INNOVATIVE RESEARCH IN HEALTH SCIENCES

Editors
Assoc. Prof. Sadettin DEMİREL, Ph. D.

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Chapter 1

Conservative and Esthetic
Consideration in Dentistry

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ABSTRACT

INTRODUCTION

Artistic elements which contain shape, symmetry, proportionality, alignment, color, and surface texture consider in every single tooth that need restorative treatment. Conservative alteration of tooth contours and contacts which include closing diastemas and the importance of illusions, correction the embrasures which preserve the health of periodontal tissues and reshaping the destructive teeth to reach the natural appearance. Treatment of discolored teeth must begin with knowing the reason of discoloration then make the treatment plan according to the case. Some cases need bleaching; others need micro abrasion and macro abrasion or veneers.

Illusions of shape

An anterior tooth's border appearance resembles two dimensions as the width and length, the depth referred to as the third dimension and play an important role in illusions for dental esthetic (Harald O Heymann & Ritter, 2018). The tooth dimension can be changed by changing the location of buccal prominence which can be called the height of contour (Harald O Heymann & Ritter, 2018).

- Illusions of width

Dimensional illusions in teeth Several methods can be used to make teeth appear either smaller or broader. By drawing the mesio- buccal and disto-buccal line angles closer together, the tooth can get thinner, and it became broader by putting the mesio buccal and disto buccal line angles further apart (Magne & Belser, 2002).

- Illusions of length

Shorter tooth could be achieved by incisively positioning horizontal features such as gingival perikymata and gingival height of contour. For achieving longer tooth the heights of contour placed from afar incisio-gingivally, the developmental depressions which are considered a vertical element should be emphasized (Harald O Heymann & Ritter, 2018).

Symmetry and Proportionality

If the sizes of the contralateral teeth are equal, tooth symmetry can be obtained (Harald O Heymann & Ritter, 2018). Dental calipers can be used for esthetic restorations for tooth which need alteration of mesiodistal dimension that exist in anterior diastema for example (H O Heymann & Hershey, 1985; Banker et al., 1982).

- The Golden Proportion

When repairing or restoring maxillary upper teeth, among the greatest significant objectives in esthetic dentistry is to create harmonic proportions between the widths of these teeth. The "golden proportion" is a key recommendation that has been developed in this subject (Mahshid et al., 2004)

The Golden Proportion of Dentistry is an equation-based method for determining the widths of the upper anterior teeth; if the lateral incisor is multiplied by one, the central incisor is multiplied by 1.6. In that front view, the visible part of that canine, which is normally the mesial part of the canine, would be 0.6 (Levin, 1978).

- RED proportion (Requiring esthetic dimension)

If the space between teeth more than 3 mm we can't close it by direct composite.

Inter canine distance: The space between the two tips of the canine can be measured with radiograph paper for giving the curve (let's say it 39 cm), Equation say: X (ideal central width)= ICD/2(1+RED+RED2).

At all cases the RED proportion could be considered 70% but it can be changed according to the case. If the teeth are too short and more composite can't be added the RED proportion will be considered 80%, and if the teeth are too long it is considered 65%. Width of central /length of central = 80% and the lateral incisor length will be 1 mm shorter than central incisor.

Location and Alignment

The general harmony and balance of the smile is determined by how equally and evenly the teeth are placed and balanced in the arch of the mouth. Malposed or twisted teeth not only distort the shape of the arch, but they may also cause problems with the teeth's apparent relative dimensions. Orthodontic correction of such flaws should always be determined, particularly if there are problems with positioning or malocclusion. Minor positioning abnormalities are frequently treatable with composite resin or facing veneering with resin or porcelain laminates when orthodontic treatment is either impracticable or costly (Saldarriaga & Peláez, 2003).

Surface Texture

The surface texture has a direct effect on the value, color saturation, and light reflection and absorption zones (Fondriest, 2005). An anterior restoration that lacks the same surface texture and luster as the adjacent natural teeth would stand out immediately (Luke S. Kahng, 1993).

When present on adjacent surfaces, developmental kinds of depressions, prominences, aspects, and enamel perikymata should all be carefully examined and repeated (Harald O Heymann & Ritter, 2018).

Color

Color as an artistic aspect and its role in conservative esthetic dentistry is by far the most complicated and poorly understood. It's an aspect with a lot of interconnected influences that all contribute to the final aesthetic result. While complicated, a simple understanding of the various components of color is important for consistently producing esthetic restorations (Harald O Heymann & Ritter, 2018).

Teeth that are lighter in color are more common in young patients with thick enamel. Furthermore, Patients with darker skin tones will typically have whiter teeth due to the contrast between the teeth and surrounding facial tissues. It is possible to create the illusion of lighter teeth (Harald O Heymann & Ritter, 2018).

Only the phenomenon of metamerism, which occurs when artifacts of different physical and chemical characteristics combine consistently with the energy of light, giving in a color appearance that is equivalent, allows for color replication of the tooth with restorative restoration (Lee & Powers, 2005; Kim et al., 2007).

Translucency has an influence on the restoration's aesthetic efficiency. The amount of light that penetrates the tooth or restoration before being reflected outward defines the degree of translucency (Johnston & Reisbick, 1997).

Conservative Alteration of Tooth Contours and Contacts

Several conservative approaches may be used to correct or significantly enhance the appearance of certain unsightly tooth contours and diastemas. The aim of this is to improve appearance while keeping as much healthy dental structure as feasible. while maintaining a good occlusion and the wellness of the tissues surrounding it. Natural tooth restructuring, embrasure correction, and diastema removal are some of the procedures available (Harald O Heymann & Ritter, 2018).

Alterations of Shape of Natural Teeth

Modifying and polishing natural teeth should always be considered to enhance their appearance and function. Furthermore, rounding sharp angles could be thought of as a prophylactic method to decrease pressure and avoid incisal edge chips and breakages (Harald O Heymann & Ritter, 2018).

There are a lot of reasons for changing the shape of natural normal teeth over time. Attrition, fractured teeth, and poor dental habits like holding objects with teeth or biting the fingernails are some of these reasons (Harald O Heymann & Ritter, 2018).

Treatment steps as the following; before starting the reshaping of any teeth, photographs, study models and line drawings should be taken to visualize the future improvement before any improvements are made for the patient (Harald O Heymann & Ritter, 2018).

There is no need to use anesthesia because the work is just on the enamel surface, the first step is doing isolation then diamond instruments and abrasive discs for finishing and polishing can be used (Sarver, 2011).

Figure 1: A, the maxillary centrals incisors exhibited wear and incisal edge breakdown due to parafunctional habits and little discoloration on the incisal third. B, Treatment of irregular and discolored incisal edges with direct composite restoration.

Alteration of Embrasures

The incisal surfaces of certain patients wear away as they get older or have bruxism habits; this may be accompanied by loss of the incisal embrasures (Harald O Heymann & Ritter, 2018).

Open embrasures maybe caused by missing laterals or canines so they may drift or be corrected by orthodontic treatment and leave the embrasure too open and they may need to reshape the moved tooth (Kurth & Kokich, 2001). Before starting the treatment, composite mockup could be made to predict the future result, then cleaning the teeth, isolate them, and adding the required composite. The final step is using finishing burs and disks. Reshaping the teeth to look more natural might be needed (Harald O Heymann & Ritter, 2018).

Figure 2: A, Peg shaped lateral. B, Reshaping and correcting the embrasure between teeth.

Correction of Diastemas

In the anterior dentition, a diastema (space between teeth) is a normal occurrence. For diastema closure, a variety of therapies can be used. The most effective treatment can be decided using a well-developed diagnosis and advanced planning (Oquendo et al., 2011). The natural approximation of erupting central incisors is often affected by an obvious labial frenum with proximally extended nonelastic substances, Bolton disparities in inter-arch teeth measurements, congenital teeth, underdeveloped or deformed teeth, excessively crowded teeth, tongue pushing, periodontal disorders, or a collapsed of the posterior bite are also reasons for diastemas (Graber & Vanarsdall, 2000). A micro filled composite resin is the ideal material for diastema closure due to its great polishability and give us the luster of the natural enamel. In patients with heavy centric contacts, the lingual aspect of the composite resin may experience considerable functional stress if the diastema is very large. The dental practitioner in these situations may decide to utilize a hybrid composite resin for the complete restoration or a hybrid for the lingual area capped with a micro filled composite resin on the facial surface (Aschheim, 2014).

Figure 3: Diastema closure. A, the aesthetic issue brought on by the space between the anterior upper centrals. B, Diastema closed.

Conservative Treatments for Discolored Teeth

In our beauty conscious culture, dental aesthetics has a significant influence (Joiner, 2006). Intrinsic and extrinsic coloration determine tooth color. The light scattering and adsorption properties of the enamel and dentin are related to intrinsic tooth color. Extrinsic stains are caused by the ingestion of tannin-rich foods and the absorption of materials used in tobacco (Joiner, 2006). Extrinsic staining can also be caused by the presence of dry mouth, this is a hallmark of radiotherapy patients. Salivary flow is reduced, which increases the demineralization ability of the teeth, allowing stains from external products to deposit more easily (Bardow et al., 2001). Bleaching, micro-abrasion, veneering, or crowning may be used to treat aesthetically unappealing tooth coloration (Abdollahi et al., 2008).

Extrinsic Discoloration: Routine prophylactic procedures can remove some superficial discolorations on tooth-colored restorations and decalcified areas on teeth; however, such cleaning cannot remove some superficial discolorations on tooth-colored restorations and decalcified areas on teeth. Mild micro abrasion or surfacing the thin, outer, discolored layer with a flame-shaped carbide finishing bur or diamond instrument may be used for conservative correction (i.e., macro abrasion) (Harald O Heymann & Ritter, 2018).

Intrinsic Discoloration: Since no restorative material is as good as safe natural tooth structure, mild discolorations are better left untreated, bleached, or

treated conservatively with micro abrasion, macro abrasion or veneers (Harald O Heymann & Ritter, 2018).

Veneers

A veneer is the restoration that replicate the color of the teeth and bonded to the front of a tooth. To repair local or widespread defects, as well as internal color changes (Harald O Heymann & Ritter, 2018).

Compressed ceramic, porcelain, processed composite, and direct composite materials are used to create veneers. Laminating is the practice of adding a small layer veneer of preformed porcelain, composite resin, or plastic material to a tooth. Laminates can effectively turn the entire tooth in a painless, conservative, and fast manner while providing long-lasting effects (Gürel & Gürel, 2003).

Since the tooth preparation requires removing approximately half as thick of the enamel and leaving the remaining part untouched until veneer placement, the veneer is regarded as among the most common minimally invasive cosmetic procedures (Pini et al., 2012).

Classification of Veneers

I. Depending on the fabrication:
- Direct method
- Indirect method.

II. Depending on the area covered:
- Partial veneers: For specific flaws or areas of inherent discoloration that only affect a small piece of the clinical crown, partial veneers are recommended.
- Full veneers: are used to restore generalized flaws or when most of the facial surface or the entire dental crown is discolored.

III. Based on tooth preparation:
- Incisal lapping on the whole veneer.
- Full veneer with window preparation.

IV. Based upon the materials & techniques used:
1- Directly produced veneers made of composite resin.
a) Direct partial veneers
b) Direct full veneers

2- Indirectly fabricated veneers
a) Etched porcelain veneers
b) Processed composite veneers
c) Castable ceramic veneers
3- Veneers for metal restorations.
V. Based on the preparation designs
1- Window preparation: the tooth's incisal edge is retained in the first step of window preparation
2- Feather preparation: the incisal edge of the tooth is prepared bucco-palatally, but the length of the incisor is not shortened.
3- Bevel preparation: the incisal edge of the tooth is prepared bucco-palatally and the length of the incisal edge is reduced slightly by 0.5-1 mm.
4- Incisal overlap preparation: the incisal edge of the tooth is prepared bucco-palatally and the length is reduced (about 2 mm), allowing the veneer to stretch to the tooth's palatal surface (Aschheim, 2014).

Indications
1. Single or numerous teeth with internal or external discoloration, chromogenic microorganisms, some types of mouthwashes, drinks like the tea, coffee, or some types of wine, and iron supplementation are examples of extrinsic factors. The internal factors can be tetracycline stains, fluorosis, hemophilia, devitalization, caries, and dental restoration products.

2. Enamel abnormalities- anterior teeth with gross enamel hypoplasia, amelogenesis.

3. The existence of a diastema.

4. Teeth with an unusual appearance or form.

5. Teeth that are misaligned when orthodontic surgery is not desired or suggested, this technique is used to provide the esthetic illusion of straight teeth.

6. There are several carious lesions and decalcifications.

7. Attrition, abrasion, and corrosion.

8. Multiple anterior teeth have been traumatized or fractured (Mitthra et al., 2020).

Contraindication
1. Teeth with inadequate enamel.

2. Adolescent permanent teeth.

3. Teeth with extreme occlusal wear trends because of para-functional behaviors Extreme periodontal activity with significant crowding.

4. Oral hygiene problems.

5. Inability to etch enamel in teeth that have been overly fluoridated.

6. Patients with a high rate of caries (Mitthra et al., 2020).

Instructions for the Patient

The patient should also be informed of the possibility of porcelain fracture.

Individuals with dysfunctional habits or situations where porcelain veneers counteract tooth structure are provided with a protecting device or occlusal guard that protects both the veneers and the opposing teeth when a person wears it (Summitt et al., 2001). The patient should be recalled after 6 months for clinical evaluation (Kihn & Barnes, 1998).

Repair of Veneers

PLVs have replaced ceramic crowns and classic porcelain-fused-to-metal crowns as an attractive option (Peumans et al., 2000). Because of their evenly glazed surface, these restorations have less plaque build-up and are simple to remove (Sá et al., 2018).

When a breakdown of the mesio-incisal region of a porcelain veneer is discovered, the patient mouth is isolated using a retractor. Initially chosen color choice has been completed. A fast mock-up of the replace with the chosen composite helps confirm the color choice. On the porcelain around the crack, a 2mm broad bevel is applied (Dent et al., 1998).

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Chapter 2

Use of Current Cad/Cam Materials in Restorative Dentistry

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ABSTRACT

INTRODUCTION

The CAD/CAM systems provided alternative esthetic restorations which is much better than the conventional restorations and it gives more strength and esthetic options. The CAD/CAM restorative materials it must be sufficient in strength to handle load and hardness of milling process, to give more clinical longevity for patients (Venturini et al., 2023).

The uses of CAD/CAM restorative materials become broad, Inlays, onlays, crowns, and veneers can all be made of it. These indications are fabricated from glass ceramics in monolithic application. The increased request for CAD/CAM restorative materials due to their big advantages, which is highly aesthetic, long lasting and biocompatible restorations (Venturini et al., 2023).

With the debut of the first chairside computer aided design/computer aided manufacture (CAD/CAM) system in 1985, ceramic restorations may be delivered in just one visit as a method of treatment (Moörmann, 2006).

The material came in the form of solid blocks ready for milling process. The grinding for both systems is restoration from the blocks is shaped or milled using wet grinding. The most important thing in the CAD/CAM system is the time saving and completion of the final restoration at the same appointment. So, the materials must be capable to withstand the rigors of milling in less than 20 minutes (Moörmann, 2006).

Few material failures could be happened due to the use of homogeneous manufacturing blocks during manufacture and for clinical use (Belli et al. 2017). Low flaws and pores present in CAD/CAM blocks compared to hand-built materials (Zhang and Kelly 2017).

Different materials showed successful uses in CAD/CAM system in clinical dentistry (Fasbinder, 2006). Presence of large number of materials in the case of digital industrial, lead to presence of numerous clinical uses such as restorative, prosthesis, dental implantology, and orthodontics. It is now challenging to choose the right material for each indication (Belli et al.2017).

Materials for repairs on CAD/CAM systems

Chairside CAD/CAM include many classifications based on the structure of the materials which makes understanding their features and clinical uses easier (Fasbinder, 2010; Fasbinder, 2012).

Tablo 1: Different types of materials used in CAD/CAM.

MATERIAL	BRAND
Adhesive ceramic Leucite-reinforced Felspathic	IPS EmpressCAD (Ivoclar) Paradigm C (3M ESPE) Vita Mark II (Vita) Sirona Blocs (Dentsply Sirona)
High-strength ceramic Lithium disilicate Zirconia-reinforced lithium silicate Lithium-silicate	IPS emax CAD (Ivoclar Vivadent) Celtra Duo (Dentsply Sirona) Obsidian (Glidewell)
Resin matrix ceramics	Hybrid nano ceramics (PICN)
Resilient ceramic (resin nano ceramic)	Lava Ultimate (3M) Enamic (Vita) Cerasmart (GC America)
Composite resin	Paradigm MZ100 (3M) Brilliant Crios (Coltene)
Zirconia (full contour)	CEREC Zirconia (Dentsply Sirona)
Provisional acrylic materials	TelioCAD (Ivoclar) Vita CAD-Temp (Vita)

- **Adhesive Ceramics (Feldspathic, Leucite-Reinforced)**

The glass components of adhesive ceramics make them brittle due to weak micromechanical adhesive bonding which etched with hydrofluoric acid. The adhesive ceramic includes two types, the first one is fine-grained feldspathic porcelain and the second one is leucite-reinforced porcelain. (Charlton et al., 2008; SARMENTO et al., 2011). These materials have high translucency which is the result of the presence of glass component which makes the "chameleon" effect (Severance, G., and Swann, L., 2009).

The chameleon effect means the capacity that reflects the shade of the tooth structure around it and thereby integrates into tooth shade (Br.Dent, 2009).

1. Leucite-reinforced glass ceramic

It contains leucite crystals approximate 40% merge in a feldspathic glass-ceramic (Höland et al. 2007). It known as ProCAD and later called IPS EmpressCAD has a crystal configuration identical to IPS Empress. EmpressCAD also has a light-scattering characteristic that enables a chameleon effect (Buso L. ve ark. 2011).

Leucite reinforced glass ceramic is available in two forms of translucency came into multi shaded blocks (Charlton et al., 2008). This material has a high Weibull modulus of 16.10 and a weak average strength (Wendler et al. 2017).

2. Feldspathic

The first CAD/CAM ceramic used in dentistry was composed of feldspathic porcelain, which has a similar composition as that of the traditional hand layered porcelain. Feldspathic CAD/CAM are still available on the market, because of their excellent esthetic properties, are mainly indicated for veneers and inlays (Wendler et al. 2017).

Vita Mark II and Sirona Blocks are feldspathic porcelain blocks with a particle measurement of approximately 4 microns (Charlton et al., 2008; SARMENTO et al., 2011).

The feldspathic CAD/CAM ceramic microstructural demonstrates two crystallization styles, one with a sodium potassium aluminum silicate and potassium sodium aluminum silicate ($AlK0.29Na0.71O3Si3$) (Ramos Nde et al. 2016). The Weibull modulus of felspathic CAD/CAM is elevated (m = 19.9) (Wendler et al. 2017).

- **High Strength Ceramic**
1. Lithium disilicate

Two successful systems (Empress 2 and IPS e.max Press; Ivoclar-Vivadent), a lithium disilicate glass-ceramic IPS e.max CAD, CAD/CAM software for processing has been created for that purpose. LDS ceramic show very small particles (0.5 to 4 μm) with different orientations (Höland et al. 2000). The milled LDS CAD/CAM is put through a two-stage crystallization procedure. Following sintering process, the final Weibull modulus (13.4) (Wendler et al. 2017).

LDS is the strongest glass-ceramic composition, having three to four times the strength of other glass ceramics (Wendler et al. 2017).

2. Zirconia-reinforced lithium silicate

Also called lithium silicate/phosphate (LSP). LSP is something to look for if you have inlays, onlays, veneers, or crowns (Belli et al. 2017). In comparison to LDS superficial pitting and many cracks were seen in the surface (Ramos Nde et al. 2016). One of the reasons for the cracking and pitting of surface may be the microcracking results from thermal instability among stages and the high local remaining stresses they cause (Wendler et al. 2017). Brand name: Celtra Duo (Dentsply Sirona)

ZRS and LS were both developed as alternatives to LDS. Unlike LDS, the glassy matrix of ZRS has 10% dissolved zirconia in addition to lithium disilicate and lithium metasilicate crystals. Because these materials have similar translucency, flexural strength, and fracture toughness to LDS higher resistance

to crack propagation, they have similar clinical indications (Wendler et. al. 2017).

