingly with a scientific fear and a sense of protection may not achieve the same result. With the post-pandemic, it is seen that scientific approaches and products that prioritize reason rather than intelligence (IQ) are becoming widespread. At this point, Generation Z, which has a high expectation from them, comes to the fore. This generation draws attention with their speed and intelligence. Speed indicates a healthy neuron structure, functional synaptic activity, and a strong database. When speed comes side by side with intelligence, truth and reality, very important results occur (Zhang, 2020). The

fact that Generation Z is a digital as well as a smart generation is revealed as a high questioning ability, which facilitates their visionary thinking, realizing, and accepting the truth, and acting scientifically. It is thought that this generation can easily internalize the post-pandemic process due to their personality traits that do not like behaviors such as handshaking and excessive socialization and like to be on their own in their individual space. For this reason, individuals who can easily adapt to post-pandemic conditions and welcome the results will probably be under the age of 15-25. These individuals are prone to accept feeling and sensation as the real reality, and they can see and live relationships and life as virtual reality due to their way of thinking that perceives that phenomena are virtuality. For this reason, it is thought that they are quite successful in using digital data and have high virtual reality constructs (Erdem, 2020; Kwok, 2020).

Pandemic Changed Perceptions and Life

It is important for scientific disciplines to consider the perceptual changes in this process as the subject of a separate study and to focus on the subject. One of the concepts discussed in the post-pandemic period is overtime, training processes and forms. In this process, it has been experienced that it is possible to produce work from home and that this can be more efficient and performant in many business areas. In this case, working and training conditions have been opened to discussion from new and unforeseen perspectives. The proposal to extend the weekend to Fridays, Saturdays and Sundays is among the issues discussed. A three-day weekend approach could lead to stronger family ties, more productive weekend holidays and more mobility in domestic and international tourism. In the European Union, this has been in practice for years in countries with a 30-hour working week. In this context, it has been realized during the pandemic that 4-day/week programs for primary, secondary, high school and higher education will be sufficient for a quality and effective educational output, and the opinions in this direction have become widely accepted. Due to

the widespread and effective use of digital communication and information technologies and artificial intelligence in the public, private and financial sectors, it has been seen that being in the office environment for one or two or three days a week may be sufficient for many jobs. A three-day weekend and four-day intensive training can increase productivity, reduce mobbing, support personal development, and provide a more economical process management. In the post-pandemic process, when it was realized that the flow of life routine was not as safe as thought, the perception of social distance and private space started to change. Environments and activities such as education, work, worship, entertainment, where it is difficult to maintain the distance to protect this area constitute an important part of life. In the case, standards should be established for a process where education and work can fit into four days, and the process should be realized through pilot applications (Tarhan, 2020).

It has been observed that many courses can be given by distance education (e-learning) under normal conditions. In this period, the possibilities of using virtual reality and augmented reality applications, which are thought to have not received the attention they deserve despite the search for alternative methods, for work, education, sports, entertainment, shopping, and worship should be investigated. It is possible to overcome the deficiencies of distance education with virtual reality applications. In this case, the space and time required for compulsory applications and processes other than virtual reality and remote communication possibilities will be considerably reduced. In a period when the active mass in business and education life has started to be Generation Z, predictions and changes are experienced very quickly. Generation Z has a profile that learns fast, gets bored quickly from facts and environments that are outside its field of interest and do not satisfy it, and has weak nostalgic desires and feelings such as returning to the past, which suggests that change will be rapid in the post-pandemic process (Zhang, 2020).

Pandemic: Chaos or Opportunity?

The answer to this question varies according to perspectives. For individuals who try to develop perceptions and behaviors in accordance with the first purity of the feeling and self, the post-pandemic is developing as a period of rapid and powerful opportunities. For those who do not care enough about universal laws and phenomena and accept a freedom limited by their individuality as indispensable, it refers to a narrowed, difficult, uncertain, and risky period (Çakıroğlu, 2020; Dündar, 2015, 2023).

Lifestyles based on philosophical backgrounds such as individualism, narcissism, hedonism, and materialism stand on two legs: Tekasür and teberrüc. Teberrüc is an emotional state based on histrionics, exhibitionism and glamourizing oneself and one's life. Tekasür, on the other hand, is a perception based on arrogance, which is based on the perception that he thinks that he and the phenomena around him really exist, that he is a self-sufficient and autonomous being (Dündar, 2023). The conditions brought about by the pandemic commonly cause psychological disorders, mood disorders and mental breakdowns such as personality disorders in these individuals. In this epidemic, where the routine and practices of normal life are distanced from, individual acquisitions change compulsorily, for example, more than one billion children cannot go to school, millions of individuals lose their jobs, there is a feeling of uncertainty, people see that their normal life course is not correct and safe, and there is a risk of contamination, disease, and death at any time. While the post-pandemic process, which is tried to be understood in a format defined by these conditions, means new perspectives, hopes and opportunities for those who think scientifically and are protected, it turns into a labyrinth of fear for those who object to the conditions, cannot accept the risks, approach the measures as restrictions, and protest the protection and security methods (Tarhan, 2020).

Conclusion and Recommendations

Covid-19 pandemic, which has affected the world is a process that includes the experimentation of man with a nano-sized molecule, who thinks that he has an invincible power and mind with the support of technology developed especially after the Industrial Revolution. While the post-pandemic period is a hope and remedy for those who think scientifically and care about protection, it is a vicious circle of uncertainties for those who make anxiety, depression, and strife a lifestyle. The shocking, encompassing and horrifying effects of the pandemic and the virus suggest that a new and different perception process may have begun. Important natural events and shocking diseases have also been perceived as a sign of a new era or perception in the historical process; many events that took place in the year Rasulullah (PBUH) was born were interpreted as such by historians, and it was thought that a period of change that would affect the world had begun. The post-pandemic process will initiate new questioning in many areas such as working life, education, politics, economy and international relations, and the need to review the knowledge, experience and perceptions acquired in the past will be felt. The conditions brought about by the pandemic may cause widespread mood disorders, mental breakdowns, and psychological disorders in individuals. The Covid-19 pandemic has had a profound impact on all societies, and this impact has been labelled as "post pandemic". This process can completely change thoughts and habits about life. This situation makes the comparison of pre-pandemic and post-pandemic conditions and awareness compulsory. During the pandemic, new perspectives may develop for work, education, sports, entertainment, shopping, and worship. The direction and speed of changes are important in this period when the active mass of life begins to consist of Generation Z. The fast-learning and nostalgic state of Generation Z may be effective in shaping the post-pandemic process. A life with a high level of protection against the danger carried by the virus, which can affect the brain, neurons, synaptic activity, and genetic data, should be considered important, and on the other hand, it should be lived with

high hope, considering that the epidemic may be a sign of an important period.

Protection of physiological health in Covid-19 cases necessitates staying away from the virus. Because Covid-19 is different from other influenza epidemics, it is a serious disease with many unknowns. It can cause sudden death by causing serious and often irreversible tissue damage in all vital organs and tissues, especially the lungs and heart. Although the average mortality rate does not exceed 3% in societies, it can produce fatal results especially in the elderly over 65 years of age, those with impaired and inadequate immune system, smokers, and those living with chronic diseases. In the meantime, it is necessary to protect and support psychology against Covid-19, as it is a disease that leaves deep traces in individual and community psychology. People with panic attacks and anxiety are people who think "my health will deteriorate, I will die" and have a high fear of death. Especially in these individuals, the philosophy of life and beliefs should be corrected first, and the correct fear-hope balance should replace the wrong fear of death. Otherwise, in accordance with the rule "the disease does not change, but the materials in the patient change", a person whose previous fear was to die from a heart attack will now fear dying from Covid-19. It should also be known that scientific fears and natural fears are not phobias.

One of the indicators that distinguishes phobia from fear is "excessive rush to cologne and disinfectant, pasta, shelves in markets; there is a disproportionate reaction in phobia. In the natural stress that develops in the case of fear, the organism increases its energy and develops a reaction to remain calm against the threat. For this reason, the sense of control that will develop this reaction should not be lost in the management of Covid-19 psychology. Otherwise, it becomes difficult to get rid of the thoughts of "I will die, something bad will happen" and the individual loses sleep at night. In such cases, the brain secretes more stress hormones, excessive stress negatively affects the immune system, and the person invites what he/she fears without realizing it. All studies show that when the

immune system is suppressed, the ability of the virus to transmit and cause disease increases. This means that instead of fighting against the virus, we unwittingly become more susceptible to the virus. Stress physiology also includes the psychosomatic consequences of stress. The body can only buffer even a momentary stress in a few hours. Individuals whose anxiety cannot be controlled live under anxiety for 45-50 minutes of an hour, leading to a chronic high stress picture. These conditions cause the brain to secrete acid chemicals, which leads to a chain of problems such as increased vascular resistance, deterioration of gastrointestinal secretions, stress on the integrity of the skin, dermatitis and, as a result, total suppression of the immune system. Since energy resources are depleted in the person who experiences "fight or flight" psychology for a long time due to stress, the immune system collapses and diseases to which predisposition is felt, and which are called "sleeping diseases" are revealed. It is important for individuals experiencing corona phobia to perform mental exercises and readings on correct faith and trust to control this anxiety and stress. The "stress, no panic" approach should be remembered here as a medically recommended emotional state that expresses a balanced state of fear-hope; it should be ensured that individuals with corona phobia, panic attacks and anxiety can pass this period in the lightest way. Controlled anxiety is essential in the Covid-19 process. For this, it is necessary to take scientific measures, to be strictly protected and to get rid of primitive approaches such as "nothing will happen to me". It should not be forgotten that new normal will make life strong, safe, healthy, and fit. In addition, not falling into the mistake of perceiving routine deaths due to Covid-19 as a number will create a high awareness and quality life platform. To come out of the process with a positive "acquired change" and to make a profitable process management, it is important to keep the level of awareness high and to draw scientific lessons from the cases, as it will be a requirement of using the mind scientifically.

One of the important ways to manage a virus outbreak is to postpone the peak of the epidemic, so that the health system is

protected from becoming unable to function due to overload. For this to happen, public institutions, individuals, local governments, and non-governmental organizations need to work together. When this environment is provided, the spread of the disease is determined by the physical compliance of individuals and their psychological state. Psychology is an integral part of physiology. "Neuro immun modulation" is an important definition in medicine, this concept emphasizes the ability of the emotional state of the individual to influence and manage immunity. Good, encouraging, positive, peaceful thoughts, speech and behavior strengthen immunity at least as much as antioxidants, vitamins, minerals, and physical activity. Endemics and pandemics, including Covid-19, are also a test and a teaching feature for humanity. This situation is not only for managers, the scientific world, and the health system, but for all individuals. While working to develop a protective vaccine against the virus and to create mass immunity, it is also necessary to update our behaviors and habits with the right ones. Developing a protective vaccine requires at least one year, while mass immunity requires two years. The most effective method to be applied in the meantime is to take ownership of the process, to change our behavior in the right, permanent and effective way, and to do this willingly and diligently. According to experts, this is the most effective and fastest solution for Covid-19. In this context, social isolation, keeping social distance (1-2 meters) and hand washing are the simplest and first behaviors to be implemented. Individual protection targeted by hand and face cleaning should be done with non-pharmaceutical tools such as soap, disinfectants, and cologne. For social protection, it is vital to suspend education, to stretch business and commercial life, to cancel collective activities, and to clean public places. The virus has also reminded the whole world that it is necessary to pay attention to scientific prevention measures and make them a lifestyle. In this context, it has been seen that it is necessary to be suspicious of external environments without obsessing. Images from many countries show that patients apply their saliva to common areas, food packaging and even food. This is common all over the world, in

every period. In cases of illness, patients endeavor to transmit their illness to other people. All this makes it necessary to be cautious, to balance socialization, and to review eating and spending habits based on out-of-home environments. A period may begin when the motto "Life is on the street!" loses its validity and it is realized that "home is the safest place". The approach that "every pandemic erase something old and starts a new life" is also valid for Covid-19. With this pandemic, it has been seen that no vital parameter will continue as before. In this context, educational technologies will also be updated. The process is an opportunity to start the effective and sustainable use of digital materials, virtual reality, and hologram techniques in education in every field and stage. Non-governmental organizations should assume more active and vital roles in this process, which can be achieved by breathing with the world but producing local solutions. If individuals do not underestimate the risk factors and create a lifestyle in accordance with scientific measures and universal general truths, the experience experienced in this process can turn into positive gains.

References

Alper, S. (2020). Possible social psychological effects of the corona pandemic: What kind of future awaits societies? https://www.birgun.net/haber/korona-salgininin-olasi-sosyal-psikolojik-etkileri-toplumlari-nasil-bir-gelecek-bekliyor-294823

Aydemir, Ö. et al. (2013). Reliability and Validity Study of Health Anxiety Scale for Turkish. *Archives of Neuropsychiatry*, 50(4), 325-31.

Bandelow. B., Michaelis, S. (2015). Epidemiology of Anxiety Disorders in The 21st Century. *Dialogues in Clinical Neuroscience*, 17(3), 327-335.

Çakıroğlu KI, Pirtini S, Çengel Ö. (2020). A Conceptual Study on the Changing Trend of Consumer Behaviour in terms of Lifestyle in the Covid-19 Process and Post-Pandemic Period. *Istanbul Commerce University Journal of Social Sciences*, 19(37), 81-103.

Cohen, MS, Hellmann, N., Levy, JA., DeCock, K., Lange, J. (2008). The spread, treatment, and prevention of HIV-1: evolution of a global pandemic. *The Journal of Clinical Investigation*, 118 (4), 1244-54.

Demircan, A. (2020) The First Preventive Medicine and Quarantine Case in Islam: How the Plague of Amvas was Overcome? Derin Tarih, https://www.derintarih.com/dosya/amvas-vebasi-nasil-asildi-2/

Dündar, Y. (2015). Sen Tanrı mısın? Ankara: Uyum Ajans.

Dündar, Y. (2016). Happiness Management. Ankara: Uyum Ajans.

Dündar, Y. (2023). Kader: Kader Matriksi, Yaşanabilir Hayat Normları. Ankara: Uyum Ajans.

Erdem, R., et all. (2020). The Effect of COVID-19 Pandemic on the Turkish Society. *Electron J Gen Med*, 17(6), 237.

Dünya Sağlık Örgütü: https://www.who.int/en/

Kıroğlu, F. (2020). Working Conditions and General Problems in Covid-19 Pandemic Environment. *Meyad Academy Journal,* 1(1), 9-90.

Kwok, KO., et all. (2020). Community responses during the early phase of the Covid-19 Epidemic in Hong Kong: Risk perception, information exposure and preventive measures. medRxiv.

Lau, JTF., et all. (2005). SARS Related Perceptions in Hong Kong. *Emerging Infectious Diseases,* 11, 417-24.

Leung, GM., et all. (2005). Longitudinal assessment of community psych behavioral responses during and after the 2003 outbreak of severe acute respiratory syndrome in Hong Kong. *Clinical Infectious Diseases*, 40(12), 1713-1720.

Li, JB., et all. (2020). Chinese Public's Knowledge, Perceived Severity, and Perceived Controllability of the COVID-19 And Their Associations with Emotional And Behavioural Reactions, Social Participation and Precautionary Behaviour: *A National Survey.* doi:10.31234/osf.io/5tmsh

Manav, F. (2011). The Concept of Anxiety. *Journal of Social Sciences,* 5(9), 201-211.

