RECENT STUDIES IN HEALTH SCIENCES

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PREFACE

This book brings together 8 chapters related to various aspects of health sciences. Also, in this book are presented of recent literature and current approaches on different health sciences. Especially this book will attract the attention of researchers and implementers, but will be of particular interest to academics and staff in the departments of health sciences.

Assist. Prof. Dr. Selen MÜFTUOĞLU

CHAPTER 1

AN EFFECTIVE AND CONVENIENT APPROACH FOR FERTILITY PRESERVATION: CRYOPRESERVATION

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INTRODUCTION

Infertility, which is defined as the inability to achieve pregnancy despite unprotected regular sexual intercourse for at least one year, is a social health problem affecting both the individuals and the public (Anwar & Anwar, 2016). The study of the World Health Organization (WHO) done with 8500 couples having infertility problems reported the causes of infertility as with 37% women factors, 8% men factors, 35% both women and men factors, and 20% unexplained cases (World Health Organization, 1992).

Assisted reproductive techniques, including ovulation induction + intrauterine insemination (OI + IUI), in-vitro fertilization (IVF), intracytoplasmic sperm injection (ICSI), embryo transfer (ET) and cryopreservation; are increasingly used in clinical applications contribute to the solution of reproductive problems in humans, to preserve the lineage of endangered animals, and to maintain the continuity of the high-yielding animal breeds.

Cryobiology is a branch of biology that studies life at sub-normal temperatures. It maintains the properties of cells, tissues, organs and organisms at low temperatures and the changes that occur in these structures after freezing or thawing. Cryopreservation, a method used in Cryobiology in the meaning of frost protection, is that the long-term storage of cells and tissues without losing their viability, without loss of function, with a minimum of injury using cryoprotectants at very low temperatures (Fahy, 1986).

Cryoprotectants are the chemicals used to prevent damages that may occur in freezing-thawing processes. They have protective effects against intracellular ice crystals and cold shock damage that may occur during the freezing process and against decristalization and membrane destabilization issues that may occur during thawing (Palasz & Mapletoft, 1996). While protecting the cells and tissues from injury, cryoprotectants on their own can cause lethal injury due to their chemical toxicity or osmotic effects (Dobrinsky, 1996). Cryoprotectants can be divided into two intracellular and extracellular which can be explained in another way of that intracellular cryoprotectants are permeable and pass through the cell membrane and the latter cannot pass through the cell membrane called non-permeable (Table 1) (R. C. Chian & Quinn, 2010; Newton et al., 1998). Intracellular cryoprotectants are replaced by intracellular water and provide dehydration. They are effective in preserving the cell structure by preventing the formation of intracellular ice crystals during the freezing and thawing processes. At least one intracellular cryoprotectant should be added into the freezing solutions.

Although, extracellular cryoprotectants are the proper chemicals for stabilization of phospholipids in the cell membranes and the formation of controlled dehydration in the cells, usually they are not used alone. In combination with the other cryoprotectants, they influence the fluid passage caused by osmotic change, and they try to minimize damage to the cell by preventing cellular swelling during dissolution. In combination with the other cryoprotectants, they affect the fluid passage according to osmotic change, and they minimize the possible

damages by preventing cellular swelling during dissolution (Palasz & Mapletoft, 1996; Sağırkaya & Bağış, 2003).

1. CRYOPRESERVATION METHODS USED TO PRESERVE FERTILITY

Today, conventional slow freezing, vitrification and ultra-rapid freezing methods are used for cryopreservation of reproductive system cells and tissues in assisted reproductive centers and experimental studies (Lee et al., 2010; Loutradi et al., 2008; Jill M. Shaw & Jones, 2003)

Slow freezing method is a slow, gradual freezing technique with the help of a programmable freezing device using less concentration of cryoprotectants (Sağırkaya & Bağış, 2003). It consists of the following stages:

1. Equilibration: Providing osmotic balance with the increasing concentrations of permeable intracellular cryoprotectants in increasing concentrations at room temperature.
2. Seeding: Controlled initiation of the formation of ice crystals by inducing between -5°C and -7°C without crystallization to reduce cold shock damage.
3. Cooling gradually with a freezing device at a temperature of 0.2°C to 2°C per minute until it reaches a temperature between -30°C and -70°C.
4. Storing in liquid nitrogen at -196°C.

The seeding process applied in the slow freezing method prevents the formation of ice crystals in an uncontrolled manner and provides sufficient time for the fluid transfer to the extracellular environment (de Paz et al., 1994) It is an important step that should be taken into consideration for the preservation of vitality after thawing.

Vitrification is the freezing of cells, tissues and organs with rapid cooling rates using vitrification solutions which are prepared with high concentrations of cryoprotectants thus having increased viscosity. A glassy appearance is obtained inside the cell without ice crystallization. Cells and tissues passed through vitrification solutions are taken into liquid nitrogen and stored until they are thawed by freezing with rapid cooling. Since the cryoprotectants used in the vitrification process are low in volume and high in concentration, they can evaporate rapidly at high temperatures (eg. room temperature) and become extra-concentrated and more toxic to the cells and tissues. They are recommended to be used in low volume due to their harmful effects. As a matter of fact lower amounts of vitrification solutions fasten the cooling rate. The cooling rate administered in vitrification is inversely proportional to the amount of cryoprotectant solution. Therefore, in order to prevent toxic and osmotic damage, care is taken in the vitrification process and cryoprotectants are used in high concentrations in low volume, and the cooling temperatures should be decreased (R.-C. Chian et al., 2004; Yavin et al., 2008).

Ultra Rapid Freezing is the freezing of partially dehydrated cells at a cooling rate of 1200-1250°C per minute with the vitrification solution

which is made of permeable cryoprotectants (approximately 2M - 4.5M) and non-permeable cryoprotectants (approximately 0.25 M - 0.5 M) (Cseh et al., 1997; Sağırkaya & Bağış, 2003).

1.1. Embryo Cryopreservation

Embryo cryopreservation is an ART that increases the chance of success of methods that help reproduction in humans, which enables experimental biomedical studies to be carried out in farm and laboratory animals, to provide animal breeding and preserve endangered species by transferring superior genetic qualities to future generations. Nowadays, the cryopreservation method is used as an often-used method for the proper storage of embryos in the transplant centers *in vitro* conditions (Campbell & Picton, 1999)

Especially in recent years, restrictions on the number of embryos to be transferred in order to prevent multiple pregnancies in clinical applications have led to increased research on the development of cryopreservation methods. Embryo cryopreservation plays an important role in the control of reproduction in mammals. The biggest advantage of using frozen embryos in ARTs is the presence of uterine polyp, fluid accumulation in the endometrial cavity, poor quality endometrium, vaginal bleeding before transfer, the necessity of fresh embryo transfer, such as ovarian hyperstimulation syndrome risk (Elder & Dale, 2019). A start has been made for the successful freezing of sperm with glycerol and to conduct embryo cryopreservation studies (Polge et al., 1949) The first successful embryo cryopreservation procedure was performed in mouse

embryos; It has been applied in humans and different animal species in the following years (Dattena et al., 2000; El-Gayar & Holtz, 2001; Lane et al., 1999; O'Kearney-Flynn et al., 1998; Whittingham et al., 1972). Embryo cryopreservation can be performed in the zygote stage, early cleavage period and the blastocyst stage. Despite the large number of developments in the field of embryo cryopreservation, no consensus has yet been reached regarding the optimal stage of development for embryo cryopreservation.

In a study comparing IVF-ET results in human embryos frozen in pronuclear stage, cleavage stage or blastocyst stage; There was no difference between implantation, clinical pregnancy, multiple pregnancies, twin pregnancy and male / female ratio between the three stages. The only difference found was the survival rate after thawing, and the survival was reported to be lower in day 3 embryos than in day 1 embryos or blastocysts (Moragianni et al., 2010). In another study, it was known that there was no difference in implantation, clinical pregnancy and live birth rates after transfer of embryos that were frozen and thawed at the zygote, day 2 and day 3 phases (Salumets, 2003). The low viability rates in the embryos obtained *in vitro* after freezing-thawing compared to *in vivo* embryos indicate that they are more sensitive to cryopreservation (Leibo & Loskutoff, 1993).

It has been reported that there are some differences between the species depending on the viability rates of the embryos after freezing-thawing, the freezing and thawing rate applied, the size and

development stages of the embryos, the permeability characteristics of the cells, the toxicity and osmotic properties of the cryoprotectants used (Edashige et al., 1999; Ludwig et al., 1998). Cryopreservation can have devastating effects on the cellular organization of embryos. After cryopreservation, destabilization and denaturation of membrane lipids and proteins, loss of function in the intracellular organelles, fractures in ZP, damage to the cytoskeleton formed by the microstructure, microtubule and intermediate fibers that play a role in the structural integrity of the cell (Dobrinsky, 1996). As a result, free radical formation, decreased ATP synthesis, impaired metabolic function of cells, apoptosis (J. M. Shaw et al., 2000) and necrosis (Baguisi et al., 1999) may develop.

1.2. Oocyte Cryopreservation

In 1948, following the introduction of glycerol as a cryoprotectant, progress has been made in freezing and storing sperm and oocytes (Pegg, 2002). (31) The first studies on oocyte cryopreservation were performed in mouse and hamster oocytes (Martino et al., 1996). When the literature is examined, it is seen that Wittingham et al performed their first live birth with the mouse purple obtained from oocytes dissolved after cryopreservation (Whittingham et al., 1972) and that in 1986, Chen et al showed that human oocytes were successfully frozen and stored (Chen, 1986). In the first studies on human oocytes, 1.2 propanediol and sucrose were mostly used as cryoprotectants; either excited or immature oocytes obtained in natural cycles were frozen (Tucker et al., 1998). When we evaluate in terms of cryopreservation,

freezing a single cell yields more successful results than freezing a tissue or cell masses, but this does not apply to mammalian oocytes.

Since the oocytes, which are the largest cells of the body, are more sensitive to temperature changes, extracellular osmotic pressure and freeze-thaw damage, the success rates in cryopreservation of mature oocytes are considerably lower than embryo cryopreservation (Kutluk Oktay et al., 2001). Mammalian oocytes are more sensitive to freezing than embryos in the zygote and cleavage periods. Arav et al. In a study with beef oocytes; reported that cryodamage was seen in different places in immature and mature oocytes and there were differences in membrane thermo-activity. The researchers stated that the damage in immature oocytes was seen in the plasma membrane, while in mature oocytes it developed in microtubules and microfilaments (Arav et al., 1996).

When the literature is examined; In oocyte cryopreservation studies using slow freezing and vitrification methods published between 1986-2008; with the use of frozen oocytes after thawing, it is seen that 936 children were born and there was no significant increase in the risk of congenital anomaly (Noyes et al., 2009). The fertilization rate per cryopreserved oocyte was 62.5% and live birth rate was 3.1% in the meta-analysis study conducted by Oktay et al. (K. Oktay et al., 2005). Oocyte cryopreservation, previously accepted as an experimental method, was accepted as a method that should be routinely presented to patients in appropriate cases where fertility is desired with the bulletin published by the American Association for

Reproductive Endocrinology (ASRM) in 2013 (Practice Committees of American Society for Reproductive Medicine & Society for Assisted Reproductive Technology, 2013).

1.3. Ovarian Tissue Cryopreservation

Although it is considered as an experimental method due to insufficient data regarding ovarian tissue cryopreservation, efficacy, safety and outcomes, which is considered to be an alternative method in protecting infertility today, it is a method that has been shown to be applicable in many living species such as cows, sheep, mice and humans (Gosden et al., 1994; Kutluk Oktay & Karlikaya, 2000; Paynter et al., 1999; Sztein et al., 1998). It is offered as an option in selected patients, especially in prepubertal age patients or cancer cases where radiotherapy or chemotherapy should not be delayed. Chemotherapeutic agents and radiotherapy used in cancer treatment can lead to decreased ovarian reserve and early ovarian failure. In these patients, cryopreservation of ovarian tissue is thought to be an effective method to protect more follicles in the tissue and provide hormonal functions (Dittrich et al., 2015).

Donnez et al. Reported the first live birth in humans following autotransplantation after dissolution of cryopreserved ovarian tissue in 2004. In 2011, 13 live births were reported worldwide and 24 live births were reported in 2013 (J Donnez et al., 2004; Jacques Donnez et al., 2013; Jacques Donnez & Dolmans, 2011). It has been reported that malignant cells that may be present in frozen tissue may have risks such as re-implantation or recurrence. Especially in

hematological cancers such as leukemia and lymphoma, there is a risk of persistence of malignant cells in the ovary. Another risk is post-transplant ischemia and graft failure (Gracia et al., 2012). Currently, a combination of a standard method and cryoprotectant has not been established in the cryopreservation of ovarian tissue. According to the American Association for Reproductive Medicine (ASRM), ovarian tissue cryopreservation is not considered as a routine standard treatment that should be applied for experimental purposes in selected cases for preserving fertility (Practice Committee of American Society for Reproductive Medicine, 2014). A simple algorithm for fertility preservation in females is represented in Figure 1 (Akdemir, 2018; Bedoschi & Oktay, 2013).

1.4. Sperm Cryopreservation

Sperm cryopreservation is the first choice in preserving fertility in adolescent male patients who are planned to undergo chemotherapy and radiotherapy, which may cause DNA damage in sperm and impairment of spermatogenesis (Picton et al., 2015). In cases where nonobstructive azoospermia has been obtained from the testicular or epididymal sperm, patients with spinal cord damage, and in patients who will undergo testicular surgery such as orchiectomy and varicocelectomy, sperm cryopreservation can also be applied to maintain fertility (Tunali, 2014). A simple algorithm for fertility preservation in males is represented in Figure 2 (Akdemir, 2018; Picton et al., 2015).

Sperm is frozen at room temperature 1-2 hours after ejaculation, following semen liquefaction or after washing. The semen cryopreservation steps are outlined in general:gently mixing with cryoprotective agents in a ratio of 1/1; placing into cryovial or straw, keeping at -80 degrees nitrogen vapor for 20 minutes and then storing in the liquid nitrogen tank. Sperm cryopreservation was defined by Sherman in 1963 and is practiced in many clinics today(Sherman, 1963). Thawing methods to be applied in cryopreservation of sperm differ according to the maturation stage of spermatozoa. Freezing and thawing sensitivity of ejaculate is higher than epididymal or testicular sperm. In sperm freezing solutions, sucrose is preferred as an extracellular agent and 5-15% glycerol is preferred as an intracellular agent. However, the most efficient results are obtained with ethylene glycol. Solutions containing additional cryoprotectants such as glycine, egg-white, and citrate are obtained to increase the viability rates of sperm after thawing. The most used for this purpose is glycerol egg yolk citrate (GEYC) (Tunali, 2014).

CONCLUSION

Fertility preservation approaches have been improved by cryopreservation. The cryopreservation of embryos and gonadal cells (oocyte or sperm) is the most common method for the solution of fertility problems that may develop due to chemotherapy, radiotherapy, surgical interventions and other non-oncological causes. Effective results were obtained with ovarian tissue cryopreservation.

Therefore it should be taken into account that it should be included in routine clinical applications.

Table 1: Summary of Cryoprotectant Agents (R. C. Chian & Quinn, 2010; Newton et al., 1998)

CRYOPROTECTANTS	CELLS/TISSUES	SPECIES
PERMEABLE AGENTS		
Glycerol	Oocyte, Embryo,Sperm	Mouse, Human, Cow
Dimethyl sulfoxide	Oocyte, Embryo, Sperm, Ovary	Mouse, Human, Cow, Rat, Dog
Ethylene glycol	Oocyte, Embryo, Sperm, Ovary	Mouse, Human, Cow, Horse
Propylene glycol	Oocyte, Embryo, Sperm, Ovary	Mouse, Human, Cow, Goat
Butyramide	Sperm	Rabbit
Malonamide	Sperm	Rabbit
Formamide	Sperm	Horse, Goose, Dog, Mouse
Acetamide	Oocyte, Embryo	Mouse, Rabbit, Pig, Rat
Propionamide	Sperm	Rabbit
Methanol	Sperm	Horse
Erythritol	Embryo	Rat
Butylene glycol	Oocyte, Embryo	Mouse, Cow, Sheep
Arabitol	Embryo	Rat
Adonitol	Embryo, Sperm	Mouse, Sheep, Human, Rat
Perseitol	Embryo	Rat
Xylitol	Embryo	Rat
MONO-DI-POLYSACCHARIDES		
Dextran	Embryo	Cat, Mouse
Sucrose	Oocyte, Embryo, Sperm, Ovary	Mouse, Human, Cow, Rat
Glucose	Sperm	Cat
Galactose	Sperm	Horse
Mannose, fructose, xylose	Sperm	Deer
Trehalose	Oocyte, Embryo, Sperm	Mouse, Human, Horse
Laktose	Sperm	Mouse, Cow
Maltose	Sperm	Mouse, Deer, Rabbit
Raffinose	Oocyte, Sperm	Mouse, Horse
MACROMOLECULES		
Ficoll, polyethylene glycol	Oocyte, Embryo	Mouse, Human, Cow
Polyvinylpyrrolidone	Embryo	Mouse
Polyvinyl alcohol	Oocyte, Embryo	Mouse, Cow, Sheep
Hyaluronan	Embryo, Sperm	Mouse, Cow, Sheep, Pig

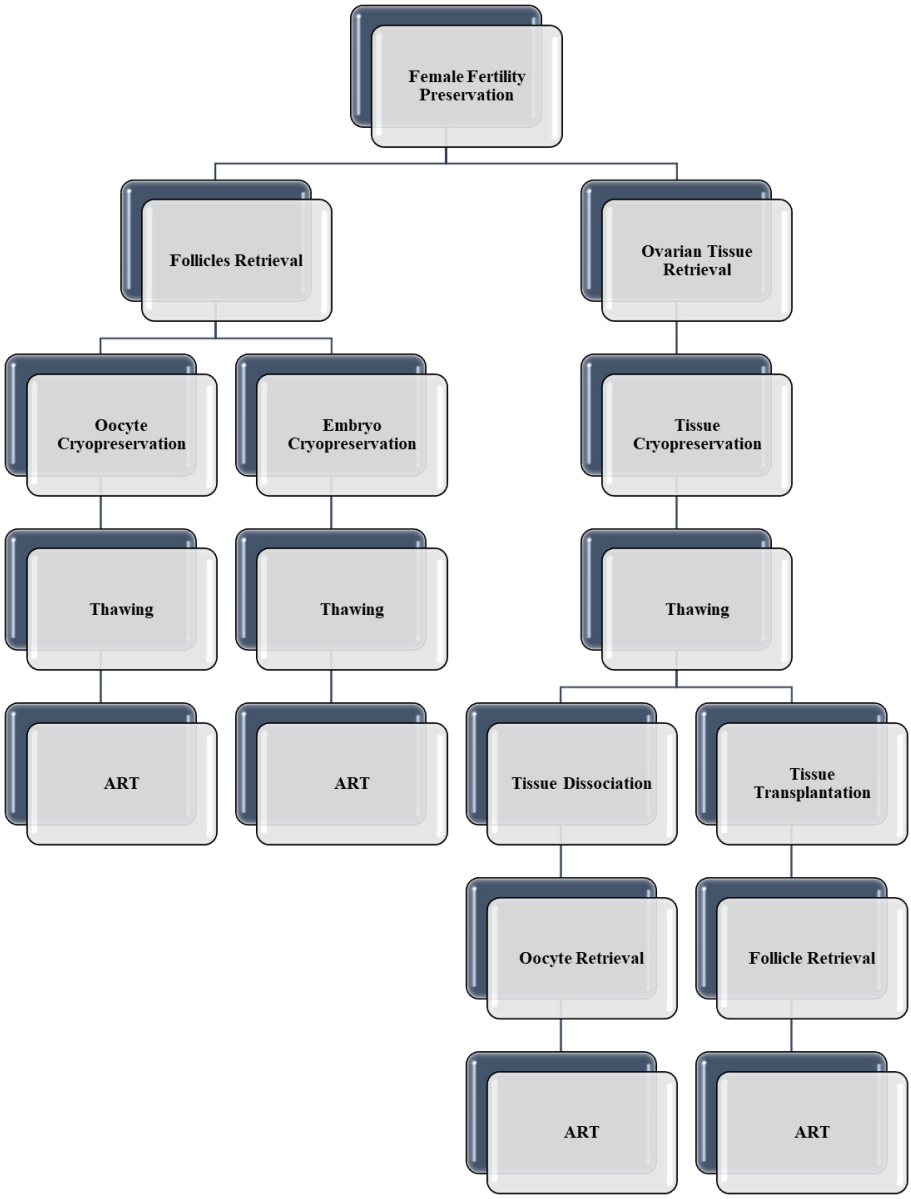

Figure 1: A Simple Algorithm for Fertility Preservation in Females (Akdemir, 2018; Bedoschi and Oktay, 2013)

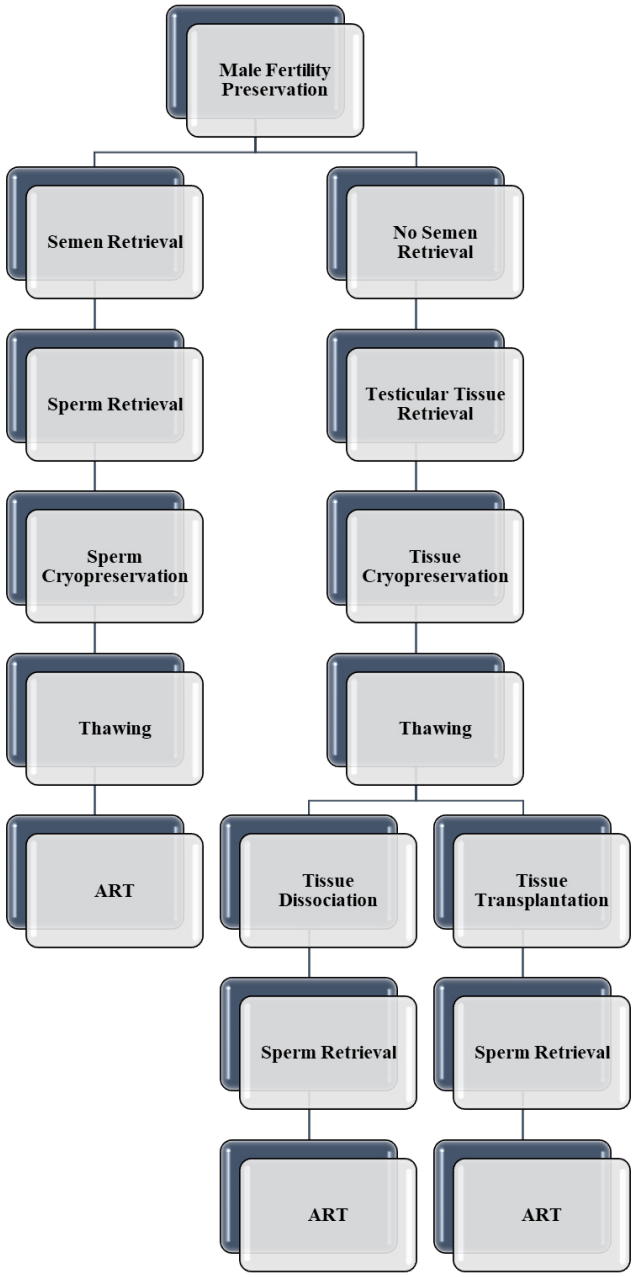

Figure 2: A Simple Algorithm for Fertility Preservation in Males (Akdemir, 2018; Picton et al., 2015)

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CHAPTER 2

ENVIRONMENT - ASSISTED LIVING TECHNOLOGIES FOR THE ELDERLY POPULATION

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INTRODUCTION

Individuals over 65 constitute an increasingly growing demographic group reflecting public change. The aging of the population which has become a global phenomenon has a tendency to grow in almost every country of the world. It is estimated that the population of the people who were 65 or over in 2019 will change and every one person out of six will be over 65 (UN, 2019) and that 80% of the elderly will be living in low and middle income countries in 2050 (WHO, 2018).