3. Lithium silicate

Lithium silicate is a glass ceramic material but a new generation of it. Zirconia is added to glass ceramic about 10% by weight. This new glass ceramic has a high load capacity and long term reliability, and it can withstand the milling and polishing. Give us a good esthetic features which facilitate using it in many indications like inlays, onlays, and crowns (Coldea ve ark. 2013)

Obsidian™ lithium silicate ceramic is a glass ceramic material which could resist chipping due to their high flexural strength and monolithic composition (Ann Arbor, 2015).

- **Resin Matrix Ceramics (RMCs)**

Termed as "hybrid ceramic" intended to bring together the benefits of ceramics' excellent aesthetics and polymers' lack of brittleness (Coldea et al. 2013).

RMCs can be classified based on their microstructure and polymerization mechanism into

a) composites made of high temperature polymerized resin with distributed fillers and a mostly organic phase. RBCs are recommended for single crowns, implant crowns, inlays, onlays, and veneers (excluding LURBCs needs to be prepared for resin bonding using air particle abrasion and the use of a universal bonding agent (Spitznagel et al. 2016)

b) RBCs needs to be prepared for resin bonding using air particle abrasion and the use of a universal bonding agent (Coldea et al. 2013; Mainjot et al. 2016). PICN materials combining the beneficial properties of composites with ceramics. The presence of network structure help decreasing the crack propagation (Coldea et al. 2013).

- **Resilient Cerami**

Termed as nanoceramics. Lava Ultimate, Enamic, and Cerasmart are types of flexible ceramic of CAD/CAM involves materials which permit for higher stress absorption by using a resin matrix rather than a glass matrix (Awada A; Nathanson D, 2015).

Lava is a nanoceramic material made of zirconia particles measuring 4-11 nm and silica particles measuring 20 nm, inserted into a matrix of strongly cross-linked polymer with 80% ceramic load. Used for inlays and onlays, not recommended for crowns (Awada & Nathanson, 2015; Albero et al., 2015).

VE (VITA Enamic) show that in some criteria has the same result of human enamel as body wear, roughness, and gloss (Mainjot et al. 2016). Its favorable using silane and hydrofluoric acid etching as a surface preparation before bonding (Spitznagel et al., 2016).

Enamic (Vita) is resin-based Leucite based and zirconia reinforced ceramic networks interpenetrating form a hybrid ceramic network. The material's mechanical characteristics fall between those of glass ceramics and those of densely loaded composites (Della Bona et al., 2014).

CERASMART is combine the greatest features of a composite and an excellent strength of ceramic. Due to its flexible nano ceramic matrix structure and entirely homogeneous and evenly distributed nano ceramic network, the material offers unparalleled physical qualities and impact dispersion (Della Bona et al., 2014).

- **Resin Composite**

For broader and more complex multi surface composite restorations, chairside CAD/CAM provides easier management of proximal shapes, contacts, and occlusal connections than incremental hand insertion of conventional composite materials (Rusin RP, 2001).

There are a couple of kinds of composite resin blocks; one of them has been employed as long-term temporization and the other type is utilized for permanent restorations. Ceramic blocks are the main material utilized for chairside CAD/CAM restorations, despite composite resin materials having ideal qualities for chairside uses (Rusin RP, 2001).

While there are two distinct approaches for Materials used in the production of resin ceramic composite (RCC) include sintered ceramic infiltration into the polymer matrix (interpenetrating phase network, or IPN), which is similar to direct composites, and distributed fillers in the polymer matrix, they have very similar characteristics and uses (Rusin, 2001).

RCCs have a translucency like that of glass-ceramics but have superior mechanical properties than those of light cured direct composites. A developed processing method is used in Paradigm MZ100, a composite block based on Z100 composite chemistry, to maximize the degree of cross-linking in the bis-GMA polymer-based composite material. It consists of 85% filled by weight with radiopaque zirconia-silica filler, with an average particle size of 0.6 microns (Rusin, 2001).

Brilliant Crios is a new reinforced composite block that contains amorphous silica and glass ceramic particles in a cross-linked methacrylate matrix (Matzinger, M. ve ark. 2018).

- **Zirconia (Full Contour)**

CEREC Zirconia was introduced in 2016 as among the most recently taken material for CAD/CAM restorations. The substance is a precolour, full-contour zirconia which could be prepared quickly and delivered in one visit (Babaier et al., 2022).

The rapid manufacturing time is due to the combination of initiate of the SpeedFire furnace, which can sinter zirconia restoration in less than 20 minutes. Zirconia possesses the least three times the flexural strength and fracture toughness of glass ceramic materials (Guazzato et al., 2004). It has a very high flexure strength suitable for crowns and limited span fixed partial dentures which could be cemented with common cements (André V., 2019).

- **Provisional Acrylic Materials**

Vita CAD-Temp (Vita)

To preserve the pulpal tissues from bacterial contamination and to preserve the periodontal tissues, accurate provisional restorations are required. In addition, it is necessary to prevent the tooth from moving out of the standard position in terms of upper or lower occlusion, and to preserve aesthetic and oral functions such as chewing and speaking. (Alt et al., 2011;Moörmann, 2006).

Utilize a range of innovative temporary blocks with the CEREC3 CAD/CAM system (Sirona, Bensheim, Germany). Due to their great strength, those substances can endure the milling process (Fasbinder, 2006). The strength and marginal accuracy of CAD/CAM provisional crowns are believed to have improved (Fasbinder, 2006).

Conclusion

Specifically, glass-ceramics are of interest to dentist among ceramic choices because they have better optical properties than polycrystalline ceramics (Arif et al., 2019). Furthermore, glass-ceramics bonded to dental substrates in a predictable and stable method using adhesive. Regardless, ceramic materials are fragile in nature (Poggio et al., 2017) and clinical research identified mass fracture which is the most common pattern of failure. Based on that perspective, usage of resin composites in CAD/CAM was investigated. These substances have enhanced optical qualities as well as elastic modules closer to the tooth surfaces, which reduces the ability to fracture and opposing tooth attrition and facilitates clinical restoration (Ludovichetti et al., 2018).

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Chapter 3

How Do Aberrant Alterations In The Gut Microbiome Affect Non-Alcoholic Fatty Liver Disease And Other Health Issues?

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ABSTRACT

Microbiota is an ecological community composed of microorganisms found in our bodies. Numerous studies on the importance of microbiota in human health have been conducted in recent years, and it has been demonstrated that qualitative and quantitative changes in microbiota are associated not only with intestinal but also with many non-intestinal diseases. The importance of microbiota in health is becoming more apparent as a growing number of studies reveal its role in autoimmune, allergic, and chronic inflammatory diseases. Bacteria, archaea, fungi, and viruses comprise this microbial community. In the formation of non-alcoholic fatty liver disease (NAFLD), microbiota stimulates fatty liver development, as well as increased energy from indigestible polysaccharides, small intestinal bacterial overgrowth (SIBO), increased intestinal permeability, increased plasma lipopolysaccharide levels, changes in tight junctions, and increased bacterial translocation. The bacterial generation of "endogenous ethanol" is another mechanism that contributes to the development of NAFLD. The intestinal microbiota continuously produces ethanol, and NAFLD is associated with higher blood and breath ethanol levels. The development and progression of NAFLD have been hypothesized to be significantly influenced by small SIBO. The impact of aberrant alterations in gut microbiota on non-alcoholic fatty liver disease and other health issues is discussed in this study.

Keywords: Microbiota, Non-alcoholic fatty liver disease, SIBO, Fatty liver.

Bağırsak Mikrobiyomundaki Anormal Değişiklikler Alkolik Olmayan Yağlı Karaciğer Hastalığını ve Diğer Sağlık Sorunlarını Nasıl Etkiler?

ÖZET

Mikrobiyota, vücudumuzda yaşayan mikroorganizmaların oluşturduğu ekolojik topluluklardır. Son yıllarda mikrobiyotanın insan sağlığındaki önemine ilişkin çok sayıda araştırma yapılmış ve mikrobiyotadaki kalitatif ve kantitatif değişikliklerin sadece bağırsak değil bağırsak dışı birçok kronik hastalıkla da ilişkili olduğu gösterilmiştir. Otoimmün, alerjik ve kronik inflamatuar hastalıklardaki rolünü ortaya koyan, giderek artan sayıdaki araştırmayla da mikrobiyotanın sağlıktaki önemi giderek ön plana çıkmaktadır. Bu mikrobiyal topluluk bakteriler, arkeler, mantar ve virüslerden oluşmaktadır. Mikrobiyota, non-alkolik yağlı karaciğer hastalığı (NAYKH) gelişiminde, sindirilmeyen polisakkaridlerden artmış enerji eldesi yanında, ince bağırsak bakteriyel aşırı çoğalması (SIBO), intestinal permeabilite artışı, artmış plazma lipopolysaccharide seviyeleri, sıkı bağlantılarda ortaya çıkan değişimler ve

bakteriyel translokasyon artışı ile karaciğerde yağlanmayı uyarmaktadır. NAYKH gelişimine katkısı olan bir diğer mekanizma endojen bakteriyel etanol üretimidir. Etanol sürekli olarak intestinal mikrobiyota tarafından üretilmektedir ve NAYKH'de artmış kan ve nefes etanol düzeyleri mevcuttur. İnce bağırsak bakteriyel aşırı çoğalmasının, NAYKH gelişimi ve ilerlemesinde önemli bir rol oynadığı varsayılmıştır. Bu çalışmada bağırsak mikrobiyotasındaki anormal değişikliklerin alkolik olmayan yağlı karaciğer hastalığı ve diğer sağlık sorunları üzerindeki etkisi tartışılmaktadır.

Anahtar Kelimeler: Mikrobiyota, Non-alkolik yağlı karaciğer hastalığı, SIBO, Yağlı Karaciğer.

INTRODUCTION

The term "intestinal microbiota" refers to all of the microbial species that present naturally in the gastrointestinal tract. Due to its part in the host's physiological development and defense mechanisms, the gut microbiota is regarded as a superorganism (Liu, S., et. al., 2016). It is made up of several kinds of microorganisms, such as bacteria, yeasts, and viruses, and it contributes to physiological, metabolic, nutritional, and immunological activities in the human body (Gerritsen J., et. al., 2011). Bacterial species are categorized taxonomically into domains, kingdoms, phyla, classes, families, genus, and species (Laterza, L., et. al., 2016). Numerous bacteria, the bulk of which are members of the phyla Firmicutes (Clostridium, Enterococcus, Lactobacillus, and Ruminococcus) and Bacteroidetes (Bacteroides and Prevotella), colonize the human intestine (Jandhyala S. M., et. al., 2015). New perspectives on intestinal microbiota have been developed as a result of recent scientific research and technological advancements like next-generation sequencing (NGS). Human cells are outnumbered by microorganisms by 1.3 times (Ghoshal U. C., et. al., 2020; Qin J., et. al., 2010). Genetics, way of life, usage of antibiotics, food, and personal cleanliness are all important factors in determining an individual's bacterial diversity (Prakash S., et. al., 2011).

New perspectives on intestinal microbiota have been developed as a result of recent scientific research and technological advancements like next-generation sequencing (NGS). Human cells are outnumbered by microorganisms by 1.3 times (Ghoshal U. C., et. al., 2020). Genetics, way of life, usage of antibiotics, food, and personal cleanliness are all important factors in determining an individual's bacterial diversity (Prakash S., et. al., 2011). A increasing corpus of recent research has revealed that dysbiosis, or problems of the gut microbiota, are linked to a number of illnesses, including gastrointestinal pain, diarrhea, asthma, diabetes, obesity, autism, and liver disease. A number of

gastrointestinal microbiota and hepatitis fibrosis pathways are involved in dysbiosis, which has a variety of etiologies including hepatitis virus, alcoholic liver disease (ALD), and non-alcoholic fatty liver disease (NAFLD). Each illness also has a unique liver metabolism (Usami M., et. al., 2015). Small intestinal bacterial overgrowth (SIBO), which has been linked to the etiology of NAFLD, has been shown in studies to modify the intestinal biota (Haitao S., et. al., 2021) (Figure 1).
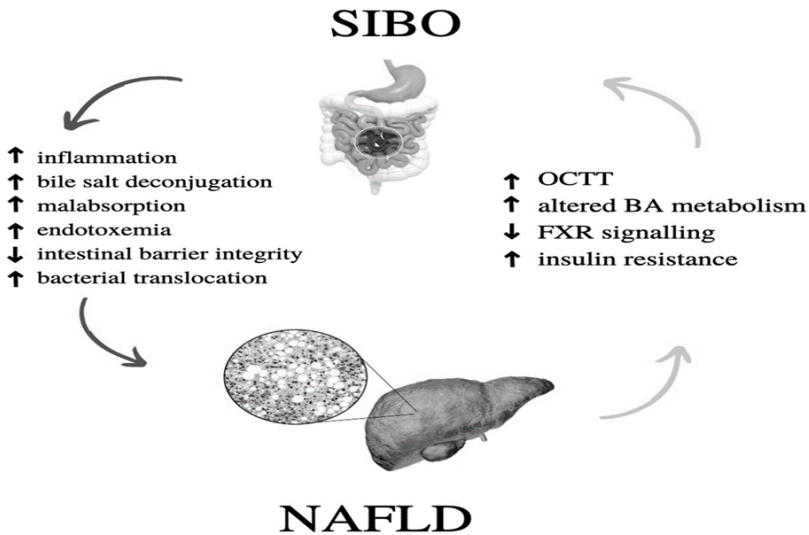
Figure 1. Possible SIBO and NAFLD interactions. OCTT—oro-ceacal transit time; BA—bile acids; FXR—farnesoid X receptor (Gudan A., et. al., 2023).

PROCESS OF INTESTINAL MICROBIOTA FORMATION

Microbiota takes on a unique structure by being affected by various factors such as environment, social life, nutrition and antibiotic use (Gudan A., et. al., 2023). It is established in the first second of life, influenced by the type of birth, such as normal or caesarean section. The environment is an important source of colonising bacteria for caesarean section babies, and these babies have less diverse gut bacteria in the first few weeks of life (Kalip K. and Atak N., 2018). Normal babies have their first contact with microbes in the birth canal, where colonisation is initiated by the mother's vaginal, gut and environmental microbiota (Grölund M., et. al., 1999) (Figur 2). Amniotic fluid, umbilical cord, placenta and uterine meconium all contain microbes according to recent studies. While Lactobacillus, Bacteroides and Prevotella bacteria are dominant in vaginal delivery, Staphylococcus, Corynebacterium, Propionibacterium and

Clostridium bacteria are dominant in caesarean section. The microbiome resulting from caesarean section has less bacterial diversity and late Bacterioidetes group bacteria colonisation (Rooks M.G. and Garrett W.S., 2016). In contrast to infants, adults have a microbiota containing Bacteroidetes and Firmicutes bacteria, whose diversity and proportional differences vary from person to person. Despite differences in the microbiome in each individual, the microbiota in healthy humans carry out common processes such as digestion, fermentation, methanogenesis, oxidative phosphorylation and the formation of lipopolysaccharides (Bäckhed F., et. al., 2015).

BACTERIAL OVERGROWTH IN THE SMALL INTESTINE

The duodenum, jejunum, and ileum, which make up the small intestine, are essential organs where digestion and nutrition absorption occur (Lynch S.V. and Pedersen O., 2016). Enterocytes, goblet cells, paneth cells, and endocrine cells make up the small intestinal epithelial cells. Enterocytes make up 95% of the cells. Enzymes like hydrolase, peptidase, carrier proteins, and receptors for different ligands are found in the microvilli of enterocytes (Caballero M.A.C., et. al., 2004). A condition known as SIBO, or small intestinal bacterial overgrowth, is characterized by an increase in bacteria in the small intestine that would typically reside in the large intestine (Osontokun B. and Kocoshis S.A., 2006). Malabsorption and increased nutritional loss are caused by intestinal villi damage, decreased synthesis of digestive enzymes, and intestinal barrier failure (Augustyn M., et. al., 2018). The inability to properly absorb carbohydrates may be caused by the loss of brush-edge disaccharidases due to mucosal injury or bacterial fermentation of sugars such sorbitol, fructose, and lactose. The metabolism of vitamins, proteins, lipids, and carbohydrates may be impacted by this (Dukowicz A.C., et. al., 2007). There are three conditions that can lead to bacterial overgrowth in the small intestine: immunoglobulin-containing mucin layer, reduced motility, and chronic achloric gastritis, which results in a shortage of stomach acid. Patients with SIBO may not have any symptoms or experience steatorrhoea or diarrhea as a result of malabsorption (Drasar B.S. and Shiner M., 1969). There is a natural system that operates under physiological circumstances to stop aberrant bacterial development in the small intestine. SIBO may manifest if one of these functional systems in the small intestine is compromised. The stomach's acidic pH, pancreatic enzymes, the proper intestinal barrier arising from the development and renewal of the intestinal wall, as well as the intestinal immune system, are a few examples of these systems. Constant diarrhea or bloating, along with abdominal pain, are symptoms of the condition. Malnutrition and anaerobic bacteria's use of

vitamins can result in vitamin shortages (B12, D, A, and E) as well as mineral losses (iron and calcium) (Wijarnpreecha K., et. al., 2020).
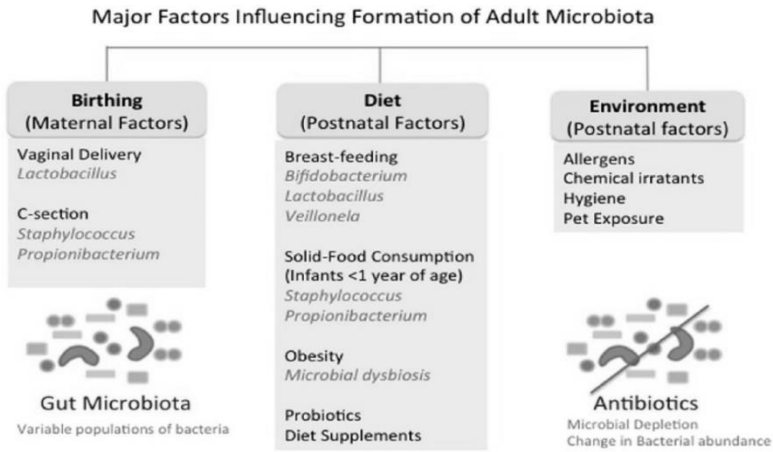

Figure 2. Shows the influences on the adult microbiota. Microbiota from the mother can pass to the baby while in the placenta, during delivery, and during breastfeeding. The newborn receives a distinct bacterial inoculum depending on whether the mother gives birth naturally or via cesarean section. Antibiotic use, nutrition, and environmental exposures can all have an impact on a child's microbiota over the course of their life (Grölund M., et. al., 1999).

BACTERIAL OVERGROWTH IN THE SMALL INTESTINE: DIAGNOSİS AND TREATMENT

Different methods have been put forth and assessed for the SIBO diagnosis. The most frequent diagnostic procedures include examinations for psychiatric symptoms, medical care, breath tests, small bowel aspiration, and culture (Losurdo G., et. al., 2020). Additionally, it is well-known that jejunal aspirate culture with a bacterial colony greater than 105 CFU/ml (colony-forming unit) is a crucial diagnostic benchmark for SIBO. However, due to its challenging process, this strategy is not favored (Wijarnpreecha K., et. al., 2020). In reality, the diagnosis of SIBO is based on thorough pathophysiological understanding, backed by an accurate evaluation of the clinical and metabolic status of patients (Rezaie A., et. al., 2023). It is not just a matter of counting the number of bacteria present. Understanding these main factors is very important in the diagnostic process. Understanding these key elements is crucial to the diagnosis procedure. Induction of remission, maintenance of remission, and therapy and adjustment of the underlying causes of SIBO are the three basic treatment modalities (Losurdo G., et. al., 2020).

PROBIOTIC AND PREBIOTIC

Probiotics are live microorganisms that strengthen the immune system, heal the body and reduce the amount of pathogenic and harmful bacteria. Probiotic bacteria usually belong to the genera Lactobacillus, Streptococcus and Bifidobacterium. Probiotic bacteria in the distal small intestine and colon are fed by undigested carbohydrates or fibres, which we call prebiotics for stronger probiotics (Ponziani F. R., et. al., 2016) (Figure 3). Gut microbiota treatment reduced intestinal inflammation and improved epithelial barrier performance in rats with fatty liver. As a result, probiotics are a new type of treatment for humans. The design of future clinical trials will undoubtedly be influenced by the considerable amount of experimental studies already available proving the positive benefits of probiotics and prebiotics (Imajo K., et. al., 2013).