Özdelikara, A. et all. (2018). Determination of Health Perception, Health Anxiety and Affecting Factors in Nursing Students. *Bakırköy Medical Journal*, 14, 275-282.

Tarhan, N. (2020). https://npistanbul.com/koronavirus/prof-dr-nevzat-tarhan-koronafobi-hayati-kisitliyor.

Tükek, T. (2020). Some Symptoms Persist in Patients. https://www.haber7.com/guncel/ haber/2983351-koronavirusu-yenen-hastalar-uzerinde-inceleme-yapildi-3-belirti-devam-edebiliyor.

Wang, Y., et all. (2020). The Impact of Covic-19 Epidemic Declaration on Psychological Consequences: A Study on Active Weibo Users. International Journal of Environmental *Research and Public Health*, 17(6), 2032-35.

Zhang, WR., et all. (2020). Mental health and psychosocial problems of medical health workers during the COVID-19 epidemic in China. *Psychotherapy and Psychosomatic*.

CHAPTER III

Cırcadıan Rhythm And Melatonın

Mehmet ÖZSAN[1]

Introduction

In a healthy individual, a balance should exist between the internal rhythms of the body and those of the external environment. Daily life exposes our bodies to primary rhythms or cycles, which encompass ultradian, circadian, infradian, and circannual rhythms. The circannual rhythm covers a yearly cycle influenced by our body, while ultradian rhythm involves multiple cycles within a day, and infradian rhythm lasts for weeks or months. Circadian rhythms, lasting approximately one day, exert significant influence on an individual's life, as we navigate our existence under the guidance of these four cycles.

Various aspects in humans, including sleep-wake cycles, body temperature, hormone levels, and specific cognitive functions, undergo fluctuations in accordance with the daily (circadian)

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rhythm. Pinealocyte cells, which are sensitive to light, produce melatonin secretion in the dark. This melatonin hormone, renowned for its heightened secretion in darkness, is emphasized as a potent antioxidant contributing to various bodily functions. The circadian rhythm in melatonin secretion becomes irregular with age, and this disruption is evident not only in physiological conditions but also in specific clinical disorders, such as mood disorders. Additionally, the brain possesses its circadian rhythm specific to its tissue, independent of the SCN rhythm (Sözlü & Şanlıer, 2017).

1-Circadian Rhythm

The term "circadian" is derived from the Latin words "circa" (approximately) and "dies" (day), denoting a roughly one-day duration. Within this timeframe, which includes features like initiation and conclusion, the circadian rhythm defines a singular cycle. It mirrors the daily physiological, biological, and behavioral alterations in an organism. Among these rhythms, the sleep-wake cycle emerges as the foremost and determining circadian rhythm in humans (Çalıyurt, 2001, Zee & Manthena 2007, Selvi et al., 2011).

Functioning as a vital regulator of diverse physiological events, the circadian rhythm exerts influence over the sleep-wake cycle, hunger and satiety, temperature regulations, gene expression, and the operation of the endocrine, gastrointestinal, immune, respiratory, cardiovascular, and metabolic systems (Sezinler, 2018).

The primary regulator of the circadian rhythm is the suprachiasmatic nucleus (SCN/SKN), consisting of a pair of structures situated in the anterior hypothalamus (Gooley & Saper 2005). The SKN controls the body's core temperature rhythm, sleep-wake cycle, and the secretion of specific hormones (growth hormone, cortisol, and melatonin). This mechanism enables the organism to synchronize its physiological functions with the external environment, maintaining rhythmic functions under varying conditions. Light plays the most significant role in regulating the rhythm, alongside other influencers like social and physical activities. Light is detected by light-sensitive retinal ganglion cells

containing melanopsin, transmitting signals to the SKN through the retinohypothalamic pathway. Light stimuli then reach the pineal gland via complex neural networks through the superior cervical ganglion, inhibiting melatonin synthesis due to the light's impact (Figure 1). The alternation between light and darkness in the external environment crucially influences circadian rhythm regulation.

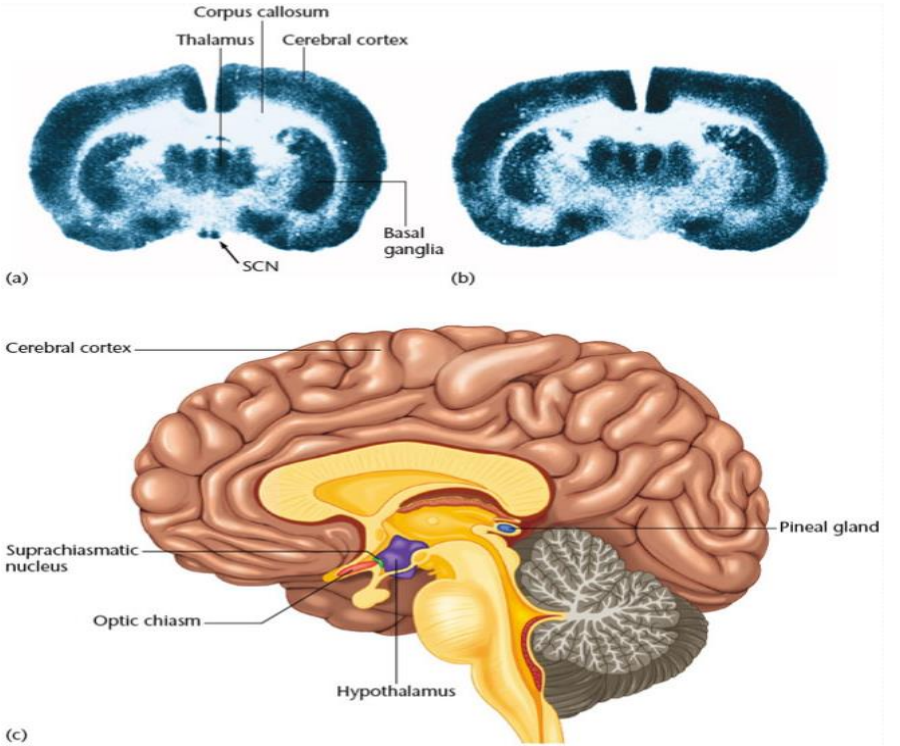

Figure 1 (Fındıklı, 2013, Thomson Higher Education, 2007).

The SCN/SKN acts as the central control center for circadian rhythms, located in the anterior hypothalamus above the optic chiasm. Damage to the SCN can disrupt the circadian rhythm, affecting the body's temperature rhythm, sleep-wake cycle, and hormone secretion (cortisol, melatonin, and growth hormone). Positioned above the optic chiasm, the SCN is sensitive to light. Zeitgeber refers to any stimulus that resets the circadian rhythm,

acting as an external factor or clock-setter affecting the biorhythm (Fındıklı, 2013). Examples of Zeitgebers include light, exercise, nutrition, temperature, work, and social preferences. These factors influence the SCN and can modify the circadian cycle (Kocar & Elçiolu, 2022).

2- Factors Affecting Circadian Rhythm

Various internal and external elements contribute to the regulation of organisms' biological clocks. Here are key factors influencing circadian rhythm:

2.1- Light

Light stands out as one of the most powerful and distinct factors affecting circadian rhythm. The biological rhythm of an organism is influenced through the interaction of the nervous and endocrine systems with light. Light plays a role in impacting the secretion of melatonin and cortisol hormones. Daylight regulates the circadian rhythm by influencing photoreceptors in the retina. SCN neurons directly receive the light signal through the retinohypothalamic system (RHT), regulating peripheral clocks in organs such as the heart, liver, and kidneys directly or indirectly (Schibler & Sassone-Corsi, 2002, Apayrı, 2012).

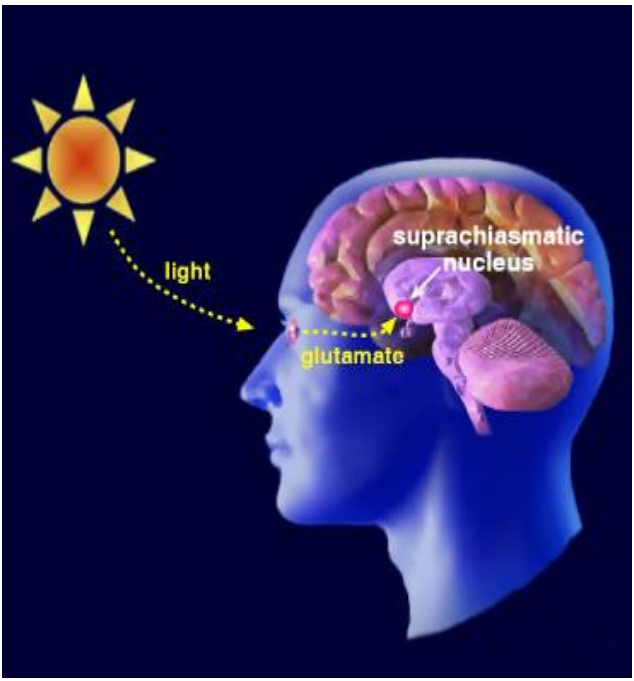

Figure 2

At the core of daily physiological functions lies the diminutive suprachiasmatic nucleus (SCN) nestled within the hypothalamus. This nucleus assumes a pivotal role in coordinating the day-to-day oscillations of the internal environment, aligning them seamlessly with the dynamic cycles of day and night and responding to the body's ever-changing states. This biological clock directs the daily expression of crucial homeostatic functions, including feeding, drinking, body temperature, and neurohormone secretion. It strategically organizes these bodily functions into nearly 24-hour oscillations known as circadian rhythms. The SCN establishes temporal order by 1) generating output signals that convey time-of-day information and 2) controlling its own sensitivity to incoming signals that fine-tune clock timing (https://www.life.illinois.edu/clockworks/pages/SCN.html)

2.2 - Sleep

Research has demonstrated that the sleep-wake cycle is the most fundamental and determining circadian rhythm in humans. The suprachiasmatic nucleus (SCN) in the hypothalamus regulates the circadian rhythm associated with the sleep-wake cycle. The melatonin receptors within the SCN underscore the significant role of melatonin hormones in circadian rhythm control. One of the key factors influencing the quality of sleep is the melatonin hormone released from the pineal gland. Melatonin is secreted in darkness, preparing the body for relaxation and sleep. Adequate sleep cannot be achieved in a well-lit environment since this hormone is not produced in the presence of light. Sleeping in a brightly lit environment disrupts the biological rhythm as cortisol is released in response to light. Unlike melatonin, cortisol is a stress hormone that attempts to keep the body awake (Kocar & Elçiolu, 2022).

2.3 - Melatonin

Melatonin, released from the pineal gland, is influenced by the environmental photoperiod. Studies have indicated that various physiological functions result from its daily secretion, leading to organized seasonal changes in mammals (Maeda & Lincoln, 1990, Dönmez et al., 2004). The pineal gland is one of the structures the SCN is concerned with. The primary function of this brain structure is to synthesize melatonin from tryptophan, influenced by darkness. This process occurs rhythmically in all mammals (Sözlü & Şanlıer, 2017). As melatonin secretion varies with the length of the night, it is responsible for synchronizing seasonal changes with circadian rhythms (Haus, 2007).

2.4 - Jet Lag

Jet lag is defined as travel (transmeridian air travel) between regions with different time zones. One of the factors disrupting the melatonin-cortisol circadian rhythm is jet lag. When a person arrives at a distant location in a short time, their internal balance cannot immediately adapt to the external environment. The body,

attempting to maintain its internal balance both at the arrival and departure locations, encounters various discomforts. Gastrointestinal problems resulting from circadian rhythm disruption, attention disorders, daytime sleepiness and fatigue, as well as nighttime sleep problems and mood disorders, may occur. Young people are more affected than the elderly (Akıncı & Orhan, 2016).

2.5 - Temperature

Body temperature is a factor that affects circadian rhythm. It is associated with wakefulness and sleep cycles. The rising temperature in the morning increases wakefulness, while the falling temperature at night enhances the tendency to sleep. Peripheral oscillators covering fibroblasts, lungs, liver, and kidneys are highly sensitive to these external temperature changes (Sözlü & Şanlıer, 2017, Oike et al., 2014).

2.6 - Nutrition

Nutrition is subject to circadian rhythm, and food intake can influence it. Specifically, meal times and eating patterns can affect the body's biological clock. Eating at night can disrupt the circadian rhythm. It is essential for nutrition to be sufficient, regular, and balanced from the perspective of circadian rhythm (Özenoğlu & Ünal, 2015). Hunger is an important factor affecting circadian rhythm. Insufficient nutrient intake can disturb an individual's biorhythm, negatively impacting their psychology. As a result, behavioral disorders may occur in individuals. For example, a deficiency in certain amino acids can lead to aggressive behavior because tryptophan is a precursor to serotonin. Since serotonin is the precursor hormone to melatonin, the absence or low levels of serotonin adversely affect circadian rhythm (Kocar & Elçiolu, 2022).

2.7 - Hormones

The circadian clocks within our body discern the optimal timing for activities and orchestrate fundamental metabolic processes, including digestion, sleep, hormone secretion, body temperature, and blood pressure, in a synchronized manner (Sözlü &

Şanlıer, 2017). Hormones play a critical and indispensable role in metabolic homeostasis by regulating the interaction between the central nervous system and metabolic organs. The variability in a hormone's rhythm determines its efficacy on the target tissue, arising from the interplay between a messenger molecule's receptor and the response of the target tissue, which may fluctuate over time. Numerous hormones are subject to circadian rhythm influence; examples include cortisol, melatonin, insulin, and thyroid hormones, which are secreted in accordance with the circadian rhythm (Haus, 2007).

2.8 - Age and Gender

The gender factor also influences circadian rhythm through the lens of the sleep factor. Studies indicate that women experience sleep problems at a higher rate than men, likely due to varying stress levels between genders that can impact sleep quality (Sezinler, 2018). As individuals age, the quality of sleep tends to diminish, accompanied by an increase in daytime napping. Changes in the central nervous system that emerge with aging contribute to altered sleep quality. The disruption in synchronization between the central and peripheral clocks, stemming from the degradation of signals from the SCN to peripheral clocks with age, results in disturbances in both central and peripheral rhythms. Additionally, the secretion of the melatonin hormone decreases and becomes irregular with aging (Kocar & Elçiolu, 2022; Otlu, 2019).

2.9 - Social Time (Shift Work)

The daily routines and work schedules of individuals can impact circadian rhythms. For instance, individuals working night shifts may find it challenging to synchronize sleep and wakefulness with their natural circadian rhythm. Those working shifts are active during hours when they should be resting according to their biological rhythm. This disruption to the circadian rhythm leads to interruptions in melatonin synthesis (Laposky et al., 2008).

3 - Melatonin

Melatonin, a natural compound belonging to the indole chemical family, shares its lineage with serotonin and its precursor, tryptophan (Figure 1). Discovered by Aaron B. Lerner in the mid-20th century (Lerner et al., 1959), melatonin is primarily synthesized by the pineal gland during nighttime under normal environmental conditions. Studies suggest that in mammals, seasonal changes are orchestrated through daily secretion, giving rise to diverse physiological functions (Maeda & Lıncoln, 1990, Dönmez et al., 2004). Melatonin is uniformly synthesized and released at night across species, synchronizing with the circadian rhythm. In mammals, the SCN governs this rhythm, and disruptions in the SCN lead to an interruption in the circadian rhythm of melatonin secretion. The circadian rhythm is fundamentally tied to the light-dark cycle (Çam & Erdoğan, 2003).