With the increase in elder population, there have been many different definitions about aging and the problems resulting from it. Biological changes caused by the accumulation of the harmful effects of various molecular and cellular damages in the course of time; sociological changes related to life transitions like retirement, movement, and the death of a friend or a spouse; the increase in the diseases such as hearing or eye disorders, osteitis and chronic obstructive lung diseases, diabetes, depression, and dementia and as a result death have all been observed with aging (WHO, 2018). In addition, the decrease in physical and mental capacity (WHO, 2018), loss of memory, (Wang & Bennett, 2012), low intensity walking speed, inactivity, and the difficulties in basic and instrumental activities of daily living show the cognitive and physical functional changes in elderly (Singh *et al.,* 2017; Gould *et al.,* 2015).

While ailments and disabilities become more common as individuals get older (Hill *et al.,* 2013), the possibility for them to experience a few problems at the same time increases, and therefore people need

more health care as they age (Hill *et al.,* 2013). In addition to the medical problems, the reality of being dependent on the family members or caregivers in performing daily activities also leads to problems like shyness, social inactivity, and inadequate nutrition in the older population (Bettio & Verashchagina, 2010).

Especially in recent years, the demand for the nursing homes where the elderly population can be cared for a longer time period and where they can be continuously assessed cognitively and physically has increased (Bettio & Verashchagina, 2010). However, meeting this demand may not provide the complete solution of the problems of the elderly (Blackman *et al.,* 2016). Furthermore, in addition to personal features, both physical and social environments may also play a role in the emergence of such problems.

The house and the district where people reside, the socioeconomic status and conditions have an important effect on the development and continuation of health behaviors. When promoting health care behaviors for the elderly, it is important to consider not only the approaches for improving losses related with age but also the approaches for strengthening recovery, adaptation and psychosocial support (WHO, 2018). It is, with this understanding, thought that the health and care of the elderly can be assisted and the burden on the health support services can also be reduced. With this regard, some researches have been carried out with new technologies to assist the elderly population, (Paulus *et al.,* 2009) and the terms like Smart Building (Leopold, 1985), Smart house (Steinke *et al.,* 2012),

Assistive Technology (Philips & Zhao, 1993) or Environment Assisted Living (Giesecke *et al.,* 2005) have emerged. This technological development and information technology have become more and more important in daily life (Paulus *et al.,* 2009).

1. TECHNOLOGIES FOR OLDER ADULTS

Assistive Technologies are defined as the services and equipment used to maintain or improve the physical and cognitive functions of the individual and to improve the general comfort and welfare of the aging and disabled population (WHO, 2019).

Assistive Technologies include:

1. To help mobility; Manual or Special Wheelchairs, Wheelchair lifts, Electric Scooters.
2. To help communication; Audio and Visual devices, Communication Boards.
3. To help improve cognition; Computer Software, Adapted or Modified toys.
4. To help self-care and nutrition; Accessories, Devices and Equipment such as modified furniture or goods, bath, toilet, and clothing (Idaho Assistive Technology Project, 2004).

2. ENVIRONMENT-ASSISTED LIVING TECHNOLOGIES

The term 'Environment-assisted Living Technologies' which has a fast development rate especially in Europe (Blackman *et al.,* 2016) and which is commonly used in research and development in Gerontechnology suggests the innovative technologies which will help

and enable older people to lead their life in a better, more healthy and safer way in the place they prefer; the concepts which relate social environment to each other and improve them and the smart systems made up of services and products (Kung & Jean-Bart, 2010). On the other hand, Environment-assisted Living Technologies have been presented as a solution which offers innovative approaches to the problems and difficulties experienced by the aging population (Blackman *et al.,* 2016) and have been defined as a type of assistive technology (Caballero-Gil *et al.,* 2018).

Technologies present in Environment-Assisted Living are those of bed sensor technology for fall prevention, smart interfaces, and technologies which provide assistive homes by integrating artificial intelligence (Sixsmith *et al.,* 2010). These technologies depend on traditional assistive technologies and universal design approaches in terms of availability and usability (Pieper *et al.,* 2011). Environment Assistive Living Technologies include 4 main coverage areas as 'health, care (Steinke *et al.,* 2012) and rehabilitation' (Nehmer & Kleinberger, 2008), 'home and supply', 'security and privacy', and 'communication and social environment' (Dupuy *et al.,* 2017). The field 'Assisted Living', which has a broad perspective, also requires the joint study of groups of experts from Medicine, Psychology, Hardware and Software (Wichert, 2010).

Environment-Assisted Living Technology has been developed to enable older people to lead a safe and independent life in their homes, to allow them to join daily life (Nehmer & Kleinberger, 2008), to help

them join public activities in the places like shopping malls or various public areas (Cardinaux *et al.,* 2011), and to help them protect their physical and mental health qualities. Moreover, Environment-Assisted Living Technology also focuses on meeting the general needs of the old people who have health problems and who require communication and safety support to overcome their loneliness, and therefore providing them solutions for their independent living (Committee on Technology of the National Science & Technology Council, 2019). This technology has also physical, mental, social and economic effects on not only the elderly but also the family members, care givers and the society as a whole because nearly 70% of the aging population is completely dependent and they require assistance in their daily living activities (Li *et al.,* 2015). It is also reported that Environment-Assisted Living Technology has the potential to lower the unregistered healthcare costs and to decrease the burden on the families, the caregivers and the society (Ganesan *et al.,* 2019).

The objectives of the Active and Assisted Living Technologies determined in the Active and Assisted Living Common Program by The Active and Assisted Living Association (AALA, 2017) are as follows;

- Lengthening the life span of people in the environment they prefer by increasing their freedom, self-confidence and mobility.
- Assisting the protection of the health and functional abilities of the elderly.
- Encouraging a morehealthy life style for the individuals at risk.

- Providing the security of the individuals.
- Preventing social isolation.
- Assisting family members, caregivers and care organizations.
- Increasing the productivity of the sources used in aging societies.
- Some of the examples stated by Technology of The National Science & Technology Council in its report on the developing technologies to support an aging population (Committee on Technology of The National Science & Technology Council, 2019) are as follows:
- Smart showers which have the ability to understand the presence of an individual in the bathroom, and which can manage the flow, direction, and heat of the water and which have also sensors to control the distribution of the soap.
- Technologies which provide information to the caregivers or the first hand service providers about the subjects such as monitoring personal care, the location of the individual, the heat of the water used, the unexpected physical and behavioral changes.
- Portable technologies which determine the incidence of the diseases and infections caused by bacteria transfer.
- Materials which are strong and affordable enough to decrease
- bacteria colonization on the devices like remote controls of the televisions.

- Oral Health and Care Devices which can be used by the elderly in situations like weak eyesight, lack of hearing, and low coordination.
- Personalized systems such as saliva biomarkers which allow the assessment of the biological conditions of the mouth at home.
- Smart Textile Products such as socks with optic fiber soles that can measure foot plantar pressure and heat and that can prevent the emergence and development of diabetic foot ulcers for individuals with neuropathy.
- Smart bandages which can detect the wounds and infection, monitor the healing process and deliver the results directly to the doctor.
- Disposable electrochemical sensors which can identify the type of the bacteria present in a certain part of the skin.
- Services which can give information to individuals about the place and cost of healthy food by comparing the food prices and informing them about the geographical location of those healthy food.
- Sensors which allow the monitoring of the blood sugar level, the heart rate and the adaptation of the medicine and which also prevents medicine toxicity and interaction.
- Technologies which will enable the blind people and people with eye-disorders to recognize their medicines, to read the medicine labels and to make them sure that they have taken the right medicine.

- Devices which will help people with hearing disability to understand the speech made in noisy environments although there are currently devices which have been designed for one to one communication at a close quarter.
- Assistive Mobility Technologies in uncontrolled environments (like lowering or raising the pavements).

3. ACTIVE ASSISTED LIVING FOR THE ELDERLY

3.1. Active Assisted Living for the Elderly with Physical Disorders

Healthy Aging is determined according to three factors: a high rate of physical and cognitive function, less chronic disease and more active participation in daily activities. It is inevitable that some physical and cognitive disorders and other age related chronic diseases will arise in the course of aging (UN, 2017). Due to physical and cognitive retardation increasing with age, the elderly people experience some limitations in daily activities, long distance walking, standing for a long time, kneeling, bending, and stature (Tkatch *et al.,* 2016). Another limitation is that they have limitations in daily living activities like eating, having a bath, going to the toilet, dressing and the instrumental activities of the daily life like communication, transportation, financial transactions, and the ability to use the telephone (Doi *et al.,* 2015; Muir *et al.,* 2010). In various fields and mostly in Biomedical Engineering, the development of advance technologies like wireless communication and monitoring human activities with wearable sensors (Muir *et al.,* 2010) may provide

benefits to the elderly population in defining their problems and finding solutions to them. Wearable and Unwearable sensors may be recommended for the elderly to carry out their daily living activities safely. However, wearable sensors are more advantageous because they are portable, light and cheaper (Liu, 2017). Therefore, they can take the first place in terms of preference.

Researches with various sensors have been carried out to monitor the daily activities of the elderly for the purpose of providing their safety (Mathie *et al.,* 2004; Parkka *et al.,* 2006; Pirttikangas *et al.,* 2006). In two of those researches (Mathie *et al.,* 2004; Parkka *et al.,* 2006) waist-worn sensors have been used for the elderly to monitor their daily living activities like sitting, standing, running, walking, climbing up the stairs. In another research, sensors on wrists, thigh and necklaces have been used to monitor activities like climbing up and down the stairs (Pirttikangas *et al.,* 2006). Another problem for the elderly is the falls which make it difficult for the elder people to perform activities at home and in social life. For this reason, fall detection system is the most important application among the systems for environment or active assisted living systems (Ganesan *et al.,* 2019). Zhang et al (2013) have introduced a home based environment assisted living system detecting falls. This multi-mode accelerometer sensor is made up of a video system with technic components such as speech recognition, voice and image. This study has established that average fall reaction time is 46.2 seconds and the fall detection validity is 94% (Zhang *et al.,* 2013). Various studies have been carried out to prevent falls by using recently developed communication

technologies and smart phones. One of those studies has been performed by Casilari et al. (2016) on a smart phone based fall detection system which is composed of 4 sensors on mounted chest, waist, ankle and wrist and a smart phone. It has been accepted that sensors on the chest, body or waist have an important role in the prediction of falls (Casilari *et al.,* 2016).

3.2. Active Assisted Living for the Elderly with Cognitive Disorders

Like memory, attention and problem solving abilities (finance management, taking the correct drugs at the right time, and using them safely) Cognitive function, plays an important role in independent daily and social life and in forming emotional reaction. These functions tend to decrease with age (Harada *et al.,* 2013). Various Medical situations like Dementia, Alzheimer, Huntington, Cerebellar Degeneration and Paralysis may also lead to cognitive disorders. Furthermore, it is known that Dementia and Alzheimer have an important effect on the performance of memory, attention, sleeping, learning, intelligence, perception and behavior and on making alterations or changes in the workings of the daily and social life (Peracino & Pecorelli, 2016). Not only physical but also cognitive disorders affect the daily life of the elder people. People with cognitive disorders may need to be hospitalized and given health-care three times more than people with other medical problems (Alzheimer's Association, 2019). In recent years various low technology interventions have come into existence to facilitate and

improve the living conditions of people with cognitive disorders. Developments in information processing and perception technologies have offered ways to solve the daily functional problems of the older adults (Ganesan *et al.,* 2019). Wearable devices like watches, accelerometers, wrist sensors, and smart phones can be given as an example for the devices used to monitor basic daily activities. Other examples constitute unwearable sensors and technologies developed for people with dementia to detect movement, location, daily living activities and total sleep hour, (Galambos *et al.,* 2013) and there are also sensors to determine how much time people with depressive disorders spend inside and outside the house for their daily activities (Eisa & Moreira, 2017).

As it happens in Alzheimer cases, there are also technologies for people with cognitive retardation such as smart home sensors to detect cognitive structure, mental state and mobility changes (Alberdi *et al.,* 2018), and to record and improve behavioral patterns in their daily living activities (Virone *et al.,* 2008). In addition, there are also other researches which make use of various technologies to monitor daily living activities of the individuals. Pressure sensors which provide fall protection and home safety for the elderly individuals by detecting them on the chair or in their bed, noise sensors which detect sound and noise in the kitchen, ground sensors which enable automatic control of the keys and mobile robots for independent daily living activities can be listed among them (Uddin *et al.,* 2018). It has been claimed that digital medicine boxes, digital reminders like calendars or electronic diaries, positioning systems like Global Positioning System (GPS) and

monitoring devices can be helpful in assisting people with cognitive disorders in terms of memory and security (Holthe *et al.,* 2018) and also helpful for memory problems (Ganesan *et al.,* 2019).

One of the problems which aging people experience is the wandering behavior. It is a cause of great risk for the person, and is often a major concern for caregivers and family members. Although dementia is cured with medicines and physical limitations, these treatments have some side effects. Lin et al. (2018) have developed an active infrared recognition system which detects wandering activities inside, and their studies have a validity rate of 98%.

3.3. Social Participation and Active Assisted Living for the Elderly

Social participation which has an important role in the improvement of the life quality of the aging population includes activities like volunteering in social projects, meeting friends, and making the most of their free time. It is especially difficult for elder people with physical or cognitive disorders to perform these activities (Ganesan *et al.,* 2019).

However, it has been reported that simplified e-mail and video phone conversations may offer elder persons certain social functions (Frisardi & Imbimbo, 2011), and that technology based games may motivate them to participate in entertaining play activities (Gamberini, 2009) and that internet based systems may help them take more social support and feel less boredom. Nevertheless, it has also been reported that such systems may also lead to some negative consequences like

providing misleading information or joining online discussion forums (Ganesan *et al.,* 2019).

4. THE BACKGROUND OF THE TECHNOLOGIES DEVELOPED FOR THE ELDERLY

Technologies designed for the elderly are also classified as 3-generation technologies (Sixsmith *et al.,* 2007; Blackman *et al.,* 2015). The first of them is the First-Generation technologies. It consists of technologies which require elder people to wear a necklace or an alarm button. It is based on a system which allows people in the call center to communicate with the older person in case of an emergency like a fall when he presses on the emergency button and which allows them to decide whether he needs first aid or not (Sixsmith *et al.,* 2007). Such technologies have provided benefits like early hospital discharge, low hospital admission rates, late admission to long term care centers and decrease in stress levels of the family members and caregivers (Sixsmith, 2000). However, the fact that elder people are physically and mentally incapable of using the devices shows that the devices have some weak sides. For example, the fact that the alarm sounds when an old person goes to bed or the fact that an older person forgets to set the alarm again after going to the toilet shows that technological devices are not effective in this age group for whom the risk for falls is high (Blackman *et al.,* 2015).

The second of them is the Second-Generation Technologies. They are those which have been developed to improve the limitations existing in the First-Generation Technologies (Sixsmith, 2000). These

technologies can detect falls and other emergency situations with sensors without requiring users to activate them (Sixsmith, 2000). For example, these sensors may determine the need to turn off the stove heating too long for individuals who have forgotten to turn it off and may warn them before the situation gets worse. Moreover, these systems may be beneficial for individuals who have difficulty in using house appliances (Blackman *et al.,* 2015).

The third one is the Third-Generation Technologies. Technologies which not only determine and report the problem but also provide solution have come into existence with the emergence and introduction of the information processing technologies (Kleinberger *et al.,* 2007). Home monitoring systems which monitor the old person besides the home environment itself, wearable sensors which can monitor the changes in both movement and activity and the life symptoms of the old person are among these technologies. It has also been reported that it may be potentially beneficial that elder people are monitored with the technology hidden in daily objects in order not to make them feel stamped (Blackman *et al.,* 2015). It is also stated that the use of such technologies that are still in a development stage is increasing day by day in assisting the individual's independence, improving his life quality and decreasing the costs involved (Kleinberger *et al.,* 2007).

Features that Assistive Technologies should have,

- New Generation sensors must be durable and affordable, and must have high sensitivity.

- Wearable and mobile devices should be less disturbing and must be easily wearable.
- They should be designed so as to improve both the physical and the cognitive abilities of the users.
- They should be developed by taking the biological, physiological and medical aspects of the users.
- System coordination and Service allocation should be performed to support the assistive technologies and appropriate framework study should be carried out for the purpose of sharing information (Idaho Assistive Technology Project, 2004).
- Universal standards should be introduced for the sensors, robots, and mobile devices in assistive technologies (Li *et al.,* 2015).
- In addition,
- Environment Assistive Living Technologies should have features like predicting and defining individual needs and preferences in advance, distinguishing people around appropriately and allowing different replies or reactions according to individual needs and situations (Queiros *et al.,* 2012).

In general, the selection process of the optimum device for the elderly (Idaho Assistive Technology Project, 2004) consists of the following steps:

1. Collecting Information: The assessment process first starts with the collection of the demographic information, then continues with collecting information about physical and mental state, daily living activities, level of independency, and the type and number of the prosthesis used.

2. Observation: The second step involves a short observation period which includes the direct study of both the individual and the environment. It is extremely important to listen to the old person and interpret his words correctly in the observation performed at his home.

3. Improving problem reporting: The third step is to improve the old person's ability to report his problems. The person should define and explain all the problems he has encountered in every environment.

4. Detailed assessment of the abilities and the environment: The fourth step, if necessary, is to make a detailed assessment about the old person and his environment. The assessment procedure starts with establishing a suitable team. It entails making more meetings with the old person and his family members, a detailed environment study and the other procedures.

5. Determining possible interventions: At this stage possible assistive devices to be used for the old person and home modifications are defined.

6. The trial of the possible interventions: It is at this stage that elder people are asked to try out the devices or home modifications to confirm that they are useful.

7. Changing interventions: Depending on the data obtained during the trial process of the device, some adjustment and adaptation operations should be performed.

8. Application and training the individual: The elder individual should be assisted in using the device or the home modification after the other steps have been completed. The elder individual and the family members should be trained in order to teach and guide them about the technology used, how to use, repair and maintain the device.

9. Monitoring the advancement: The observation and noting the use of the device or the home modification by the family members or the other caregivers to make sure that the device is used correctly by the old person and not create any risk for the user constitute the last step.

CONCLUSION

Gerontechnology which has arisen as a result of the aging population is an interdisciplinary scientific field which uses technology to ease the living conditions of the aging people (Bouma *et al.,* 2007), to improve their active living by increasing their functional capacity, independence and mobility (Sixsmith *et al.,* 2010), and to prevent social isolation by continuing the support mechanism (Sixsmith *et al.,* 2010). This field requires the cooperation of Health Sciences and Gerontechnology, Social Sciences and Engineering, Robotics and Information Processing (Bouma *et al.,* 2007). These mentioned fields have all tended to cooperate with each other to improve and develop various technologies ranging from simple devices to more complex systems for the elderly population whose physical, psychological and

social needs differ from one another and who suffer from various difficulties like the cognitive disorders (Blackman *et al.,* 2015). This cooperation has offered various new technologies like wearable sensors, devices, or robotics to assist the elderly people in their life.

Despite the fact that it has been shown by researches that developed technologies based on cooperation have beneficial effects on assisting daily living activities of the elderly, it is stated that they also cause more practical hurdles for people with cognitive disorders than those who have physical problems (Ganesan *et al.,* 2019). The fact that these technologies may lead to various security and privacy risks with regard to the sensors and the cameras (Queiros *et al.,* 2012), the high installation costs, the complexity of the installation, training and maintenance, and the ethical problems like being stamped are the factors which restrict their use (Piau *et al.,* 2014). For this reason, since it may increase the efficiency and productivity of the services provided, it is thought that more researches are required to assess the efficiency of the technological intervention on the elderly population (Ganesan *et al.,* 2019), to determine the strategies which facilitate the admittance of the devices by the users and the expectations they have (Li *et al.,* 2015), to increase the safety measures and to evaluate the coordination and harmony between the technology providers and the caregivers (Committee on Technology of The National Science & Technology Council, 2019).