Categories	Prebiotics	Probiotics
Content	Indigestible but selectively fermentable ingredients	Live microorganisms
Functions	Provide food for probiotics; increase number and improve activity of probiotics	Enhance the health and well-being of their host organisms' digestive tract
Health Benefits	Provide supportive function to probiotics	Reduce the number of pathogenic bacteria in the GIT and improve its function; improve immune system function; prevention of cellular damage from oxidative stress
Sources	Asparagus, Jerusalem artichokes, Bananas, Oatmeal, and Legumes	Yogurt, sauerkraut, Yakult, miso soup, fermented breakfast cereal and snack bars, soft cheeses, kombucha, kimchi, and sourdough
Side Effects	increase in fermentation, leading to increased gas production, bloating or bowel movement	Possibility of sepsis when given to immunocompromised patients

Figure 3. Differences between prebiotics and probiotics
(Lynch S.V., Pedersen O., 2016).

BACTERIOCIN

It is crucial for people's healthy growth and development that the foods they eat are trustworthy. Foods that we eat often have additives added to them to enhance their physical, chemical, and microbiological qualities as well as to lengthen their shelf lives (Cani PD, et. Al., 2008). Consumers have begun to demand safe and natural preservatives because some compounds have a detrimental impact on human health and, depending on the rate of use, might have harmful and carcinogenic effects (Çevik B. A. And Pirinçci E., 2017). Natural antimicrobial peptides called bacteriocins are produced by bacteria. They are protein-based, often with short chains and low molecular weight (Boğa A. And Binokay S., 2010). Particular significance is given to lactic acid

bacteria in the biocontrol of foods. In order to compete with other bacteria in the environment, lactic acid bacteria (LAB) are known to create antimicrobial peptides and tiny proteins known as bacteriocins (Zheng S. And Sonomoto K., 2018).

LIVER

Hepatic artery and portal vein are two significant blood arteries that supply the liver (Kumariya R., et. al., 2019). Hepatic portal vein and hepatic artery together supply the liver with around 75% and 25% of its blood, respectively (Clemente M.G., et. al., 2016). Blood containing oxygen is sent to the liver by the hepatic artery, which arises from the celiac artery in the abdominal aorta. Blood travels to the liver through the portal vein from the pancreas, spleen, and digestive tract organs. As a result, the liver regularly comes into contact with bacterial wastes from the intestine (Kester J.E., 2014). The straightforward elimination of these toxic chemicals from circulation is one of the liver's most crucial tasks (Abdel-Misih S.R.Z. and Bloomston M., 2010). Tight junction (TJ) protein is crucial in blocking the translocation of hazardous substances from the intestine to the portal system because endothelial and epithelial cells function as a barrier by generating a tight junction (TJ) in the intercellular area (Rui L., 2014). The disruption of the TJ in people with NAFLD can enhance intestinal permeability and bacterial translocation to the liver through the circulation, according to experimental investigations. The intestinal epithelium can be harmed, intestinal permeability can increase, and the liver can be exposed to toxic bacterial products (Zeisel M. B., et. al., 2019) as a result of gut microbiota alteration.

NON-ALCOHOLIC FATTY LIVER DISEASE

The most prevalent liver illness in the world is non-alcoholic fatty liver disease (NAFLD), which is a hepatic manifestation of metabolic syndrome (Miele L., et. al., 2009). The main risk factors for the onset and progression of NAFLD include hypertriglyceridemia, diabetes mellitus, and obesity (Suk K.T. and Kim D.J., 2019). NAFLD is characterized by excessive hepatocyte fat accumulation, which typically takes place in conjunction with obesity or liver steatosis. Although visceral fat deposition and dyslipidemia are causes of hepatic parenchyma in patients with chronic liver disease or cirrhosis, numerous studies have also demonstrated that intestinal microflora or bacterial numbers are compromised. As a result, dysbiosis, or an imbalance of bacteria in the gastrointestinal system, may be related to liver illness (Wijarnpreecha K., et. al., 2020). As a result, increased lipolysis of adipose tissue results from

hyperactivation of hormonally sensitive fatty acids (FFA/free fatty acids) (Bedogni G., et. al., 2004). Insulin resistance, which is linked, causes gluconeogenesis and slows down glycogen production. This in turn speeds up FFA production and inhibits beta oxidation. The "first strike" caused by IR that leads to lipid peroxidation may be amplified by antioxidant hepatic pathways in the cell, with excess FFA causing excess mitochondrial oxygen free radicals. Finally, necroinflammatory activity, fibrosis, and liver disorders result from the activation of many inflammatory pathways (Dietrich P. and Hellerbrand C., 2014).

The progression and development of NAFLD are reportedly influenced by a number of factors, including poor gut-liver dysfunction, small intestinal bacterial overgrowth (SIBO), and increased intestinal permeability (Dietrich P. and Hellerbrand C., 2014). NAFLD prevalence is quickly rising due to both increased genetic risk factors and a changing lifestyle. Genetic factors may contribute to the onset and progression of NAFLD, according to research (Paolella G., et. al. 2014). Haemochromatosis has been linked to NAFLD through a number of genetic polymorphisms, including those in the TLR gene, C3, MC4R, and domain-containing protein-3 patatin-like phospholipase (Cobbina E. and Akhlaghi F., 2017). All of these genes produce proteins that control the hepatic lipid metabolism (Duseja A. and Chawla Y.K., 2014). Apolipoprotein C3 (APOC3) and adiponutrin (PNPLA3) genes are linked by two notable polymorphisms.

INVESTIGATIONS INTO LIVER ENZYMES

The most frequent anomaly of laboratory results in NAFLD is elevated serum transaminase values, specifically elevated AST and ALT levels (Naik A., et. Al., 2013). The diagnosis of NASH is supported by an AST:ALT ratio of 1, although this is not adequate information. All biochemical parameters, the history, and the physical examination should be considered collectively when treating liver enzyme increases, and the aetiology should be thoroughly investigated (Bedogni G., et. Al., 2004). Patients with NAFLD and NASH may have normal levels of two crucial transaminase enzymes, aspartate transaminase (AST), also known as serum glutamic oxaloacetic transaminase (SGOT), and alanine transaminase (ALT), also known as serum glutamate pyruvate transaminase (SGPT) (Adams L.A. and Feldstein A.E., 2011). When assessing biochemical parameters, the patient's anamnesis and physical examination findings should be viewed as a whole, with particular attention paid to the rates, levels, and rate of growth of aminotransferases (Bedogni G., et. Al., 2004).

FACTORS AFFECTING THE DEVELOPMENT OF NAFDIA DUE TO INTESTINAL MICROBIOTA

Gut bacteria may have various roles in the pathophysiology of NAFLD. Hepatic toll-like receptor 4 (TLR4/Toll-like receptor 4), which is hypothesised to be involved in the development of hepatocellular cancer as well as liver inflammation and fibrosis, is continuously exposed to chemicals produced by the gut microbiota (Adams L.A., et. al., 2005). Recent research suggests that gut microbiota may play a role in the onset and progression of liver diseases by altering bile acid composition (Roh Y. S. and Seki E., 2013: Ridlon J.M., et. al., 2014). In addition, impaired choline metabolism, small intestinal overgrowth, high intestinal permeability, endogenous ethyl alcohol production by gut microflora, and impaired Farnesoid X receptor (FXR) activity have been associated with the development of liver diseases (Cobbina E. and Akhlaghi F., 2017).

CONCLUSION

The normal biology and function of intestinal epithelial cells are influenced by the gut microbiome. Multiple contributing variables, influenced by triggering factors including gut flora and food, result in complex metabolic disorders. Therefore, altering the gut microbiome may offer a fresh approach to treating or preventing NAFLD. The role of gut microbiota in NAFLD emphasizes the significance of the interactions between the gut and liver even further. SIBO and gut microbiota are recognized as being particularly significant in the etiology of NAFLD. Potentially, changing the microbiota in either a qualitative or quantitative way can lessen the impact of liver disease. Prebiotics or probiotics can alter the gut flora, which may be a crucial therapeutic approach in the management of NAFLD.

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Chapter 4

Influence of Intestinal Microbiota on Depression and Obesity

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ABSTRACT

Obesity has become a major global problem in recent years, with an increasing prevalence. The primary contributors to obesity are an increase in the consumption of high-energy foods, a decline in physical activity, and the resulting energy imbalance. It is a significant health factor that contributes to the increased risk of chronic diseases, such as cancer. The development of obesity has been the subject of numerous biochemical studies in recent years. Given the results of these studies, it is possible to conclude that the intestinal microbiota plays a significant role in the pathogenesis of obesity as well as energy metabolism. However, recent research has revealed that the intestinal microbiota has a greater impact on metabolism than previously thought. Additionally, the intestinal microbiota is crucial for the metabolism of polysaccharides and oligosaccharides and the production of short-chain fatty acids. Changes in the intestinal microbiota and microbial diversity have the most impact on glucose and lipid metabolism. The pathophysiology of obesity and depression is initiated by changes in glucose and lipid metabolism, which cause inflammation in the body. The gut microbiota is also known as the "second brain" since it controls and regulates the conditions required for a person's daily life. Many factors, including normal or caesarean section, breastfeeding or formula feeding, diet, stress, and geographical factors, affect the intestinal microbiota significantly. Disruptions in the gut microbiota affect the brain-intestine mikrobiota axis and invite a variety of diseases. Based on this information, intestinal microbiota may play a role in the treatment of obesity and depression. In this review, the relationship between gut microbiota, obesity, and depression was investigated.

Key words: İntestine, Microbiota, Obesity, Depression, Gut.

Bağırsak Mikrobiyotasının Depresyon ve Obezite Üzerindeki Etkisi

ÖZET

Obezite prevalansı, son yıllarda artarak tüm dünya için önemli bir sorun teşkil etmeye başlamıştır. Yüksek enerjili besin tüketiminin artması, fiziksel aktivitenin azalması ve bununla birlikte ortaya çıkan enerji dengesizliği obezitenin temel nedenini oluşturmaktadır. Obezite, kanser de dahil olmak üzere kronik hastalık riskinin artışında sağlık açısından önemli bir faktördür. Son yıllarda obezitenin gelişimi ile ilgili birçok biyokimyasal araştırmalar yapılmıştır. Bu araştırmalardan elde edilen bulguların ışığında bağırsak mikrobiyotasının, hem enerji metabolizması üzerinde hem de obezite

patogenezisi üzerinde önemli etkilerinin olduğunu söylemek mümkündür. Ancak yapılan son çalışmalar intestinal mikrobiyotanın, metabolizma üzerinde tahmin edilenden daha fazla etkiye sahip olduğunu göstermiştir. Bununla birlikte, intestinal mikrobiyota polisakkarit ve oligosakkaritlerin metabolizması ile kısa zincirli yağ asitlerinin üretiminde önemli fonksiyonlara sahiptir. İntestinal mikrobiyotadaki değişiklikler ve mikrobiyal çeşitlilikteki azalma öncelikle glikoz ve lipid metabolizmasını etkilemektedir. Glikoz ve lipid metabolizmasındaki değişiklikler ise vücutta enflamasyona yol açarak obezitenin patofizyolojik sürecini başlatmaktadır. Bağırsak mikrobiyotası insanın günlük yaşamı için gerekli şartların kontrolünü ve düzenlemesini sağladığı için 'ikinci beyin' olarak da adlandırılmaktadır. Normal ve ya sezeryan doğum, anne sütü ya da mama ile beslenme, diyet, stres, coğrafik unsurlar gibi birçok etmen bağırsak mikrobiyotası üzerinde önemli değişikliklere neden olmaktadır. Bağırsak mikrobiyotasında meydana gelen bozulmalar beyin-bağırsak bariyerini etkileyerek birçok hastalığa davetiye çıkarmaktadır. Bu bilgiler ışığında, gelecekte yapılacak çalışmaların intestinal mikrobiyotanın obezitenin tedavisinde potansiyel rol oynayabileceğini söylemek mümkündür. Biz bu derlemede bağırsak mikrobiyotasının obezite ve depresyon ile ilişkisini irdelemeye çalıştık.

Anahtar Kelimeler: Bağırsak, Mikrobiota, Obezite, Depresyon, Bağırsak**.**

INTRODUCTION

The term "microbiota" refers to the microbial population that can be found in the human body's various ecosystems, including bacteria, archaea, fungus, and protists (Knight R et. al., 2017:13; Khanna S and Tosh PK, 2014:13).   Joshua Lederberg introduced the term "microbiome" for the first time in 2001, defining it as "the ecological community of common, symbiotic, and pathogenic microorganisms that literally share our body space" (Lederberg J and McCray AT, 2001:13). It is also referred to as the community of microorganisms living in the human body and the genetic material of this community (Lederberg J and McCray AT, 2001:13).

Stomach and Duodenum
10^1 - 10^2 CFU/mL

Lactobacilli
Streptococci
Yeasts

Jejunum and Ileum
10^4 - 10^8 CFU/mL

Lactobacilli
Coliform bacteria
Streptococci
Bacteroides
Bifidobacteria
Fusobacteria

Colon
10^{10} - 10^{12} CFU/mL

Bacteroides
Bifidobacteria
Streptococci
Eubacteria
Fusobacteria
Clostridia
Veilonella
Coliform bacteria
Lactobacilli
Proteus
Staphylococci
Pseudomonades
Yeasts
Protozoa

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A healthy human body contains trillions of microbes (Figure 1) (Cresci GA and Bawden E, 2015:13).

Different microbiomes develop in healthy individuals as a result of factors like lifestyle and life history. To better understand the elements that affect the structure of the microbiome and affect human health, Ding and Schloss (Ding T and Schloss PD, 2014:13) applied community typing analysis to the 16S rRNA gene sequence from the human microbiome project and made three significant observations. 1) There were significant relationships between breastfeeding, gender, and educational attainment and the types of microbiomes found in various body regions; 2) there were significant relationships between breastfeeding, gender, and educational attainment and the kinds of communities found in various body regions. 3) They discovered that the gut and vagina have the most stable microbe communities, whereas the mouth cavity and vagina contain the least. The researchers came to the conclusion that there are significant differences in the human microbiome between individuals and in the individual's own body parts, and that these differences are probably caused by environmental factors like life history, lifestyle, education, and gender (Ding T and Schloss PD, 2014:13).

INTESTINAL MICROBIOTA

Microbiota is found in the gastrointestinal tract, oral cavity, skin, lungs, genitourinary system and amniotic fluid (Pelzer E. Et. al., 2017:13). Nervous tissue and intestinal microbiota contain the most microorganisms. The gut microbiome has been called the 'second brain' because it plays an active role in shaping, maintaining and homeostasis of human physiology (Sonnenburg J and Sonnenburg E., 2015:13). Gut microbiota affects the intestine, liver, brain and other organs at the molecular level. Acting as a barrier, intestinal microbiota affects metabolism by regulating absorption, digestion, bowel movement and mucosal immunity (Martin F-P J., 2017:13). The human gut microbiota now contains more than 35000 bacterial species, as opposed to the 500–1000 microorganisms that were once assumed to make up the gut microbiota (Ramakrishna B and Krishnan S., 2007:13; Frank DN et. al., 2007:13). The human microbiome project and metagenomic research on the human gastrointestinal tract have classified the gut microbiome into two groups based on their functions: high gene structure (HGC) and low gene structure (LGC). High level Akkermansia (Verrucomicrobia): Ruminococcus torque/gnavus ratio; HGC microbiomes: Anaerotruncus colihominis, Butyrivibrio crossotus, Akkermansia sp., and Fecalibacterium sp. (Le Chatelier E, et. al., 2013:13). According to reports, people with HGC have a gut flora that functions better and are less likely to be exposed to major dangers including metabolic diseases and obesity. Ruminococcus gnavus and Bacteroides genera were found in persons with LGC structure. It is recognized that both structures are connected to inflammatory bowel disease. Parabacteroides, Campylobacter, Dialister, Porphyromonas, Staphylococcus, and Anaerostipes are additional species in the gut microbiome (Swidsinski A, et. al., 2005: Joossens M, et. al., 2011:13). Firmicutes and Bacteroidetes make up the majority of the healthy microbiota in the intestine. Verrucomicrobia and Phyla Actinobacteria are next. The gut microbiota can exhibit temporal and geographical fluctuations, despite the fact that this is typically constant (O'Hara AM and Shanahan F, 2006:13).
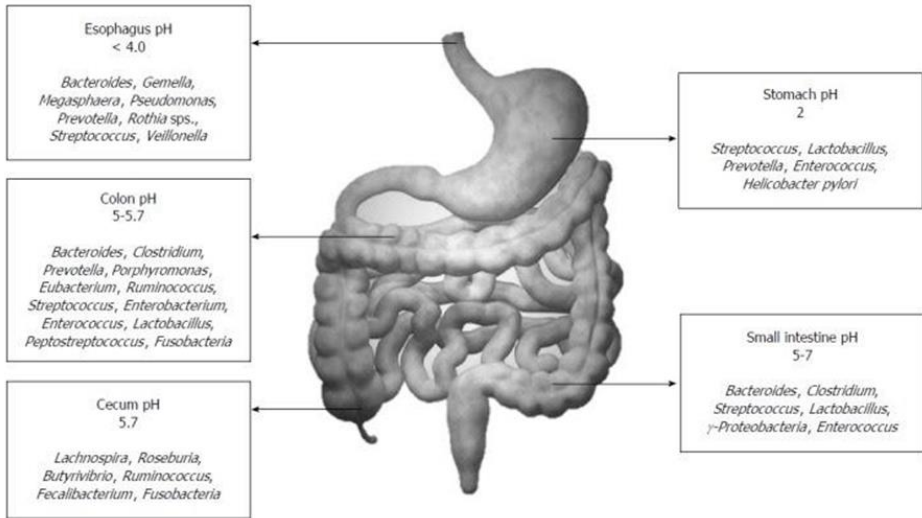
The temporal variety of the gut microbiota as it moves distally from the oesophagus into the colon is depicted in Figure 2 (Jandhyala SM, et. al., 2015:13).

The distal oesophagus, duodenum, and jejunum are where streptococcus is most commonly detected (Pei Z, et. al., 2004:13; Justesen T, et. al., 1984:13). The large intestine is where more than 70% of the body's bacteria are located. In the large intestine, Firmicutes and Bacteroidetes species are most prevalent. The ratio of incoming Firmicutes to Bacteroidetes has been linked to disease states (Ley RE, et. al., 2006:13). According to a study (Gillespie JJ, et. al., 2011:13), main pathogens such Campylobacter jejuni, Salmonella enterica, Vibrio cholera, Escherichia coli, and Bacteroides fragilis are also found in minute amounts in the human colon. Although the phylum Proteobacteria is underrepresented, a healthy microbiota is indicated by the abundance of species like Bacteroides, Prevotella, and Ruminococcus (Hollister EB, et. al., 2014:13). The lumen of the intestine is home to Bacteroides, Bifidobacterium, Streptococcus, Enterobacteriaceae, Enterococcus, Clostridium, Lactobacillus, and Ruminococcus. The major genera found in the epithelial crypts and mucus layer of the small intestine are Clostridium, Lactobacillus, Enterococcus, and Akkermansia (Swidsinski A, et. al., 2005:13).