There are discernible correlations between nighttime melatonin production and sleep. Sleep deprivation does not alter the melatonin rhythm or impact dim light secretion. Although various studies have attempted to delineate detailed melatonin profiles based on sleep stages, no conclusive relationship has been established (Çam & Erdoğan, 2003).

Melatonin acts as a transmissible marker for environmental rhythms, encompassing both circadian (sequence and duration of days and nights) (Armstrong, 1989) and seasonal (sequence of winters and summers) rhythms (Revel, 2009). This rhythmic succession involves the synthesis of melatonin by the pineal gland (Klein, 2007).

Melatonin synthesis and release are initiated in the absence of light during the night and suppressed in daylight conditions (Szymusiak & McGinty, 2008). However, exposure to light at night leads to a reduction in plasma melatonin levels. Beyond its chronobiotic influence, melatonin also harbors a hypnotic effect. By inhibiting neuronal firing in the suprachiasmatic nucleus (SCN), melatonin actively contributes to both the onset and maintenance of

sleep. The administration of exogenous melatonin orally induces a sleep-promoting, or hypnotic, effect (Sack et al., 1997). Endogenous rhythm phase shifts can be induced by manipulating exposure to light and the timing of melatonin administration. Administering melatonin in the evening advances the phase, while morning administration delays it. Conversely, light exposure follows a similar pattern: Intense light exposure in the evening delays the phase, while exposure in the early morning advances it. Properly timed application of bright light and melatonin can effectively regulate phase shifts in circadian rhythm disorders (Lewy et al., 1992)

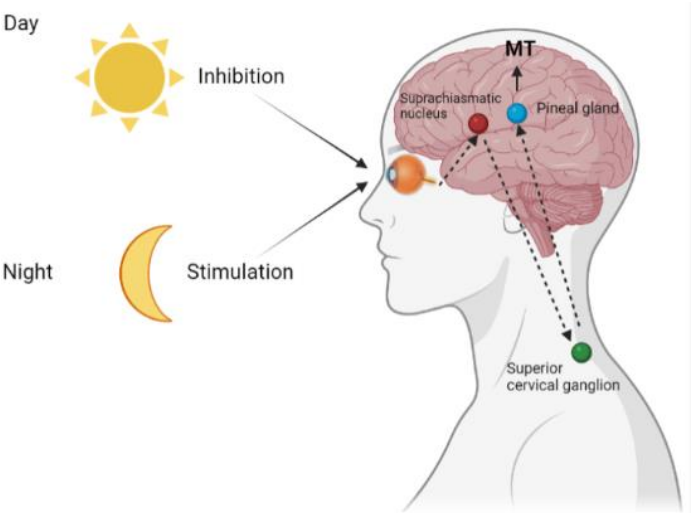

Figure 3

In the intricate orchestration of circadian rhythms across all living organisms, melatonin takes center stage as the primary regulator. Light information, transmitted via ganglion cells derived from the retina's rods and cones, as well as directly from light-sensitive ganglion cells, infiltrates the paired suprachiasmatic nucleus (SCN) nestled in the hypothalamus. These signals embark on a journey through the cervical spinal cord, loop back to the brain, and eventually find their destination in the pineal gland. During periods of darkness and sleep, when the majority of SCN neurons

remain inactive, nerve terminals release norepinephrine, instigating the synthesis of melatonin in pinealocytes. Despite the hindrance imposed by intense light on synthesis, the rhythmic production persists through the periodic activity of the SCN, a rhythm upheld in unbroken darkness (Kvetnoy et al., 2022).

3.1 Synthesis and Secretion of Melatonin

Melatonin serves as the principal product of the pineal gland (epiphysis), exhibiting a circadian rhythm in its secretion. Notably, melatonin release, which is responsive to environmental light conditions, is significantly elevated during the night, ranging from 7 to 10 times higher than during the day. Daytime light exposure stimulates receptors in the retina, transmitting signals to cells in the suprachiasmatic nucleus (SCN) through the optic nerve. These signals, in turn, generate inhibitory stimuli that prevent the upper cervical ganglion (SCG) cells from producing signals. As a result, adrenergic pathways from the SCG to the pineal gland remain inactive in well-lit environments. However, as the environment darkens at night, the inhibitory suppression on the SCG is lifted, leading to stimulation of the pineal gland through both α and β adrenergic pathways (Topal et al., 2009).

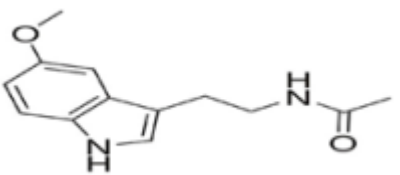

Figure 4 Melatonin, represented by the chemical formula N-acetyl-5-methoxytryptamine, is a small and lipophilic molecule.

External stimuli activate the NAT enzyme through G proteins in the primary cells of the pineal gland, known as pinealocytes. The amino acid tryptophan, transported from the blood to pinealocytes through active transport throughout the day and converted to serotonin, undergoes a chain reaction triggered by the NAT enzyme activated during the dark night, transforming it into melatonin.

Thanks to its highly lipophilic nature, the produced melatonin easily traverses the cell membrane through free diffusion and is transported in the blood, where it binds to albumin at a rate of 60-70% (Topal et al., 2009).

3.2. Melatonin's Mechanism of Action

The pineal gland and its principal hormone, melatonin, play a crucial role in regulating the endocrine rhythm, demonstrating antigonadotropic effects, providing protective effects on the nervous system, stimulating the immune system, and functioning as a potent free radical scavenger (Pekmez et al., 2004).

Melatonin, often referred to as the "youth hormone" (Mehmetoğlu, 2006), stands out as the most potent known antioxidant to date. It has been proven effective in inhibiting the impact of cancer-causing substances by generating free oxygen radicals (Mehmetoğlu, 2006). Another notable feature of melatonin as an antioxidant is its remarkable ability to reach nearly every part of cells, including the cell nucleus, extending its protective influence to vital tissues such as the brain. Consequently, melatonin exhibits antioxidant activity on a broad scale (Mehmetoğlu, 2006). The unique capability of melatonin to enter the cell nucleus represents a superior characteristic compared to other antioxidants, particularly in safeguarding DNA from oxidative damage (Mehmetoğlu, 2006).

Melatonin follows a circadian rhythm, being synthesized and released at night in all species. In mammals, the SCN (suprachiasmatic nucleus) governs this rhythm, and disruptions in SCN lesions result in the disturbance of melatonin secretion's circadian rhythm. Fundamentally, the circadian rhythm aligns with the light-dark cycle (Çam & Erdoğan, 2003).

Several perspectives propose that melatonin's ability to extend lifespan may arise from positive immune system regulation or its stress-relieving properties through the brain opioid system. Another viewpoint suggests that as individuals age, similar to the decline in serum melatonin levels, the circadian spontaneous alert system

experiences reduced adaptability. It is argued that exogenous melatonin could enhance the adaptability of the circadian spontaneous alert system by providing feedback to this system (Çam & Erdoğan, 2003).

4. Sleep and Melatonin

Essential for human well-being, sleep is intricately governed by the ebb and flow of the light-dark cycle. The journey of light exposure commences a neural pathway, starting from the retina and extending to the hypothalamic region in the brain. At the heart of this regulation is the suprachiasmatic nucleus (SCN) nestled within the hypothalamus, serving as a veritable "biological clock." This orchestrator sets in motion signals that command hormones, regulate body temperature, and modulate the delicate balance between the states of sleep and wakefulness, thereby influencing activities across the entire body (Macchi & Bruce, 2004). Melatonin-related hormones linked to sleep are suppressed due to the pineal gland's inactivity until dark hours. As sunlight fades, inhibitory signals preventing melatonin secretion decrease, stimulating the pineal gland to produce melatonin. Increasing melatonin levels reduce sensitivity to stimuli, intensifying the sensation of sleep (Arendt, 2000). Melatonin's effects on sleep are associated with its hypothermic effects and thermoregulation (Scheer & Czeisler, 2005; Tsuzuki et al., 2004).

5. Circadian Rhythm and Melatonin

Melatonin secretion follows a circadian rhythm, with releases 7–10 times higher at night than during the day. Consequently, individuals who pass away during the night often exhibit elevated melatonin levels. Plasma melatonin concentration peaks between 02:00 and 04:00 at night. In adults, secretion typically starts around 21:00–22:00 and concludes between 07:00–09:00. Time to peak levels is 1–2 hours from these periods, and the morning decline occurs 3–4 hours later. Melatonin secretion also varies seasonally, with later secretion in summer and earlier onset in winter. Prolonged

melatonin secretion is observed in short days, while short-term secretion occurs in long days (Gökçe, 2012).

Due to its anticancer properties, melatonin is used in cancer treatment, with a significant focus on breast cancer models in current studies. These studies suggest that administering melatonin during the night leads to more successful results in cancer treatment. This aligns with the optimal time for melatonin administration, emphasizing the importance of synchronizing with the human circadian rhythm (Gökçe, 2012).

Melatonin exerts its effects by binding to specific receptors in target tissues. There are three types of melatonin receptors: MT1, MT2, and MT3. Melatonin receptors are found in various peripheral tissues, including the retina, brain, pituitary gland, spleen, red blood cells, white blood cells, thyroid gland, thymus, placenta, endometrium, and the gastrointestinal system. Melatonin's circadian and reproductive effects are carried out through the MT1 receptor, while the MT2 receptor is believed to be associated with dopaminergic functions in the brain and retina (Özdemir et al., 2014). Research has shown that MT1 and MT2 receptors have a more significant impact on the circadian rhythm (Kocar & Elçiolu, 2022).

6. Conclusion

The inherent rhythm of human life, attuned to the natural cadence of day and night, encounters shifts in today's dynamic conditions, thereby influencing the circadian rhythm. Daily practices, shaped by modern technology, encompassing facets like light exposure, dietary patterns, temperature variations, physical engagement, and work hours, compounded by the nuances of contemporary living, collectively give rise to disturbances in the individual circadian rhythms.

Extensive research since the 1950s has highlighted the diverse physiological effects of the melatonin hormone, which has garnered increasing interest. Mood disorders, particularly those associated

with disruptions in the circadian rhythm, are closely correlated with plasma melatonin levels. Realignment of the circadian rhythm through not only pharmacological agents but also light therapies can contribute to improving the scenario of mood disorders. Ultimately, the circadian rhythm serves as a guide for the organism to lead a healthy life. Adhering to this rhythm, aligning the intake of food and medications with it, reduces the occurrence of diseases and issues, thereby enhancing the overall quality of life.

References

Akıncı, E., Orhan, F.Ö., (2016). Sirkadiyen Ritim Uyku Bozuklukları. Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry 8(2), s.(178-186).

Apayrı, S., (2012). Ofislerde aydınlatma tasarımının sürdürülebilirlik açısından mekan tasarımına etkileri, MSc,Haliç Üniversitesi, İstanbul, Türkiye.

Arendt, J., (2000). Melatonin, circadian rhythms and sleep. New Engl J Med; 343:1114-1116

Armstrong, S.M., (1989). Melatonin and circadian control in mammals. Experientia; 45 : 932-8.

Çalıyurt, O., (2001). Duygudurum bozuklukları ve biyolojik ritm. Duygudurum Dizisi, 5:209-214.

Çam, A., Erdoğan, M.F., (2003). Melatonin. Ankara Üniversitesi Tıp Fakültesi Mecmuası, 56(2):103-112.

Dönmez, N., Karaca, F., Belge, F., Ateş, CT., (2004). The effects of melatonin application on some haematological parameters and thyroid hormones and testosterone in male goats' non-breeding season. Veterinarski arhiv 74 (4), 281-287

Fındıklı, E., (2013). Sirkadiyen Ritim Boyutları ve Duygudurum Bozuklukları. https://silo.tips/download/yrd-do-dr-ebru-findikli-ksu-tp-fakltesi-psikiyatri-ad-49upkeyll-İzmir

Gooley, J., Saper, C., (2005). Anatomy of the Mammalian Circadian System. In: Principles and Practice of Sleep Medicine.:335-350.

Gökçe, S., (2012). Obez ve Sağlıklı Kişilerde Kan DHEA, İnsülin Rezistansı, Melatonin ve Lipid Düzeylerinin Araştırılması. Selçuk Üniversitesi Sağlık Bilimleri Enstitüsü, Yüksek Lisans Tezi, Konya, s.(31-36).

Hampden-Thompson, G. & Galindo, C. (2017). School–family relationships, school satisfaction and the academic achievement of young people. Educational Review, 69 (2), 248-265. Doi: 10.1080/00131911.2016.1207613

Haus, E., (2007). Chronobiology in the endocrine system. Advanced Drug Delivery Reviews. 59(9-10):985-1014.

https://www.life.illinois.edu/clockworks/pages/SCN.htm

Klein, D.C., (2007). Arylalkylamine N-acetyltransferase: the Timezyme. J Biol Chem; 282 : 4233-7.

Kline, B.R., (2005). Principles and practice of structural equation modeling (Second edit). NY: The Guilford Press.

Kocar, F., Elçioğlu, H.K., (2022). Circadian Rhythm And Factors Affecting Circadian Rhythm Türk Bilimsel Derlemeler Dergisi E-ISSN: 2146-0132 15(2): 29-44

Kvetnoy, I., Ivanov, D., Mıronova, E., Evsyukova, I., Nasyrov, R., Kvetnaia, T., Polyakova, V., 2022. Melatonin as the Cornerstone of Neuroimmunoendocrinology, Int. J. Mol. Sci. 23(3), 1835; https://doi.org/10.3390/ijms23031835

Laposky AD, Bass J, Kohsaka A, Turek FW. (2008). Sleep and circadian rhythms: key components in the regulation of energy metabolism. FEBS Lett.582(1):142-151.

Lerner AB, Case JD, Mori W., (1959). Melatonin in peripheral nerve. Nature 183 : 1821.

Lewy. A.J., Ahmed, S., Jackson, J.M., Sack, R.L., (1992). Melatonin shifts human circadian rhythms according to a phase-response curve. Chronobiol Int, 9:380-392.

Macchi, M.M., Bruce, J.N., (2004). Human pineal physiology and functional significance of melatonin. Front Neuroendocrinol 25:177-195

Maeda, K.I., Lincoln , G.A., (1990): Phase shifts in the circadian rhythm in plasma concentrations of melatonin in rams induced. J. Biol. Rhythms 5, 97-106.

Mehmetoğlu, İ., (2006). Bilimsel Gerçekler Işığında Gıdalar ve Sağlıklı Beslenme. Yelken Basım Yayım Dağıtım. Konya, 182-183.

Nal, M., (2018). Hastanelerde acil yardım ve afet yönetimi. Ankara: Akademisyen Kitabevi

Oike, H., Oishi, K., Kobori, M., (2014). Nutrients, Clock Genes, and Chrononutrition. Curr Nutr Rep. 3(3):204-212.

Otlu, H.G., (2019). Sirkadiyen Ritim Bozukluklarının Peroksizomal Lipid Metabolizmasına Etkisi. İnönü Üniversitesi Sağlık Bilimleri Enstitüsü, Doktora Tezi, s.1.

Özdemir, Z., Ak, O., Yüceer, H.C., Akgör,D., Aysun, D., Asparuk, Ç. (2014). Drakula Hormon: Melatonin.Başkent Üniversitesi, 16(2-6).