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CHAPTER 3

EATING DISORDERS AND FACTORS AFFECTING NUTRITION IN ELDERLY INDIVIDUALS

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INTRODUCTION

Aging refers to changes that occur during an organism's lifetime (Da Costa et al., 2016). It is the deterioration of self-regulating systems and the ability to adapt to the environment. Aging is a physiological, psychological, and social process that covers a time from the end of reproduction to death in which fertility decreases, and mortality increases (Beğer & Yavuzer, 2012). World Health Organization defines individuals over 65 as old and over 85 as very old (WHO, 2015). Especially in developed countries, the proportion of the elderly has increased significantly in recent years. The reasons for the increase in the elderly population include reduced newborn mortality rates, developments in the food production and health sector, new technologies in medicine and the prevention of infectious diseases with the production of drugs (Khaw, 1997). With the prolongation of life, physiological changes in the elderly adversely affect nutritional status (Gille, 2010). Psychological and social changes that result in loneliness and especially depression, alter the eating behavior of the elderly (Elsner, 2002). Malnutrition is a serious problem that is frequently encountered in the elderly and causes morbidity and mortality (Chen et al., 2001). Malnutrition in the elderly; is defined as improper or inadequate nutrition characterized by loss of appetite, muscle, and weight. If malnutrition is not interfered, it will worsen health status and quality of life in the elderly. The diagnosis of malnutrition in the clinic is often neglected and leads to the prolonged hospital stay. Eating is both a physiological need and social activity

(Van Buren & Sinton, 2009). Eating takes place in both the hedonic system and the hemostatic system by the control of appetite. Individual differences in these systems can create different types of eating. This can cause abnormal eating behaviors and eating disorders in individuals. In studies on eating disorders, adolescents and young women were preferred as the study group, while eating disorders in elderly individuals were neglected (Brandsma, 2007; Mangweth-Matzek et al., 2006). In this review; it is aimed to shed light on psychological and social factors as well as physiological factors affecting the nutrition of the elderly and reveal eating disorders in these individuals.

1. PHYSIOLOGICAL CHANGES IN AGING

There are some physiological changes in the human body with aging (St-Onge & Gallagher, 2010). Body composition, energy, and nutrient requirements vary. Also, the risk of dehydration is one of the most common problems due to decreased kidney function and reduced thirst (Schols et al., 2009). It is known that gastrointestinal functions and taste perception decline (Gille, 2010) and oral health is impaired with aging (Huppertz et al., 2017). All this can lead to changes in eating behavior in old age.

1.1. Body Composition

Body structure and nutritional requirements change with age (St-Onge & Gallagher, 2010). With aging, the percentage of body fat increases by about 50% and the basal metabolic rate decreases. However, energy expenditure due to physical activity also decreases. For this

reason, obesity can be observed particularly at an early age (65-75 years old), while the prevalence of malnutrition increases with older age (Elmadfa & Meyer, 2008). On the other hand, the most common change in the body structure of the elderly regardless of body weight is sarcopenia (Gille, 2010). Loss in muscle mass is accompanied by the replacement of the lost muscle with fat tissue. Inadequate energy intake, especially in individuals over 75 years of age, causes loss of muscle mass and malnutrition whereas in the elderly under 75 years of age, it can cause obesity (sarcopenic obesity) with loss of muscle mass. Depending on the age, vitamin and mineral requirements do not decrease equally, although the energy need decreases. Therefore; it is recommended to pay attention to the intake of micronutrients, whose absorption decreases, especially iron, vitamin D, vitamin B12 (Amarya et al., 2015). Decreased absorption of calcium and vitamin D in the body can lead to decreased bone mass and consequently osteoporosis (Turner, 2000).

1.2. Water Balance

Dehydration is one of the most common problems in old age; especially in individuals over the age of 65, it becomes hard to ensure adequate fluid intake (Wotton et al., 2008). With the reduction of lean body mass with old age, the amount of water, which is the most significant nutrient required for the functioning of organs, decreases in the body (Miller, 2015). In elderly individuals, decreased kidney function increases fluid loss. The reduction in the sensitivity of the osmoreceptor also impedes the feeling of thirst, causing dehydration

(Monirun & Begum, 2010). On the other hand, decreased cognitive functions in old age leads to forgetting of drinking. Also; prostate problems, urinary incontinence, and dysphagia reduce water consumption.

1.3. Perception of Taste and Smell

Decreased sensory function with aging significantly reduces the desire to eat in the elderly population. While it is thought that the loss of taste may be caused by the decrease of the number of taste buds per papillae on the tongue, deterioration in the sense of smell may be associated with changes in the olfactory epithelium, receptors and nerve pathways (Corcoran et al., 2019). The primary causes of smell dysfunction are sensorineural (e.g. chronic nasal/sinus disease, head trauma, respiratory infections) and neurodegenerative (Corcoran et al., 2019). Taste and smell disorders (irritation, touch, temperature, pain) make it difficult to enjoy healthy foods as well as to enjoy eating and food-related behaviors (Duffy, 2020). Decreased taste ability has been shown to increase the risk of malnutrition 2.5 times (Corcoran et al., 2019; Schiffman & Graham, 2000). Especially in Alzheimer's patients, some medications, including some Parkinson treatments and antidepressants, have also been shown to adversely affect taste (Corcoran et al., 2019; Murphy, 2008). Oral sensation can also be affected in poorly controlled systemic diseases such as chronic kidney disease, in usage of medicines that treat and manage systemic diseases in patients with poor oral care. Also; increased taste threshold in the elderly may lead to excessive salty and sugary foods and may

pose a risk particularly for hypertension, hyperglycemia, kidney diseases, and cardiovascular diseases (Sergi et al., 2017). The decrease in taste and smell significantly increases the risk of malnutrition, as the individual's appetite, interest in food, and lower diet quality (Corcoran et al., 2019; Schiffman & Graham, 2000). One study found that 74% of older people experienced taste impairment, while another study found that more than 60% of individuals aged 65-80 years and more than 80% of people over 80 years of age has decreased sense of taste and smell (Corcoran et al., 2019).

1.4. Gastrointestinal Function

Several changes throughout the digestive system can affect food intake as individuals age. It is important in terms of nutrition, as elderly individuals experience 85% more malnutrition while having digestive problems (Corcoran et al., 2019). Gastric acid and pepsin secretion gradually decrease with age, which may restrict the metabolism of certain foods such as vitamin B12, iron, and protein (Corcoran et al., 2019; Gille, 2010). Decreased production of gastric acid causes ulcers, malnutrition, and nutrient deficiencies (Gille, 2010). Studies have shown that reduced pepsin secretion is normal during the aging process. However, a decrease in gastric acid secretion has been associated with an increased prevalence of Helicobacter pylori infection and atrophic gastritis in the elderly population. There is also a decrease in saliva production, there are some studies showing that approximately one-third of people over 65 years of age have reduced saliva production. This reduces peristalsis and increases the

likelihood of constipation (Corcoran et al., 2019; Gille, 2010). In addition, dysphagia due to neurological diseases and dementia, insufficient fluid and fiber intake, and constipation are observed due to physical inactivity (Wellman & Kamp, 2017). Slowed peristalsis may also delay esophageal emptying, causing early saturation. Early saturation leads to reduced food intake in the elderly population (Corcoran et al., 2019; Gille, 2010). This is due to changes in susceptibility to gastrointestinal distension, which is associated with age-related receptive relaxation disorder of the gastric fundus and leads to faster gastric filling of the stomach (Corcoran et al., 2019). Besides, it may be affected by an increase in satiety hormones, CCK and PP, which slow the stomach's antral emptying rate and prolong satiety. Furthermore, the elderly have high insulin levels which can increase leptin, a hormone associated with satiety, while inhibiting ghrelin, the only known hormone to stimulate hunger.

1.5. Oral Health

Oral health has great importance in the prevention of nutritional problems (Huppertz et al., 2017). Poor oral health can be a modifiable determinant of malnutrition in old age (Kiesswetter et al., 2019). Dental caries, gum disease, inability to provide or use the dental prosthesis makes food consumption difficult (Huppertz et al., 2017). Oral health deterioration is one of the determining factors of malnutrition and increases the risk of malnutrition by causing restrictions on food choices in the elderly (Azzolino et al., 2019). Tooth loss, dry mouth, which can be caused by the use of prostheses

and multiple medications, causes difficulty in chewing and swallowing in elderly individuals. Therefore, nutritional deficiencies can be seen in the elderly and they can prefer soft and easily chewed foods (Wellman & Kamp, 2017). Studies have shown that deterioration of oral health negatively affects dietary intake (Kiesswetter et al., 2019). Since many oral health problems can be treated, oral health is very important for the treatment of malnutrition.

1.6. Chronic Diseases

One or more chronic diseases are encountered in elderly individuals (Brownie, 2006). Chronic diseases such as stroke, hypertension, diabetes, dementia, depression, cancers, arthritis, osteoporosis affect the nutrition of the elderly adversely.

Hypertension is present in about 67% of individuals aged 60 and over (Ward & Thomas, 2020). Elderly patients with stroke who have swallowing problems were found to have a worse nutritional status than those who have only the problem of swallowing (Rashid et al., 2020). Starting antihypertensive drug therapy in elderly individuals adversely affects their nutrition (Pinto & Ferri, 2019).

Studies have shown that diabetes and old age are two factors associated with an increased risk of malnutrition. Poor dietary intake or malabsorption, may be responsible for the deficiency of protein, energy and other nutrients in diabetes patients. Diabetes-related malnutrition affects various organs and systems, and changes in digestive, immune and muscle function. Consequently, malnourished

diabetic patients are more likely to have infectious or non infectious complications (Saintrain et al., 2019).

Various cancer treatments have been developed, including chemotherapy, radiotherapy, surgery, biology, and stem cell transplantation, which can be used in combination. Malignancy and its treatments have many undesirable side effects, including nausea and vomiting, oral and gastrointestinal mucositis, taste and smell changes, constipation, epigastric pain, abdominal pain, and xerostomia. Moreover, it might increase the risk of developing anorexia, early satiety, malabsorption, weight loss, anemia, and fatigue, causing various physical, psychological, or social problems. These symptoms adversely affect appetite, nutritional status, and food pleasure; thus greatly reducing the quality of life of cancer patients (Galaniha et al., 2020). Malnutrition is common in elderly cancer patients, and its prevalence varies between 25-85% (D'Almeida et al., 2020). It decreases food intake by disrupting cancer patients' distinction and perception of flavors and odors.

In elderly patients with dementia, malnutrition, involuntary weight loss, and dehydration may occur at any stage of the disease. Malnutrition in dementia can be caused by various factors such as anorexia caused by polyphagia, insufficient oral intake, depression, or hyperactivity due to patients' forgetting to eat (Cummings, 2019).

In older individuals, vitamin D and calcium levels are insufficient. Besides, it increases the risk of developing osteoporosis due to destruction of the bones during the aging process. In studies

conducted, 29% of malnourished elderly have osteoporosis, while it is only 11% in nourished elderly. Increased bone fractures are associated with osteoporosis. Such fractures may worsen with delayed healing and recovery time that come with malnutrition. Therefore, it is significant to prevent the development of osteoporosis with the help of dietary modification and supplementation (Corcoran et al., 2019).

1.7. Malnutrition

Malnutrition remains one of the most critical health problems for older people worldwide (Dent et al., 2019). Various studies have shown that nutrient intake is insufficient in elderly individuals. Especially in elderly and/or dependent individuals, a decrease in energy and protein intake is observed with aging (Sulmont-Rossé, 2019). Undernutrition is seen depending on the diseases that occur in old age. Elderly individuals with dementia also reduce food intake, as their ability to eat and drink is affected (Jones, 2019). In cancer patients, changes in taste and smell perception, dysphagia, and decreased appetite cause malnutrition (Galaniha et al., 2020). Undernutrition is common in hospitalized elderly (Kiesswetter et al., 2019). The prevalence of malnutrition and nutritional risk is high in the elderly who are hospitalized due to illness. The prolonged hospitalization period makes nutritional conditions worse (D'Almeida et al., 2020). Even when the aging process occurs normally, malnutrition is observed due to many factors such as deterioration in food intake and appetite regulation, poor oral health, swallowing difficulties and poverty (Dent et al., 2019; Sulmont-Rossé, 2019). The use of inappropriate drugs can

cause adverse effects such as taste disorders, dry mouth, constipation, nausea and reduced food intake. Studies have shown polypharmacy is the main risk factor for in malnutrition in the elderly (Bulut et al, 2019).

1.8. Drug Usage

Drug consumption is increasing considerably in the treatment of acute and chronic diseases. In patients who use one or more drugs daily, adverse effects such as xerostomia, hyposalivation, mucositis, and taste disorders may frequently occur in the oral region (Rademacher et al., 2020; Schiffman, 2018). Multiple drug use is quite common in older individuals. It can cause food-drug and drug-drug interactions, as well as negatively affect nutritional status (Gallo et al., 2019). Medicines affect the absorption, metabolism, and excretion of nutrients. The use of drugs such as angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, lipid-lowering drugs, antibiotics, non-steroidal anti-inflammatory drugs, steroids, and psychotropic agents cause taste and smell disorders. Besides, it negatively affects food intake and causes weight loss in older individuals (Schiffman, 2018). Various approaches such as consumption of zinc salts and vitamin supplements have been used to treat or improve taste and smell disorders.

2. PSYCHOLOGICAL AND SOCIAL CHANGES

2.1. Depression

One of the most common mood disorders in elderly individuals is depression, and its diagnosis and treatment are ignored in the elderly (Thomas & O'Brien, 2009). The frequency of depression is higher in unmarried women, elderly individuals with cognitive impairment, and physical disabilities. Depression has been shown to cause dementia in older individuals (Abdel-Rahman, 2012). According to World Health Organization, individuals with depression suffer from ongoing sadness, lack of interest in rewarding or entertaining activities and inability in enjoying these activities (WHO, 2017). These individuals may experience sleep and appetite disorders, fatigue, loss of concentration. Besides biological, social, and psychological factors; problems such as difficulties, losses, and unemployment can trigger depression. The prevalence of depression is high in individuals with eating disorders (Godart et al., 2015). Along with depression, appetite and weight loss can be seen.

2.2. Cognitive Features

Aging; causes an increase in cognitive loss and a decrease in quality of life (Gill & Alibhai, 2003). Inadequate intake of some vitamins, especially B6, B12, and folate, and metabolic disorders reduce cognitive capacity. In these cases, nutritional processes in the nervous system are adversely affected, the ability to learn and generate new memories decreases. The elderly with decreased cognitive capacity may experience symptoms such as not being able to prepare food and

forgetting to eat. These symptoms make progress and food intake difficult particularly in the elderly with Alzheimer's disease (Scarmeas et al., 2018; Leite et al., 2001).

Dementia affects the patient's eating behavior and causes malnutrition. Impaired nutritional status may increase the risk of mortality and morbidity and negatively affect the quality of life (Bender & Krznarić, 2020). Studies have shown that oral nutritional supplements containing long-chain omega-3 fatty acids, B vitamins, vitamin C, vitamin E, nucleotide uridilate, choline, and selenium contribute to the normal function of neuronal membranes and synapses in patients with mild cognitive impairment (Cummings et al., 2019). In another study, it was observed that the prevalence of malnutrition increased in elderly individuals with mild cognitive impairment and early Alzheimer's disease (Kimura et al., 2012). Timely recognition and adequate nutritional support can prevent or alleviate the consequences of malnutrition and reduce morbidity and mortality in older populations (Bender & Krznarić, 2020). Studies show that about 45% of Parkinson's disease patients are at risk of malnutrition. In Parkinson’s disease patients at risk of malnutrition or in malnutrition, symptoms such as dysphagia and constipation are observed more frequently compared to Parkinson's disease patients with normal nutrition.

2.3. Social Factors

Social factors such as the presence of other individuals, dependence on other people and the desire to please them are important issues

affecting food choice and consumption (Rusu et al., 2020). In order to avoid social criticism, individuals tend to behave differently when they are in public environments and feel the need to control their personal image. In the presence of other people, people usually eat more. It has been observed that older individuals have a diet that includes more diverse and healthier foods when they eat in public settings (Kimura et al., 2012). It is stated that these individuals feel the support of their families more and thus the depressive symptoms decrease, and both their nutritional and psychological state improves. On the other hand; as nutrients can reflect the attitudes and relationships between social groups, older individuals may feel embarrassed and feel psychological pressure while eating in the community due to the lack of physical skills such as pouring and dropping (Elsner, 2002). The inability to shop and prepare food alone, and thus not eating causes inadequate food intake. Moreover, family influence, economic concerns, education, occupation, and cultural norms affect the eating habits of the elderly; these factors can lead to nutritional and health problems (Bulut et al., 2019; Amarya et al., 2015).

3. EATING DISORDERS IN THE ELDERLY

Eating disorders are serious psychiatric disorders that are often overlooked in the elderly as they are generally seen in adolescents and young adults (Bulut et al., 2019). These disorders are characterized by eating or eating-related behaviors that cause physical and psychosocial deterioration of health, resulting in inadequate or excessive food

consumption (APA, 2013). According to Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 diagnostic criteria; different eating disorders are classified, mainly Anorexia Nervosa (AN), Bulimia Nervosa (BN), and Binge Eating Disorder (BED) (APA, 2013). Irregular eating and eating disorders are seen in both women and men of all ages (Mangweth-Matzek et al., 2017). Current research shows that eating disorders also occur in women and men over the age of 40. Epidemiological studies show that the general prevalence of eating disorders according to the DSM-5 criteria is 3-4% among women, 1-2% among middle-aged and older men. Eating disorders such as anorexia nervosa are the most common among young women, but eating disorders should not be ignored in older women (Gibson et al., 2018). Eating disorders are disorders caused by abnormal eating behaviors that can cause serious illness or even death when untreated (Berkman et al., 2007). It is important to control eating disorders in order to reduce diseases and deaths in old age (Lapid et al., 2010). The diagnosis of eating disorders such as AN and BN can be ignored since changes in the appearance of individuals also occur due to old age (Mangweth-Matzek et al., 2014).

3.1. Causes of Eating Disorders

Several genetic and environmental factors are effective in the genesis of eating disorders (Salafia et al., 2015). These factors are; genetic traits, personality traits, relationships between child and parent, and media influence. Factors such as the effect of genes and imbalances in the release of neurotransmitters such as serotonin are shown among

biological factors (Yilmaz et al., 2015). Conflicts that are not subconsciously resolved between individuals and their parents and situations where families are either indifferent to or overly concerned with their children are another causes of eating disorders (Brandsma, 2007). In this case; children may not be aware of their physical and emotional needs. It is known that personality traits can also affect eating disorders. Perfectionist personality trait in which eating is mainly associated with body appearance and weight is especially an important factor in the genesis of AN and BN (Polivy & Herman, 2002). Media influence also plays an important role in the formation of eating disorders. It has been observed that the ideal body perception has been internalized in the communities by the influence of the media, thereby leading to dissatisfaction and eating disorders (Uchôa et al., 2019). Older womens can experience more body dissatisfaction than men as in young womens (Quittkat et al., 2019). As women age, they experience physical and biological changes and move away from the perception of cultural beauty (Bellard et al., 2020; Brandsma, 2007). Therefore; although people mature with age, the risk of eating disorders still continues. Menopause, physical changes due to aging, and losses such as divorce and separation from children are the main causes of eating disorders in the elderly (Bellard et al., 2020).

3.2. Body Perception in the Elderly

There are changes in body perception with aging (Mangweth-Matzek et al., 2014; Peat et al., 2008). Communities are culturally pushing individuals to look younger and more beautiful, even if they age. In

women, the fear of aging and the desire to look younger and slimmer are dominant. These individuals compare themselves with their past appearances at young ages. Also, postmenopausal women gain weight, and metabolism slows down. Therefore, they may experience body dissatisfaction (Peat et al., 2008). Otherwise; cognitive control increases with age (Webster & Tiggemann, 2003). Expectations of older individuals decrease, and appearance becomes acceptable, and consequently, the importance of appearance decreases in elderly individuals. Therefore, the age factor cannot be evaluated as an positive or negative factor in body perception (Bouzas et al., 2019). Concerns about body image are often neglected in older individuals. However, they can constitute an essential feature of pathological eating behaviors in this population. Research has shown that thinness and body dissatisfaction can continue in the elderly and are closely related to fear of aging (Bulut et al., 2019).

3.3. Anorexia Nervosa (AN)

Anorexia Nervosa is an eating disorder characterized by extreme weakness, excessive dieting and behavior related to weight loss and fear of gaining weight (APA, 2013). AN criteria are the restriction of calorie intake causing low body weight, fear of gaining weight and behavior that will prevent weight gain, and the formation of a discrepancy between current body weight and perceived physical appearance. AN severity is classified according to the Body Mass Index (BMI) percentiles. In addition, restrictive and over-eating types are evaluated, which reveal the method or cause of weight loss

(Schebendach & Roth, 2017). Apart from amenorrhea, its clinical symptoms are similar to other individuals in the elderly (Lapid et al., 2010). AN is considered as a disease of adolescents. However, older patients may also be affected by AN due to chronic and recurrent disease course (Bulut et al., 2019). The reasons for the formation of anorexia in the elderly include factors such as insufficient food intake, impaired hemostatic regulation, increased taste, and odor thresholds, and slowing of gastric emptying (Landi et al., 2016). Changing hemostatic regulation and decreased gastric motility with the effect of neurotransmitters and hormones that control appetite, increases the feeling of satiety. In addition to these; While depression and loneliness cause loss of appetite, socioeconomic inequalities also decrease food intake in the elderly. AN, in the elderly; can cause morbidity, mortality, sarcopenia, protein-energy malnutrition (Wysokiński et al., 2015). In addition, since psychiatric comorbidities such as depression are observed, timely diagnosis, and planning of appropriate treatment are important (Zayed & Garry, 2017).