INTESTINAL MICROBIOTA FORMATION

Previously, it was thought that the intestinal microbiome was generated during labor and that the microbiome was already present in the GI tract and uterus (Salazar N, et. al., 2014:14). Later research (DiGiulio DB., 2012:14;

Jiménez E, et. al., 2005: Aagaard K, et. al., 2014:14) revealed that the placenta, amniotic fluid, and umbilical cord all contain bacteria. It is believed that throughout the prenatal stage, bacteria in the amniotic fluid will colonize the fetus's growing gastrointestinal tract. Newborn children are exposed to a variety of microbes during the birth process, which helps to colonize their gut microbiome. The infant's gut flora is affected by the delivery method. When a baby is delivered vaginally, the gut microbiota resembles the bacteria in the vaginal canal, whereas when a baby is delivered through caesarean section, the gut microbiota resembles skin microorganisms (Moles L, et. al., 2013; Clemente JC, et. al., 2012; Dominguez-Bello MG, et. al., 2010:14). It has been noted that compared to caesarean section neonates, vaginally delivered infants had populations of more Bacteroidetes and fewer Firmicutes (Jakobsson HE, et. al., 2014). Nutritional and environmental factors are efficient in influencing the microbiota during the early stages of colonization after birth, according to certain researches (Wall R, et. al., 2009; Koenig JE, et. al., 2011:14), despite the fact that the initial colonization pattern is complex. The infant's intestinal colonization happens in stages. Aerobic microorganisms, many of which are harmful, such as enterobacteria, staphylococci, and streptococci, colonize the intestine during the early stages of colonization. By changing the intestinal environment, these early colonizers aid in the colonization of the anaerobic microbial community (Pop M, 2012:14). During the first year of life and later, depending on environmental factors including nutrition and antibiotic use, the organization of intestinal colonization alters (Palmer C, et. al., 2007; Morowitz MJ, et. al., 2011:14). The infant's immune system and gut microbiome are impacted by weaning, breastfeeding, and the sequential administration of various food types (Schwartz S, et. al., 2012:14). The development of the brain in pregnancy is influenced by a variety of factors that alter the mother's gut microbiome, including microbial metabolites, drug-induced chemical metabolites, and inflammatory changes.
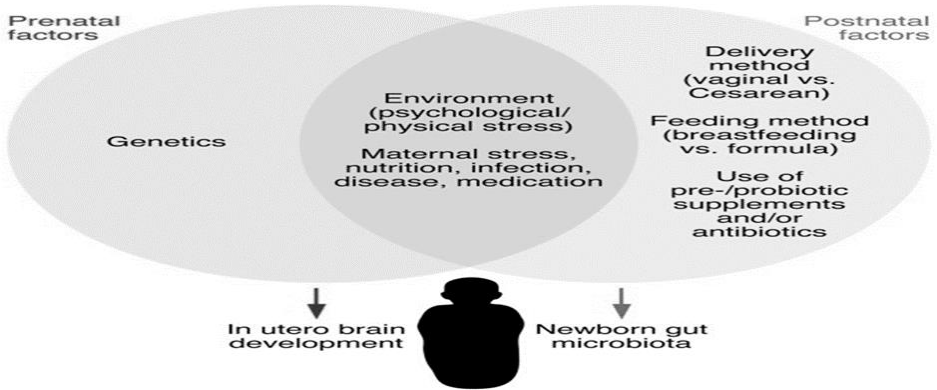
Figure-3. The mother's vaginal or skin-derived microbiota during labor (depending on the method of delivery) and numerous nutritional parameters (breastfeeding or formula feeding) have an impact on the newborn infant's microbiota after birth (Mayer EA, et. al., 2015:14).
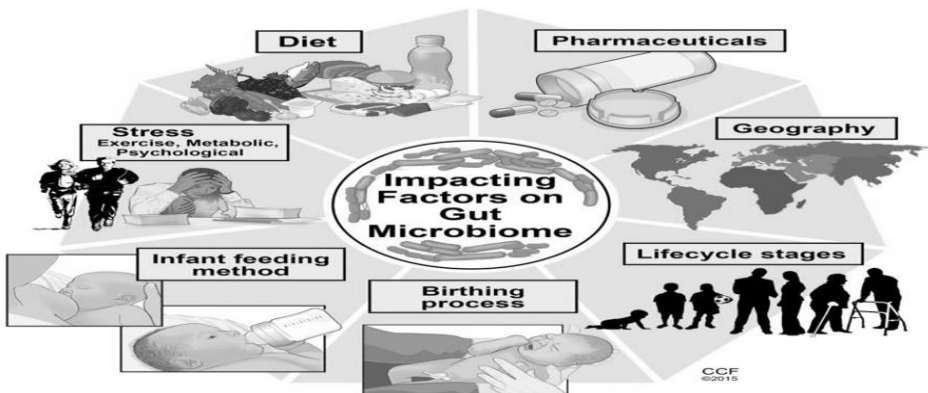
Figure-4. The infant's manner of birth and feeding, the aging process, the composition of the diet, geography, drugs, and stress can all have an im pact on the gut microbiota (Mayer EA, et. al., 2015:14).

CONTRIBUTING FACTORS TO INTESTINAL MICROBIOTA AGE

According to 16S rRNA-based sequencing studies, many taxa, including Escherichia-Shigella, Enterococcus, Leuconostoc, Lactococcus, and Streptococcus, are abundant in the first meconium (the first feces of the infant) (Gosalbes MJ, et. al., 2015:14). The Lactobacillus and Prevotella genera are the most common types of maternal vaginal bacteria that colonize the intestines of vaginally born newborns (Mackie RI, et. al., 1999:14). Streptococcus, Corynebacterium, and Propionibacterium genera predominate in the maternal flora of infants delivered via caesarean section (Mackie RI, et. al., 1999:14).

Premature babies' intestines contain members of the Bifidobacterium and Lactobacillus genera, albeit the exact species depends on feeding practices. Breastfed infants had a greater predominance of Bifidobacterium and Lactobacillus than formula-fed infants, who have Enterococcus, Enterobacteria, Bacteroides, Clostridia, and other anaerobic Streptococcus intestinal niches (Groer MW, et. al., 2014:14).

PROBIOTICS, PREBIOTICS, DIET, AND NUTRITION

Even though diet is one of the major determinants of health in humans, metabolism related to nutrition is crucial for a long and healthy life (Martin FJ, et. al., 2017:14). Following delivery, feeding the newborn breast milk or formula results in appreciable variations in the intestinal microbial makeup, according to several research (Sommer F and Bäckhed F, 2016; Brown EM, et. al., 2013). Likewise, due to several bioactive substances it contains, breast milk is superior to formula in terms of addressing the physiological needs of the newborn. These bioactive elements that make up breast milk are crucial for the development of numerous processes, including food digestion and absorption, immune system defense, and antimicrobial defense.

A balanced diet and the microbiome are positively correlated. Differences in population and culture are also linked to the composition of the gut microbiome. Actinobacteria and Bacteroidetes genera were higher in children living in Africa, while Firmicutes and Proteobacteria genera were higher in children living in Europe, according to a study (Sommer F and Bäckhed F, 2016:14; Walker AW, et. al., 2014:14; De Filippo C, et. al, 2010:15) comparing the gut microbiota of children aged 1-6 living in rural Africa and the gut microbiota of children of the same age group living in Western Europe. Actinobacteria and Bacteroidetes genera were effectively formed by the fact that children in Africa were nursed until the age of two and eaten a diet low in fat and animal protein and rich in starch, plant polysaccharides, and fiber. Additionally, the Firmicutes and Proteobacteria genera are more prevalent as a result of the fact that children in Europe are fed meals high in animal protein, glucose, starch, and fat (Qin J, et. al., 2010:15).

When there are enough probiotics, which are living bacteria, in the intestinal microbiota, they have positive benefits. In the intestinal microbiota, increasing the good bacteria (Bifidobacterium infantis, Streptococcus thermophilus, Lactobacillus casei, Lactobacillus plantarum, Lactobacillus bulgaricus, Lactobacillus acidophilus, Bifidobacterium longum, E. coli) reduces the pathogenic bacteria (Clostridial myonecrosis, Bacteroides), maintaining the

normal balance of bacteria. The immune system is bolstered and the body's resistance is increased by intestinal microbiota (Viramontes Hörner D, et. al., 2017:15). Prebiotics are food ingredients that contain indigestible oligosaccharides that promote intestinal bacterial activity and growth. symbiotic relationship between probiotics and prebiotics (Binns N., 2013:15).

DRUG

Patients' reactions to these treatments (therapeutics) vary greatly, just as there are variances in the pharmacokinetics of various pharmaceuticals. The bioactivities of inert treatments, such as prodrugs, are transformed into active forms by microorganisms in the gut microbiota (Carmody RN., 2014):15; Sousa T, et. al, 2008:15). The body is equipped with a defense system to ward against ingested infections as well as numerous other elements, including an acidic gastric environment, proper bile flow, peristaltic movements, and intestinal flora. By attaching to binding sites and releasing inhibitory chemicals in competition with other pathogens, the gut microbiota is thought to directly defend the host from pathogens. Unbalances in the gut microbiota happen when these defense mechanisms are compromised (Stecher B and Hardt WD., 2010:15).

ANTIBIOTIC

The microbial microflora of the colon is also impacted by antibiotic treatments in addition to pathogenic microorganisms. The majority of antibiotics have broad range activity, making them useful in treating a variety of illnesses. The microbial flora of the stomach suffers long-term damage as a result of antibiotics that are intended to kill pathogenic organisms (Jernberg C, et. al., 2007:15). Additionally, antibiotics are known to increase the number of bacteria that are resistant to them in the gut wall (Lofmark S, et. al., 2006:15).

STRESS

Stress is the term used to describe an organism's overall reaction to demands or pressures from the environment. Stress comes in a variety of forms, including acute, chronic, acute, and chronic, recurring acute. Stress might be minor or severe, predictable and controlled or unpredictable and uncontrollable, occur in context or out of context (Lucassen PJ, et. al., 2014:15).

The hypothalamo-pituitary adrenal (HPA) axis is activated by both psychological and physical stimuli. A hormonal reaction follows, starting with the release of corticotropin-releasing hormone (CRH), which then increases the

release of adrenocorticotropic hormone (ACTH) throughout the body, promoting the production of glucocorticoids (cortisol) in the adrenal cortex (De Palma G, et. al., 2014:15). Psychological and physical stressors also cause the release of catecholamines (noradrenaline and adrenaline). The gastrointestinal tract and gut microbiota are highly sensitive to stress and stress mediators. Enteric bacteria (microbiota) react to neurochemical mediators released by the host's intestines due to stress and this reaction initiates a bacterial infection response (Lyte M, et. al., 2011:15).

Catecholamines (adrenaline and noradrenaline) are released as a result of both psychological and physical stressors. The gut microbiota and digestive system are extremely responsive to stress and its mediators. When the host's intestines release neurochemical mediators as a result of stress, enteric bacteria (microbiota) respond to these mediators, which starts an infection response (Lyte M, 2011:15; Bravo JA, et. al., 2011; Bercik P, et. al., 2011; Bercik P, et. al., 2010:15).

OBESITY

Obesity is a complex illness characterized by the buildup of excess body fat. Body mass index defines overweight as 25.0-29.9 kg/m2, obesity as 30 kg/m2, and those with a BMI greater than 30 kg/m2 as morbidly obese and extremely morbidly obese. In numerous wealthy nations, the prevalence of obesity is rising daily (Mendez MA, et. al., 2005:15). Obesity has been linked to biological, psychological, behavioral, genetic, socioeconomic, and cultural aspects, despite the fact that the precise cause is unknown (Skelton JA, et. al., 2011:15). In obesity, an excessive calorie intake leads to a rise in body weight, and an excessive amount of energy is stored as fat and results in adiposity. The first of the elements that contribute to obesity is the rise in adipose tissue as a result of a reduction in physical activity. The causes of obesity might also be psychological. For instance, eating as a coping mechanism for mental tension might result from the loss of a close relative, life-threatening illnesses, stress, mental breakdown, etc. Children with obesity have three times as many fat cells as children with normal weight (Guyton AC and Hall JE., 2001:15). The majority of the causes of obesity are neurogenic illnesses. Obesity is brought on by ventromedial hypothalamic lesions, which increase a person's appetite. By damaging the hypothalamus, pituitary tumors in the hypothalamo-hyposiferous portal contribute to the development of obesity (Guyton AC and Hall JE., 2001:15). Genetic factors are one of the other causes of obesity. The nutritional center and the pathways that control the storage of fat and the consumption of

energy malfunction, which leads to the development of obese genes. Obesity has three single-gene (monogenic) causes: leptin receptor mutation, congenital leptin gene deficiency, and mutation in MCR-4 (Guyton AC and Hall JE., 2001:15). According to a study (Farooqi IS, 2004), genetic disorders including Bardet-Biedl and Prader-Willi syndrome contribute to obesity.

CONNECTION BETWEEN INTESTINAL MICROBIOTA AND OBESITY

More than 40 trillion bacteria make up the human gut microbiota (Sender R, et. al., 2016:15). 90% of the human gut microbiota is made up of the two main taxa Firmicutes and Bacteroidetes. The 274 genera of Bacillus, Lactobacillus, Mycoplasma, and Clostridium make up the Firmicutes phylum. In the human intestinal microbiota, the genus Bacteroidetes is the most prevalent (Ley RE, et. al., 2005:15). The gut microbiota is crucial for the digestion, absorption, and utilization of dietary nutrients (Duca FA and Lam TKT, 2014:16; Bakker GJ, et. al., 2015:16). According to studies, the gut microbiota controls how much food a person eats by releasing hormones that alter metabolism and by activating the hypothalamic centers for fullness and hunger (Kairupan TS, et. al., 2016:16).
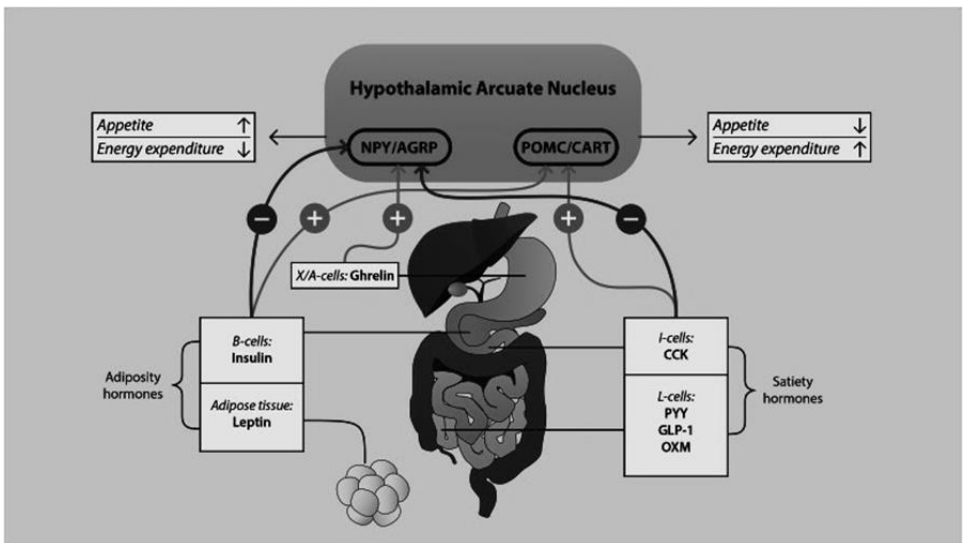
The microbiota, gut, and brain axis is a two-way signaling pathway that controls hunger, energy storage, and energy expenditure to stabilize body weight (Bauer PV, et. al., 2015:16) (Figure-5).

Figure 5 shows that the digestive tract and adipose tissue both release satiety and adipocyte signals. The NPY/AGRP and POMC/CART-containing neurons in the hypothalamic arcuate nucleus respond to these hormones either directly or indirectly. An important function of this arcuate nucleus is the control of food intake and body mass index. The orexigenic effects of NPY/AGRP neuron activity contrast with the anorexigenic effects of POMC/CART neuron stimulation. Agouti-related protein (AGRP), cocaine- and amphetamine-regulated transcript (CART), cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), neuropeptide Y (NPY), oxyntomodulin (OXM), pro-opiomelanocortin (POMC), and peptide tyrosine (PYY) are only a few of the compounds mentioned. Tyrosine has a crucial role in controlling these systems (de Clercq NC, et. al., 2016:16). It is still unclear from human investigations which particular bacteria are present or absent in the gut microbiota of obese people and whether they play a role in the onset of obesity. It was found that in obese people, Firmicutes concentration increased while Bacteroidetes concentration dropped (Ley RE, et. al., 2005:15). Bacteroidetes ratio declines in firmicutes in obese people. It must be investigated if this proportionate alteration in the gut microbiota is the primary cause of obesity or one of its secondary causes (Ley RE, et. al., 2005:15).

More so than in men, the Firmicutes: Bacteroidetes ratio rises as body mass index (BMI) rises in women (Castaner O, et. al., 2018:16). Hydrolysis of indigestible polysaccharides is provided by firmicutes bacteria. More energy and fat are consumed through feeding as a result of the increase in these bacteria's density, which also causes a similar rate of decline in Bacteroidetes (Walters WA, et. al, 2014:16). In obese people, the species of Lactobacillus and Bacteroides fragilis were positively correlated with body mass index. Bifidobacterium species were discovered to be more prevalent in lean people than in obese people and to have a negative correlation with body mass index (Castaner O, et. al., 2018:16). Obese people had a larger concentration of actinobacteria than thin people, including Bifidobacterium and Collincella species (Tseng CH and Wu CY, 2019).

ANXIETY AND ITS SYMPTOMS

More than 350 million people worldwide suffer from depression, a neuro-psychiatric condition with a high relapse rate (Ledford H, 2014). Depressive disorders include: destructive mood, inability to regulate emotion, major depression, irreversible depression, premenstrual dysphoria, substance/drug-induced depression, and depression brought on by secondary factors, according

to the Diagnostic and Statistical Information of Mental Disorders (fifth edition DSM 5). The most typical kind of depression is major depressive disorder (M Harm, 2013:16). Depressed mood (DM) or anhedonia (lack of interest or pleasure) are two symptoms. Changes in appetite or weight, sleep issues (insomnia or excessive sleep), psychomotor agitation or regression, exhaustion or energy loss, decreased thinking or attention, feelings of worthlessness or excessive guilt, and suicidal ideation are some other symptoms (M Harm, 2013:16). To ascertain if a major depressive episode has occurred or not, symptoms are gathered in accordance with DSM-5 criteria (M Harm, 2013:16). There is disagreement over whether the quantity of symptoms reflects the severity of the depression or whether the intensity of each symptom can be used as a gauge to determine whether the depression is light, moderate, or severe. As a result, rating depression scales like the Hamilton depression rating scale (HAMD) are frequently used to determine the severity of depression. The most used scale for assessing depression is now the HAMD (Hamilton M, 1960:16).

DEPRESSION AND GUT MICROBIOTA: A CONNECTION

The combination of hereditary and environmental variables causes depression (Belmaker R.H and Agam G, 2008:16). Some persons may be predisposed to depression by certain genes, psychological make-up, and stressful life circumstances (Aan het Rot M, et. al., 2009:16; Bukh J.D, et. al., 2009:16). However, research has demonstrated that the gut microbiota is crucial to the pathogenesis of depression (Forsythe P, et. al., 2010:16; Evrensel A. and Ceylan M.E, 2015:16;Dash S, et. al., 2015:16; Kundu P., et. al., 2017:16; Liang S, et. al.,2012:16). Major depressive disorder is primarily characterized by functional abnormalities of the brain, hypothalamo pituitary-adrenal (HPA) axis, immune system, and gut-brain axis. Impaired neurotransmitter release, declining neuroplasticity, and aberrant neuronal activity are all examples of brain disorders (Aan het Rot M, et. al., 2009:16; Chaudhury D, et. al., 2015:16). Dysfunction of the HPA axis is the result of negative feedback in the feeding mechanism (Leonard BE, et. al., 2005:17; Mahar I, et. al., 2014:17). The immune system alters as a result of chronic inflammation brought on by depression (Rook GAW and Lowry CA, 2008:17; Lima-Ojeda J.M, et. al., 2017:17). Abnormalities in the gut microbiota and gastrointestinal illnesses are the main causes of gut-brain dysfunction (Collins SM and Bercik P, 2009:17; O'mahony SM, et. al., 2017:17;Wilhelmsen I, 2000:17).

DISEASE OF THE BRAIN

Emotional states are significantly influenced by neurotransmitters. Neurotransmitter imbalance and depression go hand in hand (Hamon M and Blier P, 2013:17;Lener MS, 2017:17). Depression symptoms are assumed to be brought on by monoaminergic neurotransmitter deficit, or a decline in the monoamine neurotransmitters (serotonin, norepinephrine, and dopamine) associated with positive mood states like happiness (Hamon M and Blier P, 2013:17; Rm H, 2000:17). The underuse of SSRIs in some patients, however, has demonstrated the existence of other depression-related processes (Liu B, et. al., 2017:17). Other investigations (Lener MS, 2017:17; Pytka K, et. al., 2016:17; Murrough JW, et. al., 2017:17) have demonstrated that depression also alters the release of other neurotransmitters. Gamma-aminobutyric acid (GABA) release, for instance, is inhibited in depression, whereas glutamatergic and acetylcholine are hypersecreted.

Amygdala activity is increased in depressed patients because prefrontal cortex and hippocampus function is compromised, despite the fact that the prefrontal cortex, hippocampus, and amygdala all play critical roles in the regulation of emotion, stress responses, self-control, motivation, and cognitive reaction (Serafini G, 2012:17). The neurogenesis process is significantly regulated by brain-derived neurotrophic factor (BDNF). It is hypothesized that an increase in neuronal apoptosis causes the BDNF content to drop during depression. As a result, long-term antidepressant therapy increases neurotrophic factors like BDNF and stimulates neurogenesis. By lowering neuronal apoptosis, the hippocampal formation enhances mood and cognition (Aan het Rot M, 2009:16; Mahar I, et. al., 2014:17; Sahay A, 2007:18). The new neuroplasticity theory states that neuroplasticity impairment brought on by a variety of risk factors, such as neurotransmitter imbalance and inadequate BDNF, is what leads to depressive symptoms (Kraus C, et. al., 2017:19).