Özenoğlu, A., Ünal, G., (2015). Açlık ve Şiddet. MÜSBED;5(2), Samsun. s.117.

Pekmez, H., Kuş, İ., Ögetürk, M., Kutlu, S., Zararsız, İ., Sarsılmaz, M., (2004). Sıçanlarda oksitosinle indüklenmiş myometrium kasılmaları üzerine melatonin hormonunun etkisi. Fırat Tıp Dergisi.;9(1):1-5.

Revel, F.G., Masson-Pévet, M., Pévet, P., (2009). Melatonin controls seasonal breeding by a network of hypothalamic targets. Neuroendocrinology; 90 : 1-14

Sack, R.L., Hughes, R.J., Edgar, D.M., Lewy, A.J., (1997). Sleep promoting effects of melatonin: at what dose, in whom, under what conditions, and by what mechanisms? Sleep, 20:908-915.

Scheer, F., Czeisler, C.A., (2005). Melatonin, sleep, and circadian rhythms. Sleep Med Rev 9:5-9

Schibler, U., Sassone-Corsi, P.A., (2002). Web of Circadian Pacemakers. Cell. 111(7):919-922.

Selvi, Y., Beşiroğlu, L., Aydın, A., (2011). Kronobiyoloji ve duygudurum bozuklukları. Psikiyatride Güncel Yaklaşımlar-Current Approaches in Psychiatry, 3:368-386.

Sezinler, A., (2018). Sirkadiyen Ritme Bağlı Olarak Uyku Uyanıklık Durumunun Glukoz Metabolizması Üzerine Etkisi. Okan Üniversitesi Sağlık Bilimleri Enstitüsü, İstanbul, s.7- 19.

Sözlü, S., Şanlier, N., (2017). Sirkadiyen Ritim, Sağlık ve Beslenme İlişkisi. Turkiye Klinikleri J Health Sci;2(2):100-109

Szymusiak, R., McGinty, D., (2008). Hypothalamic regulation of sleep and arousal. Ann N Y Acad Sci, 1129:275-286.

Thomson Higher Education, (2007).

Topal, T., Öter, Ş., Korkmaz, A., (2009). Melatonin ve Kanserle İlişkisi. Genel Tıp Derg;19(3):137-143

Tsuzuki K, Okamoto-Miunu K, Mizuno K. Effects of humid heat exposure on sleep,thermoregulation, melatonin and microclimate. J Therm Biol 2004; 29:31-34.38

Zee, PC., Manthena, P., (2007). The brain's master circadian clock: implications and opportunities for therapy of sleep disorders. Sleep Med Rev, 11:59-70.

Zhu, L., Zee, P.C., (2012). Circadian rhythm sleep disorders. Neurol Clin, 30:1167-1191.

CHAPTER IV

The Relatıonshıp Between Apelın And Energy Metabolısm

Mehmet ÖZSAN[1]
Nurcan DÖNMEZ[2]

Introduction

In recent times, the recognition of various adipokines has transformed white adipose tissue into an endocrine organ intricately linked to overall physiological and metabolic regulation. Apelin, initially acknowledged for its effects on the cardiovascular system and fluid balance, has now been identified as an adipokine with broader physiological implications. The broadening of its role has positioned Apelin alongside influential factors like leptin and adiponectin, establishing it as a significant contributor to energy

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metabolism. Noteworthy is Apelin's impact on glucose and lipid metabolism, coupled with its ability to influence insulin secretion. Research findings, spanning both animal and human studies, consistently highlight elevated plasma concentrations of Apelin in conditions such as type 2 diabetes and obesity (Bertrand et al., 2015).

The discovery of the APJ receptor in humans can be traced back to 1993, unveiling sequence homology with angiotensin II receptor type 1 and earning the acronym AGTRL1 as a G-protein-coupled receptor (GPCR) (Castan – Laurel et al., 2011). Apelin, identified in 1998 from the bovine stomach, acts as the endogenous ligand for the G-protein-coupled receptor APJ. Apelin exhibits various isoforms, including Apelin-36, Apelin-17, Apelin-13, and Apelin-13', originating from its 77-amino acid precursor, preproapelin, through diverse enzymatic reactions (Şahin & Saral, 2015; Drougard et al., 2016). Recognized as an adipokine, apelin is expressed in multiple regions of the central nervous system, particularly the hypothalamus, as well as various peripheral tissues throughout the body (Hu et al., 2021). The functional apelin's role is diverse, contingent upon its tissue presence and bodily fluid localization (Dagamajalu et al., 2021).

Glucose initiates the release of apelin within the intestinal epithelial cells, and the liberated apelin facilitates the transportation of glucose from the intestinal lumen into the bloodstream. The interaction between glucose and apelin results in an increase in the glucose levels within the portal vein, prompting a hastening of insulin secretion and an augmentation in insulin sensitivity (Fukaya et al., 2007; Delaere et al., 2010; Dray et al., 2013). Apelin stimulates the absorption of glucose in the intestinal epithelium, thereby amplifying portal blood glucose and insulin secretion, which plays a role in maintaining glucose homeostasis. Furthermore, there is a proposition that apelin employs various regulatory pathways, involving the binding of apelin to APJ in central glucose metabolism (Hu et al., 2021).

Locations of the Apelinergic System

Research conducted in some laboratory animals (rats, mice) and human tissues has reported widespread expressions of Apelin and the apelin's receptor in the central nervous system (CNS), cardiovascular, circulatory, digestive, and reproductive systems, as well as in adipose tissue and striated muscles (Kawamata et al., 2001; Medhurst et al., 2003).

Signaling Pathways of Apelin and Its Physiological Effects in Peripheral Tissues

The cellular-level effects of Apelin within the organism stem from the activation of distinct G proteins by the APJ receptor, varying according to the cell type. Fundamental signaling involving Apelin is reported to engage a specific G protein subtype, Gαi/0 (Hosoya et al., 2000). Multiple studies consistently show that via this pathway, Apelin initiates intracellular messengers, leading to the activation of ERK, protein kinase B (PKB or Akt), and p70S6 kinase, while simultaneously inhibiting forskolin-mediated cyclic adenosine monophosphate (cAMP) production (Masri et al., 2004; D'Aniello et al., 2009).The vasodilatory impact of the Apelin/APJ system on circulation is purported to occur through the activation of the PLCβ-PKC pathway via calmodulin-mediated eNOS (Tatemoto et al., 2001). The increase in intracellular calcium ions (Ca^2+), stemming from the phospholipase C-β and protein kinase C cascade, leads to the proportional activation of calmodulin, subsequently ensuring the activation of nitric oxide synthase (NOS) (Sevim 2018).

The involvement of the APJ/apelin pair in multiple signaling pathways is suggested, with APJ predominantly binding to G protein, allowing apelin to 1) inhibit adenylate cyclase, resulting in a restrained increase in cAMP (Lee et al., 2010; Knauf et al., 2013). Recent revelations highlight the pivotal roles played by apelin and APJ not only in energy metabolism but also in the cardiovascular system, fluid homeostasis, angiogenesis, and the neuroendocrine system (Newson et al., 2013; Picault et al., 2014; Birsen 2018).

Apelin, along with its receptor APJ, actively participates in a myriad of physiological processes through diverse signaling pathways. On a cellular level, the apelin/APJ system plays a role in promoting the proliferation of endothelial progenitors during the cardiovascular system's formation. Simultaneously, it exhibits an anti-inflammatory impact on activated T lymphocytes, contributing to immune system regulation (Kidoya et al., 2012). Furthermore, apelin stimulates the growth of endothelial cells, especially concerning retinal angiogenesis (Eyries et al., 2008). Studies have detailed its influence on retinal vascular development in mice and noted lower plasma apelin levels in individuals with heart conditions (Zhang et al., 2009). Apelin is celebrated for its cardioprotective qualities, shielding against oxidative stress and apoptosis, thereby boosting heart contractility. In addition, apelin prompts a reduction in blood pressure through the nitric oxide (NO) pathway. Apelin's influence also reaches the digestive system, where intestinal apelin prompts the proliferation of gastric cells, secretion of duodenal bicarbonate, release of enteric cholecystokinin, and production of gastric acid (Knauf et al., 2013).

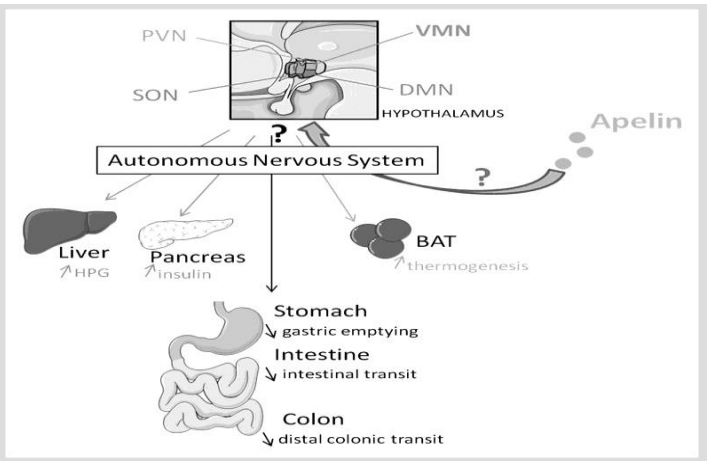

Figure 1 Communication in glucose metabolism occurs between the hypothalamus and diverse peripheral organs. Among the various nuclei that play roles in this process are the supraoptic

nucleus (SON), paraventricular nucleus (PVN), dorsal medial nucleus (DMN), and ventromedial nucleus (VMN) (Knauf et al., 2013).

Energy Metabolism and the Relationship with Apelin

Metabolic disorders, particularly the energy metabolism, which can lead to conditions such as obesity and type 2 diabetes, are particularly influential in any alterations in the stabilization of glucose homeostasis. This intricate system involves hormonal and neural regulations, with the hypothalamus playing a crucial role as the central hub for integrating various neural and peripheral cues. Nutrients, sensory nerves, and adipokines like leptin and adiponectin are also included in this integration process. Recent studies highlight the significant role of an adipokine called apelin, which can induce notable changes, especially in hypothalamic neurons, during this process (Knauf et al., 2013).

Apelin and the apelin receptor are distributed extensively within the central nervous system, with a notable presence in the hypothalamus. Apelin messenger RNAs (mRNAs) are identified in diverse nuclei responsible for regulating behavioral responses, endocrine processes, and maintaining energy homeostasis, including the paraventricular, arcuate, and supraoptic nuclei (Reaux et al., 2001). Apelinergic neurons are indicated by positive nerve fibers of apelin in the hypothalamus, revealing apelin's dual role as both a circulating peptide and a neurotransmitter. The uncertainty persists regarding whether peripheral plasma apelin can reach the hypothalamus and impact apelin levels within the hypothalamus to this day (Castan-Laurell, 2011).

When investigating the interplay between the energy metabolism and the apelinergic system, it becomes evident that the apelinergic system actively participates in glycolipid metabolism, type 2 diabetes, insulin resistance-sensitivity, and obesity (Sevim, 2018). Initially identified within adipose tissue (Tatemoto and Rinsho, 2000) and subsequently confirmed as a product of adipocytes (Boucher et al., 2005), apelin is acknowledged as an

adipokine. The connection between apelin and insulin has been validated in both in vivo and in vitro settings (Boucher et al., 2005).Apelin expression in adipocytes rises in various mouse models associated with obesity and hyperinsulinemia. In addition to its involvement in cardiovascular and fluid homeostasis, apelin actively contributes to the regulation of food consumption, cell proliferation, and angiogenesis. Consequently, the correlation between apelin and metabolic disorders, including obesity and type 2 diabetes, has emerged as a central focus in recent research (Castan-Laurell et al., 2011).

Circulating apelin concentrations,released from adipose tissue, elevate in obesity (Boucher et al., 2005; Castan-Laurell et al., 2012). It is believed to collaborate with insulin in regulating energy metabolism and contributing to diabetes recovery. Reports indicate that apelin adjusts insulin levels and insulin receptor numbers within the organism (Chaves-Almagro et al., 2015; Hu et al., 2016).

Empirical investigations have demonstrated that exogenous application of apelin inhibits adipogenesis in white adipose tissue while promoting adipogenesis in brown adipose tissue (Masaki et al., 2012; Than et al., 2015). Additionally, apelin enhances glucose entry into skeletal muscle and adipose tissue, leading to a reduction in plasma glucose levels. It induces an increase in energy expenditure without altering nutrient consumption, resulting in a decrease in the proportion of adipose tissue (Birsen, 2018).

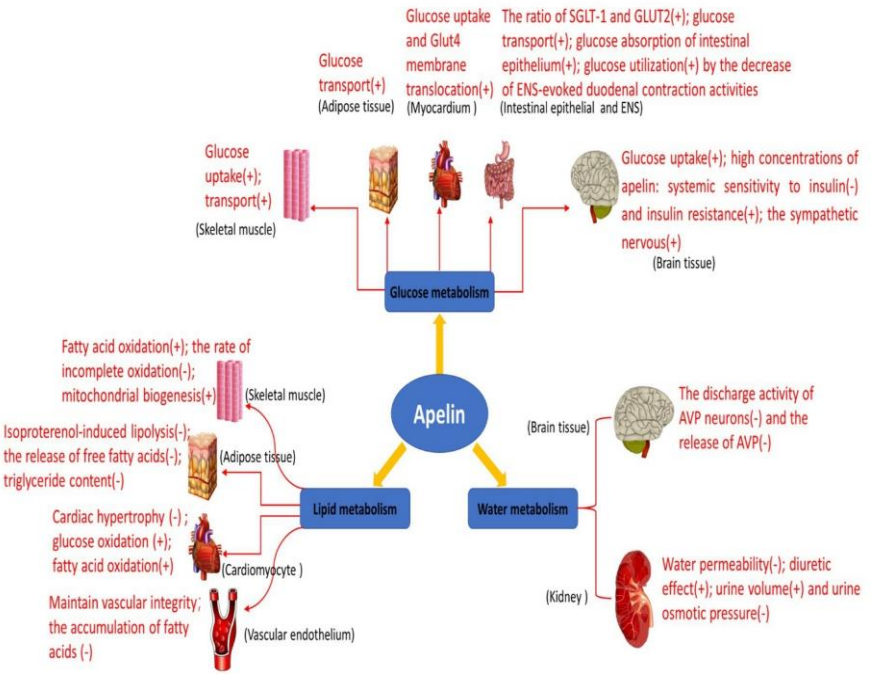

Figure 2 Apelin's Role in Glucose Metabolism, Lipid Metabolism, and Fluid Homeostasis: Unveiling its Biological Functions (Hu et al., 2021).

Apelin and Glucose Metabolism

Nutrient metabolism and the delicate balance of energy homeostasis are meticulously governed by a network of endocrine, paracrine, and autocrine factors that intricately communicate. Critical organs like skeletal muscle, liver, adipose tissue, and pancreatic β cells play a crucial role in maintaining this balance. Disruptions in energy equilibrium, particularly those resulting in insulin resistance, are fundamental to the development of obesity Within this intricate web, adipocytes release factors, including adipokines, which can either directly support or impede the development of insulin resistance based on their fluctuations. The functions of leptin and adiponectin have been thoroughly

investigated in this regard (Tishinsky et al., 2012; Farooqi and O'Rahilly, 2014; Bertrand et al., 2015).