3.4. Bulimia Nervosa (BN)

It is defined as the display of compensatory behaviors such as repeated uncontrolled binge eating attacks and vomiting to prevent weight gain (APA, 2013). Individuals with BN experience overeating events at least once a week for three months according to DSM-V criteria. In addition, excessive self-assessment is seen with compensatory behaviors such as vomiting, laxative use, diuretics, excessive exercise, and fasting. BN is classified according to the

frequency of compensatory behaviors (Schebendach & Roth, 2017). The occurrence of BN formation in older ages is seen less frequently than other eating disorders (Elran-Barak et al., 2015). Most of them are early-onset. Situations in which elderly people are not supported and neglected by their families and body dissatisfaction can trigger eating disorders. These individuals may turn to the act of vomiting with the desire to attract the attention of their families, control the change in their bodies, and improve their self-esteem (Podfigurna-Stopa et al., 2015).

3.5. Binge Eating Disorder (BED)

Binge eating disorder is an eating disorder characterized by eating large amounts of food and eating repetitions in a very short time compared to most people (APA, 2013). After eating, negative feelings such as depression, shame, and feeling guilty are experienced rather than compensatory behavior. Individuals cannot control how much or what food they eat during binge eating episodes. These attacks occur at least once a week for three months. Individuals with BED are accompanied by obesity and mood disorders, particularly psychiatric disorders (Guerdjikova et al., 2012). Anxiety, depression, low self-confidence, and personality traits can be influential in the formation of this eating disorder. These factors continue to appear as long as the eating disorder continues, and as a result, individuals are concerned about their body weight and appearance. Its frequency increases with advancing ages mostly before menopause, then decreases (Marcus et al., 2007). It is significant to keep it under control as obesity resulting

from BED may cause disorders such as dyslipidemia, insulin resistance, and hypertension (Podfigurna-Stopa et al., 2015). Like other eating disorders, BED has a higher risk of mortality and worse prognosis in older individuals than in young people (Bulut et al., 2019).

CONCLUSION

Depending on aging, physiological, psychological, and social changes occur in human body. These factors affect the eating behavior of the elderly and show their significant effect on nutritional status. Decreased muscle mass in the body, loss of taste and smell, impaired oral health, problems in fluid balance, and decreased gastrointestinal function are the main physiological changes. These changes cause loss of appetite and insufficient fluid and nutrient consumption. In addition; depression and associated unhealthy nutritional status and eating disorders can occur in elderly individuals who experience significant cognitive losses, become lonely, and cannot get enough support from their relatives. Psychological factors underlie the occurence of eating disorders. Changes in body perception that occur with age, loneliness and depression can trigger eating disorders. Eating disorders; causes weakness, malnutrition, obesity, and related diseases. Eating disorders in the elderly are often overlooked and associated with morbidity and/or mortality. Since nutritional problems are related to multiple factors, a multidisciplinary approach is significant at this point. Therefore; with early diagnosis, appropriate treatment should be designed with a team of healthcare professionals

such as doctors, nurses, dieticians, physiotherapists, and psychologists.

In this review; the factors affecting the nutrition of the elderly have been tried to be enlighted and eating disorders in these individuals have been revealed. However, studies in the literature in this field are limited. It is useful to conduct studies, where long-term evaluations are done, and various factors are investigated in more detail. In future studies, nutritional problems, including malnutrition, and the underlying psychological factors should not be ignored during appropriate treatment.

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CHAPTER 4

LABIAL ADHESIONS IN PREPUBERTAL CHILDREN

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INTRODUCTION

Labial adhesion (labial fusion/labial synechia/ labial agglutination) is a gynecological pathology characterized by fusion of labia minora completely or partially at midline. The line of adherence is between clitoris and posterior fourchette (Figure 1). The lesion generally starts from posterior vestibule and proceeds anteriorly to the urethra.

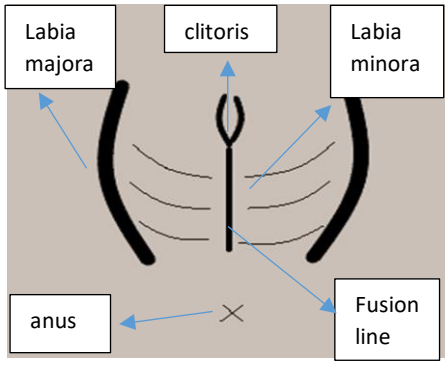

Figure 1: Schematic representation of labial adhesion

It is diagnosed by gentle retraction and inspection of the labia and appears as a thin greyish line in the middle, referred to as the raphe. Labial adhesion can be complete or partial. If the adhesion is complete, urethral meatus, hymen and vaginal opening cannot be identified. In these patients, absence of vagina and an imperforate hymen must be excluded by close examination of the raphe. Partial adhesions can occur just below the clitoris, in the middle or just above posterior fourchette, however, mostly occur posteriorly. The most common presentation of adhesion is that involving more than 75% of the total length.

1. EPIDEMIOLOGY

Labial adhesion is most commonly seen in children at 0-2 years of age (1.8%), especially before toilet training period. Its incidence is higher at 13-23 months of age (3.3%). Since most of the children are asymptomatic, it is generally unnoticed and is assumed that the incidence is much higher. In a study on pre-pubertal girls, the incidence of labial adhesion (including minimal fusions of 2 mm) is reported as 38.9%.

2. ETIOLOGY

The etiology is predicted to be the decreased level of estrogen in serum at pre-pubertal age. Its absence in newborns, who have high levels of estrogen supply from mothers, supports this thesis. Besides this, chronic irritation and infection also may cause micro-traumas on the skin and trigger formation of fibrinous exudate during the healing process, which lead to synechias at midline. Vulvovaginitis, diarrhea, diaper dermatitis, inadequate hygiene, masturbation, straddle injury, female circumcision and sexual abuse may be the provoking factors for synechia formation. Lichen sclerosis also leads to treatment-resistant labial adhesions. Candidal vulvovaginitis due to uncontrolled diabetes or recent antibiotic use can increase risk of adhesions in children. Steven Johnson syndrome; Graft-versus-host disease and Behçet's Disease also reported to be rare causes of labial adhesions.

3. CLINICAL MANIFESTATIONS

Labial adhesion is usually asymptomatic, but especially in cases with near-complete fusion; pooling of urine, difficulty in urination, post-void urinary dribbling, pollakuria, dysuria, bacteriuria, hematuria, vaginal pain or discharge, vaginitis, urinary tract infections (UTI) and even hydronephrosis can be seen. Acute renal failure due to labial adhesion is also reported in postmenopausal woman that also support the thesis that low estrogen level is a predisposing factor. Urinary tract infections occur 3-5% of girls in the normal population, however, may be seen up to 40% among those with labial adhesions.

4. TREATMENT

Treatment of labial fusion is controversial. Even though there are studies which conclude that treatment is not necessary, many studies suggest that treatment should be given to prevent complications like urinary tract infections, vulvovaginitis and hydronephrosis. Asymptomatic patients with minimal adhesion (less than 50% of the total length) only require observation. In symptomatic patients or patients with more than 50% adhesions, medical (topical) treatment is recommended as a first choice, however, there is not a precise duration of treatment for any form of topical treatment modalities. The most common method used as topical treatment is applying topical estrogen-containing (estradiol 0.01%) creams twice a day, for 2 weeks. Most common side effects of topical estrogen use are irritation, erythema, breast enlargement and tenderness, pigmentation of vulva and minimal vaginal bleeding due to stimulation of endometrium.

These side effects are rarely seen and regress after cessation of treatment. The side effects may be minimized with optimum time and amount of application to avoid unnecessary systemic absorption of estrogen. In some studies, the treatment is continued for 4-12 weeks, but the risk of side effects like vulvar hyperpigmentation and gynecomastia may increase then. Studies show that the efficacy of topical estrogen cream is 50-100%. Success rates are higher in patients with a thin, translucent raphe. The estrogen containing cream must be applied with fingertips or Q-tip with soft local pressure or gentle traction for a successful resolution.

There are some studies on the efficacy of topical steroids (betamethasone 0.05%) in the treatment of labial fusion as an alternative to topical estrogen. It can also be used as an adjunctive therapy. The basis of this treatment modality was the success in nonsurgical method of managing phimosis in young boys with steroids Patients with recurrent adhesions, refractory to local estrogen therapy, were treated with topical betamethasone and success rate was 68% after twice daily application for 4-6 weeks. Some studies suggest that there is less recurrence with steroids when compared to local estrogen treatment. Side effects of local steroid treatment include erythema, pruritus, folliculitis, skin atrophy and fine hair growth.

If the adhesions do not resolve with topical treatment in symptomatic patients, or in adhesions with severe symptoms like urinary retention and hydronephrosis; surgical or manual separation can be a solution. Manual separation is performed by gentle retraction of the labia

laterally under local anesthesia. Lidocaine ointment or prilocain lidocaine combination can be used in local anesthesia. Forceful separation may result in more local damage and inflammation and lead to fibrosis and increased rate of recurrence. In selected cases, sedation or general anesthesia is required. The decision is based on the density of the adhesion and child's ability to tolerate the procedure. Surgical incision and suture over-sewing is rarely required, only in very thick adhesions that does not respond to any medical treatment and manual separation. Topical estrogen creams are suggested after the procedure. Although the duration and frequency of postoperative therapy has not been specifically studied, once or twice daily applications for 2-4 weeks is mostly recommended.

5. PROGNOSIS

Recurrence rates generally differ between 11 and 14% either with topical or surgical treatment. In some studies, it is reported as higher, 41-55%. Bland emollients like petrolatum oil is advised twice a day for at least 1 month to prevent recurrences after adhesion is resolved. Parents should be informed about the possibility of recurrences during the course of treatment. Risk of recurrence decrease with increasing age. Adhesions tend to recur until puberty in some patients and may resolve spontaneously with the development of puberty.

6. PREVENTION

Hygiene of this region is important in prevention of infections and agglutination of the labia. Stool contamination must be avoided by regular changing of the diaper. Local factors like harsh cleaning that

will cause local irritation during cleaning of this region must also be avoided. It is assumed that wet-wipes change the pH of the skin and can cause irritation leading to labial adhesion; however, there are not enough controlled studies that support this thesis. Some studies confirm that leaving the diaper decrease the incidence of labial fusion. Besides, vulvar area shouldn't be cleaned with soaps, shampoos or cleansers with inappropriate pH that can cause irritation in the dermis.

CONCLUSION

Since labial adhesion is usually asymptomatic, it is not usually recognized by parents. As genital examinations may be a taboo for some families, it is usually underdiagnosed in children. Besides, it may also be forgotten or missed out during physical examination. Routine vulvar examination should be performed in all of the infants; especially in infants and children with urinary tract infections. Parents should be informed about the importance of perineal care and the possibility of recurrences.

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CHAPTER 5

THE ROLE OF LIFESTYLE AND NUTRITION IN INFERTILITY

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INTRODUCTION

Fifty years ago, women often struggled not to get pregnant, however, today the problem is just the opposite (Saldeen-Saldeen 2004: 722). In recent years, the prevalence of infertiliy is rising considerably. Infertility is defined as the absence of pregnancy after regular unprotected intercourse for 12 months or more (WHO, 2020).

INFERTILITY TYPES

There are two types of infertility: primary and secondary (National Family Planning Service Guide Family Planning and Reproductive Health, 2005).

1.Primary Infertility

Despite having unprotected intercourse of couples 2-3 times a week for at least 1 year, no pregnancy occurs.

2. Secondary Infertility

Although, the couples have a history of pregnancy that resulted in live birth; pregnancy does not occur after unprotected intercourse for 12 months.

Infertility Prevalence

Infertility has been drawing attention especially for the last 20 years. The prevalence of infertility varies by region and country. The World Health Organization (WHO) estimates that there are 60-80 million infertile couples worldwide (Cengiz et al. 2015: 247). Infertility affects approximately 8-10% of married couples in developed

countries and 15-20% of married couples in developing countries (Kırca-Pasinlioğlu 2013: 165). According to the study on primary and secondary infertility prevalence between 1990-2010 in 190 countries and regions; among women aged 20-44 who became pregnant, 1.9% could not give live birth (primary infertility) and 10.5% of women who got pregnant and has made at least one live birth could not have another child (secondary infertility) (Mascarenhas et al. 2010: 3). Turkey is one of the countries with high infertility rates (Rutstein-Shah 2004: 34); the prevalence of infertility varies between 3.2 and 20.0% (Gokler 2014: 160). According to Nutrition and Health Survey in 2013, at the end of the reproductive age, primary infertility rate for women has been shown to be 4 percent in Turkey (Turkey Demographic and Health Survey, 2013).

Causes Of Infertility

There are several reasons for female and male infertility. These are;

1. Factors causing infertility in women (45-50%)
2. Factors causing infertility in men (30-40%)
3. Idiopathic infertility (22-28%)

1. Factors Causing Infertility in Women

In 45-50% of couples infertility occurs as female origin (Yumru-Öndeş, 2011: 58).

- Ovulatory disorders
- Tubal and peritoneal factors

- Problems such as uterine, cervical, and uncommon pathologies cause infertility in women.

2. Factors Causing Infertility in Men

In 30-40% of couples, infertility occurs as male origin (Yumru-Öndeş, 2011: 57).

- Sexual factors
- Urinary system infections
- Congenital anomalies
- Varicocele
- Hormonal disorders
- Immunological factors
- Problems such as idiopathic semen disorders lead to infertility in men.

While the most common cause of male infertility is producing less or damaged semen, the most common cause of female infertility is ovulation disorders (AWHONN 2014: 264).

3. Idiopathic Infertility

Although there has been a regular unprotected intercourse for a year, they are cases where pregnancy has not occurred and no identifiable problem has been diagnosed during their examination (Algül 2013: 12). Infertility occurs in 22-28% of couples for unexplained reasons.

Factors Affecting Infertility

Age, smoking, alcohol consumption, stress, systemic diseases such as diabetes, hypertension, obesity, celiac; and lifestyle changes such as physical activity and nutrition can be counted as the factors causing infertility.

Age factor

Today, the age of childbearing has increased, since women think of getting married and having children after taken a job and starting their career. The average maternal age at the time of first birth has approached the age of 30. Many women give birth to their first child, 35 or older. In the natural fertile population, the median age at the last birth for women is 40-41 (Eijkemans et al. 2014: 1305; Borght- Wyns 2018: 1; Baldwin 2019: 1). Increasing ovulation disorders with advancing age have decreased the frequency of ovulation and the disruption of the luteal phase that leads to decreased chance of conception. Several studies have shown that delaying fertility also increases the risk of infertility (Borght-Wyns 2018: 9).

Diabetes mellitus

In a study, aspermia and azoospermia were observed in male individuals with high risk of diabetes (Glazer et al. 2017: 1474). In another reported study, the poor blood glucose control (HbA1c $\geq$ 7%) was significantly associated with reduced the motility of abnormal semens (Omu 2013: 34).

Obesity

Obesity is a problem affecting more than 600 million adults worldwide (Broughton-Moley, 2017: 1). It affects adversely fertility in both genders, and if both married couples are obese, the risk of infertility increases (Yılmaz-Yardımcı 2015: 4; Bosdou et al. 2019: 1). Increasing body mass index (BMI) can cause the infertility because of reducing the parameters such as semen quality, motility and testosterone level in male individuals (Yılmaz-Yardımcı, 2015: 3). According to results of the study carried out by the National Institute of Environmental Health Sciences (NIEHS); a 3-point increase in BMI can increase the men´s infertility by 10% (Omu 2013: 33). Obesity of male individuals is associated with increased prevalence of azoospermia or oligozoospermia and high sperm DNA damage (Piché et al. 2018: 19). Furthermore, progressive sperm motility was found to be significantly higher in overweight male individuals than in the obese group (Baydilli et al. 2020: 103). In obese women, fertility is lower than in women with normal weight (Pantasri-Norman 2013: 90). The level of hormones such as estrogen and progesterone may decrease in women with increased BMI while parameters such as leptin, insulin and luteinizing hormone lead to anovulation (Yılmaz-Yardımcı 2015: 4). Weight loss of obese women with polycystic ovarian syndrome (PCOS) can positively impact on the fertility. Also, there was a relationship between smoking, hypercaloric diet, plastic product use and ovulation dysfunction (Kalem et al. 2017: 745; Zhang et al. 2020: 5). Obesity affects the female reproduction by disrupting hormone metabolism and follicular environment (Pantasri-Norman

2013: 90). The effect of obesity on the risk of subfertility has also been proven by scientific researches (Bosdou et al. 2019: 2). Physical activity, diet modification and weight loss especially after bariatric surgery may have a positive effect on fertility as it can increase fertilized oocyte count, pregnancy and live birth rates (Broughton-Moley 2017: 6; Bosdou et al. 2019: 7). Although the effect of obesity on women´s infertility is well defined, the principles of treatment have not been clarified yet (Broughton-Moley 2017: 840). On the other hand, the obesity causes infertility in men through the azoospermia.

Hypertension

When the effects of hypertension on semen parameters and drugs used in the treatment of hypertension were examined, it was observed that hypertension caused erection problems directly or as a side effect of the drugs (Omu, 2013). The volume, concentration, motility and the total number of semen, and the total number of motile semen have decreased by administration of antihypertensive drugs; especially beta-blockers (Guo et al., 2017). Consequently, the fertility is negatively affected due to the decreased semen count.

Celiac disease

Womens with positive symptoms of celiac disease, the risk of general and idiopathic infertility are three times higher than in healthy women (Kutteh et al., 2019; Castaño et al., 2019; Schiepatti et al., 2019). Women with celiac disease can reduce the risks of abortion and infertility by following a gluten-free diet by eliminating wheat, and rye from their diets (Kutteh et al., 2019). The main mechanism of

celiac disease reduced the fertility is unknown. The evaluation of micronutrient status is important in the treatment of infertility, since it is under influence of nutritional elements associated with celiac disease such as selenium, zinc, iron and folate deficiencies (Pieczyńska, 2018). The balanced and adequate nutrition of adolescent girls can prevent the effect of the celiac disease on reproductive health (Pogačar & Micetic-Turk, 2020).

β-thalassemia

Thalassemia is a common genetic disorder that involves the formation of abnormal hemoglobin. It is caused by defects in polypeptide chains which are produced incorrectly due to mutation in a patient with thalassemia. There are two main types of thalassemia; alpha and beta. In the patient with thalassemia, the body can not be oxygenated enough due to hemoglobin deficiency (Helmi et al., 2017). The iron overload has the toxic effect on the infertility for the reproductive organs, especially in women with beta thalassemia. Its mechanisms are based on disturbances in the secretions of luteinizing hormone and follicle stimulating hormone (Shiadeh et al, 2020).

Lifestyle And Infertility

Lifestyle habits such as stress, caffeine intake, physical activity levels, and sleep quality can impact on female and/or male fertility (Piché et al., 2018).

Stress

Mens received infertility treatment were found to have more severe depression and anxiety than the fertile mens. These depressive disorders can lead to decreased testosterone levels, reduced semen volumes and causing infertility (Wdowiak et al., 2017). A study conducted on women nurses, the duration to conceive in nurses working more than 40 hours in a week is prolonged (Gaskins et al., 2015). As a result, stress delays fertility in female individuals and decreases fertility in male individuals.

Smoking

Since smokers are exposed to heavy metals, polycyclic hydrocarbons, nitrosamines and aromatic amines during smoking, every stage of the reproduction is adversely affected, such as folliculogenesis, embryo transport, uterine blood flow (Borght & Wyns, 2018; Dechanet et al., 2010). The effect of cigarette smoking depends on the dose, and it is associated with other toxic substances and hormonal status. The individual sensitivity, dose, time and type of exposure may also play roles in human fertility (Dechanet et al., 2010). The smoking of mens impairs the production, motility, morphology of sperms and an increase damage of sperm DNA (Borght & Wyns, 2018). In consequence, the smoking adversely affects the reproductive health in both genders.

Alcohol

Chronic alcohol consumption in women causes an increase in estrogen levels, decreased secretion of follicle stimulating hormone and impaired ovulation (Borght & Wyns, 2018). In men, the deterioration of spermatogenesis leads to a decrease in sperm count and testosterone levels. However, the mechanisms of these effects have not been studied in detail (Sharpe, 2010; Panth et al., 2018). Studies reported on alcohol and infertility showed that the moderate alcohol consumption did not have a significant effect on sperm count.

Caffeine

Investigations found that there were no relationship between semen parameters and caffeine intake from coffee, tea and cocoa drinks (Lyngsø et al., 2017; Ricci et al., 2017; Soylu et al., 2018). On the other hand, it has been demonstrated that cola containing caffeine and other additives, and non-alcoholic beverages containing caffeine have a negative effect on the volume, number and concentration of semen (Ricci et al., 2017).

Physical activity level

The calorie restriction and excessive physical activity in women may lead to decrease in the frequency of ovulation, poor endometrial development and amenorrhea (Borght & Wyns, 2018), while an increase in the intensity of physical activity has a negative effect on semen parameters (Hayden et al., 2018). Consequently, excessive physical activity affects fertility negatively in both genders.

Nutrition And Infertility

According to a reported study, the healthy diet is a factor that increases the chance of getting pregnant (Jahangirifar et al., 2019). Intake of more monounsaturated fat, vegetable protein, high fiber with lower glycemic index carbohydrates, lower trans fat are also associated with the fertility in both genders (Chavarro et al., 2007). Therefore, couples with infertility may increase their chances of getting pregnant with nutritional interventions before starting infertility treatment.

Excessive salt consumption

Excess salt consumption causes hypertension, cardiovascular diseases and chronic kidney diseases (Wang et al., 2015; Lee & Cho, 2016). In a study conducted with rats, it was found that high salt intake negatively affects the reproductive functions of the rats by inhibiting follicle development (Wang et al., 2015). According to the results of the study on zebrafish, it has been revealed that excessive salt intake increases hyperlipidemia, inflammation, spermatogenic defects and infertility, while low salt intake can improve infertility by increasing spermatogenesis (Lee & Cho, 2016).