ABNORMALITIES OF THE IMMUNE SYSTEM

In the pathology of depression, inflammation is evident. Depression develops as a result of immune dysfunction and ongoing inflammation (Barden N, 2004:18;Juruena MF, et. al., 2004:18; Kunugi H, 2010:18;Schiepers OJ, 2005:18; Lindqvist D, et. al., 2007:18). Depression is thought to be caused by neuroglia dysfunction-induced neuroinflammation and neuroplasticity degradation, according to the cytokine, neuroinflammation, and inflammation hypotheses (Schiepers OJ, 2005:18).

DYSFUNCTION OF THE GUT-BRAIN

Patients with depression frequently exhibit gut-brain dysfunction, including changes in the gut microbiota, metabolism, appetite, and functional gastrointestinal disorders (Logan AC and Katzman M, 2005:18;Jiang H, et. al., 2015:18; Naseribafrouei A, et. al., 2014:18). Major depression is a systemic condition in addition to a mental disorder. Patients frequently suffer from a variety of dysfunctions, including peripheral dysfunction, immunological dysregulation, brain dysfunction, including gut brain dysfunction, and HPA axis abnormalities (O'mahony SM, et. al., 2015:18). In mammals, the brain-gut axis transmits messages in both directions between the brain and the gut. Through a number of channels, including nerves, the HPA axis, and the immune system (Liang S, et. al., 2018:18), it links the brain and gut. Depression is likely brought on by factors including disease and psychological stress that interfere with the brain-gut axis' normal function (O'mahony SM, et, al., 2011:18; Scott LV, et. al., 2013:18). The gut-brain axis plays a key role in the operation of numerous systems, including those involved in metabolism, immune, endocrine, and neurological systems. The gut-brain axis is altered by abnormalities in the gut microbiota, which impacts the brain and behavior. The structure and operation of the gut-brain axis are also impacted by changes in the brain (Mayer EA, et. al., 2015:18; Kelly JR, et. al., 2016:18). The gut-brain axis influences the brain and behavior, which are significant contributors to mental disorders, in accordance with the gut microbiota hypothesis (Kelly JR, et. al., 2016:18; Rieder R, et. al., 2017:19). By controlling the joint operations and structuring of the gut-brain, gut microbiota has an impact on the growth and maturity of the HPA axis. The blood-brain barrier is regulated, neurotransmitter synthesis and recognition are impacted, neuralgias and neurogenesis are affected, myelin is formed, and the immune system's function has an impact on the development and function of the brain (Sudo N, 2014:19; Gareau MG, et. al., 2007:19; Eutamene H and Bueno L, 2007:19; Sudo N, et. al., 2005:19;Honda K and Littman DR, 2016:19; Thaiss CA,et. al., 2014:19;Kim S, et. al., 2017:19; Ogbonnaya ES, et. al., 2015;Castillo-Ruiz A, et. al., 2018:19; Erny D, et. al., 2015:19). All of these important functions are impacted by the gut microbiota.
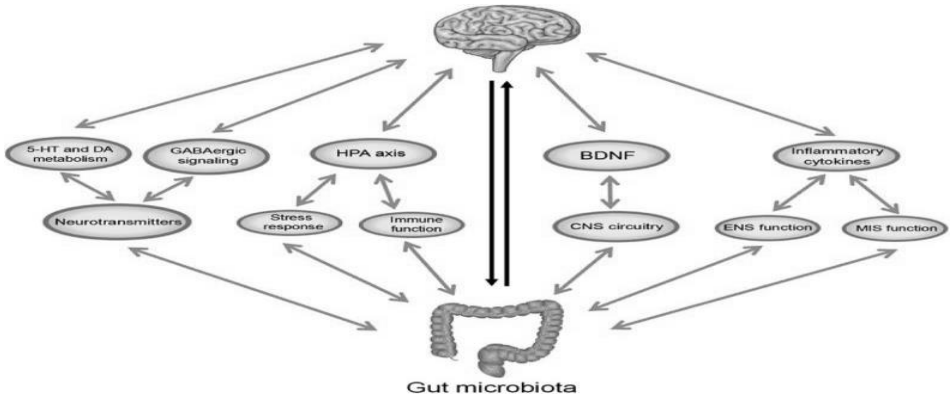
Gut microbiota

The mechanism of abnormalities in the microbiota-gut-brain axis that cause depression is depicted in Figure 6 (Du Y, et al., 2020:19).

Clinical research has revealed that depressed patients' gut flora differs significantly from that of healthy controls. According to several research, the diversity and richness of the microbiome reduced in patients (Kelly J.R, et. al., 2016:19). Prevotellaceae substantially increased in the mucosal flora, Prevotella increased while Faecalibacterium and Ruminococcus dropped at the genus level, and Bacteroidetes and Proteobacteria increased while Firmicutes reduced at the phylum level (Liu Y, et. al., 2016:19). According to reports, the variety of Lactobacillus and Bifidobacterium has decreased (Aizawa E, et. al., 2016:19). The specific differences between depressive patients and controls are still up for debate, despite the fact that all of these investigations have shown aberrant gut flora in depressed individuals. These variations are likely the result of various diagnostic and categorization criteria and faecal microbiota detection techniques (Zheng P, et. al., 2016:19; Lin P, et. al., 2017:19).

According to research using animal models, the intestinal microbiota of depressed animal models was comparable to the intestinal microbiota of depressed people when comparing sad animal models to animals in the control group. Firmicutes and Lactobacillus species were found to be declining while Bacteroidetes species were increasing (Park AJ, et. al., 2013:19; O'mahony SM, et. al., 2009:20; Yu M, et. al., 2017:20). Stress alters the gut microbiome, which makes people more vulnerable to depression. Through its impact on the brain and the body's stress system, chronic stress alters the gut microbiota (Holdeman LV, et. al., 1976:20; Galley JD, et. al., 2014:20; Bailey MT and Coe CL, 1999:20). Weaning and diet are two elements that directly affect gut flora. By upsetting the gut microbiome, poor diets cause depression (Yatsunenko T, et. al., 2012:20; Frei R, et. al., 2012:20). The normal gut flora is disrupted by

the use of refined meals, excessive saturated fats, sweets, and dietary additives, which increases vulnerability to depression (Slyepchenko A, et. al. 2017:20; Owen L and Corfe B, 2017:20;Noble EE, et. al., 2017:20). Malnutrition and dysfunction in the microbiota-gut-brain axis are intimately related (Bereswill S., et. al., 2014:20; Oriach CS, et. al., 2016:20). By altering the gut microbiome, antibiotics, ongoing stress, and starvation cause depression (Ng KM, et. al., 2013:20).

INTESTINAL   MICROBIOTA   AND   DEPRESSION-OBESITY RELATIONSHIP

Adolescence is a time when depression and obesity are both widespread issues (Kessler RC, et. al., 2005:20; Skinner AC and Skelton JA, 2014:20). Some potential mechanisms relating depression and obesity include biological, genetic, behavioral, and lifestyle factors. With the disruption of hunger and dietary patterns, signs of depression in teenagers include weight gain or loss, incapacity to exercise, and excessive ingestion of foods high in carbohydrates (Privitera GJ, et. al., 2013:21; Privitera GJ, 2008:21; Stice E, et. al., 2005; Nierenberg AA, et. al., 1998:21; Spoor ST, et. al., 2006:21; Witherspoon D, et. al., 2013:21). These elements raise the likelihood of obesity (Witherspoon D, et. al., 2013:21). Obesity and depression are positively correlated (Shelton RC and Miller AH, 2010:21; Luppino FS, et. al., 2017:21). Obesity is associated with a 58% greater risk of depression among depressed individuals, and obesity is associated with a 55% higher risk of depression over time (Luppino FS, et. al., 2017:21).

CONCLUSION

We indicated in this article that the gut microbiota, sometimes known as the "second brain," is home to a variety of bacteria. Prenatal, postnatal, and perinatal variables all have an impact on the gut flora. The gut microbiota is impacted by the baby's gestational age, cesarean delivery method, and breastfeeding or formula feeding choices. Our gut microbiota is significantly influenced by factors such as age, diet, usage of probiotics and prebiotics, drug and antibiotic use, stress levels in the environment, and genetics. Metabolic syndromes and psychiatric illnesses are brought on by problems with the gut brain barrier or the intestinal mucosa. Obese people are those whose body mass index is greater than 30 kg/m2. Obesity is brought on by an excessive buildup of bodily fat. Obesity is caused by a variety of variables, including genetic, environmental, and socioeconomic factors. Obese people had higher

concentrations of Firmicutes and lower concentrations of Bacteroidetes, it was found. A neuropsychiatric illness called depression is characterized by symptoms like weariness lasting longer than two weeks, mood swings, and decreased enjoyment in activities. The most prevalent kind of depression is major depressive disorder. Depression is brought on by a variety of reasons, including gut-brain problems in major depressive disorder, dysregulation of the gut microbiota, immunological abnormalities, and brain and HPA axis dysfunction. By disrupting the gut flora, factors like poor food or malnutrition can also cause depression.

Adolescence is when depression and obesity are most prone to co-occur. Depressive thoughts and the want to eat that is brought on by this can also be avoided if the degeneration of our gut microbiota is stopped by balancing factors like nutrition, food, drug use, and everyday stress. Obesity and depression are mutually reinforcing processes. To better comprehend and further explore the underlying mechanisms of gut-obesity depression, new knowledge, additional research, and clinical investigations are required.

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Chapter 5

A Clinician's Perspective on The Diagnosis and Treatment of Primary Hyperparathyroidism

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ABSTRACT

INTRODUCTION
Definition

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterized by high or inappropriately normal parathormone (PTH) levels accompanied by hypercalcemia. PHPT is a disease caused by abnormal secretion of PTH in response to plasma calcium that occurs in one or all four parathyroid glands as a result of inherited or acquired changes in genes (Wilhelm et al, 2016;151:959-68).

PHPT is considered to include three clinical phenotypes: classical PHPT characterized by overt target organ involvement, asymptomatic PHPT with mild asymptomatic hypercalcemia, and in normocalcaemic PHPT, normal albumin-corrected and ionised serum calcium levels are accompanied by persistently high PTH levels..

Epidemiology and Pathogenesis

PHPT is common among women, usually in the postmenopausal period, with a male to female ratio of 1:4. The prevalence of PHPT varies by geographıc regıon and race, with a prevalence of 0.86. For normocalcemic PHPT, a range of 0.4% to 11% has been reported (Wermers et al, 2015; 297-308). Until the 1970s, PHPT was known as a symptomatic disease characterized only by severe clinical symptoms, but since then, asymptomatic cases of PHPT have been detected with the routine measurement of serum calcium levels, leading to a fivefold increase in the incidence of the disease compared to baseline (Bilezikian et al; Lancet. 2018;391:168-78).

The aetiological distribution of patients with PHPT is as follows: solitary parathyroid adenoma in 80%, hyperplasia in 10-15%, multiple parathyroid adenomas in 5% and parathyroid carcinoma in less than 1% (Bilezikian et al; 2016;2:16033).

The etiology of PHPT is not clearly known There is evidence that ionizing radiation can be relevant to the development of PHPT. The role of genetic factors in the development of PHPT is not clear, but genes that regulate the cell cycle are to blame.(Thakker et al, 2016;280:574-83). Examples of genes implicated in the development of PHPT include CCND1 encoding cyclin D1 and multiple endocrine neoplasia (MEN1) encoding menin. Approximately 5-10% of PHPT patients are inherited or familial. Tumor suppressor genes are responsible for MEN1 syndrome and familial isolated primary hyperparathyroidism (FIHP), while MEN 2A syndrome is characterized by mutation of RET, a proto-oncogene. CDKN1B is involved in MEN 4 syndrome (Pardi et al, 2017;12).

LABORATORY ASSESSMENT

The first diagnostic test for suspected PHPT in primary care requires measurement of albumin-adjusted serum calcium level followed by PTH levels.Renal functions and 25(OH)D level should also be known for optimum evaluation of PTH. Phosphorus and bone alkaline phosphatase levels are not required for the diagnosis but are instructive. Urinary calcium is not a diagnostic criterion in PHPT, but knowledge of excretion is important for stone formation. It is a criterion for the differential diagnosis of familial hypocalciuric hypercalcemia and for the decision of surgical treatment of asymptomatic cases (Bilezikian et al, 2014 ;99:3561-9). Current recommendations for the assessment of a patient with PHPT are presented in Table 1 (Bilezikian et al, 2014 ;99:3561-9). In addition to lumbar spine and hip DXA measurements, the distal third of the radius bone should also be measured in PHPT patients.Patients should be evaluated with abdominal X-ray, ultrasonography or CT, as stones and/or nephrocalcinosis are frequently seen even in incidentally discovered PHPT patients (Cipriani et al, 2015;100:1309-1315.)

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Table 1: Clinical and laboratory evaluation in primary hyperparathyroidism

In the blood sample Serum parathyroid hormone, calcium, phosphate, alkaline phosphatase, renal function tests, 25-hydroxyvitamin D3
Urine sample In 24-Hour urine calcium and creatinine measurement
Fracture risc assessment Bone mineral density by dual-energy x-ray absorptiometry
Vertebral spine assessment Lumbar vertebrae radiography Lumbar vertebrae by computed tomography Vertebral fracture assessment by dual-energy x-ray absorptiometry
Renal stone assessment Urinary calcium >400 mg/day Abdominal imaging by plain radiography Urinary ultrasonography Urinary computed tomography scan

Modified from Bilezikian JP, et al. (Bilezikian JP, et al., 2014; 99:3561–3569)

PHPT is diagnosed by laboratory tests. High PTH level accompanying hypercalcemia confirms the diagnosis. In PHPT, serum calcium levels may intermittently fall into the normal range on repeated laboratory tests, and a pattern of recurrent hypercalcaemia is compatible with the diagnosis of PHPT. Inappropriately normal (>20 pg/ml) PTH levels in a patient with hypercalcemia are consistent with a diagnosis of PHPT (Yu et al, 2009;71:485-93). The drugs to be questioned in the differential diagnosis of PTH-induced hypercalcemia are thiazide diuretics and lithium. Non-parathyroid causes of hypercalcemia such as malignancy or granulomatous diseases are confirmed by severely suppressed PTH levels and thus PHPT is ruled out. Some substances can interfere with PTH measurement, the agent to consider when low PTH levels are encountered is biotin. In this case, the test should be repeated a few weeks after stopping the biotin.

In the differential diagnosis of PHPT, the first disease to be excluded is FHH, a rare genetic disorder of the calcium-sensing receptor (CASR). Due to the high penetrance of FHH, almost all patients have hypercalcemia in young adulthood. In FHH, 24-hour urinary calcium is low (<100 mg) and the calcium clearance/creatinine clearance ratio is <0.01. Genetic testing can be performed for subtypes of FHH. It is important to differentiate PHPT from FHH, there is no indication for surgery in AHH, and since the problem in AHH is a genetic defect, it is not curative.

Secondary and tertiary hyperparathyroidism must be made in the differential diagnosis of PHPT. In secondary hyperparathyroidism, serum calcium level is low or normal although PTH is high. This condition most commonly develops secondary to vitamin D deficiency and osteomalacia. Tertiary hyperparathyroidism is defined as the occurrence of a hypercalcemic state as a result of autonomic function of severe secondary hyperparathyroidism due to advanced renal failure. This effect can occur in dialysis patients but can also occur after kidney transplantation.

Radiology or nuclear medicine has no role in the process of diagnosing PHPT. Imaging scans help to determine the anatomical location in preparation for treatment.

First, PHPT is diagnosed with laboratory techniques and then localization studies are performed before treatment. $Tc^{99}M$ -sestamibi imaging is the most commonly used method. Ultrasonography is highly effective in detecting parathyroid pathology in the neck when performed by an experienced endocrinologist or radiologist, but may not be sufficient for mediastinum. Magnetic resonance imaging, computed tomography, preferably 4-dimensional

computed tomography are the preferred imaging modalities if it cannot be detected by classical localization studies.

CLINICAL PRESENTATİONS OF PHPT
Symptomatic PHPT

Classical PHPT is a multisystem disorder affecting the skeletal, renal and urinary, gastrointestinal, central nervous and cardiovascular systems. In addition to overt hypercalcemia, clinical manifestations include bone pain and fractures (especially vertebral), X-ray findings of osteitis fibrosa cystica, nephrolithiasis, nephrocalcinosis and renal failure. Other clinical features of classic PHPT include muscle weakness, polyuria and polydipsia, peptic ulcer disease, pancreatitis, and neurological symptoms ranging from mild mental impairment to coma. Classical PHPT is now less common with routine measurement of calcium levels

Asymptomatic PHPT

The majority (>80%) of PHPT patients are detected in the 'asymptomatic PHPT' stage, thanks to the easy availability of biochemical tests. Individuals with asymptomatic PHPT do not have the skeletal and renal findings described in classical PHPT. Most patients with PHPT are discovered incidentally with the detection of hypercalcemia in routine laboratory tests. Serum calcium levels are moderately elevated, usually 1 mg/dl lower than the high limit of normal. Serum phosphate levels are usually mildly low, rarely severe hypophosphatemia may develop. Alkaline phosphatase levels may be elevated, but often remain within the normal range (Bilezikian et al, 2014;99:3561-9).

Levels of 25-hydroxyvitamin D (25OHD) between 20-29 ng/mL are generally defined as insufficiency, while levels <20 ng/mL are defined as deficiency. In PHPT, 25OHD levels are usually <20 ng/mL, while 1,25-dihydroxyvitamin D (1,25(OH)D), which is activated vitamin D is detected high-normal or high.

Normocalcemic PHPT

After complete exclusion of secondary hyperparathyroidism, patients with normal calcium levels despite elevated PTH levels are classified as NPHPT. NPHPT can be asymptomatic or symptomatic. (Cusano et al, 2013; 98:2734-2741).

EVALUATION OF CLASSİCAL SYMPTOMS

In the presence of severe hypercalcemia in patients with PHPT, that is, when serum calcium levels exceed 12 mg/dL, symptoms related to the hypercalcemia itself, such as polyuria, polydipsia, constipation, anorexia, emesis, dehydration, dysrhythmias, and mental status disturbance, even coma, are evident.Today, patients with PHPT usually present with main target organ effects.

Skeletal manifestations

 Skeletal symptoms may include fragility fractures, bone deformities and skeletal pain. Classically, osteitis fibrosa cystica describes the radiographic features of the condition, in which brown tumors, lytic lesions, subperiosteal bone resorption of phalanges and bone cysts are seen (Misiorowski et al, 2017;58:380-5). BMD loss is seen primarily in the cortical bone regions. Spongy regions are partially preserved, as in the spine. There is an increased risk of fracture in the vertebrae and peripheral bones in PHPT(Bandeira et al,2014;58:553-61).

Renal manifestations

Currently, the main renal manifestations of PHPT are hypercalciuria and nephrolithiasis. While the prevalence of clinically symptomatic kidney stones is 10-20%, the prevalence of nephrolithiasis detected by imaging techniques without causing any clinical symptoms is much higher (Cipriani et al, 2015;100:1309-15). Renal failure characterized by an estimated glomerular filtration rate (eGFR) <60 ml/min is 15-17%.

Neuropsychological features

PHPT can cause a wide range of non-specific problems, including depression, anxiety, fatigue, poor quality of life (QoL), sleep disorder and cognitive impairment.

Other symptoms

When PHPT is symptomatic, the rheumatologic neuromuscular, cardiovascular, and gastrointestinal systems can be commonly affected. Gastrointestinal problems such as pancreatitis and peptic ulcer disease are seen in classical hyperparathyroidism (Bilezikian et al, 2016;2:16033).

TREATMENT OF PHPT

Surgical treatment

The treatment of primary hyperparathyroidism is surgical. Surgical treatment is recommended for all classic PHPT patients and asymptomatic PHPT patients who fulfill even one of the surgical criteria (Bilezikian et al, 2014 ;99(10):3561-9): Hypercalcemia >1 mg/dL above normal; fracture; kidney stones, hypercalciuria and other stone risk factors; T-score <-2.5 at any site; and age <50 years (Table 2).

Table 2: Parameters indicating surgery in patients with asymptomatic primary hyperparathyroidism

Parameter	Criteria for parathyroidectomy
Clinical finding	Age <50 years
Laboratory findings	Serum calcium>1 mg/dL exceeded the upper limit of normal Creatinine clearance <60 mL/min urinary calcium (>400 mg/day)renal stones or increased risk
Radiological findings	Reduced Bone mineral density by dual-energy x-ray absorptiometry to a T-score <-2.5 at any site by dual-energy x-ray absorptiometry Vertebral fracture detected by imaging methods Renal calculi or nephrocalcinosis on imaging

Adapted from Bilezikian JP, et al. (Bilezikian JP, et al., 2014; 99:3561–3569)

Non-surgical management

Patients who are not suitable for surgical treatment are placed on a follow-up program.Surgical indications are assessed by performing serum calcium and PTH testing every six months, DXA testing annually or biennially, annual urinary calcium measurements and high-level skeletal and renal scanning when necessary.