The Apelin receptor (APJ) fulfills a range of functions in both physiological and pathological contexts within the body, including functions related to maintaining fluid balance, regulating anxiety and depression, and influencing cardiovascular and metabolic health. Recent studies are increasingly linking apelin to glucose metabolism and insulin sensitivity. As a result, the Apelin/APJ system emerges as a compelling target for therapeutic interventions, promoting glucose absorption, improving overall glucose utilization, and mitigating insulin resistance.. It's important to highlight that disturbances in apelin concentrations are documented to exert detrimental effects on the body (Hu et al., 2021).

Apelin, a bioactive peptide, dynamically contributes to the orchestration of energy metabolism. Its impact extends to glucose and lipid metabolism, along with the modulation of insulin secretion. Evidence from studies on animals and humans consistently indicates elevated circulating apelin levels in cases of obesity and type 2 diabetes (Bertrand and Castan Laurell, 2015). When scrutinizing the interplay between apelin and energy metabolism, it becomes evident that apelin exerts a substantial influence on glucose metabolism, exhibiting diverse effects in a dose-dependent manner. Apelin not only plays a pivotal role in glucose metabolism but also significantly impacts insulin sensitivity, enhancing insulin sensitivity and facilitating glucose uptake by muscles. Although insights into its influence on lipid metabolism remain incomplete, suggestions abound that apelin affects energy expenditure, thermogenesis, and the browning of adipose tissue. Moreover, apelin holds promise in addressing metabolic conditions, such as obesity, by influencing the browning of white adipose tissue (Hu et al., 2021).

Currently, apelin is recognized as a novel hypothalamic player contributing to the control of glucose metabolism in the brain. Peripherally, intravenous apelin injections enhance insulin sensitivity in both normal and obese/diabetic mice. Studies hint at a

controversial role for apelin in regulating food intake. While low doses of central nervous system apelin improve glycemia in normal mice, an abnormal increase in hypothalamic apelin expression is linked to fasting hyperglycemia. Despite these nuances, there is a consensus that apelin significantly impacts the control of glucose homeostasis (Drougard et al., 2016).

In skeletal muscle, apelin assumes a crucial function in preserving standard glucose homeostasis and supervising carbohydrate metabolism. Research suggests that the capacity of apelin to decrease glucose levels is associated with the activation of AMPK and eNOS (Dray et al., 2008; Bertrand et al., 2015; Hu et al., 2021).

Elevated apelin levels in the hypothalamus, persisting over time, correlate directly with increased hepatic glucose production, paving the way for type 2 diabetes. Yet, the molecular mechanisms underpinning the adverse effects of prolonged high apelin levels in the brain, and their repercussions on energy consumption and thermogenesis, remain incompletely understood. The gut-brain axis emerges as a crucial regulator in glucose homeostasis. Detecting nutrients and/or hormones in the duodenum furnishes the hypothalamus with vital information regarding the nutritional status of the organism. This complex mechanism, orchestrated by hypothalamic neurons, governs the release of nitric oxide (NO), consequently overseeing the entry of glucose into tissues (Duparc et al., 2011; Breen et al., 2013). In an experimental study elucidating apelin's effects on the gut-brain axis in glucose metabolism, it was observed that, in obese/diabetic mice, the reduction in duodenal contraction activities stimulated by ENS in response to apelin resulted in improved glucose utilization and increased NO release in the hypothalamus (Fournel et al., 2017; Hu et al., 2021).

In intestinal epithelial cells, apelin triggers the secretion of apelin, fostering the enhanced conveyance of glucose from the intestinal lumen to the bloodstream. This interaction between glucose and apelin results in elevated portal vein glucose levels,

subsequently triggering insulin secretion, expediting insulin release, and enhancing overall insulin responsiveness (Fukaya et al., 2007; Delaere et al., 2010; Dray et al., 2013). Through its role in augmenting glucose absorption within the intestinal epithelium, apelin actively contributes to maintaining glucose homeostasis by elevating portal venous glucose concentrations and enhancing insulin release. Moreover, it is postulated that apelin engages multiple regulatory pathways, including binding to APJ in central glucose metabolism (Hu et al., 2021).

The Relationship Between Apelin and Lipid Metabolism, Its Role in Thermogenesis

Limited research has explored the involvement of apelin in lipid metabolism. Current evidence suggests that apelin impedes isoproterenol (a β-adrenergic agonist)-induced lipolysis in both isolated adipocytes and differentiated 3T3-L1 adipocytes. This inhibitory effect operates via a pathway that includes Gq, Gi, and AMPK (Bertrand et al., 2015; Zarkesh et al., 2023). Moreover, apelin reduces the liberation of fatty acids from 3T3-L1 adipocytes, and this decrease corresponds to the amount of peripheral lipoproteins encapsulating the lipoproteins.

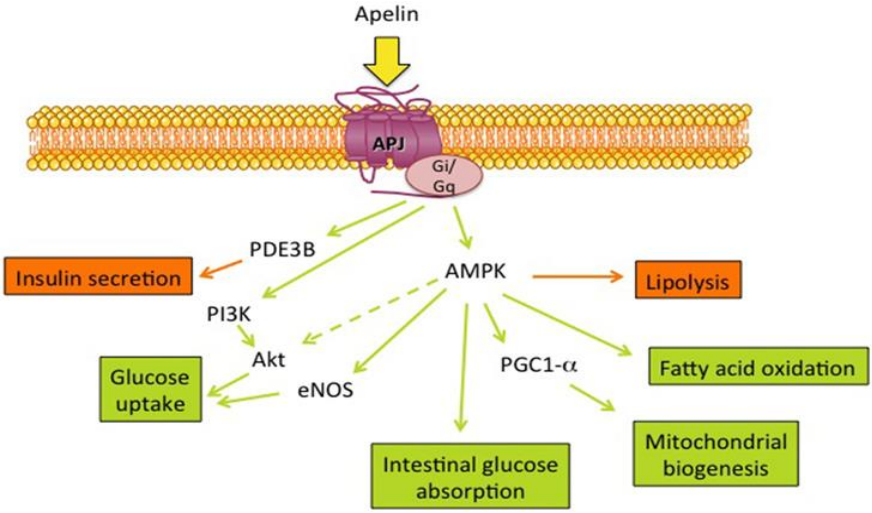

Figure 3 When considering the metabolic impacts of Apelin and its key signaling targets, Apelin, the ligand for the G protein-coupled receptor APJ, can impact diverse metabolic processes (green arrows/boxes) and, in addition to lipolysis, can also suppress insulin release via distinct signaling routes (orange arrows/boxes): PDE3B, phosphodiesterase 3B; AMPK, AMP-activated protein kinase; PGC1-a, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; eNOS, endothelial NO synthase; PI3K, phosphatidylinositol 3-kinase, and Akt. (Bertrand et al., 2015).

Apelin possesses a mechanism susceptible to AMPK activation, and by augmenting the quantity of peripheral lipoproteins enveloping lipoproteins, it can diminish the liberation of free fatty acids (FFA) from 3T3-L1 adipocytes. Nevertheless, investigations on human fat tissue samples or individual fat cells have indicated that apelin has negligible impact on basal or isoproterenol-induced lipolysis (Chaves-Almagro et al., 2015).

Exploration on obese and insulin-resistant mice has revealed that persistent apelin treatment increases fatty acid oxidation in muscles by promoting AMPK activation (Attane et al., 2012). Moreover, within the context of diminished heart function associated

with obesity, chronic apelin treatment has been recognized to hinder fatty acid and glucose oxidation. Studies conducted on skeletal muscle cells suggest that prolonged apelin intervention in mice with obesity and insulin resistance enhances fatty acid oxidation in muscles by activating the AMPK pathway, concurrently diminishing the incomplete oxidation rate of extended-chain fatty acids. This impact correlates with an elevation in the expressions of PGC1a, NRF-1, and TFAM, known to amplify oxidative phosphorylation in mitochondria and promote the generation of new mitochondria (Alfarano et al., 2015). Apelin can similarly amplify mitochondrial biogenesis in myocytes by advocating for lipid utilization (Bertrand et al., 2015). This enduring effect is associated with an increase in oxidative phosphorylation in mitochondria and the promotion of mitochondrial biogenesis, mirrored in the expressions of PGC1a, NRF-1, and TFAM (Chaves-Almagro et al., 2015).

Adipose tissue emerges as a intricate yet pivotal regulator in overseeing metabolic functions. Despite white fat tissue employing lipids to furnish energy substrates, brown fat tissue (BAT) and the phenomena of browning/thermogenesis contribute to storing chemical energy as heat, thus actively participating in maintaining core temperature and thwarting obesity (Geurst et al., 2015). BAT adipocytes are distinguished by a dense concentration of mitochondria containing uncoupling protein 1 (UCP1). Activation of this protein segregates mitochondrial respiration from ATP synthesis, culminating in "non-shivering thermogenesis" and the generation of heat (Drougard et al., 2016).

The evaluation of the reaction to apelin therapy has been carried out by investigating thermogenesis, where there is an augmentation in energy expenditure (Drougard et al., 2016). Brown fat tissue (BAT) possesses a heightened mitochondrial concentration and UCP1 content, granting it the ability to separate fatty acid breakdown separate from ATP generation and produce heat (Lam et al., 2009). The apelin/APJ signal bolsters the differentiation of brown adipocytes by increasing the expression of adipogenic and thermogenic transcription factors through the PI3K/Akt and AMPK

signaling pathways. Apelin has the potential to mitigate the inhibitory impact of TNF on the development of brown adipose tissue. Moreover, apelin has been documented to reinforce enhance the fundamental activity of brown adipocytes by magnifying the expression of PGC1 and UCP1, thereby enhancing mitochondrial biogenesis and consumption of oxygen (Than et al., 2015). Nevertheless, the involvement of apelin in regulating thermogenesis is not comprehensively comprehended and persists as intricate (Hu et al., 2021).

References

Alfarano, C., Foussal, C., Lairez, O., Calise, D., Attané, C., Anesia, R., et al. (2015). Transition from metabolic adaptation to maladaptation of the heart in obesity: role of apelin. Int. J. Obes. 39, 312–320.

Attane, C., Foussal, C., Le Gonidec, S., Benani, A., Daviaud, D., Wanecq, E. (2012). Apelin treatment increases complete Fatty Acid oxidation, mitochondrial oxidative capacity, and biogenesis in muscle of insulin-resistant mice. Diabetes 61, 310–320

Bertrand, C., Valet P, Castan-Laurell, I., (2015). Apelin and energy metabolism. Front Physiol. 6: 115.

Birsen, İ., (2018). Apelin'in iskemi/ reperfüzyon hasarına karşı mide mukozasını koruyucu etkisinde kapsaisine duyarlı duysal liflerin ve N. Vagus'un rolü. Doktora tezi. Akdeniz Ünv. Sağ. Bil. Enst. Antalya.

Breen, D. M., Rasmussen, B. A., Côté, C. D., Jackson, V. M., and Lam, T. K., (2013). Nutrient-sensing mechanisms in the gut as therapeutic targets for diabetes. Diabetes 62, 3005–3013.

Boucher, J., Masri, B., Daviaud, D., Gesta, S., Guigne, C., Mazzucotelli, A., Castan-Laurell, I., Tack, I., Knibiehler, B., Carpene, C., Audigier, Y., Saulnier-Blache, J.S., Valet, P., (2005). Endocrinology 146(4):1764-71. doi: 10.1210/en.2004-1427. Epub.

Castan-Laurell, I., Dray, C., Knauf, C., Kunduzova, O., Valet, P., (2012). Apelin, a promising target for type 2 diabetes treatment? Trends Endocrinol Metab. 23: 234-241.

Chaves-Almagro, C., Castan-Laurell, I., Dray, C., Knauf, C., Valet, P., Masri, B., (2015). Apelin receptors: From signaling to antidiabetic strategy. Eur J Pharmacol. 763: 149-159.

Dagamajalu, S., Rex, D. A. B., Philem, P. D., Rainey, J. K. ve Prasad, T. K. (2021). A network map of apelin-mediated signaling. Journal of Cell Communication and Signaling, 1-7

D'Aniello, C., Lonardo, E., Iaconis, S., Guardiola, O., Liguoro, A.M., Liguori, G.L., Autiero, M., Carmeliet, P., Minchiotti, G., (2009). G Protein-Coupled Receptor APJ and Its Ligand Apelin Act Downstream of Cripto to Specify Embryonic Stem Cells Toward the Cardiac Lineage Through Extracellular Signal-Regulated Kinase/p70S6 Kinase Signaling Pathway. Circ Res. 105: 231-U265.

Delaere, F., Magnan, C., and Mithieux, G., (2010). Hypothalamic integration of portal glucose signals and control of food intake and insulin sensitivity. Diabetes Metab. 36, 257–262.

Dray C., Knauf C., Daviaud D., Waget A., Boucher J., Buleon M., (2008). Apelin stimulates glucose utilization in normal and obese insulin-resistant mice. Cell Metab. 8, 437–445.

Dray, C., Sakar, Y., Vinel, C., Daviaud, D., Masri, B., Garrigues, L., et al. (2013). The intestinal glucose-apelin cycle controls carbohydrate absorption in mice. Gastroenterology 144, 771–780.

Drougard, C.A., Fournel, A., Duparc, T., Valet, P., (2013)Hypothalamic Actions of Apelin on Energy Metabolism: New Insight on Glucose Homeostasis and Metabolic Disorders. Horm Metab Res; 45(13): 928-934.

Drougard, A., Fournel, A., Marlin, A., Meunier, E., Abot, E., Bautzova, T., Duparc, T., Louche, K., Batut, A., Lucas, A., Le-Gonidec, S., Lesage, J., Fioramonti, X., Moro, C., Valet, P., Cani, P.D., Knauf, C., (2016). Central chronic apelin infusion decreases energy expenditure and thermogenesis in mice. *Scientific Reports*. 6, Article number: 31849.

Duparc, T., Naslain, D., Colom, A., Muccioli, G. G., Massaly, N., Delzenne, N. M., (2011). Jejunum inflammation in obese and diabetic mice impairs enteric glucose detection and modifies nitric oxide release in the hypothalamus. Antioxid. Redox Signal. 14, 415–423

Eyries, M., Siegfried, G., Ciumas, M., Montagne, K., Agrapart, M., Lebrin, F., Soubrier, F., (2008). Hypoxia-induced apelin expression regulates endothelial cell proliferation and regenerative angiogenesis. Circ Res; 103: 432-440

Farooqi, I.S., O'Rahilly, S., (2014). 20 years of leptin: human disorders of leptin action. J. Endocrinol. 223, T63–T70.

Fournel, A., Drougard, A., Duparc, T., Marlin, A., Brierley, S. M., Castro, J., (2017). Apelin targets gut contraction to control glucose metabolism via the brain. Gut 66, 258–269. Fukaya, M., Mizuno, A., Arai, H., Muto, K., Uebanso, T., Matsuo, K., et al. (2007). Mechanism of rapid-phase insulin response to elevation of portal glucose concentration. Am. J. Physiol. Endocrinol. Metab. 293, E515–E522

Hosoya, M., Kawamata, Y., Fukusumi, S., Fujii, R., Habata, Y., Hinuma, S., Kitada, C., Honda, S., Kurokawa, T., Onda, H., Nishimura, O., Fujino, M., (2000). Molecular and functional characteristics of APJ. Tissue distribution of mRNA and interaction with the endogenous ligand apelin. J Biol Chem. 275: 21061-21067.