Milk and milk products

Due to the high galactose content of dairy products, it was observed as a result of an *in vivo* study that they reduced ovulation in rats and caused early ovarian failure (Gaskins & Chavarro, 2018). While a high intake of low-fat dairy and dairy products have a protective effect

on oligozoospermia, an excessive intake of high-fat dairy and dairy products have been associated with an increased risk of oligozoospermia (Chavarro et al., 2007; Dizavi et al., 2018). Brucella causes infection in the testicles. Any inflammation of the epididymis (sperm is stored, and where the membrane as mature sperm motility boiler) to reduce the sperm count, or sperm motility reduction leads to impaired function (Sayar, 2019). It can be performed with combined antibiotic therapy for the treatment of brucella, but infertility can be seen in these patients (Sayar, 2019; Akinci, 2006). In a study conducted in Turkey, epididymoorchitis was detected in 17 of 134 male patients with brucellosis. Combined antibiotic therapy was given to these patients for 6-8 weeks. After antibiotic treatment, recurrence occurred in one patient, permanent oligospermia in three patients and permanent aspermia in one patient (Akinci, 2006). More studies are needed to explain the relationship between brucella and human infertility (Sayar, 2019; Akinci, 2006).

Red meat

As well as being a good source of protein, red meats contain high amounts of saturated fat, which may cause a decrease in semen concentration (Panth et al., 2018). High consumption of red meat increases the risk of infertility and is negatively affected the embryonic development (Gaskins & Chavarro, 2018).

Fish

Seafood is considered a good source of omega-3 fatty acids. Besides, it is the main source of mercury exposure (Gaskins & Chavarro, 2018;

Mínguez-Alarcó et al., 2018). A reported study found that women with unexplained infertility had higher blood mercury concentrations than their fertile counterparts. Additionally, a higher seafood consumption has been associated with high blood mercury concentrations in this population (Gaskins & Chavarro, 2018).

Egg

The egg, which constitutes an important part of the daily diet in terms of nutritional value, can have positive effects on reproduction. However, poultry eating pesticide-containing feed may lead to infertility following the pesticides remain in eggs (Hamid et al., 2017). In a study on rats, it was revealed that the consumption of quail eggs may increase the fertility in mens due to the increase in sperm concentration and sperm motility (Okoye et al., 2017).

Nuts

Nuts are rich in monounsaturated fatty acids, vitamin E, polyphenols, other macro and micronutrients. According to the study, 60 g/day mixed nuts (walnuts, almonds, hazelnuts) were added to the Western diet consisting of a high amount of sugary drinks, potatoes, fast food, refined grains, oils and salt for 14 weeks (Salas-Huetos et al., 2018). It has been observed that it positively affects on total sperm count, sperm motility and morphology.

Probiotics

In a study on probiotics, a probiotic mixture with antioxidant and anti-inflammatory activities was given to zebra fish for 21 days and as a

result, it affected the sperm quality positively (Valcarce et al., 2019). In another study, it was found that kefir, a probiotic food, has positive effects on lead toxicity in rats (El- Kewawy, 2018). Therefore, consumption of kefir can be used to prevent reproductive damage caused by lead.

Honey

Consumption of natural bee honey has been shown positive effects on sperm count, motility and morphology (Wally, 2018). Also, the luteinizing hormone responsible for sperm production increased the level of follicle-stimulating hormone and testosterone hormones. Contrary to this study, the consumption of natural bee honey negatively affects the semen parameters in rats (Abdullahi et al., 2019). Bee pollen is rich in flavonoids with anti-inflammatory and antioxidant effects (Hesami et al., 2018). An individual with idiopathic infertility has been observed to improve semen quality and testosterone levels as a result of bee pollen supplementation.

Mediterranean diet

The Mediterranean diet is characterized by high intake of fruits, vegetables, legumes, poultry products, whole grains, low intake of red meat and saturated fatty acids (Karayiannis et al., 2017; Salas-Huetos et al., 2019) which have the anti-inflammatory and antioxidant properties. Total sperm count and motility were higher in individuals who complied with the Mediterranean diet (Karayiannis et al., 2017). This situation may be associated with fish consumption rich in omega-

3 fatty acids and increased intake of fruits and vegetables rich in antioxidants such as beta-carotene, vitamins E, C in this type of diet.

Vitamins

Various studies have revealed that adequate intake of antioxidant vitamins such as carotene, vitamin C, E, D, B12 and folic acid can positively affect male and female fertility (Salas-Huetos et al., 2019).

Antioxidant vitamins

Antioxidants are compounds that are produced by the body or taken with nutrients, protect the body against high reactive oxygen species (ROS) and prevent cell damage (Gupta et al., 2017). There are two types of antioxidants: enzymatic and non-enzymatic. Enzymatic or endogenous antioxidants; represents the main antioxidant system and includes superoxide dismutase (SOD), catalase and glutathione peroxidase. Non-enzymatic antioxidants, also known as exogenous antioxidants, are natural compounds that can be found in diets rich in vegetables and fruits; includes trace elements such as selenium and zinc consist of microelements such as β- carotene, vitamin C, vitamin E, L-carnitine. Oxidants and antioxidants are in balance in the human body. The increase in reactive oxygen types causes oxidative stress (OS), which is defined as an imbalance between oxidant and antioxidants. This can affect male and female reproductive systems, causing infertility. In various studies, oral antioxidant supplements are used in the treatment of OS-induced infertile male individuals. This treatment positively affected the semen parameters of some male individuals. More research is needed to identify the benefits, optimal

doses and possible risks of treatment with antioxidants (Henkel et al., 2019; Sekhon et al., 2010).

Carotenoid has been associated with high sperm motility in young men. Since it is an antioxidant, it is protective against ROS formation that can adversely affect sperm motility. (Karayiannis et al., 2017). Tomato juice contains lycopene, a component of the carotenoid family, which increases sperm motility. Reported study found that regular consumption of tomato juice increases sperm motility in infertile patients (Yamamoto et al., 2017). In another study, the application of lycopene supplements to infertile individuals revealed that a decrease in lipid peroxidation and DNA damage after decreasing oxidative stress were observed (Durairajanayagam et al., 2014).

Vitamin C is a water-soluble and reactive oxygen species (ROS) scavenger. It is present in seminal plasma at concentrations 10 times higher than serum. By decreased ROS production, sperm cells were protected from DNA damage, and so the concentration and mobility of semen can significantly increase (Agarwal & Sekhon, 2010; Ilić et al., 2018; Rafiee et al., 2016). The effect of vitamin C on sperm quality depends on the dose. In studies, a dose of 1000 µg/l of vitamin C positively affects the motility of spermatozoa, while higher dosages can decrease sperm motility (Agarwal & Sekhon, 2010; Mendiola et al., 2010). There is a positive relationship between male individuals intake of vitamin C and β-carotene and fertilization (Li et al., 2019).

Therefore, it seems to be a positive relationship between semen quality and vitamin C intake.

Vitamin E, which has antioxidant properties, dissolves in lipids; it cleans free radicals formed during the normal activity of oxidative enzymes and increases the activity of various antioxidants (Agarwal & Sekhon, 2010). Studies have reported that vitamin E is effective in the treatment of infertile men with high ROS levels (Agarwal & Sekhon, 2010; Alta et al., 2018). Consequently, vitamin E positively affects reproduction in both sexes.

Vitamin D

The reported studies found that men with severe vitamin D deficiency had a lower rate of motile spermatozoa and there was a significant increase in sperm production as a result of vitamin D treatment (Bosdou et al., 2019; Jensen et al., 2018). Adequate intake of vitamin D improves the motility and morphology of sperm. However, high-dose vitamin D supplements did not alter semen quality in infertile men. Also, in men with vitamin D deficiency vitamin D and calcium supplements had no effect on semen quality or live birth rate. (Jensen et al., 2018). Women with vitamin D below 25 (OH) D> 20 ng / mL were also found to have lower ovulation. More studies are needed to clarify duration and dosage of vitamin D supplementation (Bosdou et al., 2019). After all, getting enough vitamin D may increase the fertility in both male and female.

B vitamins

Increasing homocysteine levels in deficiency of B vitamins may lead to miscarriages in the early period (Avşar et al., 2013). According to the study, serum homocysteine levels of women with unexplained infertility were found higher than fertile women (Liu et al., 2019).

It is thought that the effect of B12 deficiency on infertility is related to folic acid deficiency or high homocysteine level (Avşar et al., 2013). Low B12 level has been reported to cause primary infertility and recurrent fetal loss (Ibeh et al., 2019). In studies reported *in vivo* or *in vitro*, plasma vitamin B12 concentrations were found to be lower in infertile men than in fertile men. Vitamin B12 has been shown to increase sperm count, sperm motility, and semen quality by decreasing sperm DNA damage (Banihani, 2017). The positive effects of vitamin B12 on semen quality may be due to its decrease in homocysteine toxicity, increasing the amount of nitric oxide produced and reducing the accumulation of ROS (Banihani, 2017).

Folate helps DNA replication by purine biosynthesis (Schisterman et al., 2019). It can also affect spermatogenesis through DNA methylation and regulation of DNA function. However, folate and zinc are interdependent for proper use. Zinc adequacy is extremely important for folate bioavailability. The study showed that women with idiopathic infertility use more folic acid supplements and their folate levels are higher than other women (Murto et al., 2014). In women with idiopathic infertility, folic acid use or high folate levels in infertility treatments did not have a positive effect on pregnancy

outcome. In these women, high folic acid intake or high folate levels after infertility treatment did not increase the likelihood of a healthy baby. In the study, it has been observed that folic acid supplementation significantly improves sperm quality in subfertile men (Mendiola et al., 2010). According to the results of another study, patients with oligospermia and asthenopermia who received a dose of 400 μg folic acid supplements twice daily for three months, were observed to have significant increase in their sperm density (Xie et al., 2019). As a result, giving folate and zinc supplements to men undergoing infertility treatment improved semen quality.

Vitamin-like substances

Substances such as carnitine and coenzyme Q10 also have positive effects on male fertility.

Carnitine

Carnitine, an exogenous antioxidant, protects the DNA and membranes of semen cells from ROS-induced damage. Carnitine oral supplementation has a positive effect on semen motility and semen concentration (Agarwal & Sekhon, 2010). Spermatozoa supports the spermatogenic process using energy produced by carnitine and acetylcarnitine in semen metabolism. Carnitine protects semen and cell membrane against ROS-induced DNA fragmentation and apoptosis. Regular intake of carnitine and acetylcarnitine has been shown to improve semen quality and function. In addition, low carnitine levels have been suggested as one of the contributing factors to semen disorders such as azoospermia and asthenospermia. Vitamin

E and C protect sperm from DNA damage, while carnitines energize sperms (Adewoyin et al., 2017).

Coenzyme Q10 (CoQ10)

CoQ10 is one of the most important antioxidants in seminal plasma. Endogenous CoQ10 is significantly related to sperm count and motility and it protects sperm DNA against oxidative damage. However, there is no evidence that CoQ10 increases live birth or pregnancy rates (Balercia et al., 2009). According to the study, male patients with infertility were given orally 200 mg of CoQ10 for 30 days and no difference in sperm motility was observed (Chayachinda et al., 2020).

Minerals

Adequate supply of minerals such as iodine, zinc, selenium, copper, iron has positive effects on fertility. Both excess and deficiency of minerals affect reproduction in genders (Xie et al., 2019; Adewoyin et al., 2017).

Zinc

It is an important mineral for male reproductive stages. In men, the synthesis of sex hormones is essential for sperm production and motility (Grieger et al., 2019). Zinc acts as more than 80 cofactors in spermatogenesis (Schisterman et al., 2019). In various studies, it was found that zinc values in seminal plasma of infertile men are significantly lower than in fertile men (Zhao et al., 2016). As a result, it was observed that when infertile men were given zinc

supplementation, semen volume and sperm motility increased. Zinc is an important mineral, since its deficiency may be associated with negative pregnancy outcomes in women (Grieger et al., 2019). More studies are needed on how circulating zinc in female individuals helps conception at the level of oocytes and early embryos.

Selenium

Selenium is an important trace element for maintaining human body homeostasis (Qazi et al., 2018). Since selenium is an antioxidant mineral, it affects fertility positively by alleviating oxidative stress in male and female infertility. Selenium also supports the growth and maturation of oocytes. Studies have shown that low selenium levels are associated with pregnancy complications (Qazi et al., 2018). However, its relationship with oocyte development and fertilization has not been studied to a great extent (Grieger et al., 2019). Although the reported studies are insufficient, selenium supplementation was shown to increase semen motility, but there was no positive effect on semen quality (Mendiola et al., 2010; Qazi et al., 2018; Mintziori et al., 2020). Selenium supplementation is important for male infertility as it eventually increases semen motility.

Copper

In animal studies, copper deficiency has been shown to reduce fertilization rate and oocyte healing rate (Grieger et al., 2019). On the other hand, it has been reported that women with low plasma copper concentrations are protected against any risk of pregnancy complications compared to women with high plasma copper. This

suggests that copper has an important role for placentation. Studies have shown that women with abortion and infertility have lower serum copper levels compared to pregnant women (Chyra-Jach et al., 2020). The role of copper in male infertility is still not fully understood. On the other hand, excessive intake of copper may be toxic because it produces reactive oxygen species.

Iron

It is an essential mineral for proper sperm development and function. Although it is not proven, even minimal decrease in iron levels may be significant for male reproductive health (Gabrielsen et al., 2019). The increase in copper and iron may have an important role in the pathogenicity of women with unexplained infertility (Hussien et al., 2017). Serum iron levels were found to be higher in women who had a miscarriage compared to pregnant women (Skalnay et al., 2019). After all, the lack or excess of iron negatively affects reproductive health.

Iodine

Thyroid dysfunction plays an important role in infertility in women and men. Thyroid dysfunction can cause menstrual disorders, abortion and spermatogenetic abnormalities. Rats with hypothyroidism have been shown to have impaired reproductive functions (Trokoudes et al., 2006). In a reported study, spermatogenesis was negatively affected in men with hypothyroidism. Also, sperm morphology was found to be different than in healthy men (Fakhar-I-Adil et al., 2020). Most women with hyperthyroidism have anovulation. This was not the primary cause of infertility in women, but was associated with

menstrual disorders. Therapy for thyroid disfunction may be helpful in women with anovulation or unexplained infertility (Onwubuariri et al., 2020).

Heavy Metals

Cadmium (Cd)

Cadmium is a heavy metal with toxic effects on reproductive functions (Li et al., 2016). A high amount of Cd was found in the semen of infertility patients. This is a factor that leads to low sperm quality (Zhang et al, 2019). According to the study, it was found that semen volume, motility and sperm morphology decreased in Chinese men exposed to high Cd (Li et al, 2016).

Lead

Lead negatively affects the reproductive system of both women and men (Assi et al., 2016; Gandhi et al., 2017). Lead causes abnormal spermatogenesis, chromosomal damage, changes in serum testosterone levels and infertility in men. It leads to pregnancy hypertension, abortion, infertility, preterm labor and preeclampsia in women.

Fiber

Fruits, vegetables, dried legumes and whole grains consumed in the daily diet are sources of pulp. These foods positively affect fertility in both genders thanks to the pulp and nutrients they contain (Lee & Cho, 2016; Salas-Huetos et al., 2017; Martenies & Perry, 2013). However, exposure to pesticides in fruits and vegetables leads to a

decrease in the number of semen, leading to impaired spermatogenesis and reduced semen mobility. Studies have found that in men who consume fruits and vegetables with high pesticide total sperm content are 49% lower than those who consume low pesticide content (Martenies & Perry, 2013). The harmful effects of fruits and vegetables with high pesticide content should not be overlooked (Hayden et al, 2018).

Unsaturated Fatty Acids

Omega-3 supplementation causes increased semen production and increased motility in the seminal fluid of male individuals. The previous studies have shown that the ideal ratio of omega-6/omega-3 is 1. However, since the amount of omega-6 increased in Western diets, this ratio increased from 25: 1 to 40: 1 (Safarinejad, 2012). In other studies, it was suggested that the omega-6 / omega-3 ratio should be 2. In some Western countries, the omega-6 / omega-3 ratio has been reported to be 15-20 / 1 (Matorras et al., 2020). The ratio of omega-6 / omega-3 in the cell membrane is very important in maintaining normal sperm integrity and function (Safarinejad, 2012). The excessive intake of trans fats and saturated fats causes infertility in men by leading to low semen quality and in women, by disrupting ovulation (Çekici, 2019). In addition, omega-3 supplements may increase fertility in women and men (Saldeen & Saldeen, 2004; Collodel et al., 2020). Men with sperm abnormalities have decreased level of docosahexaenoic acid (DHA), increased oleic acid level and increased omega-6/omega-3 ratio in the sperm membrane. Decreased

docosahexaenoic acid content in the sperm membrane is associated with poor sperm quality (Nasrallah et al., 2020). It has been reported that there are about near thirty saturated (SFA), monounsaturated (MUFA) and polyunsaturated fatty acids (PUFA) related to sperm parameters in human seminal fluid (Collodel et al., 2020). Compared to normozoospermic individuals, in patients with altered sperm parameters; high palmitic, stearic, oleic, linoleic, arachidonic and DHA levels were detected in spermatozoa. Higher levels of omega-6 PUFA (linoleic acid and arachidonic acid) and lower omega-3 PUFA (α-linoleic acid, eicosapentaenoic acid and docosahexaenoic acid) were detected in spermatozoa and blood plasma of infertile men. Besides, fertile men were found to have a lower omega-6 / omega-3 ratio compared to infertile ones. Consequently, omega-3 supplements may increase fertility in women and men.

CONCLUSİON

Infertility can occur due to some reasons in both genders, and its prevalence is increasing day by day. Diabetes, obesity, hypertension, celiac disease, poor eating habits, exposure to heavy metals and pesticides can cause the infertility. Additionally, changeable lifestyle habits such as stress, smoking, chronic alcohol consumption, caffeinated drinks containing various additives and excessive physical activity can lead to infertility in men and women. Adequate dietary intake of vitamins, minerals and polyunsaturated fatty acids positively affects fertility in both genders. As a result of the studies carried out, it is understood that carnitine and coenzyme Q10, which are vitamin-

like substances, support reproductive health, especially in male individuals. Furthermore; adding nuts, probiotics, prebiotics, bee products, especially honey and pollen to the diet may increase fertility. In consequence; adequate and balanced nutrition which comprises the intake of fruit, vegetables, legumes and whole grains containing pulp, consumption of white meat and eggs instead of red meat with high saturated fat content, and compliance with a Mediterranean diet rich in omega-3 fatty acids can positively affect fertility. However; it is clear that the studies on infertility have been inadequate, although infertility rates have increased in recent years. More researches are needed especially to comprehensively identify the appropriate doses of nutritional supplements such as vitamins and minerals to be taken daily and the possible risks in case of overdose.

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CHAPTER 6

SOCIAL COGNITION AND LANGUAGE

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INTRODUCTION

1. Social Cognition and Language

Language is a systematic coding that develops in an individual with social development starting from birth and continuing for a long time. In this context, language, which plays a role in interaction with people, contains many social cognitive processes. These processes include creativity, continuity, and the transformation of collective representations into intrinsic representations. At the same time, these social cognitive processes are also effective in the use of language (Holtgraves & Kashima, 2008). Therefore, social cognition and language can be considered as intertwined processes.

Although the language is effective in social cognition processes, it is a kind of cerebral cortical function. Language has been the subject of research since ancient times, as it is one of the most important tools in social communication and interaction with people, and in the studies conducted 150 years ago, leading information about the neural infrastructure of the language was obtained.

As a result of the autopsy studies carried out 150 years ago by Broca and Wernicke, important data were obtained for explaining the language network in the brain. These studies also led to research on brain functions. Today, most neurologists classify patients with language disorders as the motor (Broca) or sensory (Wernicke) or a combination of the two (Rutten, 2017).

2. Cortical Localization Studies in the Language Field

Paul Broca (1824–1880) can be the first scientist to present the scientific information about the cortex. In 1861, Broca claimed that damage to the left hemisphere of the brain affected the ability to speak. In modern neuropsychology and neurology, this discovery of Broca is regarded as the beginning of studies on the localization of functions in the brain. The most famous case of Broca in his works that enabled the definition of the area called Broca today is Leborgne, also known as Mr. Tan. Louis Victor Leborgne (Mr. Tan) spent 21 years of his life in the hospital. He spent the last periods of his life being treated under Broca's control. The reason he became known as Mr. Tan was that the only word he could say was ‘tan’. It was observed that Leborgne understood what was spoken but could not respond (Hale, 2007, p. 98).

Broca, who performed the autopsy on Leborgne who died in 1861, determined that there was a lesion in the left part of the brain (Figure 1). The brain of Leborgne is now displayed in the Paris Musee Dupuytren museum (Dronkers, Plaisant, Iba-Zizen, & Cabanis, 2007).

Figure 1. Brain photograph of Leborgne (Dronkers et al., 2007)

In 1876, Carl Wernicke described a new aphasia type characterized by interpretation, different from speech (Barker, 1905). Wernicke, in his studies, aimed to explain the expression of language, the storage of images, the formation of semantic memory, and the connections between mental processes and neural structures. He focused particularly on mental images, memory, and the representation and recalling of words (Edwards, 2005, p. 9).

Realizing that some patients with aphasia did not understand what was said but understood its grammatical and emotional content, Wernicke discovered that this was due to the lesions in the posterior and superior temporal lobes. These patients could speak, but they could not organize and control the content of the words (Purves et al., 2004, p. 639). Patients with this type of aphasia, which is completely different from the type of aphasia described by Broca, appear to speak fluently but cannot make sense of the words. Wernicke states that there are two important characteristics in sensory aphasia. The first is the loss of perception of the vocabulary and as a result it is not possible to

make a sense of the word. In these patients, loss of interpretation occurs without hearing loss. Secondly, it is seen that incorrect or misplaced words are used frequently during speech (Edwards, 2005, pp. 9-11).