Pharmacological Management

Cinacalcet is a calcimimetic agent which binds to the calcium-sensing receptor to lower serum calcium levels in non-operative patients with serum calcium levels >1 mg/dL higher than normal or symptomatic hypercalcemia. Serum calcium levels normalize in >70% of patients (Peacock 2005;90:135-141). Patients with low bone density may be given bisphosphonates or denosumab to treat osteoporosis.

Nutrition Recommendations

Calcium intake

Dietary calcium restriction means that the parathyroid tissue can sense the reduced calcium intake and is more stimulated to produce and release PTH into circulation. Contrary to common perception, normal calcium intake is recommended for PHPT patients according to their needs, not calcium restriction. 800 mg/day for female younger than 50 years and male younger than 70 years; 1000 mg/day for female older than 50 years and male older than 70 years (Rosen et al, 2011;14:79-84).

Vitamin D

Despite clinical observations linking higher biochemical indices of PHPT with low 25-hydroxyvitamin D levels, structural skeletal indices measured by quantitative CT or HRpQCT are not so clearly associated. To restore vitamin D sufficiency, Vitamin D2 must be used in reasonable amounts, starting with 1000 IU per day (Bilezikian et al, 2014;99:3561-9).

Hydration

Adequate hydration, use of diuretics if possible and avoidance of immobilization are the main precautions in a hypercalcemic patient. 2000 ml of fluid intake per day is recommended in outpatients.

CONCLUSION

In PHPT, PTH secretion is inappropriately high for serum calcium concentration, but sometimes the PTH level may be within the laboratory reference range. Conversely, in normocalcemic PHPT, the PTH level consistently rises above the normal reference range.Tertiary hyperparathyroidism associated with end-stage renal disease should be excluded in the definition of PHPT. It is extremely rare that hypercalcemia associated with malignant tumors is associated with ectopic secretion of PTH. Another aspect of the differential diagnosis is FHH. The urinary calcium/creatinine clearance ratio may be helpful as a differentiating point. For patients requiring treatment, the curative solution is parathyroidectomy. Pharmacologic approaches are available for other patients who do not meet surgical requirements or are not suitable for surgery.

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Chapter 6

Nano-Based Drug Delivery System for Cancer

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ABSTARCT

INTRODUCTION

The study of science, engineering, and technology at the nanoscale is referred to as nanomedicine. The word is Greek in origin and means "dawrf" but it is a synonym for "billionth" in science the concept and idea of nanotechnology originally was first introduced to the world when the physicist Richard Feynman who worked at he California Institute of Technology in 1959 said that ' there's enough space at the bottom' (Bayda et al, 2019). Nearly ten years after Richard first developed a method for manipulating and reshaping individual atoms, professor Norio Taniguchi first used the word "Nanotecnology." The advent of the scanning tunneling microscope in 1981, which allowed researchers to observe individual atoms for the first time, marked the beginning of nanotechnology. We are now able to observe, manage, and modify atoms at the molecular level thanks to nanotechnology. Atoms are in charge. for the creation of everything around us, including the food we eat, the clothes we wear, and even our own bodies. When nanotechnology is used in the field of medicine, it is called "nanomedicine." Nanomedicine, despite being new to the field of medicine, It has demonstrated exceptional potential in treating and diagnosing a wide range of medical and life-threatening conditions, including COVID-19 and cancer. Unlike the common believe Cancer is a disease in which dysfunctional cells are formed and widening into surrounding tisses, not abnormally growing tissues (Hausman, 2019). When it comes to detecting cancer, the current methods used can only detect when a visible change has already occurred to the tissue, at which point thousands of cells have already multiplied and even metastasized. In addition to current technology only being able to identify the presence of a cancer but not its characteristics or the nature of the tumor, which require painful and expensive biopsies.

Thus, nanotechnology can be used to address two issues: detecting changes as soon as they occur and identifying disease characteristics. Antibotics that binds to receptors which are commonly found on cancerous and non-cancerous cells can be coated onto nanoparticles detected on MRI(magnetic resonance imaging) and CT(Computed tomography) scans furthermore this concept can be applied to various molecular makers, meaning that specific stages and types of cancers could be recognized using nanotechnology (Bayda et al, 2019). Curative effecincy, poor blood-distributing, steadiness, solubility, and intestinal take in; a lack of selectivity; side effects; and fluctuations in plasma concentration are some of the few of the burdensome problems that the traditional usage of drugs displays in the remediation of many diseases therefore nano- based Drug delivery systems (NDDS) have been created to get over these restrictions and disadvantages. NDDS provides accurate drug delivery and targeting, preventing negative side-effects, necessitating decreased dosages, and protecting the molecule from

degradation (Shi et al, 2010). Recent developments in nanotechnology suggest that drug carriers made of nanoparticles with ideal physicochemical and biological properties can range in size from 1 to 1000 nm (small-size, raised drug accumulation and curative effects, ability to overpass cell or tissue blocks, planned drug delivery) (Dang, 2020). the application of nanoparticles as medication-carriers can significantly reduce the unpleasant side effects of conventional medications used to treat many chronic diseases such as cancer, asthma, hypertension, human immunodeficiency virus (HIV), and diabetes.

Controlling the rate of drug release from compounds or doses, in addition to the rate of medication delivery to absorbent membranes and surfaces, as well as the rate of drug release at specific sites are among the goals of drug delivery systems. Bearing in mind that the ability to control drug release and its distribution in the body are the two main components of drug delivery systems. When choosing the best method for delivering nano-based drugs, the biophysical and biochemical possessions of the aimed drugs choosen for therapy plays a key role. In order to reduce toxicity problems, nanoparticles have been mainly used recently with natural products. Creating them in drug-loaded nanoparticles is also a popular green chemical strategy due to the fact that they reduce the amount of potentially harmful substances in the biosynthetic process. As a result, the use of green nanoparticles to carry drugs is likely to reduce their negative effects. Their bioactivity can be improved by modifying the size, shape, water resistance and surface properties of the nanostructures (Patra et al, 2018). Some of the features of ideal nano-based drug distribution systems include that they are harmless, biocompatible, degradable, and physiologically stable both in vivo and in vitro. It should be limited to the required location only. The avarage of release of the drug must be predictable and controlled. No leakage during transportation. In addition, the transportation system should be easy to prepare or reasonably clear in terms of reproduction and economical.

Nanomaterials used in drug delivery system
Biopolymeric nanomaterials

Biopolymeric nanomaterials are more convient compared to the artifical polymers, as they are biodegradable, biocompatible and harmless in nature, many are presently being researched and developed to deliver drugs to specific desired sites such as polymeric micelles, dendrimers, liposomes, solid lipid nanoparticles (SLNs), metallic nanoparticles (magnetic, gold), nanofiber ,nanotubes and nanospheres (Mu et al, 2020).

POLYMERIC MICELLES

Polymeric micelle are nano-sized drug delievery system charatertericzed by a core-shell structure originated from self-assembly of amphipililic block co-polymers in aquerous solution (Zhang et al. 2014). an inner core and outter corre are the two parts that make up polymeric micelles . the existence of essential and modified features of polymeric micelles makes them particularly well fitted for drug delivery purpose. the co-polymers hydrophilic shell, which consists of hydrophilic non-biodegradable polymers such as poly(alkylacrylic-acide), poly(N-Isopropylacrylamide), and poly(ethylene-glycol), maintain stability in hydous medium and allows interconnections with plasmatic proteins and cell membrances (Eskiler etal, 2015). paclitaxel, doxorubicin, tamoxifen, camptothecin, and porphyrins are some Different non-polar medications that are surrendered in the hydrophobic core of the micelles to allow for their regulated release. The hydrophobic core could be made of a biodegradable, non-biodegradable, or only marginally biodegradable water-dissoluble polymers, such as poly(propylene oxide) (PPO), poly(-benzyl-L-aspartate) (PBLA), poly(L-lactic acid) (PLLA), poly(lactic-co-glycolic acid) (PLGA), poly(-caprolactone) (PCL) (Eskiler et al, 2015).

Polymeric micelle has a size that ranges between 10 to 100 nm that guarantees great durability, sterility and prolonged blood circulation (Patra et al, 2018). Furthermore polymeric micelles contains polymer chain that alter their stability and its crucial in drug deli-every to prevent interactions between single polymer chain and the loading drug.

DENDRIMERS

Dendrimers have comes along way in the last 25 years since their inceptions originally created as a wonder molecule of chemistry. Hyper branched globular particles with a distinctive three-dimensional structure are called dendrimers. Dendrimers is now a fourth class of polymers its mainly used for entrapment of drugs by non-covalent interaction (Pandey and Mahara, 2017).

A core initiator, internal layers made up of repeated units that are radially linked to the interior core and the most recent interior generations are connected to the exterior (terminal functionality) are the three componentsthat make dendrimers (Eskiler et al, 2015).

Types of dendrimer

1. PAMAM Dendrimers: These are employed in gene transfection because they have a positive charge on their surface.

2. PPI Dendrimers: Applications in Biology and Material Science

3. Limited use of liquid crystalline (LC) dendrimers for DNA delivery

4. Application of core shell (tecto) dendrimers in nanomedicine, including drug distribution

5. Chiral dendrimers: Potential applications include chiral hosts for enantiomeric resolutions and chiral catalysts for asymmetric synthesis.

6. Peptide dendrimers are used at delivery systems for drugs and genes in the biomedical field.

7. Hybrid dendrimers: They could be used to deliver drugs.

8. PAMAM-organosilicon (PAMAMOS) inverted dendrimers: Potential uses in nano-lithography, photonics, electronics, chemical catalysis, and other fields.

9. Glycodendrimers: They may be used to deliver medications to lectin-rich tissues at specified sites (Pandey and Mahara, 2017).

Due of their special characteristics, dendrimers have been intensively researched for application in cancer therapy. Dendrimers have been loaded with various chemotherapeutic drugs to boost their curative efficacy, and it has been demonstrated that these chemicals preferentially aggregate in cancer cells by negetive targeting. Dendrimers, besides, it can be coupled with a wide range of cancer-aiming ligands (such as biotin, folic acid, amino acids, peptides, aptamers, and monoclonal antibodies), allowing them to actively target and cure cancer cells (Pandey and Mahara, 2017). In addition Dendrimers are also effective as drug delivery methods for silencing genes.Folic acid and methotrexate are two of the most efficient site-specific targeting medicines that are delivered using dendrimers (Mu et al, 2020).

LIPOSOMES

Liposomes, also known as bilayer vesicles, are composed of cholesterol and phospholipids(Mu et al, 2020). Where the phospholipids that make up the liposomal determine the physical and alchemical features such as (volume, permeabilization, charge consistency, steric barrier). Liposomes are either single-layered or multi-layered (MLV, 100 nm-20 m). Small single-layered vesicles (SUV), which range in size from 25 to 100 nm, and large single-layered vesicles (LUV), which range in size from 100 to 1000 nm, are the other two kinds of single-layered liposomes (Karami et al, 2018).

It is anticipated that liposomes will have a promising future for use in industrial production, as they are characterized by several advantages such as high encapsulation efficiency, excellent targeting and low toxicity (Mu et al, 2020), which are among the primary goals in the use of nanomaterials.Due to its distinctive features such as its size, having both hydrophobic and hydrophilic

structures, improved therapeutic effects, biocompablity, etc., it has been successfully used in cancer treatment as well as in gene therapy research (Eskiler et al, 2015). Liposomes consist of a structure that includes an inner hydrophilic layer and a hydrophobic layer that are trapped within lipid bilayers, which offers special capabilities. The liposomes transport the drugs into the cells through the use of endocytosis or fusion, which allows the release of the drug without causing any side effects and is protected from breakdown by plasma enzymes (Patra et al, 2018). The liposomes can also be readily changed either by coating the outer exterior of linking several exterior conductors PEG-like specialized antibodies and peptides to target cancer tissues.

SOLID LIPID NANOPARTICLES (SLNs)

A novel carrier for colloidal drugs such as polymeric nanoparticles, dendrimers, liposomes and SLN some of the drug delivery challenges like weak drug loading ability, issues with unsettled size and features and unrestricted drug release can be overcomed . SLNS which range in size from 10 to 1000 nm is of great interest due to its special properties that make it stand out from other materials like its small volume, wide exterior area, elevated drug tolerance, confinement adequecy, decreased toxicity, outsanding physical stabilization, restrictied drug release, prentention from drug degradation, and avoidance of organic solvents. In addition, SLNS has a solid lipid structure that is solid at normal temperature, also the loaded molecule's ability to fit tightly into a delivery system depends on its lipid structure (Reddy and Shariff, 2013).

SLNS is frequently used to combine drugs with lipophilic and hydrophilic carriers that do not have harmful effects. This is due to the fact that the basic structure of SLNS is made up of lipids and its biocompatiblty, which is crucial to the drug loading at a high rate (Tekade et al, 2017). SLNS while used as drug delivery systems has been demonstated to enhance the cytotoxic outcomes of drugs along with reduce harmful outcomes on Normal cells. in order to load lipophobic and hydrophilic medicines in the lipid structure as well as to allow gene distrubution The coating of SLNs has also received more focus recently. raised cellular cumulation of the medication caused by negative or active aiming has been said to help overcome P-gp based MDR resistance.

Metallic nanoparticles

High drug loading capacity, functionalization viability, and lack of immunogenicity are some of the compatiable features that Metallic and inorganic nanoparticles has shown as a drug carriers(Eskiler et al,2015). Gold,silver and Platinum which are metal- based nanoparticles have been tested as a drug delivery

systems as (Qian et al) utilized gold nanoparticles (AuNPs) combined with cetuximab [an epidermal growth factor receptor (EGFR) that's being aimed from a monoclonal antibody) and showed that cetuximab indeed enhanced cytotoxicity in both EGFR-positive non-small cell lung cancer(NSCLC)both in vitro and in vivo. Compared with cetuximab alone, cetuximab combined with AuNPs substantially repressed reproduction and emigration of EGFR-overexpressing NSCLC cells and accelerated apoptosis. Furthermore, a significant reduction in tumor weight and tumor volume was observed in a mouse lung cancer model with little or no damage after treatment with AuNP-integrated cetuximab (Patra et al, 2018).

Nanospheres

Hollow nanospheres can be made via micro emulsion polymerization or by coating colloidal decorations with a fine layer of polymer material, then removing the template that are biodegradable and biocompatible. Biodegradable nanospheres and non biodegradable nanospheres are two categories that nanoshoeres can be put in. Biodegradable nanospheres contain albumin nanospheres, polypropylene dextran nanospheres, gelatine nanospheres, modified starch nanospheres, and polylactic acid nanospheres, poly-lactic acid (PLA), poly -D- L-glycolide (PLG), poly-D- L-lactide-co-glycolide (PLGA), and poly-cyanoacrylate (PCA) (Eskiler et al, 2015). The hollow gold nanosphereshas attracted tremendous amount of interest as claimed by the latest findings of hollow gold nanospheres's possessing outsanding chemical and physical properties for drug distrubtion.

As a result of the fact that hollow gold nanospheres have distinct alchemical and physical features for drug delivery, they are tremendous interest. According to the recent results, the hollow temple of the nanosphere produces the least amount of mass and enhances the loading of useful substances and drugs, which is essential for drug delivery. The drug is released through diffusion. Depending on the synthesis of the polymer matrix and its ability to imbile fluids, rapid release of the drug is possible. They can also avoid the rapid filtering of phagocytes, which leads to a blood circulation that lasts longer. In addition, nanosphere have the ability to release the existing drug over a long period of time. Nanospheres are considered one of the most desirable types of nanomaterials for drug delivery for several reasons, including their non-toxicity or low toxicity as well because they can pass through cell and tissue barriers to arrive the desired parts. Moreover, the ligand's binding to the sphere's superficial makes site-specific targeting easier. The polymeric nanocarrier releases the drug not only by

diffusion but also by responding to environmental, thermal, biological or chemical events with site specificity (Pathak et al, 2019).

Nanofibres and nanotubes

Nanofibers and nanotubes are made by electrospinning from the majority of polymer materials by virtue of easy process and control mainly in two ways either self-assembled from peptide amphiphiles, or formed on carbon dioxide surfaces. despite the significant concerns regrading their safety, carbon nanotubes have seen an increase in intereset in the nanomedicine filed given the uniqueness of Electrospun continuous nanofibres as a result of their depiction of macroscopic structures in one dimension and nanostructures in two dimensions (Sreekant, 2013). Electrospun continuous nanofibres are smother to make comparing to carbon nanotubes which have high air pollution concern. Electrospun continuous nanofibres of the biodegradable polymer poly(lactic-co-glycolic acid) (PLGA) packed with dexamethasone in neural prosthetic applications has been utilized. The surface of the nanofibre was coated with the frontal polymer poly(3,4-ethylenedioxythiophene), which was then put on the microfabricated neural microelectrodes that were inserted into the brain (Contreras-Cáceres, 2019).

CONCLUSION

Given that nanotechnology has the unique ability to outdo the drawbacks and restrictions of classic medicines like harsh side effects, lack of absorption and inability to site specificity target, it is anticipated in the future to increase the usege of nanotechnology in medicine, especially in drug delivery quickly. with the possiblity of developing new methods that carry a specific therapeutic treatment using drug delivery technologies developed to treat cancer or diabetes. When creating target-specific drug delivery systems, metallic, organic, inorganic, and polymeric nanostructures, such as dendrimers, micelles, and liposomes, are commonly taken into account. These nanoparticles are specifically added to drugs that have limited solubility and poor absorption to increase their effectiveness. Note that the effectiveness of nanostructures such as delivery systems varies according to their sizes, shape, and innate biophysical/chemical properties. The polymers must be biocompatible and biodegradable.

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Chapter 7

Alternative Strategies for Control of Necrotic Enteritis in Poultry

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ABSTRACT

In the poultry industry, intestinal tract infections are a significant problem, resulting in severe economic losses. Necrotic enteritis (NE) caused by *Clostridium perfringens*, which may be clinical or subclinical form, is an important infection that results serious economic losses in the poultry industry. The previous studies showed subclinical NE can cost higher than 5 cents per animal, and the annual cost of necrotic enteritis to the global industry is predicted to be about $6 billion, including output losses and control steps. *C. perfringens* formerly known as *Bacillus welchi*, is a Gram-positive, rod-shaped, anaerobic bacterium. Although type A toxin of *C. perfringens* is the main responsible for the NE, most studies mention a new type called Type G, which contains the NetB toxin. The bacterium is widely present in nature, including in the intestinal flora of healthy animals. The predisposing factors with the colonization of the bacterium in the intestinal flora of the animal is inevitable for NE infection in chickens. The clinical cases have a high mortality. Although mortality is low in the subclinical cases, it causes more serious economic losses. The use of antibiotic growth factors has played an important role in protection against NE, increasing feed utilization rates and animal productivity. However, the use of antibiotic growth factors has been banned due to increasing antibiotic resistance in animals. Currently, many studies are being conducted on the research of new alternative products to antimicrobial growth factors in the fight against NE. In this chapter, we focused on phytogenics, probiotics, vaccines, and other feed additives that can be used as an alternative to growth factors in the control of NE.

Keywords: Alternative strategies, Clostridium perfringens, Control, Necrotic Enteritis, Poultry

INTRODUCTION

Poultry production is one of the most vibrant parts of the sustainable agricultural production system and has increased significantly since 1970 compared to other animal food producing industries (Vaarst et al., 2015:609-620). The health status of poultry is directly related to intestinal health, including the immune system, microbiota, and structural integrity of the intestines. The digestive tract's condition has an impact on absorption, nutritional digestion, and metabolism as well as disease resistance and immunological response. Any problems in the gastrointestinal system of chickens can result in enteric infections (Kelly and Conway, 2001:612-613). Therefore, enteric diseases are the most important problems resulting economic losses in the poultry production due to reduced weight gain, high mortality, cost of treatment, and raised risk of antimicrobial residues in poultry products offered for human consumption. Although biosecurity measures are applied at the highest level in poultry industry, there is always a risk of developing bacteria-based infections due to the commensal bacteria placed in the intestinal flora of the animals (M'Sadeq et al., 2015a:1-11).