Hu, H.L, He, L., Li, L.F., Chen, L.X., (2016). Apelin/APJ system as a therapeutic target in diabetes and its complications. Mol Genet Metab. 119: 20-27.

Hu, G., Wang, Z., Zhang, R., Sun, W., Chen, X., (2021). The Role of Apelin/Apelin Receptor in Energy Metabolism and Water Homeostasis: A Comprehensive Narrative Review. Frontiers in Physiology, 12.

Kawamata, Y., Fukusumi, S., Hosoya, M., Fujii, R., Hinuma, S., Nishizawa, N., Kitada, C., Onda, H., Nishimura, O., Fujino, M., (2001). Molecular properties of apelin: tissue distribution and receptor binding. Biochim Biophys Acta. 1538: 162-171.

Kidoya, H., Kunii, N., Naito, H., Muramatsu, F., Okamoto, Y., Nakayama, T., Takakura, N., (2012). The apelin/APJ system induces

maturation of the tumor vasculature and improves the efficiency of immune therapy. Oncogene; 31: 3254-3264

Knauf, C., Drougard, A., Fournel, A., Duparc, T., Valet P., (2013). Hypothalamic Actions of Apelin on Energy Metabolism: New Insight on Glucose Homeostasis and Metabolic Disorders. Horm Metab Res; 45(13): 928-934.

Lee, D.K., Ferguson, S.S., George, S.R., O'Dowd, B.F., (2010). The fate of the internalized apelin receptor is determined by different isoforms of apelin mediating differential interaction with beta-arrestin. Biochem Biophys Res Commun; 395: 185-189

Masaki, T., Yasuda, T., Yoshimatsu, H., (2012). Apelin-13 microinjection into the paraventricular nucleus increased sympathetic nerve activity innervating brown adipose tissue in rats. Brain Res Bull. 87: 540-543.

Masri, B., Morin, N., Cornu, M., Knibiehler, B., Audigier, Y., (2004). Apelin (65-77) activates p70 S6 kinase and is mitogenic for umbilical endothelial cells. Faseb J. 18: 1909.

Medhurst, A.D., Jennings, C.A., Robbins, M.J., Davis, R.P., Ellis, C., Winborn, K.Y., Lawrie, K.W.M., Hervieu, G., Riley, G., Bolaky, J.E., Herrity, N.C., Murdock, P., Darker, J.G., (2003). Pharmacological and immunohistochemical characterization of the APJ receptor and its endogenous ligand apelin. J Neurochem. 84: 1162-1172.

Newson, M.J.F., Pope, G.R., Roberts, E.M., Lolait, S.J., O'Carroll, A,M., (2013). Stress-dependent and gender-specific neuroregulatory roles of the apelin receptor in the hypothalamic-pituitary-adrenal axis response to acute stress. J Endocrinol. 216: 99-109.

Picault, F.X., Chaves-Almagro, C., Projetti, F., Prats, H., Masri, B., Audigier, Y., (2014). Tumour co-expression of apelin and its receptor is the basis of an autocrine loop involved in the growth of colon adenocarcinomas. Eur J Cancer. 50: 663-674.

Reaux, A., De Mota, N., Skultetyova, I., Lenkei, Z., El Messari, S., Gallatz, K., Corvol, P., Palkovits, M., Llorens-Cortes, C. J., (2001). Neurochem. 77, 1085

Sevim, B., (2018). Kardiyopulmoner Hastalıklarda Serum Apelin Düzeyleri. Doktora Tezi. Dicle Ünv. Sağ. Bil. Enst. Diyarbakır.

Şahin, A., Saral, S., (2015). Nöroendokrin Bir Peptid: Apelin. ODU Journal of Medicine. e41-e47,

Tatemoto, K., Rinsho, N., (2000). Search for an endogenous ligand of the orphan G protein-coupled receptor--discovery of apelin, a novel biologically active peptide. Nihon rinsho, Japanese Journal of Clinical Medicine, 58, 737-746.

Tatemoto, K., Takayama, K., Zou, M.X., Kumaki, I., Zhang, W., Kumano, K., Fujimiya, M., (2001). The novel peptide apelin lowers blood pressure via a nitric oxide-dependent mechanism. Regul Pept. 99: 87-92.

Than, A., He, H.L., Chua, S.H., Xu, D., Sun, L., Leow, M.K.S., Chen, P., (2015). Apelin Enhances Brown Adipogenesis and Browning of White Adipocytes. J Biol Chem. 290: 14679-14691.

Zarkesh, M., Safarian, M., Asghari, G., Daneshafrooz, A., Yuzbashian, E., Hedayati, M., Mirmiran, P., Khalaj, A., (2023). Is Habitual Dietary Intake of Fats Associated with Apelin Gene Expression in Visceral and Subcutaneous Adipose Tissues and Its Serum Levels in Obese Adults? *Public Health Genomics.* 26 (1): 16–23.

Zhang, Z., Yu, B., Tao, G.Z., (2009). Apelin protects against cardiomyocyte apoptosis induced by glucose deprivation. Chin Med J (Engl); 122: 2360-2365

CHAPTER V

Ahmet Alperen PALABIYIK[1]
Esra PALABIYIK[2]

Introduction

The vascular network that connects lymphoid organs such as lymph nodes, tonsils, thymus and spleen to each other is called the lymphatic system. It progresses simultaneously with the venous circulation mechanism. The main function of the lymphatic system is to ensure that the excess interstitial fluid coming out of the blood capillaries is discharged into the tissue spaces. It also plays an active role in important functions such as fat absorption in the intestine, immune surveillance and inflammation resolution. Lymph fluid carries the antigens and antigen-presenting cells that will serve in the immune response to the lymph nodes. Lymphs contain lipids, immune cells, macromolecules, and fluid. Lymph collected by capillary lymphatic vessels is emptied into collecting vessels. As can be seen, collecting lymphatics exhibit luminal valves that act reversibly to capillary lymphatics, allowing the progression and maintenance of unidirectional flow (Azhar et al.,2020).

As a result of a dysfunction in this mechanism of the lymphatic system, the balance is disrupted. Obstruction and dysfunction of the

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lymphatic system lead to lymphatic stasis, leading to the accumulation of protein and fluid in the interstitial space. This situation causes edema (Warren et al., 2007).

Dysfunction in the lymphatic system occurs especially as a result of the lymphatic system carrying more load than it should and the insufficiency of the lymphatic vessels. In addition, a decrease in carrying capacity as a result of disruption of the lymphatic system mechanism is among the important reasons (Özdemir et al., 2020).

To summarize the situation, we can define lymphedema as a disease that occurs as a result of a loss of function in the lymphatic system mechanism.

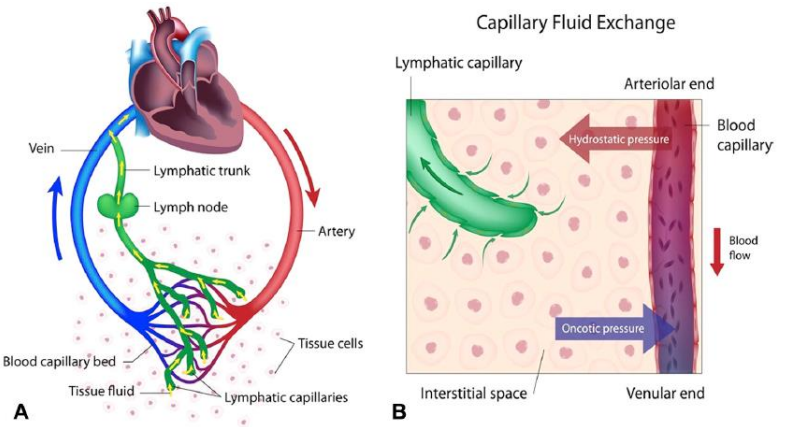

Figure 1. *Lymphatic circulation.* ***A****. Return of tissue fluid to the bloodstream by lymphatic drainage.* ***B****. Excess of the limit in the interstitial space is collected through lymphatic capillaries. The fluid is filtered by blood capillaries and approximately 90% is absorbed. It then returns to venous microcirculation. Approximately 10% of the fluid is lymph and is rich in protein. This fluid is drained by lymphatic capillaries. If there is a disruption in this systematic of lymphatic drainage, lymphedema occurs (Grada & Phillips 2017).*

Lymphedema

Lymphedema is a common human disease that is difficult to explain because it has a very complex mechanism and is not studied sufficiently (Rockson, 2021).

The formation of lymphatic fluid, its transfer to another area or the outflow of this fluid, and the imbalance in the vessels that lose their ability to function are among the most well-known causes of lymphedema. Lymphedema is defined as a persistent disease that can cause the accumulation of large amounts of fluid. Although it is commonly seen in the extremities, it can also develop with lymphatic dysfunction. This situation causes a psychological burden. Therefore, it appears as a crippling disease (Brix et al., 2021).

Apart from its exact causes, lymphedema most commonly manifests itself with intense swelling, secondary infection, atrophic changes in the skin and regional pain (Kayıran et al., 2017).

Many treatments are available for lymphedema, but there is no clear treatment method. However, correct diagnosis and treatment can prevent the progression of the disease and the undesirable effects that may occur (Grada & Phillips 2017).

Epidemiology

Lymphedema is stated as a disease that is often ignored and diagnosed incorrectly. Although the number of people struggling with lymphedema is not known exactly, it varies between 140-300 million people worldwide (Brix et al., 2021). According to studies conducted in various countries (France, Turkey, United Kingdom, Canada and more), approximately 70-79% of patients are women (Keeley et al., 2019). Compared to male individuals, the incidence of lymphedema is higher in female individuals (female:male; 4.6:1) (Neuhüttler & Brenner, 2018) However, the actual prevalence of lymphedema varies depending on etiology. Accordingly, primary lymphedema, which is seen at birth but is often seen in the lower extremities and occurs after situations such as ankle sprain, insect bite, and arthroscopic knee surgery (Rockson & Rivera, 2008; Grada

& Phillips 2017), is seen in 1 in 100,000 people and mostly occurs in childhood. 19% of the disease is seen in adults (Misra & Carroll, 2023). Secondary lymphedema, which occurs as a result of iatrogenic or post-disease damage to the normal lymphatic system, is seen in 1 in 1000 people (Grada & Phillips 2017). It affects approximately 15 million people worldwide. One of the most important factors for this is the attack of the Wuchereria bancrofti parasite on the lymph nodes. This condition is also defined as filariasis (Fimbo et al., 2020).

Etiology, Classification and Pathophysiology

Lymphedema is a special type of edema caused by a problem that occurs during lymph formation or drainage (Lee et al., 2015). Its pathophysiological processes, heterogeneity and basic causes have not been fully clarified (Brix et al., 2021). However, it is possible to evaluate it as congenital or acquired primary and secondary forms (Lee et al., 2015).

Primary Lymphedema

The incidence of primary lymphedema is 1 in 100,000 people (Grada & Phillips 2017). This extremely rare disease is associated with a strong genetic background mediated by hereditary or spontaneous mutation in 25-30% of primary lymphedema patients (Telinius & Hjortdal, 2019). In this form, the disorder in the lymphatic system is congenital. This damage may cause lymphedema in individuals' lives, or it may not show any symptoms (Lee et al., 2015). Dysfunction in primary lymphedema occurs due to damage that causes a structural or functional disorder that negatively affects drainage properties (Mortimer & Rockson, 2014).

The primary form may be circumscribed, but it is also associated with mixed syndromes. In a high percentage of cases, it is incomplete penetrance and is inherited in an autosomal dominant manner (Greene et al., 2015).

More than twenty genes (i.e., VEGFR-3, CCBE1, FOXC2, GATA2, GJC2, PTPN14, SOX18, CCBE1, FAT4, ADAMTS3,

FBXL7, GJC2, KIF11, ITGA9, REEKIN, PIEZO1, EPHB4, CALCRL, and CELSR1) have been associated with anomalies in the lymphatic system (Oliver et al.,2020; Maltese et al., 2019). Genetic mutations in the vascular endothelial growth factor-C (VEGF-C) and endothelial growth factor receptor-3 (VEGFR-3) signaling pathways are highly influential in 30-50% of patients with primary lymphedema (Greene et al., 2015; Aspelund et al., 2016).

Although the genetic history of primary lymphedema was investigated, the time of disease onset according to age was also taken into account. Considering this situation, 3 separate groupings were made (Kerchner et al., 2008);

- congenital lymphedema: in those younger than 1 year of age,

- lymphedema praecox: in the age group between 1 and 35 (the group where the disease is most common),

- lymphedema tarda: Primary lymphedema is seen in those older than 35 years of age.

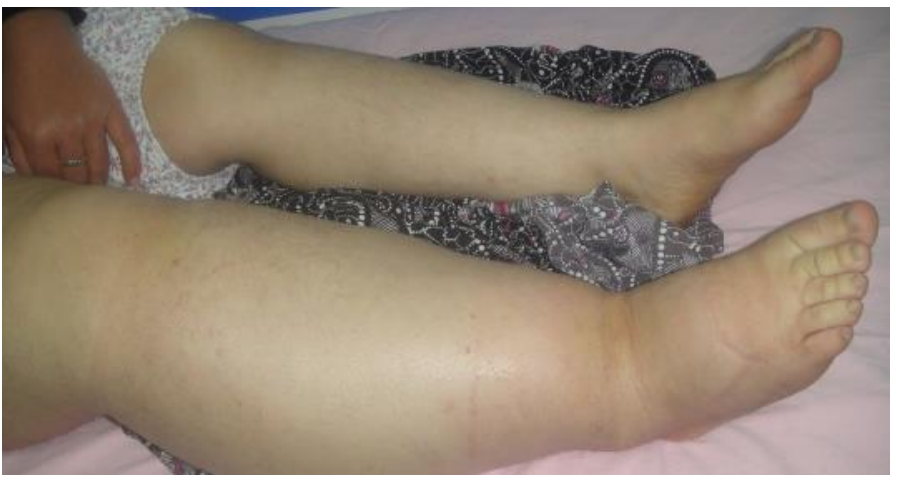

Figure 2. *Primary lymphedema in the right lower extremity (Toktaş et al., 2015)*

Secondary lymphedema

Secondary lymphedema is more common than primary lymphedema. It is supported by research that it occurs in approximately 1 in 1000 people. The disease was diagnosed in individuals aged between 50-58 (Grada & Phillips 2017). Secondary lymphedema may occur due to the persistence of diseases and infections developing in healthy lymphatic vessels, tissue damage, vascular occlusion and imbalance in the lymph nodes as a result of conditions such as trauma, surgical procedures and obesity. Therefore, secondary lymphedema is considered an acquired disease (Kerchner et al., 2008; Grada & Phillips 2017; WHO, 2021). It may also occur as a result of malignancy and related therapeutic processes (Grada & Phillips 2017). Radiation therapy, in particular, is very effective in the development of the disease (Ad et al., 2010). Other conditions that contribute to the development of secondary lymphedema include congestive heart failure or kidney diseases (Brix et al., 2021). Both chronic venous hypertension and venous ulcers are among the most effective causes of deterioration of lymphatic function (Grada & Phillips 2017). The most common type of secondary lymphedema is breast cancer-related lymphedema (BCRL). Breast cancer treatment is approximately 15-20% effective in the development of lymphedema (Mortimer & Rockson, 2014). As a result of the examination of patients diagnosed with BCRL, the incidence was found to be 15.5% (Cormier et al., 2010). In addition, it has been suggested that VEGFR2, VEGFR3, RORC, GJC2 and FOXC2 genes may be effective in secondary lymphedema that develops after breast cancer treatment (Newman et al., 2010; Muambangu & Lukenze, 2018; Michelini et al., 2016).