As a result of his studies, Wernicke discovered the sensory speech center and formed the basis of localizationism, where different regions in the brain were thought to be associated with each individual mental function. At the same time, Wernicke stated that mental functions were complex by showing that speaking was associated with different regions in the brain (Rutten, 2017, p. 23). In the monograph he published in 1874, he explained that multiple regions in the cortex were connected together through fiber pathways and that traces in cognition, thinking and consciousness were formed through these connections

In his study, the *Symptom Complex of Aphasia* (*Der aphasische Symptomenkomplex*, 1874), Wernicke adapted Meynert's thoughts on speaking and language functions. In this study, which included reports of 10 aphasic patients, four types of aphasia were included according to Wernicke's model. Of these, three patients had motor aphasia, two had sensory aphasia, four had conduction aphasia, and one had global aphasia.

In his studies, Wernicke stated that patients with advanced sensory aphasia, who spoke fluently but had a complex and unintelligible speech, especially those with no physical symptoms due to stroke or brain damage, exhibited the clinical picture of confusional conditions,

and therefore, their conditions may be misdiagnosed by considering that they have dementia or psychiatric disorder (confusion or delusion). Susanna Adam, Wernicke's first patient in the field of sensory aphasia, can be shown as an example.

In his book *Symptom Complex of Aphasia* Wernicke gave the following information about Susanna Adam:

“Susanna Adam, 59 years old, came on March 1, 1874, with complicated speech complaints with symptoms of vertigo and headache. Although she correctly expressed her headache and dizziness complaints, she added the meaningless word "begraben" (buried) to every speech. Adam, who did not have any physical disorder, was first diagnosed with dementia and taken to the psychiatry department” (Wernicke, 1874, p. 39).

After these symptoms were observed in some cases similar to that of Adam, it was determined by the evaluation of the symptoms that there was no dementia condition but a neurological disorder and that these patients had a type of aphasia later called sensory aphasia (Bogousslavsky, Boller, & Iwata, 2019, p. 6).

A second case contributing to Wernicke's studies in this area was Susanna Rother, 75 years old. Rother's speech suddenly deteriorated on November 2, 1873. Although there was not adequate clinical information about Rother, it was known that the patient had been suffering from weakness in her left leg for 10 years. The patient, who gave completely complex answers to the questions asked, died on December 1. Following Rother's death, Wernicke's examination of her

brain formed the basis of his theories. In his autopsy studies, Wernicke observed that there was a lesion in the left temporal fold of Rother's brain. He claimed that the lesion in this area, today called the Wernicke's area, might have been the cause of aphasia. However, the case could not be re-examined because the brain was not kept as it was in Broca's patients (Rutten, 2017, p. 41).

Figure.2 The area where the lesion was seen in the autopsy of Susanna Rother (Binder, 2017).

In addition, Luria, who has made significant contributions in the field of aphasia with his studies, has defined phonemic (sensory) aphasia as the loss of ability to distinguish the characteristic features of sounds. In addition, patients' difficulty in understanding words, naming objects, repeating or writing words in temporal lobe lesions were evaluated as secondary disorders due to the disorder in phonemic hearing (Cole, Levitin, & Luria, 1979/2010, p. 133). In his studies, Luria revealed the connections of lesions in different regions of the left hemisphere of the brain with impaired phonemic hearing and obtained findings supporting the Wernicke's explanations about the

Wernicke area, Luria's research revealed that lesions in different areas of the left hemisphere of the brain were linked to impaired phonemic hearing. He obtained findings supporting Wernicke's explanations for the Wernicke's area, which he said was responsible for sensory aphasia (Figure 3).

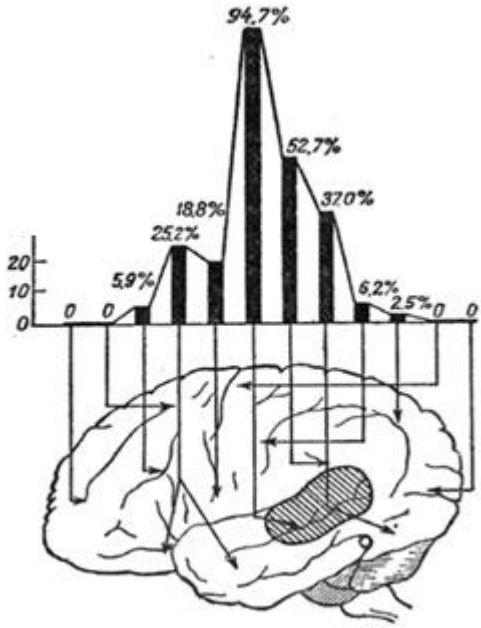

Figure 3. Luria's percentage indicators of areas in the left hemisphere that are linked to impaired phonemic hearing (Rutten, 2017, p. 195).

2.1. Wernicke's area

The interpretation of a heard voice is different than its perception. Auditory memory is needed to recognize a word. It is suggested that this task in the brain is performed by the area located in the middle and posterior part of the superior temporal gyrus, designated as the

Brodmann's area 22 (Figure 4). This area is called Wernicke's area. Wernicke defines this area as the area in which auditory word images are stored. Damages in this area are characterized by difficulty and distortions in the perception of auditory language, and at the same time, speech disruption is observed (Reinvang, 1985, p. 27).

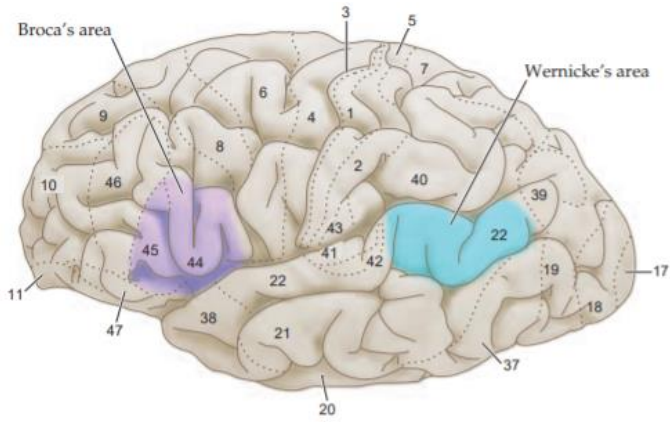

Figure 4. Major regions of the brain and Wernicke's area (Purves et al., 2004, p.638).

The Wernicke's area receives input from the hearing cortex and determines the meanings of the words through its cortical connections. The Wernicke's area is also connected with the visual cortex areas in both hemispheres. This function ensures the understanding of the written language. In addition, messages perceived in the Wernicke's area are transmitted to the Broca's area via the arcuate fasciculus (association band between the Broca's area and Wernicke's area, which connects the two). The arcuate fasciculus is also responsible for repetition-related functions (Figure 5). Therefore, a disorder that will occur in the Wernicke's area also negatively affects repetition (Dokur, 2013).

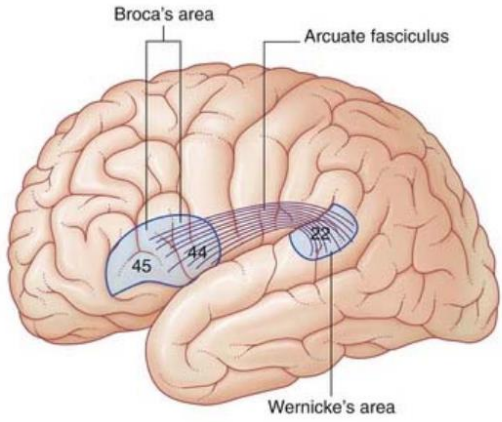

Figure 5. Wernicke's area, Broca's area, and arcuate fasciculus

2.2. Wernicke's Aphasia

Wernicke's aphasia is completely different from the type of aphasia described by Broca 10 years ago. In these patients, apart from Broca's aphasia, it is seen that the patient speaks fluently but cannot make sense of the words (Edwards, 2005, p. 9). These patients can speak, but they cannot organize and control the contents of the words (Purves et al., 2004, p. 639).

Wernicke's aphasia is characterized by fluent, paraphasic speech, in which auditory interpretation is reduced. Speech is produced involuntarily and has a mixed grammatical structure. It appears to be incomplete in content. In Wernicke's aphasia, repetition is also often impaired, depending on the level of auditory comprehension. The patient's spoken language is impaired, sometimes real words are used, but neologism (making up new words) is common. In addition,

semantic paraphrases (the use of a word with a similar meaning) are also common (Freitas, 2012).

Unlike Broca's aphasia, patients with Wernicke's aphasia usually do not notice the mistakes they make during the speech. Since patients have the appropriate melody and intonation, other people often think that they speak a foreign language (Hillis, 2007). A person with another language does not notice any oddities when talking to a patient with Wernicke's aphasia, but a person using the same language can detect the patient's verbal paraphrases, newly made-up words, and grammatical errors (Dokur, 2013).

Problems in naming objects or actions may appear in different forms, severe deterioration may occur as well as clinical pictures where there is no problem (Reinvang, 1985, p. 27). In particular, fatigue, anxiety, or emotional discomfort can lead to an increase in naming problems (Kargın, 1993). Repetition is similar to spontaneous speech, i.e. the patient has a fluent speech, but it is not meaningful (Hillis, 2007).

Patients with Wernicke's aphasia have difficulty in understanding what they hear as well as understanding what they read. Unlike Broca's aphasia, the patient's writing is fluent, but reading and writing are often severely distorted, as is often the case with speech; the content of the writing is meaningless, and the writing consists of a series of letters that do not form a meaningful word. This is explained by the fact that visual symbols are associated with auditory word images stored in the Wernicke's area (Kirshner, Webb, & Duncan, 1981).

In Wernicke’s aphasia, depending on the level of auditory interpretation, an impairment seen mostly in repetition as well. Patient’s spoken language is impaired, sometimes it is noticeable that the patient is using real words, however, neologism is common. Furthermore, it is also common in semantic paraphasias (using wrong words in the context).

Carl Wernicke's theory, which was instrumental in the introduction of Wernicke's aphasia, is based on the psychic reflex arc and the sejunction hypothesis. Carl Wernicke has defined other types of aphasia in addition to Wernicke's aphasia in the framework of his theory.

3. Basis of Carl Wernicke's Theory

In his studies, Wernicke investigated the connections between central nervous system functions and psychological phenomena and formed his theory to develop a formulation that could explain psychic life (Eling, 1994, p. 67). Wernicke's theories of localization are well known in the fields of neurology, neurosurgery, and neuropsychology, but have low popularity in the field of psychiatry. However, Wernicke regarded neurology and psychiatry as an integral whole. Wernicke, who wanted to establish a new school of somatic thought in psychiatry, carried out his studies at the University of Breslau for this purpose (Lanczik & Keil, 1991). In Breslau and Hella, he contributed to the training of valuable students and assistants. Hugo Liepmann, Karl Bonhoeffer, Karl Heilbronner, Kurt Goldstein, Ludwig Mann, Heinrich Lissauer, Richard Cassirer, Otfrid Foerster, Max Kauffmann,

Berthold Pfeifer, Edmund Förster, Karl Kleist, Erwin Nissl von Mayendorf are some of his students (Tesak, 2005, p. 9).

While Wernicke's linguistic theory showed that the number of localized functions in the brain was limited, it also revealed the importance of neural connections of these centers with other areas in the cortex. Therefore, Wernicke can be considered neither a localizationist nor a holistic. Wernicke's revealing the connections between language and brain functions can be explained by the term 'connectionism' (Eling, 1994, p. 67).

In his theory, Wernicke described the process of cortical processing of the formation of conceptual information. Here, the term concept refers to the tools that are effective in the formation of consciousness. According to Wernicke (Gage & Hickok, 2005):

1. The concepts are spread over a large area in the form of images or traces of memory on the cerebral cortex.
2. Single memory traces are localized with cortical sensory and motor areas.
3. The anatomical basis of connections between cortical symbols that support conceptual information is provided by transcortical fiber pathways.
4. The processes that provide learning and concept formation are realized by synchronization of cell activations.

Wernicke's views on the neural basis of conceptual knowledge are included in his study dated 1874, the Symptom Complex of Aphasia.

In this work, Wernicke explained the functional neuroanatomy model of the language and described the various aphasia states that form the basis of this model (Wernicke, 1874). This monograph, which contains information about the sensory speech center, enabled Wernicke to gain a worldwide reputation. Wernicke describes the nature of conceptual symbols in the cortex as follows:

“The conceptual symbol of the word "bell" is shaped by the way visual, tactile and auditory perceptions are connected with each other. These memory images represent the characteristic features of the object, i.e. the bell” (Wernicke, 1874, p. 36).

He then continued his studies in this field with Theodor Meynert, the founder of the comparative anatomy of the nervous system (Lanczik & Keil, 1991). Meynert's view that projection and association systems are separate from each other is one of the cornerstones of Wernicke's theory about brain functions. According to Wernicke, the main perceptual and motor functions have local areas. In language, each word has an auditory and movement image; these motor and sensory effects are stored in certain areas. Wernicke suggests that these effects form the mind through interaction in projection areas on association pathways (Koehler & Lanska, 2014, p. 749).

Wernicke drew attention to two types of sensory aphasia and stated that aphasia was a clinical picture between the two extreme conditions. These two points are the areas where the motor and sensory structures are located in the brain (Figure 6).

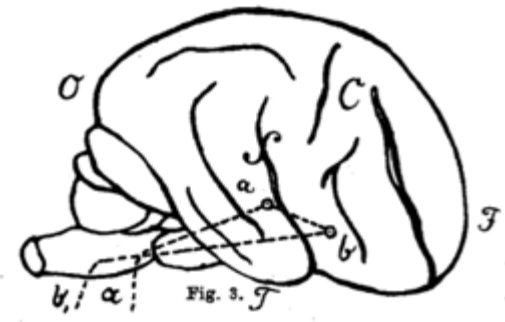

Figure 6. Areas related to the occurrence of aphasia, according to Wernicke: (a) auditory images are stored around the central connection point of the auditory nerve and the center located in the first temporal gyrus; (b) motor images associated with speech-sound production in the frontal region; (C) central sulcus; (F) frontal lobe; (O) occipital lobe; (T) the temporal lobe (Wernicke, 1874, p. 19).

Aphasia occurs if there is a deterioration in the pathway between (α - a) or (β - b). (a). The disappearance of the areas results in the loss of names (auditory images), but concepts continue to form and remain (visual and sensory images). The speech capacity is largely maintained. Here, the image of the spoken word disappears, so it is often observed that an unintelligible mixture of words, called word salad, is produced (Koehler & Lanska, 2014, p. 749). The patient perceives the words he/she hears as meaningless noise. In milder cases, because what is said cannot be made sense, it sounds like a foreign language, but as the patient is able to fully perceive single sounds, he/she can slowly achieve correct perception by achieving integrity. The severity of symptoms varies depending on the extent and severity of the pathological condition in the first temporal lobe (Eling, 1994, p. 77-78).

According to Wernicke's aphasia scheme (Figure 7), the conditions that cause sensory aphasia and motor aphasia are as follows (Kohler & Lanska, 2014, p. 749):

1. Damages to the auditory nerve center causing cortical sensory aphasia.

2. Damages to the central auditory nerve pathway causing subcortical sensory aphasia.

3. Damages that occur in the central auditory nerve pathway causing transcortical sensory aphasia.

4. Damages to the visual motor center related to speech-sound production in the frontal region, which causes cortical motor aphasia.

5. Damages to the motor speech nerve pathway that cause subcortical motor aphasia.

6. Damages that occur in the nerve pathway between transcortical motor aphasia, the center of concept, and the motor visual center related to speech-sound production.

7. Damages in the nerve pathway between the central auditory center causing the connection aphasia and the center of the motor images associated with speech-sound production.

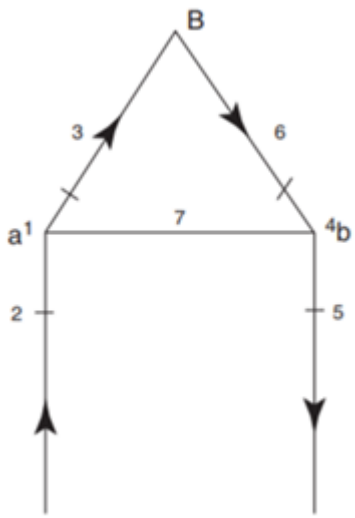

Figure 7. The scheme Wernicke defines for aphasia. a, the auditory nerve center point and its surroundings, this center contains the auditory images in the first temporal gyrus; b, motor images associated with speech-sound production in the frontal region; B, concept center (Kohler & Lanska, 2014, p. 749).

3.1. Psychic Reflex Arc and Sejunction Hypothesis

The psychic reflex arc, which forms the basis of Wernicke's theory, shows various disorders and states of consciousness, and the connections between these two (Wernicke, 1900, p. 10-17). According to Wernicke, the psychic reflex arc originates from the subcortical afferent pathway and extends to the sensory projection area, and then advances towards the center of thought (Figure 8). Complex links between preliminary thoughts and goals are recognized in the thought center. A connection is established between the targets and the motor projection areas. Thinking processes take place in the thinking center. processes take place in the thinking center. Wernicke

suggests that purposeful movements emerge from motor projection areas (verbal expression, reaction, and early movements) as a result of connections to the nervous system and are a function of consciousness and thus are part of the symptomatology of mental disorders (Franzek, 1990).

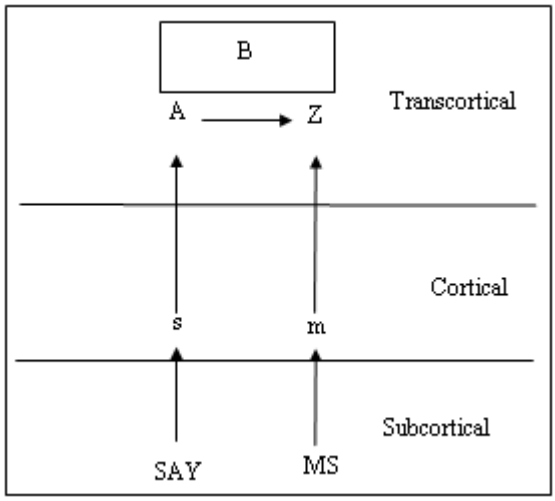

Figure 8. Psychic reflex arc according to Wernicke. B = center of thought; A= preliminary thoughts; Z= targets; m= motor projection areas; s= sensory projection areas; SAP= subcortical afferent pathway; MS = movements, symptomatology (Franzek, 1990).

4. Carl Wernicke's Scientific Background

Carl Wernicke was born on May 15, 1848, in a small town of Upper Silesia. Wernicke, who completed his high school education in Oppeln, began his medical education at the University of Breslau upon his mother's request. He then joined the French-Prussian War in 1870 as a military surgeon (Eling, 1994, p. 61).

In 1871, Wernicke started to work as an assistant in the psychiatry department next to Heinrich Neumann. Later, upon Neumann's request, Wernicke went to Vienna to study neuroanatomy under the supervision of neuroanatomist and psychiatrist Theodor Meynert. Wernicke worked at the Charite Hospital in Berlin from 1876 to 1878. In 1885, due to a special study on neurological diseases, he started to work in the department of psychiatry and neurology in Breslau. Five years later he became the head of the neurology department at the university hospital in Breslau (Koehler & Lanska, 2014, p. 748).

In the next two decades, this hospital in Breslau has become the center of studies in the field of neuropsychology. Concepts such as apraxia, agnosia, and asymbolia of distinguished scientists such as Liepmann, Goldstein, Kleist, and Foerster were developed here. In the early 1900s, upon the deterioration of Wernicke's relationship with the university, he accepted the position of chairmanship of the Clinic of Psychiatry and Neurology (Klinik für Psychiatrie und Neurologie) in Wernicke Halle. In 1905, Wernicke died as a result of an accident (Eling, 1994, p. 62).

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CHAPTER 7

THE EFFECT OF VITAMIN D ON BONE METABOLISM

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INTRODUCTION

Vitamins have important functions for metabolism. Many vitamins are involved in the structure of enzymes and proteins involved in the metabolism to regulate biological events. Vitamins are necessary for various biochemical functions and are either inadequately synthesized by the organism or are not synthesized at all, therefore they are taken by the diet (Akkoyun et al., 2014).

Vitamin D is a fat-soluble, secosteroid hormone, which plays a role in bone formation by increasing the absorption of calcium and phosphate through the intestines and stimulating osteoid maturation and mineralization. Vitamin D is the primary function of bone tissue in children and bone reconstruction in adults; to maintain the necessary concentration of calcium and phosphorus for mineralization (Akpınar and İçağasıoğlu, 2012). There are two sources of vitamin D; the first one is cholecalciferol (vitamin D_3) and the second one is ergocalciferol (vitamin D_2). Both are metabolized in the same way, so both are called vitamin D (Aydoğdu et al., 2015). In order to evaluate vitamin D levels, 25-hydroxyvitamin D (25-OH D) level should be examined (Uçar et al., 2012).

Adequate vitamin D intake and maintaining optimal vitamin D levels in the serum are not only important for the metabolism of bone, calcium and phosphorus, but also for general health and well-being. Vitamin D deficiency and deficiency as a global health problem is likely to be a risk for broad-spectrum acute and chronic diseases (Pludowski et al., 2012). The most common causes of vitamin D

deficiency include inadequate vitamin D intake, limited sunlight exposure, and inadequate synthesis of skin and kidneys (Uçar et al., 2012). Vitamin D deficiency which causes deficiency in osteoid mineralization is "rickets" in children, or "osteomalacia" in adults (May, 2015). In addition to the deterioration of bone formation, it causes proximal muscle weakness and disruption of neuromuscular coordination, thus increasing the risk of falls and fracture risk, causing pain and functional limitation negatively affect quality of life (Akpınar and İçağasıoğlu, 2012).