Necrotic enteritis (NE) caused by *C. perfringens* is the most prevalent infection in poultry, especially occurring in broilers (Cooper et al., 2013:92-97). Necrotic enteritis is characterized by inflammation and necrosis of the gastrointestinal tract, with a crucial decrease in growth performance, and a large increase in herd mortality in clinical cases. The annual losses due to NE are assessed at approximately $6 billion (Sarmah et al., 2021). An economically important of necrotic enteritis in broiler production, the gradual elimination of the use of antimicrobial feed additives as growth factors in the outcome of a significant problem re-emerged (Sarmah et al., 2021).

Several predisposing factors have placed the occurrence of necrotic enteritis. These factors include infectious bursal disease virus (IBDV), coccidiosis, and indigestible non-starch polysaccharides such as oats, wheat, rye, or barley, and high protein diets (M'Sadeq et al., 2015a:2434-2444). Antinutritional factors such as dietary lectins, trypsin inhibitors, tannins, and mycotoxins also play a role in the development of infection (Annett et al., 2002:598-601). In addition, *C. perfringens* strains capable of producing NetB toxin play a role in the pathogenesis of the infection. Mortality is higher in strains that can produce TpeL toxin with NetB (Cooper et al., 2009a:55-60). The epithelial surface of the small intestine is damaged by predisposing factors and increases the viscosity of the intestinal contents, creating an ideal environment for the growth and multiplication of bacteria (Helmboldt et al., 1971:775-780, Timbermont et al., 2011:341-347).

The microbiota, intestinal wall thickness, bacterial fermentation, and catabolism are all specifically altered by antibiotics. Antibiotics' characteristics have been utilized successfully to raise animal performance. They contribute positively to animal health status, nutrient availability, and growth performance (Carlson et al., 2018). Therefore, antimicrobials as feed additives not only improve the growth of poultry and feed conversion rate, it also controls outbreaks of enteric diseases (Kim et al., 2011:75-82). In 1999, 4.7 million kg, or 35% of all antibiotics administered in Europe, were used in animal feed. It is speculated that 11.15 million kg of antibiotics are used in animal feed annually in the USA (M'Sadeq et al., 2015b:2434-3444). Especially due to the emergence of antibiotic-resistant super bacteria in recent years, many studies conducted in order to develop new alternative strategies to antimicrobial growth factors (Yılmaz Çağırgan, 2022; Eid et al., 2018:25-34; Lee et al., 2022:1-17). Tetracycline, bacitracin, lincomycin, and penicillin G were previously used as antimicrobial growth factors in poultry feed (Castanon, 2007:2466-2471, Tuncer, 2007:1-9). Extensive and unconscious usage of antibiotics has accelerated the emergence of resistance in *C. perfringens* isolates globally (Kilic, 2004:29-36). A study reported that *C. perfringens* strains isolated from pig feces developed multiple resistance to clindamycin, lincomycin, erythromycin, and tetracycline antibiotics and contained tetracycline resistance genes in their plasmids (Teuber, 1999:755-763). The use of antimicrobial growth factors was gradually reduced in various countries and was completely banned in 1999 due to the rise in bacteria that are resistant to antibiotics and the significant risk to human health (Yilmaz Cagirgan, 2022). In Turkey, antimicrobial growth factors used in poultry diets were banned in 2006 (Cepoglu et al., 2016). The phenotypic and genotypic antibiotic resistance of *C. perfringens* isolated from pig and chicken feces were investigated in a study (Li et al., 2021). The study results investigated that *C. perfringens* strains were highly resistant to sulfonamides (sulfisoxazole and trimethoprim-sulfamethoxazole) and gentamicin (91%), whereas they were moderately resistant to ceftiofur (2.6%), doxycycline (5.6%), linezolid (2.1%), vancomycin (0.4%), and amoxicillin-clavulanate (1.3%) (Li et al.,2021).

Etiology

C. perfringens (formerly *Bacillus aerogenes capsulatus*, *Bacillus perfringens*, *Bacillus welchii* or *Clostridium welchii*) was first described by William H. Welch in 1891 (Lucey et al., 2004:1193-1195). *C. perfringens* was isolated by from a 38-year-old man's autopsy, in which gas bubbles were observed in infected blood vessels, and was identified as a new bacterium

(Lucey et al., 2004:1193-1195). Later, the gas-forming property has been associated with the symptoms of gas gangrene seen in British and French soldiers during World War I (Lucey et al., 2004:1193-1195).

C. perfringens, a Gram-positive, non-motile, encapsulated, and spore-forming bacillus, is an aerotolerant anaerobic bacterium. It can be found in decaying vegetation, feces, soil, and natural microbiota of animals and humans (McClane, 2012:465-498). The causative agent can isolate from soil, feces, and farm environments (Craven et al., 2001). In a study of chickens less than two weeks old transferred from hatcheries to breeder houses reported that chickens could be contaminated with *C. perfringens*, indicating that this may occur during transportation from the hatchery to farms or due to contaminated equipment and water (Husta et al., 2021:1708).

C. perfringens can produce a large number of toxins that produce the development of infection in animals and humans. The alpha, beta, gamma, epsilon, and iota toxin production are used to identify bacterial type A to G. The alpha toxin can detect in all *C. perfringens*, including Types A, B, D, E, and G, whereas beta toxin is in Types B and G, Iota toxin is only in Type E, and Epsilon toxin is found in Types B and D. Toxins may not detect in all field strains of bacteria. The most of the toxin genes are encoded on large plasmids including NE toxin B (NetB). The avian NE toxin, known as NetB, significantly harms the poultry industry globally by degrading poultry performance and increasing morbidity and mortality. In addition to toxins of *C. perfringens* contains various enzymes in lecithinase, hemolysin, hyaluronidase, collagenase, DNase (deoxyribonuclease), and amylase toxins that cause tissue damage (Husta et al., 2021:1708; Carli, 2022:329-334).

The Important Toxins of C. perfringens

Alpha-toxin (CPA/PLC): Alpha-toxin, which is synthesized by all strains of *C. perfringens*, is a lecithinase (phospholipase) weighing 43-kDa, also known as phospholipase. It hydrolyzes lecithin into phosphorylcholine and diglyceride. Since most cell membranes contain lecithin, it is destroyed by the alpha toxin structure. CPA causes vasoconstriction, reducing blood flow to tissues and creating an anaerobic environment that helps *C. perfringens* grow. Alpha toxin is encoded by the CPA gene, which has an active and immunogenic domain. These include a C-terminal β sandwich domain that is necessary for both toxic and cytolytic activity and an N-terminal α-helical domain that surrounds the enzyme's sole active site (Liu et al., 2020:179)*.*

Beta-toxin (CPB): *C. perfringens* types B and C can produce this toxin that is a necrotic and lethal effect on tissue. CPB is highly sensitive to environmental conditions and resistant to heat. It can be easily inactivated with trypsin and other proteolytic enzymes (Nagahama et al., 2015:396-406). Beta toxin consist of two-layer channels that include phosphatidylcholine and cholesterol, which are selective against cations such as Na^+, K^+ (Kiu et al., 2018:1-15). It has been reported that the toxin has an affinity for neuromuscular junctions and disrupts the Na^+ and K^+ balance with cation-selective channels formed in these regions, causing depolarization. Beta-toxin is encoded by a virulence plasmid carrying the *CPB* gene (Kiu et al., 2018:1-15).

Epsilon toxin (ETX): This toxin is considered as enterotoxin and neurotoxin. The *ETX* gene, which is produced only by type B and D strains, is encoded by plasmids. It shares structural similarities with the aerolysin toxin made by a species of *Aeromonas*. Epsilon toxin is the reason for enterotoxaemia in goats and sheep. It is activated in the intestines by a protease such as trypsin. The toxin causes increased intestinal permeability and endothelial damage in blood vessels. The ε-toxin is currently thought to be the most powerful of all the toxins produced by *C. perfringens* (Alves et al., 2014:102-107).

Iota toxin (ITX): Iota toxin produces by *C. spiroforme*, *C. perfringens* type E, and *C. difficile*. ITX includes two parts known as binding (Ib) and enzyme component (Ia). The *iap* and *ibp* genes on plasmids, encode the binding component. Targeted cells' receptors are bound by Ib, which then moves Ia into the cytosol of the cells. Actin, death, and cell rounding are caused by Ia ADP-ribosylates (Sakurai et al., 2009:208-228).

Enterotoxin (CPE): *Clostridium perfringens* enterotoxin (CPE) produced by A, C, D, and E types causes food poisoning and non-foodborne diarrhea, however, there is no information about the production by Type B. The *cpe* gene, which regulates the release of enterotoxin, can be transferred on a chromosomal or plasmid (Freedman et al., 2016:73). It has been determined that the *cpe* gene is chromosomally transported in the factors causing food poisoning and it is caused by plasmids in strains obtained from other diseases and animals (Freedman et al., 2016:73). Molecular analyses have revealed that the *cpe* gene has a C-terminal region and an N-terminal domain. The C-terminal region binds to claudin receptors, while the N-terminal region, which is critical for por formation, membrane insertion, and mediates oligomerization. The toxin disrupts the claudin receptor connections in intestinal epithelial cells. In addition, it binds and necrotizes the

human ileal and colon epithelium and can induce apoptosis by the caspase-3 pathway (Miseon and Fatemeh, 2019:124-129).

Beta2-toxin: The β2-toxin encoded by the *CPB2* plasmid has a 15% sequence similarity with the β-toxin and is a pore-forming toxin. *C. perfringens* producing β-2 toxin have been linked to intestinal illnesses such enterocolitis in horses and necrotic enteritis in piglets (Silva et al., 2015:1027-1034). However, the β2-toxin gene has also been detected in *C. perfringens* isolated from healthy animals, and the role of this toxin in disease formation has not been clearly explained (Benz et al., 2022:15-27).

Perfringolysin O (PFO): Perfringolysin O is a pore-forming cholesterol-dependent cytolysis also known as toxin or perfringolysin. PFO is a water-soluble monomer that is secreted and that identifies and binds membranes via cholesterol. Large pores are created on the target cell membranes by this toxin using cholesterol as a receptor. It is encoded by the *pfoA* gene, gas gangrene is also associated with tissue necrosis and destroys polymorphous nuclear leukocytes in the affected areas (Verherstraeten et al., 2015:1702-1721).

Delta toxin: Delta toxin is the toxin that three hemolysis released by *C. perfringens* type C and B strains. Delta toxin is cytotoxic for cells that have ganglioside GM2 in their membranes. Secreted Delta toxin (290 amino acids; 32619 Da), *C. perfringens* β-toxin (43% identity) is a basic protein that represents a crucial homology with NetB (40% identity), and to a lesser extent, *Staphylococcus aureus* leukotoxins and alpha toxin. Unlike β-toxin, which does not bind to gangliosides, recombinant delta toxin uses GM2 as a receptor (Manich et al., 2008).

Necrotic enteritis B-like Toxin: An essential virulence element in the pathophysiology of poultry NE, a disease that significantly damages the global poultry industry's bottom line, is the NE B-like toxin (NetB) secreted by *C. perfringens*. It has been reported that NetB toxin is cytotoxic to chicken hepatoma cells (LMH) and chicken embryo fibroblast cells (DF-1), affecting the viability of the chicken macrophage cell line (HDII). NetB has been evaluated as a new toxin associated with poultry NE caused by *C. perfringens* (Islam et al., 2021:187-194). The pathogenicity of NetB on chickens has shown that it produces the characteristic lesions of necrotic enteritis. In addition, the removal of cholesterol by a cholesterol depletion test performed on LMH cells revealed both oligomers and monomers of the NetB molecule. The results indicate that the NetB toxin can detect the

membrane molecules different from cholesterol in the libidinous layer of the cell (Islam et al., 2021:187-194).

TpeL toxin: The pathogenesis of NE is thought to be enhanced by *C. perfringens* type A/G strains. TpeL transports the glycosyltransferase enzyme to the cytoplasm of host cells thanks to its autocatalytic activity, glycosyltransferase activity, and several transmembrane domains. By independently mediating host cell entrance, TpeL blocks Ras signaling and triggers cell death. There is disagreement regarding when TpeL is produced; some studies claim that it occurs during sporulation, while others link it to vegetative growth (Paredes-Sabja et al., 2011:384-388).

Clinical Symptoms

The infection characterizes in subclinical and clinical cases. The clinical case of the infection is characterized by a fluffy and tangled coat, immobility, loss of appetite, dehydration, severe depression, and diarrhea (Carli, 2022:329-334). In a study reported that animals showing clinical symptoms usually die within a few hours, and mortality rates can be up to 1% per day (Helmbold and Bryant, 1971:775-780). There are no obvious clinical symptoms in the subclinical form. With a low mortality rate, weight loss takes shape in the animal due to chronic intestinal damage, a decrease in digestion and absorption, and causes production losses (Timbermont et al., 2011:341-347). Due to intestinal damage during subclinical infection, bacteria can reach the bile duct and bloodstream. High numbers of *C. perfringens* colonization in the liver result in cholangiohepatitis. The infected liver has a pale appearance with large and red or white foci (Sasaki., 2000:59-67). Although no clinical signs were observed in the infected chickens, indicating that liver lesions were observed in the meat examination performed during slaughter (Dahiya et al., 2006:60-88).

The main pathological findings are localized in the small intestine, especially in the ileum and jejunum. However, lesions may also occur in the rectum, kidney, and liver. The lesions can be detected from the outside due to the thinning of the intestinal wall and the appearance of a bulge filled with gas. The intestinal contents are brown and smelly. The yellow-brown pseudo membrane can be seen in the intestinal mucosa layer. The mucosa is hyperemic and necrosis has occurred. In subclinical cases, there are colorless, depression-shaped ulcers adhering to the mucosal surface (Carli et al., 2022 and Casewell et al., 2003:159-161).

PREVENTION AND CONTROL STRATEGIES

The incidence of necrotic enteritis has raised on broiler operations in recent years due to the prohibition of antibiotics as a feed additive (Yadav et al., 2022). Alternative strategies have been developed to defend animal health status and the productivity of livestock (Qi et al., 2023:1-7, Seal, 2013:526-533; Shamshirgaran et al., 2022:6441-6453). These alternative strategies include regulating the intestinal microflora, enhancing the immune response, and decolonizing the pathogen as well as reducing its effects through management, vaccination, feeding strategies, and feed additives (M'Sadeq et al., 2015b:1-11).

Vaccine and Phage Therapy

Vaccination can be used as an alternative to antimicrobial growth factors for the purpose of protection against necrotic enteritis, and various studies have been conducted against the prevention of NE (Cooper et al., 2009b:92-97, Duff et al., 2019:6319-6325). A category of viruses known as bacteriophages, which are abundantly present in nature, have a life cycle connected to bacteria. The spread of phages within their host (lytic cycle) results in the cell's destruction. Hence, bacteriophages can be used as an alternative to antibiotics (Huang et al., 2022:676). Details on the previous studies related to phage and vaccination are given in Table 1.

Table 1. Research on vaccination and phage therapy

Used technology	Strain(s)	Evidence	Reference
Phage Therapy	Podovirus phage	Decreased clinical severity, mortality rate, and intestinal lesion score *C. perfringens* reduction in caecal content	Hosny et al., 2021
Phage Therapy	LysCP28 endolysin encoded by orf28 from *C. perfringens* bacteriophage BG3P	In vitro 3.08 units-log reduction in *C. perfringens* in duck meat	Lu et al., 2022
Phage Therapy	φCJ22 phage	The moderate and high levels of phage decreased the mortality in broilers	Bae et al., 2021
Phage Therapy	CpeP_HN02 lytic phage belonging to the podoviridae family	*C. perfringens* reduction in chicken samples	Tian et al., 2022
Vaccination	Recombinant *Lactobacillus casei* ATCC 393 strain harboring alpha toxin	Mucosal (IgA) and humoral immune response (IgG) elicited in BALB/c mice after oral inoculation	Alimolaei et al., 2018
Vaccination	Recombinant *C. perfringens* alpha toxin	Decreased intestinal lesion score, lower level of *C.*	Valipouri et al., 2022

		perfringens in the cecum content, and weight loss	
Vaccination	Recombinant C. *perfringens* epsilon and beta toxin	Up to 90% of immunized mice were protected from an experimental challenge by the epsilon-beta fusion toxoid	Langroudi et al., 2013
Vaccination	Recombinant *Salmonella enterica* harboring fructose-biphosphate-aldolase, pyruvate ferredoxin-oxidoreductase and hypothetical proteins of *C. perfringens*	Vaccinated chickens developed serum and mucosal antibodies against clostridial and salmonella antigens.	Kulkarni et al., 2008
Vaccination	Recombinant *Clostridium perfringens* Epsilon toxin mutant Y30A-Y196A	IgG response detected in rabbits	Bokori-Brown et al., 2014
Vaccination	Recombinant *C. perfringens* with CnaA, FimA, and FimB pilus antigens	Reduced the severity of infection and an increase in IgY titers in broilers	Lepp et al., 2019

In a study, CnaA, FimA, and FimB pilus antigens of *C. perfringens* were used as vaccine target sites against NE. The study result showed that only the combination of CnaA and FimB vaccine reduced the severity of infection in broilers after exposure to *C. perfringens* CP1 isolate, and also provided an increase in IgY titer compared to control and pre-vaccination groups (Lepp et al., 2019:7-13).

Alpha-toxin plays a role in NE infection in poultry. The researcher investigated the protection of recombinant *Lactobacillus casei ATCC 393* strain harbored alpha-toxin in BALB/c mice. Mucosal (IgA) and humoral immune response (IgG) were obtained in BALB/c mice vaccinated orally with recombinant *L. casei* harboring alpha-toxin strain, indicating may be a successful vaccine candidate against necrotic enteritis (Alimolaei et al., 2018, 251-257).

Another study was performed with recombinant *C. perfringens* alpha toxin gene containing 203 amino acids. After three doses of intramuscular vaccination, broilers were challenged with *C. perfringens* type A strain (1.0 x 10^9 CFU/bird). The experiment results indicated that decreased count of *C. perfringens* in the fecal contents, fewer in the intestinal lesions of jejunum, and higher antibody titers compared to un-vaccinated and infected groups (Valipouri et al., 2022).

A study in Egypt investigated the efficacy of podovirus phage in the treatment of NE. The phage isolated from the cecum content of healthy chickens and characterized by evaluation with various stability tests. Arbor Acres broilers infected with *C. perfringens* were administered phage by oral probe for six days, once daily, after *C. perfringens* challenge. The mortality rate, enteric lesions, and enumeration of *C. perfringens* were recorded during the experiments. The results demonstrated that phage therapy reduced the clinical severity of the infection, intestinal lesion score, and mortality. In addition*, C. perfringens* count in the fecal content with phage therapy was decreased compared to the control group, indicating phage therapy may be an alternative strategy in the treatment of NE (Hosny et al., 2021:409-421).

The study using *C. perfringens*-specific phage φCJ22 reported that the high and medium concentrations of phage φCJ22 demonstrated an antimicrobic effect against wild *C. perfringens*, the groups decreased necrotic enteritis lesions, lowered *C. perfringens* number in the fecal content, and mortality rates remained unchanged in broilers growth performance in the experiment (Bae et al., 2021:302-313).

The member of Podoviridae family lytic phage vB_CpeP_HN02 was used to determine the efficiency on chicken breast infected with *C. perfringens*. The aseptically cut 2x2 cm squares pieces were sterilized with UV before application. During sampling, chicken breast pieces were transferred to the buffer solution, and centrifuged, then cells were collected and the phage amount was determined. The study results determined that the decrease in the number of *C. perfringens* was proportional to the phage density. HNO2 phage showed a good antimicrobial effect by a lytic activity test (Tian et al., 2022).

Phytogenics, Probiotics and Essential Oils

The prohibition of the use of antibiotic growth factors as feed additives, the most of research was focused on the new alternatives that will prevent the commensal *C. perfringens* from forming necrotic enteritis in poultry, increase feed conversion rates and the growth performance of the animals. The various plant extracts, phytogenic feed additives, probiotics, and essential fatty acids have been subject to previous studies due to their natural structure, low toxicity at certain doses, and their action without residues in animal carcasses (Si et al., 2006). Clove and thyme essential oils on broiler chickens were added to the rations of birds infected with *C. perfringens*. The added essential oil concentrations were detected by the agar dilution method. The results demonstrated that thyme and clove essential oils alleviate intestinal damage and reduce the amount of *C. perfringens* in the intestine (Eid et al., 2018:25-34).

In a study, two distinct essential oil mixtures were tested in vitro and in vivo for their ability to inhibit the growth of *C. perfringens* bacteria. The study results showed a significant reduction in bacterial counts and intestinal lesions, improved fattening performance, and induced immune response compared to the untreated groups, suggesting that essential oil mixture can be used as an efficacy and safe in alternative contrast to antibiotics in the treatment of infection in broilers (Gharaibeh et al., 2021:4527).