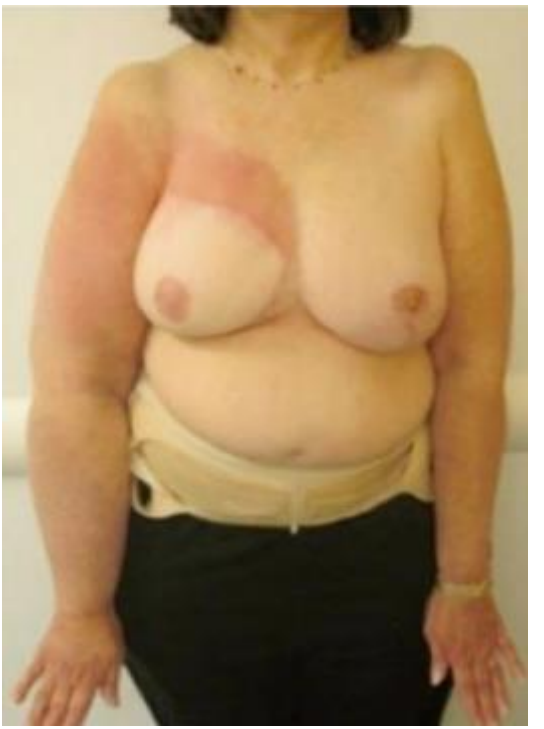

Figure 3. *Secondary lymphedema in the right arm (64-year-old patient with cellulite after BCRL treatment) (Greene, 2015)*

Histopathology

Although there is no distinguishing or direct diagnostic finding for lymphedema, a few situations can be mentioned (Sleigh & Manna, 2022). These;

-Early stages of dermal edema,

-It is the thickening of the Stratum corneum, the outermost part of the epidermis. That is, the cells are loaded with a high amount of keratein, a protein structure,

-The number of papillae in the epidermis increases and becomes thin and long,

-Observation of thickness in the non-cornified epidermis due to the increase in the number of epidermis cells,

- Thickening of the dermal vessel walls,

- Fibrillary collagen and thickening of the upper dermis with increasing fibroblast.

Historical and Physical Features

It is very difficult to diagnose primary and secondary lymphedema because they are very similar to each other. Therefore, a more detailed examination is very important. While primary lymphedema is a congenital disease, secondary lymphedema is an acquired disease. In the early stages of lymphedema, a simple swelling and edema are seen, but this is not taken into consideration much. In addition, since the diuretic treatment is insufficient, no effect is observed in reducing the swelling. In the early stages of the disease, there are distinct dimpled images and a soft skin structure. Elevating the extremities is an important step in reducing swelling. However, as the disease progresses, a reversible situation occurs in the physical structure and elevation does not have any effect.

Lymphedema can cause a decrease in quality of life because it causes intense psychological problems for patients (Sleigh & Manna, 2022).

History - If the diagnosis is primary lymphedema; The story of previous generations needs to be taken in detail. If the cause is not clear, conditions such as cancer, burns or injury should be evaluated.

Signs and Symptoms - Edema in the extremities is common. The skin, which has a scaly appearance, thickens. A skin with tiny blisters and swellings appears. A lymph fluid leaking from the skin is seen (Mortimer, 2000).

Extremity - If the size of the extremity where the disease occurs is less than 20%, the disease is mild or moderate; if it is more than 20%, it is severe (Lund, 2000).

Treatment

Lymphedema is known as a disease that tends to progress continuously. Therefore, it is critical to make an early diagnosis and start treatment without wasting time. The person performing the treatment is as important as the type of treatment to be performed. These treatments should be carried out by a specialist doctor, therapist or physiotherapist (Sleigh & Manna, 2022). Although there is no fully clarified treatment for lymphedema, research continues unabated. The most important thing here is to start treatments in the early stages. Because as lymphedema progresses, it causes some damage to the lymphatics (lymphatic vessels) (Sabbagh et al., 2019). There is a common goal in all types of treatment. This aim is to stop the development of the disease by reducing the leaking lymph fluid and improving the lymphatic system mechanism (Ogawa, 2012; Apich, 2013).

It is possible to group lymphedema treatment as conservative treatment, surgical treatment and drug treatment. Conservative treatment is the most commonly used treatment method as it is very effective in reducing the volume of the lymphedematous extremity. In drug treatment, antibiotics are generally used more than other drugs. Because it is more useful to prevent lymphangitis and cellulite formation. It is not preferred in surgical treatments due to the damage that may be caused to healthy tissue or the lymphedema area. (Özdemir et al., 2020).

Conservative Treatment

Complex Decongestıve Therapy (CDT) - Consisting of two treatment processes and four components, CDT includes skin care, manual lymphatic drainage (MLD), compression therapy and exercises. In the first stage, it is aimed to reduce the extremity volume to the highest level through skin care, MLD, and exercises. This process varies between approximately 4-6 weeks and is done every day. Following this stage, the second stage is started. The purpose here is to evaluate the results obtained (Executive Committee, 2016). CDT treatment improves the quality of life of

patients in terms of achieving the desired results. For this reason, it is considered very valuable and the first treatment that should be applied (Noh et al., 2015; Jeffs et al., 2018; Mobarakeh et al., 2019).

Taping, extracorporeal shock wave therapy (ESWT), acupuncture, photobiomodulation therapy, endermotherapy - vacuum suction therapy, intermittent pneumatic compression (IPC) and low-frequency-low-intensity electrotherapy techniques are among the complementary methods of CDT therapy (Bergmann et al, 2021). Since these techniques are used for research purposes, they may not be applied routinely. Therefore, it is very important to conduct new studies that include more comprehensive and advanced techniques (Tzani et al., 2018).

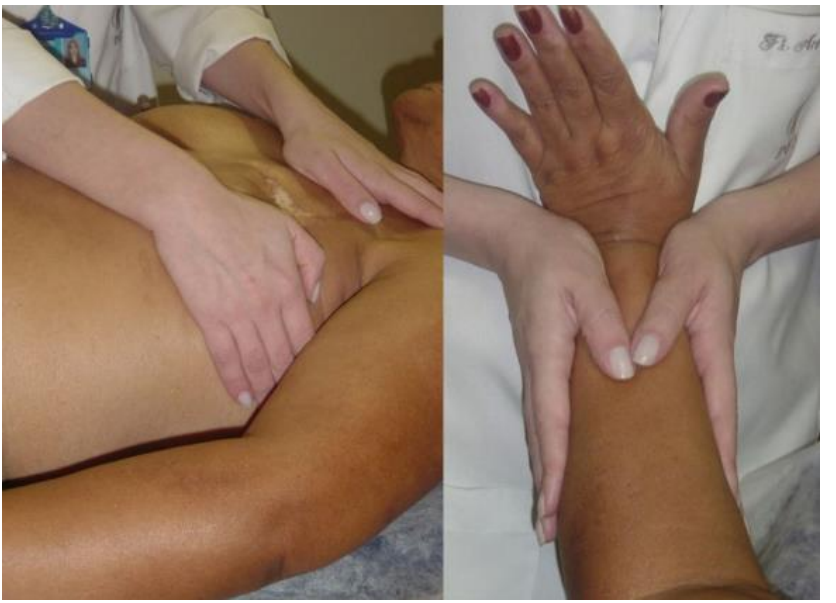

Figure 4. *Manual lymph drainage treatment (in the diagnosis of BCRL) (Bergmann et al, 2021).*

Drugs Treatment

Diuretic drugs, which are frequently preferred in the treatment of lymphedema, are no longer recommended because they may

disrupt electrolyte and fluid balance (Brix et al., 2021). *Benzopyrones* are very effective at hydrolyzing proteins, which activates the lymphatic transport pathway. Therefore, although it is thought to have a positive effect on the absorption of lymphatic fluid, it has not been fully supported by studies. On the contrary, liver damage may occur with continuous use of benzopyrones (Brix et al., 2021). *Ketoprofen*, used in a preliminary study, showed an effective result on lymphedema. This anti-inflammatory compound also caused some positive changes in tissue histopathology by downregulating granulocyte-colon stimulating factor-1 (GCSF) (Rockson et al., 2018). T cells play a role in the emergence of lymphedema. They do this by inhibiting lymphatic angiogenesis and increasing connective tissue in the tissue. *Tacrolimus*, which is used as an immunosuppressive drug and is sensitive to CD4 + T cells, could prevent the formation of lymphedema and also had a beneficial effect after lymphedema developed (Gardenier et al., 2017). Lymphedema was induced by removal of the superficial inguinal lymph node, popliteal lymph node, deep inguinal lymph node, and femoral lymphatic vessel. In the secondary lymphedema mouse model created, treatment with the use of *hyaluronidase* was beneficial and reduced volume in the extremity (Roh et al., 2017). Mutations in the VEGF-C and VEGFR-3 pathways develop lymphedema in high percentages. Therefore, administration of VEGF-C through various techniques (such as gene therapy, injection) increases lymphatic pump function and lymphangiogenesis. According to this information, positive effects of *Lymfactin*® (a combined adenoviral VEGF-C) administered to patients with lymphedema in combination with lymph node transfer have been reported (Hartiala et al., 2020).

If a general evaluation is made regarding drug use, it is seen that the drug treatments applied do not have the desired effect on lymphedema or their reliability is not clearly stated. However, if the studies are made comprehensive, alternative treatment options can be offered (Rockson, 2016).

Surgical Teratment

There is also a focus on research on the development of surgical procedures among the methods used to treat lymphedema. Because the healing effect of modern surgical methods used on dysfunctions in lymphedema patients has been observed.

It is possible to divide surgical procedures into two subgroups. These are physical and excisional methods. Physiological methods aim to develop new ways to improve fluid flow status and direct lymphatic flow to the venous system. In other words, it includes interventions to be used to clean the leaking lymphatic fluid through surgical methods. Excisional methods aim to remove tissues or parts of them affected by lymphedema (Sabbagh et al., 2019).

Table 1. *Classification of applied surgical methods.*

Physiological Procedures	Lymphvenous Anastomosis (LVA) Vascularized Lymph Node Transfer (VLNT)
Excisional Procedures	Suction Assisted Lipectomy (SAL) The Charles procedure

Vascularized Lymph Node Transfer (VLNT) - It is a method applied to improve physiological functions in lymphedema patients (Masia et al., 2016; Mardonado et al., 2017). However, the application is performed when there is damage to the lymph vessels or when lymph nodes are absent, that is, in the advanced stages of the disease (Schaverien et al., 2018). VLNT is a very effective procedure in deciding between proximal anatomical (orthotopic) or distal non-anatomical (heterotopic) lymph node flap placement. Additionally, the combined application of lymphovenous bypass and vascularized lymph node transplantation has a synergistic effect (Masia et al., 2016; Mardonado et al., 2017). VLNT is especially used in the treatment of breast cancer-related lymphedema. Treatment following removal of breast tissue (mastectomy) is the transplantation of a deep inferior epigastric artery perforator (DIEP) flap with a chimeric inguinal vascularized lymph node flap into the armpit (Schaverien & Coroneos, 2019).

Lymphvenous Anastomosis (LVA) - The LVA method can be applied if the patient still has some functionality in the lymphatic system. To determine this functionality, ICG lymphography should be used. It provides effective results in determining lymphatic system function other than subdermal lymphatics.

The purpose of LVA is to bypass the shadows where the blockage occurs and to transmit the lymph directly to the venous channel without passing it through the thoracic duct (Chang et al., 2016). In other words, communication is provided between blood vessels and lymphatics (Sabbagh et al., 2019). Although regional anesthesia is applied in this procedure, general anesthesia is preferred to take precautions against problems that may occur during the procedure (Chang et al., 2016). Recovery is often observed after LVA surgery. However, the use of pressure clothing should continue. In LVA application, more successful results were obtained in the upper limbs than in the lower limbs.

VLNT and LVA applications are the most preferred procedures in lymphedema patients (Sabbagh et al., 2019).

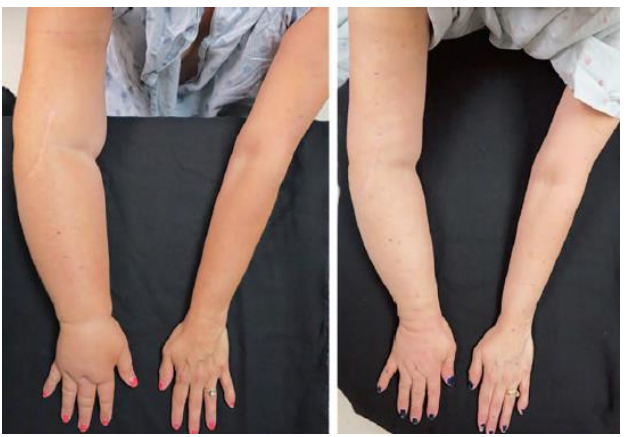

Figure 5. *(Left)-Lymphedema in the right arm associated with breast cancer treatment, %81. (Right) - Decrease in volume after VLNT and LVA application, %56 (After a 12-month follow-up period)(Chang et al., 2016)*

Suction Assisted Lipectomy (SAL) - In cases of chronic lymphedema and fibroadipose soft tissue hypertrophy, SAL application is mostly preferred (Schaverien & Coroneos, 2019). Since a small physiological improvement occurs with this application, it is necessary to wear compression garments and bandages to prevent the risk of recurrence of the disease (Boyages et al., 2015; Greene et al., 2017).

The Charles procedure - This method is known as skin grafting, which is the complete removal of the skin and subcutaneous tissue in the area affected by lymphedema. The main purpose of this method is to reduce the thickness/swelling in the area where lymphedema develops and to prevent the formation of inflammation. However, it has ceased to be a used technique because it does not provide useful results in continuous application (Sabbagh et al., 2019;).

Table. 2. *Evaluations of surgical practices.*

Intervention	Potential benefits	Potential limitations
ARM	Preserves the arm sentinel node and may prevent breast cancer-related lymphedema	Oncological safety is not com-pletely established
LYMPHA	May preemptively prevent breast cancer-related lymphedema	Lengthens the operative time for axillary lymph node dissection May require multiple surgical teams
SAPL	Restores limb volume and function in chronic lymphedema	Requires long-term patient compliance with a stringent compression regimen following the procedure Not optimally effective if hydro-static edema is not well-controlled before surgery
LVA	Minimally invasive Rapid recovery	Variable success rate Durability of the surgical response may be variable Not feasible in later stages of lymphedema if vascular channels are not amenable to surgical anastomosis
VLNT	Can potentially restore both circulatory and immune lymphatic function Feasible in later, more advanced stages of lymphedema	More invasive with longer anesthesia times, Risk of donor site lymphedema Variable success rate

**ARM indicates axillary reverse mapping; LVA, lymphaticovenous anastomosis; LYMPHA, lymphatic microsurgical preventive healing approach; SAPL, suction-assisted protein lipectomy; and VLNT, vascularized lymph node transfer. (*Rockson, 2021)

Complications

-Chronic swelling in the extremity brings about dysfunction.

-Recurrence of fungal and bacterial infections is a common occurrence.

-Lymphitis and cellulite conditions are repeatable. This causes increased damage to the lymphatic system.

-Ulceration, the treatment process of which is quite difficult, can be seen very frequently.