Structure, Functions And Metabolism Of Vitamin D

Vitamin D is a group of sterols with hormone-like functions. Fat-soluble vitamins are examined in the group. D vitamins are called calciferols. About ten different compounds are known which exhibit vitamin D effect. Among these, the most important biological and chemical aspects are cholecalciferol (vitamin D_3) and ergocalciferol (vitamin D_2) (Öngen et al., 2008). Because cholecalciferol and ergocalciferol are metabolized in a similar way, they are referred to by their common name as vitamin D (Hatun et al., 2003; Göçoğlu, 2010).

Colecalciferol (vit D_3) is made of 7- dehydrocholesterol on the skin under the influence of ultraviolet radiation at wavelength of 290-315 nm and this endogenous production is the main source of vitamin D (Glerup et al., 2000; Holick, 2005). Cholecalciferol is a natural vitamin D. Ergocalciferol (vitamin D_2) is caused by plant origin and exposure to ultraviolet rays of ergosterol most commonly found in yeasts and fungi. But there is not much in nature.

It is used mostly for strengthening of dairy products. Vitamin D_2 is separated from vitamin D_3 by having a double bond between carbon 22 (C22) and carbon 24 (C24) and containing methyl group in carbon 24 (C24). This leads to the fact that the biological activity of vitamin D_2 is 3-10 times less than D_3 (Armas et al., 2004; Bikle, 2007).

Vitamin D has different aspects than other vitamins. These will be summarized first; They can be synthesized in the body, subcutaneous 7-dehydrocholesterol is converted to vitamin D_3 under sun or UV light (Holick, 2005). It is converted into vitamin D_2 under the same conditions in ergosterol found in vegetable oils. Secondly; active shapes are not coenzyme. They usually act on the DNA to produce some proteins. Vitamin D_3 has no activity but active forms can occur. The active form is 1.25 dihydroxycalciferol. This form generally has hormone-like functions (Glerup et al., 2000).

The main function of vitamin D in metabolism is to regulate the balance of calcium and phosphorus of the organism together with parathormone by providing intestinal calcium and phosphorus absorption. Calcium requirement causes the secretion of parathormone in metabolism. For this reason, parathormone plays an important role in the regulation of vitamin D metabolism (Hatun et al., 2003). In the absence of vitamin D, calcium absorption is 10-15% and in the presence of vitamin D, this rate is up to 30-80% (Ataş et al., 2008).

Among the general functions of 1,25 dihydroxy vitamin D_3 (1,25 (OH) 2D), the active metabolite of vitamin D, is to maintain the

plasma calcium level. 1.25 dihydroxy vitamin D_3 increases Ca absorption from duodenum and P absorption from ileum.

It also prevents the loss of calcium in the kidneys and increases bone resorption. 1,25 dihydroxy vitamin D_3 also reduces parathormone synthesis and increases insulin production (Öngen et al., 2008).

Vitamin D_2 and vitamin D_3 are absorbed through the intestine, and vitamin D is circulated through binding proteins. The metabolism of the D_2 and D_3 vitamins is similar. Since they are dissolved in fat, they are located in the lipid components of many tissues such as skin, liver and intestine (Gürdöl & Ademoğlu, 2010). Vitamins D_2 or D_3 are not biologically active. All forms of vitamin D are transported in serum by binding to vitamin D binding protein (DBP); only 1-3% are found free (Özkan & Döneray,2011). Vitamin D transported to the liver with binding proteins is converted into 25-hydroxy vitamin D (25 (OH) D) by 25-hydroxylase enzyme (CYP27A1) in the liver (Öngen et al., 2008; Murray et al., 2004). 25-hydroxylase enzyme is the most important enzyme in vitamin D synthesis, 25-hydroxy vitamin D, the body's vitamin D vitamin provides the best information about the parameter (Holick, 2005; Özkan & Döneray, 2011; Wilkinson et al., 2000).

The 25-hydroxy vitamin D_3 is the most prevalent of the circulating vitamin D. At the same time, 25-hydroxy vitamin D_3 is the most stored form in liver, skeletal muscle and fat tissue. An important part of 25-hydroxy vitamin D is introduced into the enterohepatic circulation. A disruption in this circulation causes vitamin D

deficiency (Üstdal et al., 2003). 25-hydroxy vitamin D_3 is also bound to globulin, a vitamin D binding protein in the blood. The 25-hydroxy vitamin D_3 transported to the kidneys by its 1-α-hydroxylase enzyme (CYP27B1) constitutes the active metabolite 1,25 dihydroxy cholecalciferol by hydroxylation or the inactive metabolite 24 by its 24th carbon, 24,25-dihydroxy vitamin D_3. 1,25-dihydroxy cholecalciferol controls its synthesis by inhibiting 1-α-hydroxylase activity by stimulating 24-hydroxylase activity (Gürdöl & Ademoğlu, 2003; Üstdal et al., 2003). Recently, 1-alpha hydroxylase enzyme is found in the intestine, epidermis, macrophages, prostate, breast, pancreas and parathyroid glands outside the kidney. Therefore, it is emphasized that adequate levels of 25-OH-D levels in non-renal tissues are necessary for active vitamin D production (Mutlu & Hatun, 2011).

Vıtamin D Levels, Resources And Requirements

In order to evaluate the level of vitamin D in the person, 25 (OH) D levels, which have a half-life of 2-3 weeks and which show both vitamin D intake and endogenous construction, should be examined. The biological active form 1,25 $(OH)_2D$ is not suitable for ideal measurement. Because the half-life is as short as 4-6 hours and circulating levels are 25 (OH) D 1000 times lower.

Several studies have been conducted to identify vitamin D deficiency and deficiency and to determine the normal range of 25 (OH) D levels. In the light of these studies; If vitamin D deficiency is between 21 and 29 ng / mL, vitamin D deficiency is higher than 30 ng / mL, if

the 25 (OH) D levels are less than 20 ng / mL, the adequate range is 40-60 ng / mL and if it is higher than 150 ng / mL it is considered to be vitamin D intoxication (Holick 2005; Wacker 2013). The average of the measurements in March and September of the year should be determined and the vitamin D level should be determined in the individuals.

Whose should controlled the level of vitamin D?

- People with bone disease (osteomalacia, osteoporosis, paget, etc.),
- People with symptoms of musculoskeletal symptoms suggesting a lack of vitamin D,

• Those with risk factors for vitamin D deficiency and deficiency (dark-skinned people, those who do not sufficiently benefit from sunlight, the elderly, obese, frequent pregnant women with short intervals, breastfeeding women, malabsorption cases, anticonvulsant and glucocorticoid drug use etc (Fidan et al., 2014).

Vitamin D is not widely distributed in nature but is taken by three basic routes. Firstly; vitamin D is either taken directly from the food or enriched by adding vitamin D to the food. Second, substances containing vitamin D are enriched in vitamin D by exposure to ultraviolet light as a precursor molecule. Finally, vitamin D deficiency can be prevented by direct skin exposure to sunlight (Gözükara 2011).

Under normal conditions, 90-95% of vitamin D is synthesized by the effect of sunlight. No food source other than fatty fish, even if consumed above normal, vitamin D requirement can not meet. Cod

fish oil and salmon, sardine, mackerel are the best sources of greasy fish. Cooking 3-4 times a week of fatty fish can meet the needs of the adult individual. However, foods such as milk, egg yolk, butter, sweet potatoes, oats, broccoli, parsley, moss and mushrooms contain high amounts of vitamin D. However, vitamin D requirements cannot be met with the normal consumption of these foods (Ataş et al., 2008; Fletcher et al.,2002; Baysal 2004). The recommended intake levels were 400 IU in infants between the ages of zero and one, 600 IU / day in individuals older than one year (1-70 years), and 800 IU / day in individuals aged 71 years and older. Pregnant and breastfeeding women should receive 600 IU / day of vitamin D. Obese individuals and anticonvulsants, glucocorticoids and AIDS treated individuals, vitamin D intake levels should take 2-3 times (Baysal 2004).

Deficiency And Toxicity Of Vitamin D

The best source to meet the need for vitamin D is the sun's rays. However, in some cases, the synthesis of vitamin D is not sufficiently realized. Vitamin D can be obtained in an amount equal to 2000 IU of vitamin D taken by sunbathing (15-30 minutes) for sufficient time for the skin to become slightly pinkish. There are some beliefs that there will be more vitamin D in the body with much sunbathing. However, some compounds that do not exhibit vitamin D activity such as lumisterol, crown, suprasterol, which do not show vitamin D activity with excessive sun exposure, occur. In addition, the person who has long contact with the sun also has no vitamin D toxicity. Because the skin is thin and the subcutaneous fat layer is low in elderly people, the

formation of vitamin D by sunbathing is less. In addition, the upright or oblique appearance of sun rays affects the synthesis of vitamin D. In our country, the sun rays are slanted from November to April, the effect of sunbathing is very small. The ozone layer in the atmosphere keeps the ultraviolet rays. In the morning and evening hours and winter days when the sun is inclined, ozone decreases the formation of vitamin D because it holds the rays. For this reason, vitamin D does not occur during sunbathing in northern countries 4-6 months of the year. In the summer when the sun comes up, sunbathing between 10.00 and 16.00 increases the risk of skin cancers. For this reason, people use preservatives. Vitamin D formation is reduced in the skin. Since the glass breaks the sun's rays, sunbathing behind the house prevents the formation of vitamin D.

Due to the clothing style, the formation of vitamin D in women can be less. Vitamin D formation decreases in people who work indoors and who do not leave during the day (in the home or in the office). In people with dark skin, vitamin D formation is less than that of clear-skinned people. Air pollution reduces the formation of vitamin D. Vitamin D is not enough in obese individuals, the need for vitamin D is higher in these individuals (Baysal 2004).

Vitamin D; inadequate intake or absorption (inadequate intake with diet, inadequate sunlight, malabsorption, gastrectomy, small intestinal disease, pancreatic insufficiency), sequestration (obesity), defective 25-hydroxylation (biliary cirrhosis, alcoholic cirrhosis), increased vitamin D catabolism (anticonvulsants, steroids, antiretroviral), loss of

VBP (nephrotic syndrome), defective 1-alpha 25-hydroxylation [hypoparathyroidism, renal failure, 1-alpha hydroxylase deficiency (VDD, rickets, Type I)], target organ resistance to calcitriole (hereditary VDR, rickets, type II) deficiency caused by acquired diseases (primary hyperparathyroidism, granulomatosis diseases, lymphoma) causes various disruptions in metabolism (Gürlek&Kumar, 2001). The most important environmental factor affecting vitamin D levels is season. The level of vitamin D is at the highest levels in late summer, while the end of winter is at the lowest levels (Dawson-Hughes et al., 2005; Özkan & Döneray, 2011). Bone demineralization leading to rickets and osteomalacia is the most important deficiency symptom (Champe 2007). In many studies, vitamin D deficiency has increased in Type I diabetes, multiplesclerosis, rheumatoid arthritis, osteoarthritis, Crohn's disease, various cardiovascular diseases, and also in many cancer types due to vitamin D deficiency (Mutlu & Hatun, 2011).

When high levels of vitamin D are toxic, calcium and phosphate levels increase in serum. This causes the accumulation of calcium in the kidneys and blood vessels, weakness in the muscles, gastrointestinal disorders, the inability of the kidney to fully perform its functions, and in the case of excess it causes liming in the soft tissues with the joints (Akkoyun et al., 2014).

Vitamin D And Bone Metabolism

Vitamin D is one of the oldest known hormones in terms of growth, development and healthy skeletal structure from birth to death.

Adequate vitamin D_3 synthesis or dietary intake is essential for lifelong bone health. The main function of vitamin D is to provide the levels of calcium and phosphorus necessary for the growth of bone tissue in children and for the reconstruction and mineralization of bone in adults. Vitamin D deficiency leads to problems such as an increase in bone building-destruction rate, osteoporosis and osteomalacia, and increased risk of fracture in the hip and other bones (Öğüş et al., 2015).

Rickets

The effects of vitamin D on the prevention of childhood bone diseases have been known for many years. Vitamin D deficiency is the problem of the whole world and is now defined as pandemic (Holick & Chen, 2008). Rikets, which have bending flexion in Latin, is a disease of growing organism and it is accompanied by osteomalacia in advanced ages (Wharton & Bishop, 2003). Rikets disease develops in children between 4 months and 3 years of age who do not receive adequate vitamin D support during the winter months because of low vitamin D content of mother's milk: hypocalcemia, convulsion, bending of muscles, muscle weakness, tooth failure and growth retardation (Holick, 2007; Dimitri & Bishop, 2007).

There is no threshold 25-OH D level for vitamin D deficiency in children. In studies investigating vitamin D deficiency and deficiency, different threshold values were taken as criteria. 'British Paediatric and Adolescent Bone Group' by 25-OH D level of 10 ng / mL was reported to be impaired in bone mineralization and 25-OH D level <10

ng / mL if vitamin D deficiency, 10-20 ng / mL between vitamin D is defined as insufficiency (Saggese et al., 2015). American Child Endocrinology Association 25-OH D level; Insufficiency between 15-20 ng / mL; Deficiency if <15 ng / mL; <5 ng / mL is considered to be a severe deficiency (Özkan & Döneray, 2011). However, there are studies suggesting that the increase in PTH, which is one of the expected findings in vitamin D deficiency, develops when the 25-OH D is below 30 ng / mL and the threshold value for vitamin D deficiency is taken as 30 ng / mL (Han et al., 2013). In 2016, the rapor Endocrine Society 'published a consensus report on this issue. In this report; 25-OH D level; Vitamin D deficiency was <12 ng / mL, vitamin D deficiency was 12-20 ng / mL, and normal vitamin D level was> 20 ng / mL (Munns et al., 2016).

In epidemiological studies conducted in different parts of the world, vitamin D deficiency in healthy children and adolescents is reported as 7-68% and vitamin D deficiency is reported as 19-61% (Saggese et al., 2015). In Turkey, age, gender, and although it may change with the seasons prevalence of vitamin D deficiency in children and adolescents has been reported as 8-61% (Özkan & Döneray, 2011). In 2011, the Ministry of Health of 6-17 month old children and mothers in Turkey levels of vitamin D and iron-deficiency anemia status determination and assessment of vitamin D deficiency in 2,504 children in the study of the programs 26.8%, and vitamin D deficiency was found to be 66.7% (Tezel 2013).

Adolescent period is the most critical period for skeletal development. The height burst in puberty is associated with an increased need for Ca and vitamin D. Vitamin D deficiency is common in this period. Therefore, it is recommended that adolescents with vitamin C and vitamin D support routinely during puberty period (Özkan & Döneray, 2011).

Osteomalasia

Low levels of vitamin D are not only simple biochemical disorders; In addition, it causes physiological, clinical and pathological findings such as an increase in bone building-destruction rate, osteoporosis and mild osteomalacia and increased likelihood of fractures in the hip or other bones (Akpınar & İçağasıoğlu, 2012).

In the case of osteomalacia bone mineralization is normal (or increased), but bone mineralization is not smooth (hence low bone mineral density) (May 2015).

Causes of Osteomalacia

1. Decreased synthesis of skin

- Inadequate exposure to sunlight
- People over 70 years old
- Dark-skinned people

2. Decrease of bioavailability

- Malabsorption (Postgastrectomy, Gluten enteropathy, Pancreatic insufficiency, Cystic Fibrosis, Crohn's Disease, Biliary Obstruction etc.)
- Obesity

3. Increases in catabolism

- Glucocorticoid and anticonvulsant drug use

4. Reduction of 25 (OH) D synthesis

- Liver failure

5. Increase of 25 (OH) D excretion

- Nephrotic syndrome

6. Reduction of 1,25 $(OH)_2$D vitamin synthesis

- Chronic renal failure
- Hyperphosphatemia

7. Tumor-induced osteomalacia

- Tumor secretion of Fibroblast Growth Factor 23

8. Genetic Diseases

- Vitamin D-Dependent Ripple (Type 1, Type 2 and Type 3)
- Autosomal Dominant Hypophosphatemic Rickets
- X linked Hypoposphatemic Rickets (Fidan et al.,2014).

Osteoporosis, Fall and Fracture

Since low 25 (OH) vitamin D levels cause secondary hyperparathyroidism and cause bone resorption through osteoclasts, they may accelerate and aggravate osteopenia and osteoporosis in adults (Holick 2007). Vitamin D; By keeping PTH levels at physiological healthy levels, it increases osteoblastic activity and supports bone mineralization and consequently decreases the risk of falling and fracture (Holick 2007; Dawson-Hughes et al., 2005). There is evidence that the fracture risk is lower in patients with 25 (OH) D vitamin levels> 30 ng / mL (Wacker 2013).

There is a positive relationship between 25 (OH) vitamin D and lower extremity functions, proximal muscle strength and physical activity (40). Vitamin D deficiency affects the antigravity muscles of the lower extremity, especially for postural balance and gait (Akpınar & İçağasıoğlu, 2012). There is a significant correlation between 25 (OH) vitamin D levels and falls in the elderly. Muscle strength, postural and dynamic balance can be increased with vitamin D supplementation (Bischoff-Ferrari et al., 2012).

Vitamin D Deficiency Prevention and Treatment Approach

Institute of Medicine (IOM) to prevent vitamin D deficiency; In the first year, 400 IU of vitamin D supplementation is recommended for infants, 800 IU / day for those aged between 1-70 and 800 IU / day for those over 70 years of age. These doses recommended by IOM may increase the level of 25 (OH) D to 20 ng / mL, which is thought to be sufficient for bone health, but is not sufficient for the levels of 30 ng /

mL recommended by the Endocrine Community. Therefore, in order to prevent vitamin D deficiency, the Endocrine Society in its practice guidelines; 400-1000 IU per day for the first year in infants (safe up to 2000 IU), 600-1000 IU per day for children and adolescents between 1-18 years old (safe up to 4000 IU), -2000 IU (safe up to 10,000 IU) recommends vitamin D support. However, in obese people, patients with Malabsorption syndrome may require higher doses of glucocorticoid and antiepileptic drug users.

According to the endocrine community;

- Infants with vitamin D deficiency between 0-1 years of age; Maintenance therapy of 400-1000 IU / day in order to keep the blood 25 (OH) D levels above 30 ng / mL for 6 weeks at 2000 IU / day or 50,000 IU / week vitamin D_2 or D_3,
- In children with vitamin D deficiency between 1-18 years; Maintenance therapy of 600-1000 IU / day in order to keep the blood 25 (OH) D level above 30 ng / mL for six weeks or 2000 IU / day or 50,000 IU / week vitamin D_2 or D_3,
- In all adults with vitamin D deficiency; Maintenance therapy of 1500-2000 IU / day to maintain blood 25 (OH) D level above 30 ng / mL for 8 weeks at 6000 IU / day or 50,000 IU / week vitamin D_2 or vitamin D_3,
- In obese patients, patients with malabsorption syndrome and those who use drugs that affect vitamin D metabolism, high dose, at least 6000-10,000 IU / day vitamin D treatment and

maintenance therapy at a dose of 3000-6000 IU / day is recommended.

The strategy of administering 50,000 IU of vitamin D twice a month treats vitamin D deficiency or deficiency without any toxicity for up to six years and prevents recurrence (Wacker 2013).

CONCLUSION

Vitamin D is a vitamin that is also classified as a fat-soluble steroid hormone, which increases the absorption of calcium and phosphate from the gut and affects bone metabolism. The main function of Vitamin D is the reproduction of bone tissue; provide the necessary calcium and phosphorus levels for mineralization (Öğüş et al., 2015).

Many individuals in the community say that their vitamin D levels are low in their blood despite their good nutrition. There are two reasons for this. First of all, since vitamin D has information about its association with chronic diseases such as rheumatoid arthritis, cancer, asthma, diabetes, vitamin D assessment has started to be done in routine health screening. However, vitamin D has been considered as a vitamin that has been associated with bone development for many years. Individuals have more information about vitamin D as the vitamin D evaluation is included in routine tests. In spite of the fact that individuals think that they are fed well, the second reason for low vitamin D levels is the lack of knowledge about the sources of vitamin D (Baysal 2004). When the studies about this subject are examined; In Ankara, 420 children between the ages of 1-16 have identified vitamin D deficiency in the spring months as 8% and deficiency as 25.5%

(Akman et al., 2011); In 2008-2010, 440 children between 0-16 years of age and adolescents found vitamin D deficiency to be 40% in another study (Andıran et al., 2012).

Uçar et al. (Uçar et al., 2012) In 2012, the rate of vitamin D deficiency in 513 adult patients in the winter-spring-summer months was 20.7% and the deficiency was 51.8%.

Bolland et al. Found women in New Zealand to have healthy post-menopausal 1606 women and 378 male patients in the middle and advanced age group with a vitamin D level of <50 nmol / L (<20 ng / mL) and 73% and 39%, respectively. They examined seasonal changes in vitamin D deficiency (Bolland et al., 2007). In a study by Yoon et al. In Korea, they found vitamin D deficiency in children under 2 years of age to be 29.8% when they took 30 ng / ml as cut off (Yoon et al., 2011).

Vitamin D deficiency / deficiency is common in our country and in the world. Since the sun's rays have not been used sufficiently for various reasons, the consumption of vitamin D-rich foods and the use of vitamin D supportive therapy in physician control have increased.

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CHAPTER 8

CLINICAL EVALUATION OF THE UPPER RESPIRATORY TRACT AND CURRENT APPROACHES IN PATIENTS WITH OBSTRUCTIVE SLEEP APNEA SYNDROME

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INTRODUCTION

Sleep breathing disorders cover a large group of diseases and the most important part of these diseases consists of “sleep apnea syndrome”. Since it constitutes 90-95% of all cases, when sleep apnea syndrome is mentioned, practically "obstructive sleep apnea syndrome" (OSAS) is understood (Lawrance,1997). Obstructive sleep apnea syndrome is a syndrome that is accompanied by recurrent episodes of upper airway obstruction throughout the sleep period, often with a decrease in arterial oxygen saturation and sleep interruption in general. OSAS is observed in 1–5% of adult males and 1.2–2.5% of females in the community (Aydın, 2005,pp 66-68). It has been stated that more than 7 million of approximately 31 million adults over 65 years old in the USA have OSAS and 46% of them have moderate or severe disease. It has also been reported as a more common disease than asthma in the adult population (Agrawal,2002, pp1626-1630). Although polysomnography is the gold standard diagnostic method used in the diagnosis of OSAS and determining its severity, it does not provide information regarding the pathophysiology of apnea (Köktürk, 1998, pp 187-192). However, the detection of obstructive pathology in these patients is extremely important in terms of both prognosis and planning the appropriate treatment. It is important and necessary to evaluate the anatomical and physiological narrowing of the upper respiratory tract by performing a detailed ENT examination after the diagnosis and staging phase of the disease.In addition to examination methods, techniques such as cephalometric examinations, radiological examinations such as CT and MRI, and acoustic and fluoroscopic

measurements are also used to evaluate craniofacial abnormalities and upper respiratory tract (Olson,2005,pp 329-359). The methods used in advancing technology are changing and developing.