-Although cutaneous hemangiosarcoma is rare, it can lead to fatal consequences.

-Skin deterioration may limit individuals' movement. This may cause psychosocial problems in the patient. Complication cases are classified in Table 3 (Grada & Phillips, 2017).

Table 3. Undesirable conditions that may develop with lymphedema.

Potential complications
Physical
Heaviness and discomfort
Decreased range of motion
Recurrent skin infection
Elephantiasis verruca nostra
Recurrent skin ulcers
Cutaneous angiosarcoma
Psychological
Depression
Anxiety
Negative body image

Risk Factors

Genetic factors and related diseases that are effective in the emergence of lymphedema have been studied by many researchers. Knowing what these factors are is very critical. Because the treatments to be applied to sick individuals can be shaped accordingly. Genetic factors, obesity, radiation and infection are considered the most important risk factors in the development of lymphedema (Hespe et al., 2015).

Conclusion

Generally speaking, lymphedema occurs as a result of disruption of the lymphatic system or drainage boundaries. Since it causes an increase in limb volume, it has a negative impact on the quality of life. Various treatment applications have been carried out for congenital (primary) and acquired (secondary) lymphedema classes, but the desired result has not been fully achieved. Although they were beneficial in the short term, they could not show this effect in the long term. There is always a need for more innovative research and advanced technologies and techniques to be used for lymphedema, which has no definitive treatment.

References

Ad, V. B., Cheville, A., Solin, L. J., Dutta, P., Both, S., & Harris, E. E. (2010). Time course of mild arm lymphedema after breast conservation treatment for early-stage breast cancer. *International Journal of Radiation Oncology* Biology* Physics*, *76*(1), 85-90. doi:10.1016/j.ijrobp.2009.01.024

Apich, G. (2013). Konservative Therapie des Lymphödems–Lymphologische Rehabilitationsbehandlung. *Wiener Medizinische Wochenschrift*, *7*(163), 169-176. doi:10.1007/s10354-013-0205-5

Aspelund, A., Robciuc, M. R., Karaman, S., Makinen, T., & Alitalo, K. (2016). Lymphatic system in cardiovascular medicine. *Circulation research*, *118*(3), 515-530. doi:10.1161/CIRCRESAHA.115.306544

Azhar, S. H., Lim, H. Y., Tan, B. K., & Angeli, V. (2020). The unresolved pathophysiology of lymphedema. *Frontiers in physiology*, *11*, 137. doi:10.3389/fphys.2020.00137

Bergmann, A., Baiocchi, J. M. T., & Andrade, M. F. C. D. (2021). Conservative treatment of lymphedema: the state of the art. *Jornal Vascular Brasileiro*, *20*. doi:10.1590/1677-5449.200091

Boyages, J., Kastanias, K., Koelmeyer, L. A., Winch, C. J., Lam, T. C., Sherman, K. A., ... & Mackie, H. (2015). Liposuction for advanced lymphedema: a multidisciplinary approach for complete reduction of arm and leg swelling. *Annals of surgical oncology*, *22*, 1263-1270. doi:10.1245/s10434-015-4700-3

Brix, B., Sery, O., Onorato, A., Ure, C., Roessler, A., & Goswami, N. (2021). Biology of lymphedema. *Biology*, *10*(4), 261. doi:10.3390/biology10040261

Chang, D. W., Masia, J., Garza III, R., Skoracki, R., & Neligan, P. C. (2016). Lymphedema: surgical and medical therapy. *Plastic and reconstructive surgery*, *138*(3S), 209S-218S. doi: 10.1097/PRS.0000000000002683

Cormier, J. N., Askew, R. L., Mungovan, K. S., Xing, Y., Ross, M. I., & Armer, J. M. (2010). Lymphedema beyond breast cancer: A systematic review and meta-analysis of cancer-related secondary lymphedema. *Cancer*, *116*(22), 5138-5149. doi:10.1002/cncr.25458

Executive Committee. The diagnosis and treatment of peripheral lymphedema: 2016 consensus document of the International Society of Lymphology. Lymphology. 2016;49(4):170-84. PMid:29908550.

Fimbo, A. M., Minzi, O. M., Mmbando, B. P., Barry, A., Nkayamba, A. F., Mwamwitwa, K. W., ... & Aklillu, E. (2020). Prevalence and Correlates of Lymphatic Filariasis Infection and Its Morbidity Following Mass Ivermectin and Albendazole Administration in Mkinga District, North-Eastern Tanzania. *Journal of Clinical Medicine*, *9*(5), 1550. doi: 10. 3390/ jcm90 51550.

Gardenier, J. C., Kataru, R. P., Hespe, G. E., Savetsky, I. L., Torrisi, J. S., Nores, G. D. G., ... & Mehrara, B. J. (2017). Topical tacrolimus for the treatment of secondary lymphedema. *Nature communications*, *8*(1), 14345. doi:10.1038/ncomms14345

Grada, A. A., & Phillips, T. J. (2017). Lymphedema: Pathophysiology and clinical manifestations. *Journal of the American Academy of Dermatology*, *77*(6), 1009-1020. doi:10.1016/j.jaad.2017.03.022

Greene, A. K. (2015). Epidemiology and morbidity of lymphedema. *Lymphedema: Presentation, Diagnosis, and Treatment*, 33-44. doi:10.1007/978-3-319-14493-1_4

Greene, A. K., Slavin, S. A., & Brorson, H. (Eds.). (2015). *Lymphedema: presentation, diagnosis, and treatment*. Springer. doi:10.1007/978-3-319-14493-1

Greene, A. K., Voss, S. D., & Maclellan, R. A. (2017). Liposuction for swelling in patients with lymphedema. *New England*

Journal of Medicine, *377*(18), 1788-1789. doi:10.1056/NEJMc1709275

Hartiala, P., Suominen, S., Suominen, E., Kaartinen, I., Kiiski, J., Viitanen, T., ... & Saarikko, A. M. (2020). Phase 1 Lymfactin® Study: short-term safety of combined adenoviral VEGF-C and lymph node transfer treatment for upper extremity lymphedema. *Journal of Plastic, Reconstructive & Aesthetic Surgery*, *73*(9), 1612-1621. doi:10.1016/j.bjps.2020.05.009

Hespe, G. E., Nitti, M. D., & Mehrara, B. J. (2015). Pathophysiology of lymphedema. *Lymphedema: Presentation, diagnosis, and treatment*, 9-18. doi:10.1007/978-3-319-14493-1_2

Jeffs, E., Ream, E., Taylor, C., & Bick, D. (2018). Clinical effectiveness of decongestive treatments on excess arm volume and patient-centered outcomes in women with early breast cancer-related arm lymphedema: a systematic review. *JBI database of systematic reviews and implementation reports*, *16*(2), 453. doi:10.11124/JBISRIR-2016-003185

Kayıran, O., De La Cruz, C., Tane, K., & Soran, A. (2017). Lymphedema: From diagnosis to treatment. *Turkish journal of surgery*, *33*(2), 51. doi:10.5152/turkjsurg.2017.3870

Keeley, V., Franks, P., Quéré, I., Mercier, G., Michelini, S., Cestari, M., ... & Moffatt, C. (2019). LIMPRINT in specialist lymphedema services in United Kingdom, France, Italy, and Turkey. *Lymphatic research and biology*, *17*(2), 141-146. doi:10.1089/lrb.2019.0021

Kerchner, K., Fleischer, A., & Yosipovitch, G. (2008). Lower extremity lymphedema: Update: Pathophysiology, diagnosis, and treatment guidelines. *Journal of the American Academy of Dermatology*, *59*(2), 324-331. doi:10.1016/j.jaad.2008.04.013

Lee, B. B., Antignani, P. L., Baroncelli, T. A., Boccardo, F. M., Brorson, H., Campisi, C., ... & Yamamoto, T. (2015). IUA-ISVI

consensus for diagnosis guideline of chronic lymphedema of the limbs. *Int Angiol*, *34*(4), 311-32.

Lund, E. (2000). Exploring the use of CircAid® legging in the management of lymphoedema. *International Journal of Palliative Nursing*, *6*(8), 383-391. doi:10.12968/ijpn.2000.6.8.9063

Maltese, P. E., Michelini, S., Ricci, M., Maitz, S., Fiorentino, A., Serrani, R., ... & Bertelli, M. (2019). Increasing evidence of hereditary lymphedema caused by CELSR1 loss-of-function variants. *American Journal of Medical Genetics Part A*, *179*(9), 1718-1724. doi:10.1002/ajmg.a.61269

Mardonado, A. A., Chen, R., & Chang, D. W. (2017). The use of supraclavicular free flap with vascularized lymph node transfer for treatment of lymphedema: a prospective study of 100 consecutive cases. Journal of surgical oncology, 115(1), 68-71. doi:10.1002/jso.24351

Masia, J., Pons, G., & Nardulli, M. L. (2016). Combined surgical treatment in breast cancer-related lymphedema. Journal of reconstructive microsurgery, 32(01), 016-027. doi:10.1055/s-0035-1544182

Michelini, S., Vettori, A., Maltese, P. E., Cardone, M., Bruson, A., Fiorentino, A., ... & Bertelli, M. (2016). Genetic screening in a large cohort of Italian patients affected by primary lymphedema using a next generation sequencing (NGS) approach. *Lymphology*, *49*(2), 57-72.

Misra, S., & Carroll, B. J. (2023). Comprehensive Approach to Management of Lymphedema. *Current Treatment Options in Cardiovascular Medicine*, *25*(8), 245-260. doi:10.1007/s11936-023-00991-8

Mobarakeh, Z. S., Mokhtari-Hesari, P., Lotfi-Tokaldany, M., Montazeri, A., Heidari, M., & Zekri, F. (2019). Combined decongestive therapy and reduction of pain and heaviness in patients

with breast cancer-related lymphedema. *Supportive Care in Cancer, 27*, 3805-3811. doi:10.1007/s00520-019-04681-9

Mortimer, P. S. (2000). Swollen lower limb—2: Lymphoedema. *BMJ*, *320*(7248), 1527-1529. doi:10.1136/bmj.320.7248.1527

Mortimer, P. S., & Rockson, S. G. (2014). New developments in clinical aspects of lymphatic disease. *The Journal of clinical investigation*, *124*(3), 915-921. doi:10.1172/JCI71608

Muambangu, J.P. & Lukenze J., T. Genetic Risk Factors of Secondary Lymphedema in African Breast CancerPopulation. J. Oncol. Res. Ther. 2018, 4, 147.

Neuhüttler, S., & Brenner, E. (2006). Beitrag zur Epidemiologie des Lymphödems. *Phlebologie*, *35*(04), 181-187. doi:10.1055/s-0037-1622142

Newman, B., Lose, F., Kedda, M. A., Francois, M., Ferguson, K., Janda, M., ... & Hayes, S. C. (2012). Possible genetic predisposition to lymphedema after breast cancer. *Lymphatic research and biology*, *10*(1), 2-13. doi:10.1089/lrb.2011.0024

Noh, S., Hwang, J. H., Yoon, T. H., Chang, H. J., Chu, I. H., & Kim, J. H. (2015). Limb differences in the therapeutic effects of complex decongestive therapy on edema, quality of life, and satisfaction in lymphedema patients. *Annals of rehabilitation medicine*, *39*(3), 347-359. doi:10.5535/arm.2015.39.3.347.

Ogawa, Y. (2012). Recent advances in medical treatment for lymphedema. *Annals of vascular diseases*, *5*(2), 139-144. doi.org/10.3400/avd.ra.12.00006

Oliver, G., Kipnis, J., Randolph, G. J., & Harvey, N. L. (2020). The lymphatic vasculature in the 21st century: novel functional roles in homeostasis and disease. *Cell*, *182*(2), 270-296. doi:10.1016/j.cell.2020.06.039

Özdemir, Ö. Ç., Yıldırım, B., & Ebru, K. O. S. E. (2020) Lenfödemde Alternatif Tedavi Yöntemleri. *Izmir Democracy University Health Sciences Journal*, *3*(1), 1-7.

Rockson, S. G. (2016). Lymphedema. *Vascular Medicine*, *21*(1), 77-81. doi:10.1177/1358863X156208

Rockson, S. G. (2021). Advances in lymphedema. *Circulation research*, *128*(12), 2003-2016. doi:10.1161/CIRCRESAHA.121.318307

Rockson, S. G., & Rivera, K. K. (2008). Estimating the population burden of lymphedema. *Annals of the New York Academy of Sciences*, *1131*(1), 147-154. doi:10.1196/annals.1413.014

Rockson, S. G., Tian, W., Jiang, X., Kuznetsova, T., Haddad, F., Zampell, J., ... & Nicolls, M. R. (2018). Pilot studies demonstrate the potential benefits of antiinflammatory therapy in human lymphedema. *JCI insight*, *3*(20). doi:10.1172/jci.insight.123775

Roh, K., Cho, S., Park, J. H., Yoo, B. C., Kim, W. K., Kim, S. K., ... & Lee, S. (2017). Therapeutic effects of hyaluronidase on acquired lymphedema using a newly developed mouse limb model. *Experimental Biology and Medicine*, *242*(6), 584-592. doi:10.1177/153537021668857

Sabbagh, M. D., Agko, M., Huang, T. C., Manrique, O. J., Román, C., Reynaga, C., ... & Chen, H. C. (2019). Surgical management of lower extremity lymphedema: a comprehensive review. *Indian Journal of Plastic Surgery*, *52*(01), 081-092. doi: 10.1055/s-0039-1688537

Sapountzis, S., Ciudad, P., Lim, S. Y., Chilgar, R. M., Kiranantawat, K., Nicoli, F., ... & Chen, H. C. (2014). Modified Charles procedure and lymph node flap transfer for advanced lower extremity lymphedema. *Microsurgery*, *34*(6), 439-447. doi:10.1002/micr.22235

Schaverien, M. V., & Coroneos, C. J. (2019). Surgical treatment of lymphedema. *Plastic and reconstructive surgery*, *144*(3), 738-758. doi:10.1097/PRS.0000000000005993

Schaverien, M. V., Badash, I., Patel, K. M., Selber, J. C., & Cheng, M. H. (2018, February). Vascularized lymph node transfer for lymphedema. In *Seminars in plastic surgery* (Vol. 32, No. 01, pp. 028-035). Thieme Medical Publishers. doi:10.1055/s-0038-1632401

Sleigh BC, Manna B. Lymphedema. In: StatPearls. StatPearls Publishing, Treasure Island (FL); 2022. PMID: 30725924.

Telinius, N., & Hjortdal, V. E. (2019). Role of the lymphatic vasculature in cardiovascular medicine. *Heart*, *105*(23), 1777-1784. doi:10.1136/heartjnl-2018-314461

Toktaş, H., Çevik, H., Dündar, Ü., & Güleç, Ö. (2015). Lenfödem tedavisi. *Kocatepe Tıp Dergisi*, *16*(4), 269-272.

Tzani, I., Tsichlaki, M., Zerva, E., Papathanasiou, G., & Dimakakos, E. (2018). Physiotherapeutic rehabilitation of lymphedema: State-of-the-art. *Lymphology*, *51*(1), 1-12.

Warren AG, Brorson H, Borud LJ, Slavin AS. Lympedema: a comprehensive review. Ann Plast Surg 2007;59:464-72.

WHO. Fact sheet. Lymphatic Filariasis. Available online: https://www.who.int/newsroom/fact sheets/detail/lymphaticfilariasis (accessed on 4 February 2021).