1. UPPER RESPIRATORY TRACT ANATOMY:

The upper airway consists of the nose, pharynx, larynx, and extrathoracic trachea. Although the most important part of our subject is the pharyngeal airway that starts from the nasopharynx at the top and ends in the glottic space at the bottom, the importance of the nose cannot be ignored. It is classified anatomically as nasopharynx, oropharynx, and hypopharynx. It is about 15 cm long and extends from the base of the skull, to the lower edge of the cricoid cartilage at superior and to the lower edge of the sixth cervical vertebra at posterior. There is an accumulation of lymphoid tissue known as the pharyngeal tonsil in the mucous membrane of the posterior wall and roof of the nasopharynx. The oropharynx is the continuation of the oral cavity from the oropharyngeal isthmus. It is limited to the soft palate from the top, the tongue base from below, the palatoglossal and the palatopharyngeal plicas from the sides. It extends from the soft palate to the upper edge of the epiglottis. The dimensions of the tonsilla palatina located on both sides of the oropharynx vary from person to person. While it is generally large in children, it is usually smaller in older ages and is not often seen. Commonly, the tonsilla palatina has the largest diameter of 2 cm and usually does not fill the distance between the palatine arches. (Qureshi, 2003,pp 643-651)

The soft palate is a mobile fibromuscular fold attached to the posterior edge of the hard palate. The soft palate is supported by the palatine aponeurosis created by the expanding tendon of the tensor veli palatini muscle. The tongue base is mainly attached to the floor of the mouth and fills most of the oral cavity during rest. The hypopharynx is the laryngeal part of the pharynx. It extends from the lower edge of the epiglottis to the lower edge of the cricoid cartilage. It is associated with the cervical 4-6 vertebrae in the posterior. Pyriform recess is located on both sides of the larynx entrance. (Omur, 2004, pp 62-69)

2. PHYSIOPATHOLOGY

The most common structural anomaly in patients with sleep breathing disorder is pharyngeal collapsibility, whose severity and level vary from person to person. (Picture 2) A collapse in the upper respiratory tract occurs physiologically at the end of expiration and this situation is called "static collapse". In cases with apnea, in addition to this collapse that occurs at the end of expiration, a closure called "dynamic collapse" occurs instead of enlargement in the lumen during inspiration. In conclusion, while obstructive apnea is a problem that occurs in expiration mechanically, it is considered as an inspiratory disease biologically due to hypoxemia or hypopnea during sleep. (Fogel, 2004,pp159-163)

The width of the upper airway depends on the balance between the pressure forces (negative intraluminal pressure and increased tissue-extraluminal pressure) that have the characteristics of collapsing the airway and the factors (the contraction of the pharyngeal dilator

muscles) that try to provide airway openness. The factors causing anatomical stenosis or obstruction in the upper airway can be anywhere from the nose to the epiglottis level. Structurally, upper respiratory tract stenosis is the most common pathology. On top of these, when other factors also develop, obstructions in the upper respiratory tract easily occur. (Schwab,1998, pp 347-352)

3. CLINICAL EVALUATION

The main evaluation methods to be followed in the diagnosis of patients presenting with complaints of respiratory arrest during sleep or snoring are as follows;

I.-Anamnesis and Physical Examination

II-.ENT examination

III-.Endoscopic Examination Methods

IV-.Imaging methods (CT, MRI, Cephalometric analyses)

V-Acoustic Analysis Techniques

3.1. Anamnesis and Physical Examination:

Measuring the height and weight of patients with obstructive sleep apnea is the first application to be performed in general physical examination. Body mass index (BMI) is used for the evaluation of obesity. According to the classification made by the World Health Organization; BMI below 18.5 was determined as Underweight, 18.5 - 24.9 Normal Weight, 25.0 - 29.9 Overweight, 30.0 - 39.9 Obese, and over 40.0 Morbid (severe) Obese.

Romero-Corral A et al. (2010, pp 711-719) have found a significant relationship between BMI and the frequency of OSAS in their study. OSAS risk has been observed 15 times more common in patients with a BMI above 30 than those with BMI within normal limits. One of the parameters that should be particularly evaluated in patients with OSAS is the width of the neck circumference (Hoffstein,1992, pp 377-381). Neck circumference should be measured at the level of the cricothyroid membrane. Normal values are accepted less than 17 inches (43.18 cm) in males and less than 15 inches (38.10 cm) in females. In the study by Katz I et al. (1990, pp 1228-1230) sleep apnea syndrome has been found in approximately 25-30% of males with a neck circumference greater than 17 inches.

3.2. ENT Examination:

Although many factors are held responsible in the etiology of OSAS, it is necessary to evaluate the upper respiratory tract in detail in order to determine the possible obstruction areas in URT, where obstruction actually occurs and which has the characteristics of collapsing, and to determine the findings that may cause an increase in the severity of obstruction.

3.2.1. Craniofacial Skeletal Structure:

In the first evaluation of the patient, the structure of the maxilla and mandibula and dental occlusion are shortly evaluated. When evaluating maxillary hypoplasia, it is benefited from the plane extending from the nasion to the subnasal.(Kim,2011,pp 185-193) The vertical line descending from the nasion should normally pass through

the subnasal. If the subnasale remains posterior to this vertical line, it is possible to talk about maxillary hypoplasia. Again, in the horizontal Frankfort position, if there is more than 2 mm distance between the vertical line descending from the vermillion border and the protrusion, there is retrognathism. Patients with retrognathism have a high risk of obstruction at the oropharynx and hypopharynx level since the tongue base and soft tissues will move posteriorly. (Onerci, 2003,62-69)

3.2.2. Nasal Examination:

In addition to creating obstruction on their own, endonasal deformities cause collapse of the pharynx by increasing the negative intraluminal pressure in the pharynx by increasing the nasal resistance. In addition, nasal anatomy should be known in patients who will use CPAP and deformities should be corrected when necessary. In nasal examination, the external roof, septum, internal nasal valve and concha are examined. If there is deviation of the septum, it should be treated first.

3.2.3. Oral Cavity and Oropharynx Examination:

Examination of the oral cavity begins with the determination of the neutral position of the tongue and soft palate. The size and position of the tongue is determined. One of the most frequently used methods in tongue evaluation is the modified mallampati classification (MMC). In the Friedman modification of the Mallampati classification (Friedman, 1999, pp 1901-1907), which is used to determine the relationship between the positions of the tongue base and palate in the oropharyngeal examination of the patients, the appearance of the soft

palate is evaluated in the sitting position, with the mouth open and the tongue in the neutral position. (Figure 1)

After the oral cavity, the oropharynx formed by the soft palate, tonsil, uvula and pharyngeal walls should be examined. The soft palate can have very different configurations by nature. It can be shortly classified as low, thick, bilobular, or with close localization to the posterior pharyngeal wall. If the length of the uvula exceeds 1 cm, it is considered long. The size of the tonsils is also important. The tonsils, that narrow the oropharynx and thus the respiratory tract, are responsible for sleep apnea more or less. In various studies, a relationship between tonsil size and AHI has been determined. (Schlossan, 2004, pp 347-352). In addition, large posterior plica mucosa, large mucosal loops originating from the lateral and posterior pharyngeal wall, low arched palate due to downward extension of the soft palate, Floppy or omega-shaped epiglottis, and excess aryepiglottic plica are other findings that can be detected during examination.(Stuck, 2008,pp 411-436)

3.3. Endoscopic Examination Methods

3.3.1. Awake Fiberoptic Endoscopy:

Fiberoptic endoscopy performed while the patient is awake allows the imaging of all upper airways from the nose to the trachea. After nasal topical anesthesia, a nasopharyngolaryngoscopic examination is performed with a fiberoptic endoscope in patients in the sitting and/or supine position. Starting from the nasal entrance, the nasal mucosa, concha, nasopharynx, dorsal side of the soft palate, lateral pharyngeal

walls, oropharynx, hypopharynx, tongue base, supraglottic and glottic region are examined endoscopically. (Schwap,1998,pp 1617-1637) In addition, massive lesions that cause obstruction in the upper airway can also be detected.

3.3.2. Muller Maneuver:

Evaluation of the diameter of the upper airway during negative intraluminal pressure is important to determine surgical treatment. The Müller maneuver is based on the determination of the region that has a tendency to collapse and a tendency to mimic apnea that occurs during sleep by creating a collapse in the upper airway or the region that collapsed. This examination method is a non-invasive method that can be applied easily and saves time. The endoscope is advanced to the retropalatal region and the patient is asked to make a forced inspiration while the nasal passage is closed by the doctor and the patient has closed his/her mouth. (Togeiro,2010,pp 230-235) By repeating the müller maneuver in both the retropalatal and retrolingual regions, the collapse occurred in these regions is evaluated subjectively (Figure 2). However, this technique cannot show different levels of obstruction simultaneously. At the same time, it should be known that the application cannot provide an assessment equivalent to that during sleep, since the application is performed while the patient is awake and in a sitting position. Terris et al. (Terris,2000, pp 1819-1823) have determined that the evaluation performed with the Müller maneuver varies from clinician to clinician, besides, patients cannot always provide negative pressure that can cause obstruction. In

addition, the effect of the Müller maneuver on the success rate of surgical operations is a controversial issue. In a study related to this, the opinion that retrolingual obstruction was overlooked during the evaluation with müller has been suggested as one of the reasons for the low surgical success rate in sleep apnea patients who underwent uvulopalatopharyngoplasty (Katsantonis,1989, pp 677-680).

3.3.3. Simulated Snoring Techniques:

In order to evaluate the physiological changes occurred during snoring in sleep, Herzog et al.(Herzog,2006,pp 1456-1462) have defined an examination method based on endoscopic examination of URT during Simulated snoring, which is based on imitation of snoring, as an alternative to the Müller maneuver for evaluation in polyclinic conditions. In this method, while the patient is awake, he/she makes a forced inspiration with his/her mouth open. Meanwhile, the upper airway is examined with flexible endoscopy and the occurred obstructive pathologies are evaluated. In their later study, they have compared Simulated snoring with sleep endoscopy and have stated that simulated snoring provides quite similar results with sleep endoscopy. The advantages of the simulated snoring method are that it is non-invasive, can be performed while the patient is awake, requires less equipment and effort, and there is no possibility of side effects (Herzog,2015, pp 2541-2550). Again in 2015, when Huo et al. have compared the Müller maneuver and simulated snoring method, they have showed that the simulated snoring technique was more effective in detecting obstructions in the retroglossal area (Huo,2015, pp 661-

667). For this reason, simulated snoring method can be a good alternative to Müller maneuver in terms of being applied in outpatient clinic conditions in pre-surgical planning.

3.3.4. Drug-induced Sleep Endoscopy (DISE):

When the fiberoptic endoscopic examination is performed while the patient is awake, it can be misleading in showing the obstruction area during sleep, since muscle tone differs from sleep state. Pringle and Croft (Pringle, 1991, pp559-562) have applied the fiberoptic endoscopy technique in sleep for the first time in 1991 and have suggested that the determination of the obstruction area where snoring originated with this technique was superior to the results of the Müller maneuver with the fiberoptic endoscopy performed while awake (Certal, 2016, pp 768-774).

The application is performed in a quiet and dark environment in which there is general anesthesia equipment and in the presence of an anesthesiologist. The patient is placed in a supine position. It is important to apply intranasal topical anesthetic and decongestant to the patient before the procedure. In addition, an anticholinergic agent is administered half an hour before to prevent the negative effects of secretion. Throughout the procedure, the patient is monitored in terms of oxygen saturation and cardiac rhythm monitoring.

Although different medications have been used to provide sedation, a combination of Propofol and midazalom is frequently used today. Sedation is started with fast-acting sedatives such as midazolam (Dormicum), and propofol (dipirivan) infusion (50-100 μg/kg/min) is

continued until snoring and apnea occur. Care is taken for the patient to maintain spontaneous breathing. Areas with stenosis are generally at the level of the soft palate, lateral pharyngeal wall, tonsils, tongue base, epiglottis, and hypopharynx. Although there are different opinions about the grading of the findings, there is currently no classification system that a consensus has been achieved on. The most commonly used ones for this purpose are the classification system defined by Pringle and Croft (Pringle,1991, pp 559-562) and the VOTE (velum, oropharynx, tongue base, epiglottis) classification defined by Keziran(Keziran,2011,pp 1233-1236)(Table 1).

In studies comparing DISE examinations using different anesthetic medications, no significant difference was found between the results (Carrasco, 2014, pp 181-187). Since the findings are evaluated subjectively by clinicians during DISE, results may vary according to the examiner. In their study of Keziran et al. (Keziran, evaluating the compatibility among examiners, it has been found that DISE showed moderate to significant reliability. Another advantage of DISE is that it allows to see the opening at the level of the pharynx and tongue base by mandibular advancement maneuver, particularly in patients with maxillofacial problems, and thus to identify patients who will benefit from the use of oral devices (Bachar, 2008, pp 1397-1402).

3.3.5. Natural Sleep Endoscopy:

Due to the opinions that drug-induced sleep may be different from the natural sleep physiology, it has become necessary to visualize the upper respiratory tract during sleep. For this purpose, for the first time

in 1978, Borowiecki et al. (Borowiecki,1978, pp 1310-1303) have wanted to perform sleep endoscopy in the natural process without using sedative medications, however, this was not possible in routine practice.

In this regard, Park et al. (Park, 2019, 730-734) have been able to evaluate URT during natural sleep in about 26 patients and have compared their findings with drug-induced sleep endoscopy. They have stated that the area where the stenosis detected the most in patients during sleep was the soft palate and tongue base. In addition, a statistically significant level of compatibility has been detected between the two techniques.

3.4. Imaging Methods

3.4.1. Lateral Cephalometry:

Lateral cephalometric examinations are standard lateral radiographs of the head and neck used to examine upper airway craniofacial and soft tissue structures. For cephalometric examination, radiographs are taken at the end of expiration with the teeth in centric occlusion and with the tongue touching the teeth, after stabilizing the head in a natural position. The natural position of the head can be achieved by the Frankfurt horizontal (the line drawn from the external canthus to the tragus) plane parallel to the ground or by the patient looking at his/her own pupilla in the mirror. Determining reference points of bone and soft tissues on this graph and making distance, angle and area measurements is called cephalomatric analysis. With this method, craniofacial and soft tissue anomalies that play a role in the

pathogenesis of sleep apnea syndrome can be revealed. Possible craniofacial skeletal anomalies such as retrognathia, micrognathia, maxillary retroposition, posterior airway stenosis, soft palate hypertrophy can be determined in patients with OSAS. Cephalometry can also be used to determine the effectiveness of oral prostheses in snoring patients. Advantages of cephalometry include ease in imaging, being more common than Magnetic Resonance Imaging (MRI) and Computerized tomography (CT), not having a weight limit, and not being as expensive as CT and MRI.The disadvantages are that the device requires standardization of the scanning technique and soft and bone tissues can only be evaluated in 2 dimensions. (Neelapu, 2017,pp 79-90)

3.4.2. Computerized tomography

It displays the soft and bony structures of the upper airway in high quality. It is a widely available, non-invasive, easily applicable, but expensive and imaging method with radiation exposure that provides detailed information due to its superior bone and soft tissue resolution. It can be used in the area measurement of the upper airway. Volumetric reconstructions can be made from the axial plan sections of the upper respiratory tract. With dynamic CT studies, important information has been provided on how the upper airway diameter is affected by the respiration phases (Passos,2019). Compared to MRI, soft tissue contrast resolution is limited.

3.4.3. Magnetic Resonance Imaging

In the light of the developments in MRI technique, Barrera et al. (Barrera, 2009, pp 423-425) have defined sleep MRI technique to detect obstructive pathology in OSAS patients. However, the biggest difficulty in applying this technique is that the apnea periods of the patients cannot be caught. Because many authors emphasize that the apnea periods provided with sedative agents to be given, as in sleep endoscopy, are different from the situation that will occur during physiological sleep.

With dynamic MRI and especially ultrafast MRI and cine-MRI, an image can be obtained in 0.8 seconds. The use of MRI in patients with OSAS has been tried to correlate with EEG changes during sleep, and many neurophysiological studies have been conducted.

Collapse areas can be measured by applying various sequences in the evaluation and obtaining cine-MR images (Moriwaki,2009, pp 187-191). To understand sleep MRI, it is also necessary to know the anesthetic agents given. For this purpose, propofol and dormicum are used as in sleep endoscopy.

3.4.4. Fluoroscopy

It is an imaging method that provides dynamic examination of URT while awake and asleep. This technique was initially used to examine soft palate mechanics and diagnose OSAS in children. During the examination, the tongue and pharyngeal area is covered with a thick layer of barium, and the head should be 30 degrees high for better

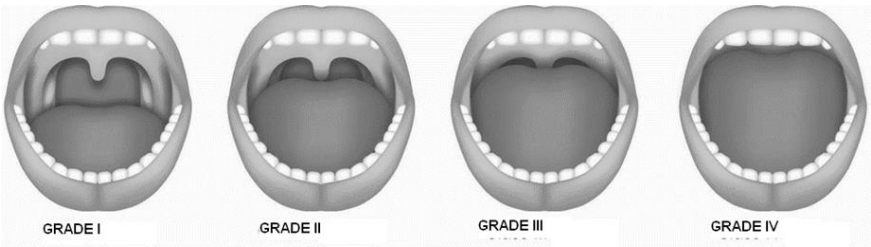
visualization of the hypopharynx. Its superiority to other imaging methods is that it can dynamically monitor changes in URT and soft tissues during sleep apnea. The disadvantage is that the measurements of the cross-sectional dimensions of the URT and bone structure cannot be made. The presence of radiation exposure makes routine use impossible. (Thakkar,2007,pp 785-805)

3.5. Acoustic Evaluation Methods

Acoustic pharyngometry is a relatively new method that is used to evaluate the cross-sectional areas of the airway using the acoustic reflection technique. In the acoustic reflection technique, sound stimuli sent from a sound source are sent to the object being measured by passing through a wave tube. Sound stimuli and reflection from the object are recorded by the computer system with a pressure sensitive receiver. Proper analysis of the reflected waveform enables the impedance profile of the object to be established. (Kendzerska, 2019, pp 2019-2026) In acoustic pharyngometry, sound stimuli sent in the audible frequency range are compared with responses reflected from the airway. If the entrance size of the airway is known, the size of the reflection indicates changes in airway size. The time between reflections gives the distance between changes depending on the speed of the sound. In this way, it is possible to determine the cross-sectional area at a certain distance of the airway. Reflection of oral acoustic stimuli is used to learn the cross-sectional areas of pharyngeal cavities up to the oral cavity and larynx level. (Viviano,2002, pp 129-149)

CONCLUSION

It is important to define the location and pattern of the upper airway collapse to correctly plan the treatment approaches for OSAS patients. In addition, different airway obstruction features of patients have an impact on determining the severity of the disease, so defining an accurate surgical treatment for OSAS patients will reduce unnecessary costs. All of the techniques for evaluation of upper airway have their advantages over each other as well as their limitations. With the developing technology, newer techniques will be added to the evaluation methods of OSAS patients in the future. Comparative studies with large series on this subject will also be a guide in evaluating the superiority of the techniques.



Grade 1: All soft palate, uvula, plicas and tonsils are seen
Grade 2: While the entire uvula is visible, the plicas and the upper part of the tonsils are visible.
Grade 3: Only the soft palate and hard palate can be fully seen.
Grade 4: Only the hard palate can be seen

Figure 1: Modified Mallampati Score (Friedman M.,2005)

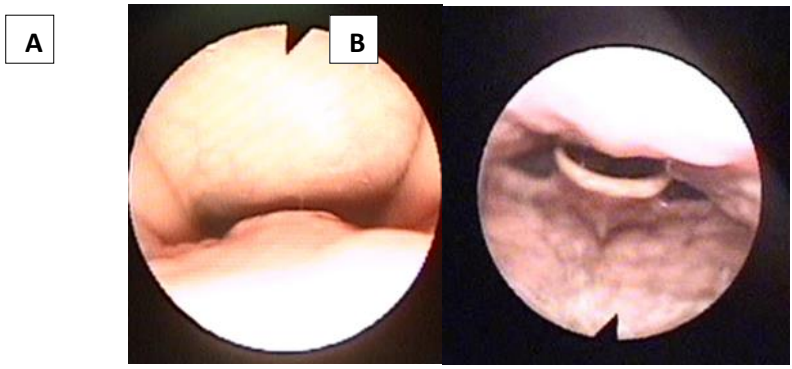


Figure 2: A: Anteroposterior collapse pattern at retropalatal level with MM

B: Anteroposterior collapse pattern at retrolingual level with MM (Ozcelik M.,2009)

STRUCTURE	DEGREE OF OBSTRUCTION[a]	CONFIGURATION[c]		
		A-P	LATERAL	CONCENTRIC
Velum				
Oropharynx lateral walls[b]				
Tongue Base				
Epiglottis				

Figure 3: The VOTE classification for evaluation of URT during DISE (Keziran,2011)

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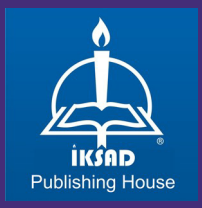

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