In a study, the effects of lauric acid were examined in relation to the prevention of necrotic enteritis and the manipulation of microbiota. *C. perfringens* and *Eimeria* spp. were used in the experimental challenged and the animals were treated with lauric acid. It has been reported that the microbiota in the jejunum were different from those in the cecum and the microbiota change was more important in the jejunum. The cecum microbiota remained steady, even though *Eimeria* spp. and *C. perfringens* dramatically decreased species diversity in the jejunal microbiome (Yang et al., 2019).

A study investigated the effect of various essential oils (herbs, spices and peppermint oil, anise, and clove), prebiotics, and probiotics (*Enterococcus, Pediococcus, Bifidobacterium*, and *Lactobacillus* spp.), and stimbiotic supplements against NE infection in broilers. The study results indicated that broilers fed with stimbiotic only or combined diet had higher growth performance at 21 and 30 days compared to the control group, however, none significant difference were detected in body weight between the stimbiotic and combined groups, suggesting that stimbiotic feed additive may improve performance in the fight against necrotic enteritis (Lee et al., 2022:1-17).

The effect of turmeric on *C. perfringens* was tested in 3000 one day old Cobb broilers. The presence of *C. perfringens* and the average chick mortality rate were reported to be significantly reduced in the treatment groups, indicating that the use of turmeric powder in the broiler diet can reduce necrotic enteritis by reducing *C. perfringens* and can be a good source of non-antibiotic growth promoters to reduce antibiotic resistance in poultry (Ali et al., 2020:209-218).

The effect of *Bacillus subtilis* and *Bacillus velezensis* probiotics on the development of necrotic enteritis, intestinal health, and growth performance in chicks has been investigated. It was determined that the chickens fed with low-energy ration and probiotics had a higher feed conversion rate and body weight compared to the negative control group. Chickens fed the probiotic and standard energy diet showed a better feed conversion rate from day 21 than the negative control. An increase in duodenal and jejunum villus height to crypt depth has been observed in chickens fed a low-energy diet containing probiotics. It has been found that probiotic administration significantly reduces the relative liver

weight in both energy groups. These results further indicate that *Bacillus* spp. can improve broiler performance and intestinal health, and therefore can be an alternative to antibiotic growth factors in broiler industry (Ramlucken et al., 2020:331-341).

A study investigated silver (Ag) nanoparticles on poultry performance, antimicrobial activity against *C. perfringens*, and immunity levels on experimentally induced necrotic enteritis in broilers. Treatment with Ag nanoparticles, *C. perfringens* has been reported to reduce colonization in the intestine, the severity of clinical symptoms, and mortality compared to the untreated infected group, as well as alleviate pathological lesions in the intestine and liver. Although Ag nanoparticles have no effect on immune organs, it has been noted that they have a positive effect on the integrity of intestinal health. However, Ag nanoparticles found residues in the muscles. Therefore, procedures for obtaining the routes of chicken meat produced for human consumption need further study on the size, route of administration, and washout time of Ag nanoparticles (Salem et al., 2021:6783-6796).

In another study, the effect of *Clostridium butyricum* on necrotic enteritis was investigated. *C. butyricum*, which is thought to have a probiotic function, was added to the diets of the chicks in the experimental group before they were infected with *C. perfringens*. Animals fed diet for a specified period (21 days) were infected with *C. perfringens*. The results showed that although *Clostridium butyricum* strengthens the intestinal barrier structure, it does not prevent intestinal lesion formation, reduces the relative abundance of *C. perfringens* in the intestine and causes an increase in anti-inflammatory interleukins. Researchers have concluded that *Clostridium butyricum* is not a sufficient probiotic to prevent necrotic enteritis (Huang et al., 2019:2309).

CONCLUSION

Necrotic enteritis infection is a serious threaten to the poultry operations, which can result serious economic losses. After the global restrict on the use of antibiotics, there was a need to research efficient antibiotic alternatives to control necrotic enteritis infection. Prebiotics, probiotics, symbiotics, essential oils, herbal extracts, and preventive vaccines are effective antibiotic alternatives that can be used in combination with biosafety applications to reduce the negative impact of necrotic enteritis in poultry. In addition to the fight against the recommended substances and the elimination of predisposition factors are important for the fight against necrotic enteritis. Further studies need to be developed and updated to better understand *C. perfringens* toxin types and to discover new alternatives.

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Chapter 8

Irrigation Activation Methods in Endodontics from Past to Present

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ABSTRACT

Irrigation of the root canal is an essential process during root canal treatment. Although syringe irrigation is the common practice, it is not applicable to the apical section of the root canal, isthmuses, or oval extensions. Acoustic and hydrodynamic stimulation of the irrigant has been developed and has been demonstrated to improve the cleaning efficiency. However, the physical mechanisms behind these cleaning processes are not fully understood. No matter how effective it is, it is not possible to purify root canals 100% of microorganisms with any irrigation activation system.

Keywords: gentlewawe, laser, irrigation activation, root canal treatment, enterococcus feacalis

INTRODUCTION

It has been reported in the literature that the main factor causing pulp and periodontal tissue damage is bacterial infection. Dentists have a difficult time removing microorganisms in infected root canals [1]. The root canal system has a complex morphology, which makes it difficult for dentists to completely remove intraradical microorganisms. In addition, intra-cannals bacteria can form biofilms that are resistant to antimicrobials [2]. If bacteria and by-products are not removed, they can lead to long-term inflammation and slow healing. Although the number of microorganisms is sufficiently reduced as a result of adequate irrigation with sodium hypochlorite, the most widely used irrigation solution with appropriate canal instrumentation and different concentrations, stubborn bacteria such as Enterococcus faecalis cannot be completely removed from the root canal [2-4]. It is recommended to activate the irrigation solutions used during root canal preparation to destroy intraradicular microorganisms and provide three-dimensional chemomechanical disinfection. Irrigation solutions; It can be activated in the canal with the help of devices such as sonics, ultrasonics and lasers [5]. In recent years, the search for new techniques and methods in this regard continues.

IRRIGATION ACTIVATION METHODS
STANDARD NEEDLE IRRIGATION

This is the most commonly used irrigation technique in dental practices. In this method, the solution is applied to the root canal either passively or actively using a needle. Activation occurs when the needle tip moves up and down through the root canal [6].

The main benefits of using a standard needle irrigation technique include: The deeper the needle penetrates into the canal, the more volume of the irrigation solution that can be pumped out of the root canal [7]. However, the literature has shown that standard needle irrigation only penetrates the irrigation solution 1 mm below the needle tip of the needle. This means that the irrigation technique is not as effective in very narrow canals [8].

MANUAL DYNAMIC ACTIVATION

Vapor-lock is one of the main reasons why it is so difficult to apply root canal irrigation through apical canal, and this is why new irrigation activation methods are used to increase the rate of penetration of the solution through the root canal into the dentin tube. [9]. One of these methods is manual dynamic activation, which involves the use of gutta-percha cones placed apically in the root canal filled with irrigation solution [10]. In order for this method to be

successful, the irrigation fluid must interact directly with the canal walls. or this technique to be effective, the irrigation solution must be in direct contact with the canal walls. In literature, it has been reported that an effective hydrodynamic effect will be created with up and down 2-3 mm oscillating strokes with gutta-percha compatible with the apical preparation of the root canal. Manual dynamic irrigation due to the hydrodynamic effect has been reported to provide superior intracranial disinfection compared to conventional needle irrigation. [6].

BRUSHES

Brushes are employed to clean the canal walls and trigger irrigation. It is done by rubbing the root canal walls with light pressure. EndoBrush (C&S Microinstruments Ltd., Markham, Ontario, Canada), CanalBrush (Coltene Whaledent, Langenau, Germany) and NaviTip FX (Ultradent Products Inc., Southern Jordan, UT) have been developed for this purpose [11]. NaviTip FX is a brush-coated 30 gauge irrigation needle. NaviTip FX was found to be more effective than regular needle irrigation when it comes to disinfecting the third coronal layer of root canal walls. [12]. EndoBrush, on the other hand, is a spiral-shaped endodontic brush made of nylon bristles placed on a bent wire. This product is sold with the aim of eliminating debris and a smear layer from the root canal walls in a more efficient manner. There are studies in the literature reporting that EndoBrush is effective in root canal disinfection [11].

IRRIGATION ACTIVATION METHODS WITH PREPARATION

These irrigation systems include the Quantec E, which is prepared and activated by SymbronEndo in Orange, CA, and the Self Adjusting File system (SAF) which is installed by ReDent-Nove Ltd. near Ra'anana in Israel. Plus, there's the XP Endo Finish and XP Endo Finish R, which is installed by FKG Dentaire in La Chaux - des-Fonds, Switzerland.

Quantec E is a system of root canal disinfection that is composed of a pump and two solution reservoirs, as well as a tube that allows for continuous irrigation during the preparation process. Compared to conventional needle irrigation, Quantec E has been found to be more effective in disinfecting the root canal coronal third, while maintaining a similar level of efficacy in the remaining root canal. [13]. In contrast, this situation, there are also studies in the literature reporting that there is no difference between the two systems [14].

SAF stands for preparation and irrigation root canal treatment System". This system is designed to provide root canal treatment at a minimally invasive level. The SAF system is composed of a hollow tube composed of a nickel titanium cage,

with a rough external surface. The tip of the file is asymmetrical, with the center of the tip being located on the outside of the tube. This is in contrast to the symmetrical center of the tip found on all traditional Nickel Titanium Rotary files. It has been reported that when SAF is used for preparation and irrigation in oval root canals, the possibility of remaining inaccessible areas is reduced because it contacts all the walls [15].

The XP-Endo Finisher file is a 21 mm long, non-cutting Ni-Ti rotary file system produced with Max-Wire technology. Max-Wire technology ensures that the files are in the martensitic phase and flat shaped below 37 ° C, while it passes into the austenitic phase at body temperature within the root canal system and takes a curved (spoon-shaped) shape at a depth of 1.5 mm in the last 10 mm of the file It goes into an austenitic stage when it's at body temperature inside the root canal and takes on a spoon-shaped shape at the bottom of the file, which is about 1.5mm deep. The spoon shape that the XP-Endo Finisher file takes at body temperature, when used with irrigation solutions in the root canal, enables the cleaning of irregular areas that are difficult to reach without making any changes in the dentin and original root canal anatomy [16, 17]. The manufacturer recommends that the XP-E Finisher file should be used at an rpm of 800-1000 and a torque of 1 Ncm with an amplitude of 7-8mm [18]. If you're looking for a new version of this file, the FKG Dentaire R file is a great option. It's designed to be used in cases where you need to regenerate your root canal. Studies have shown that it can remove debris and Ca(OH)2 from both oval and curved canals, which can help you get more of the filling material out of your root canal when you use different retreatment techniques. [20]. It has also been reported to reduce the amount of residual bacteria in the canals when used on molars and premolars [21].

PRESSURE EXCHANGE SYSTEMS

RinsEndo (RinsEndo, Duerr-Dental, Bittigheim-Bissingen, Germany) and EndoVac (Discus Dental, Culver City, CA, USA) are irrigation activation systems that work with the negative pressure principle.

RinsEndo uses the negative pressure principle to perfume your product. It's made up of a head, a solution reservoir, and cannulas. The solution, which is flowed with a syringe with a volume of 65 microliters, vibrates at a frequency of 1.6 Hz, making approximately 100 pulsating movements per minute and is transported into the root canal with the RinsEndo needle. In addition, the cycle of injecting and sucking into the canal with lower pressure is repeated 100 times per minute compared to the syringes used in the conventional technique [22].

The EndoVac root canal irrigation activation system utilizes negative pressure to deliver the irrigation solutions applied to the root canal into the apical area without

applying any pressure [23]. The system involves the attachment of macrocannulas (or microcannulas) through tubing to an irrigation syringe and the use of a dental unit's highly aspirated saliva ejector.Kumar et al. [24] reported that EndoVac increases irrigation efficiency, reduces solution extrusion and complications. In addition, EndoVac has been shown to cause less extrusion of irrigation solution into periapical tissues and reduce accidents due to NaOCl extrusion [25].

SONIC SYSTEMS

In 1985, Tronstad et al., conducted the first trial of root canal treatment using a sonic instrument. Sonic irrigation operates at a frequency of 1-6 kHz and produces a lower shear stress than ultrasonic irrigation [26]. The energy produced by sonic instruments has a higher amplitude and is more reciprocating than ultrasonic irrigation. The oscillation patterns produced by sonic devices differ from those of ultrasonic devices. EDDY (VDW, Munich, Germany), EndoActivator (Dentsply Tulsa Dental Specialties, Tulsa, OK, USA), MM1500 Sonic Air (Micro-Mega, Besançon, France) and Vibringe (Vibringe BV, which are designed to provide irrigation activation using sonic energy) Amsterdam, Netherlands) are examples of these systems [27].

ULTRASONIC SYSTEMS

It is known that ultrasonic energy has been used for many years to facilitate root canal cleaning and disinfection in endodontics [28, 29]. Ultrasonic energy produces higher frequencies but lower amplitudes compared to sound energy. Ultrasonic tips oscillate at 25-30 kHz, which is higher than human hearing threshold (>20 kHz) and works with transverse vibration. [6].

Endodontic ultrasonics is a technique used to remove obstructions in the oral cavity, activate irrigation, place TMAs, and remove broken instruments from the canal [28]. It can be used either with the use of simultaneous ultrasonic instruments and irrigation, or passively. Passive ultrasonic irrigation is a technique in which the activation is done without the use of instruments. [29]. When ultrasonic activation is used with an irrigant source, it is called ultrasonic irrigation [30]. In order for ultrasonic tips to work effectively, they must be able to move freely in the canal lacking of touching the canal wall [31]. On ultrasonic irrigation, it is not possible to check the dentin preparation and thus the form of the prepared root canal. At the end of the preparation, in addition to the perforations, highly irregularly shaped canals are obtained. Therefore, ultrasonic irrigation should not generally be identified as being a different choice to traditional hand files. On the other hand, the endodontic literature defends that passive ultrasonic activation is more advantageous after canal preparation is completed [6].

LASER ASSISTED IRRIGATION SYSTEMS

The word "laser" is short for "light amplification by stimulated emission of radiation" or "LASER". After Maiman developed the ruby laser in 1960, dentists started to look into the different uses of lasers. First, they looked at how the ruby laser could be used on hard dental tissue to help slow down the process of demineralisation. In 1964, a team of dentists wrote a paper on the Ruby laser and its uses in dentistry, published in the Journal of the American Dental Association. The paper was titled "Ruby laser and the use of hard dental tissues in dentistry" and was published under the title "Goldman et al." . They reported a decrease in the permeability and demineralization of enamel in acid-treated teeth after laser irradiation [32].

Weichman and Johnson (1971) reported the first endodontic laser use in 1971 for the in vitro creation of apical plugs using high-powered carbon dioxide in vitro in teeth that were apically incomplete. However, clinical applications of endodontics lasers began in the late 1990s with the development of fine and flexible fiber endodontic tip systems. Today, endodontic lasers are used in a wide range of procedures, including pulp capping / pulppotomy, root canal cleaning and disinfection, oral obturation, endodontics root canal treatment and apical surgery. [32].

Sterilization efficiency of root canals of lasers including Nd:YAG, Argon, Diode, CO2 and Er:YAG has been proven in many studies [34, 35]. Some research results have shown that the use of lasers with appropriate parameters eliminates microorganisms in infected root canals [36]. Microphotographic recordings; shows that activation of the laser irrigation solution creates a cavitational effect in the root canal by fluctuating at high speed after the root canal is filled with the irrigation solution. The thermal effect of the laser beam causes contraction and expansion of liquid molecules, creating secondary cavitations in the irrigation solution in the canal [37, 38]. A study by DiVito and colleagues (39) showed that the application of 17% of EDTA/Er:YAG by Diode laser for 20/40 seconds resulted in a very good cleaning of root canals with open dentin tube.

A study by Saghiri and colleagues (40) showed that when Diode laser was applied with 17% of the EDTA/BioPure MTAD solution to root canals, the smear layer is removed but melting areas are formed on dentin surface of samples treated with EDTA.

Another study by de Groot and colleagues (41) looked at the results of laser activation in an irrigation solution and compared it to passive ultrasonic or manual irrigation. The results showed that laser activation is more effective than manual irrigation in the removal of dentin debris. In another study, the effects of argon on the smear layer were studied. The argon laser was used to remove the dentin layer

from the middle root canal and the dentin layer was observed to be removed from both the middle and the apical region of the dentin. [42].

PIPS is a laser-activated irrigation system that uses a fiber optic tip with Er:YAG lasers. The fiber optic tip is used to activate the system [39]. The laser pulses are sent out at 15 Hz and average 0.3 W for 50 μs. This energy causes the water molecules to react with a high power of 400W. To activate the system, the root canal is filled with irrigation solutions and a special fiber optic tip is put at the orifice. If enough Er:YAG energy is absorbed, the solution will be heated to above the boiling point and a vapor bubble will form at the tip. The bubble will expand and then collapse when it reaches its maximum size. In some cases, this will cause a second bubble to grow. The bubble moves the solution three-dimensionally, creating successive shock waves that create a strong current.

Shock waves that occur in the entire solution ultimately affect the canal walls, showing the cleaning and disinfection effect [43, 44]. In contrast to traditional laser applications, PIPS tip doesn't need to be inserted into the canal but is simply inserted into the pulp chamber, thus eliminating the need to create wider channels.

It has been demonstrated that PIPS can efficiently penetrate the apical section of the canal as well as canal branches of irrigation solutions used in the treatment. It also has been demonstrated that it can efficiently remove both vital as well as devital tissues. It disinfects the dentinal tubule. [45].

SWEEPS is the most recent development in the use of lasers for endodontic irrigation. Its operating system is similar to that of PIPS, but differs in the manner in which the impact pulse is sent to the pulp chamber. This is achieved through the insertion of a fiber tip in the pulp chamber, which is used in conjunction with the Er;YAG laser, which has a 2940 nm wavelength. The difference in mode of action between SWEEPS and PIPS is the mode in which the pulse pulse pairs are sent to the solution, as opposed to PIPS, which is fired at the end of each emission cycle with a one-square waveform laser. This mode of action accelerates the collapse of the laser induced bubbles, resulting in an increase in shock wave emission, even in the most narrow root canals. The magnitude of the pressure waves produced by SWEEPS is greater than that produced by PIPS, which produces a single Er:YAG pulse [46]. The goal of SWEEPS is to increase the shock waves coming out of collapsed bubbles in tight spaces like root canals by creating synchronized laser pulses. Once the first bubble that's been induced by the laser starts to collapse, you send a second pulse to the liquid, and a second bubble is created. This growth of the second cavitation bubble makes the main bubble collapse faster, leading to a violent collapse where shock waves come out. Secondary bubbles are also very close to root canal walls when they collapse, creating a shear flow that can pull particles out of the surface. Shock waves are also coming out of secondary bubbles near root

canals, which still travel super sonic when they get to the walls, which could make the cleaning mechanism even better [47].

GENTLEWAVE

GentleWave is a new type of irrigation system that's designed to clean your root canal with little to no shaping. It creates a strong hydrodynamic cavity in the degassed liquid inside your tooth, which sends out a wide range of sound waves [48]. The manufacturer says it can be used in cases where tooth strength needs to be maintained and the root canal preparation needs to be minimally invasive [49] .Traditionally, root canal preparation makes the root more fragile by causing too much material loss. But there's no evidence that minimally invasive preparation makes the root structure harder to break. [50, 51].

The WG generates a powerful, high-velocity shear force that penetrates the access cavity and disperses the irrigation solution into the root canal. In particular, the bursting of the microbubbles produces an acoustic field composed of broadband frequencies which travels in solution throughout the root canal system, eliminating organic and inorganic residue and removing microorganisms from the root canal system (52, 53). However, the WG also offers negative pressure irrigation activation which eliminates the potential for apical overflow of the irrigation solution (54). The WG is compatible with NaOCl and EDTA, as well as distilled water. The system dispenses the irrigation solution from the head through the tooth at a speed of 45 ml/min, with the excess irrigation solution being removed simultaneously. [55, 56].

Extrusion of NaOCl into perioperative tissues can result in a variety of adverse outcomes, including postoperative discomfort, oedema, and necrosis[57]. In studies conducted with the use of the GW system, it was found that, in comparison to the standard needle irrigation method and the endoVac method used in the studies, negative apical pressures were produced by the GW system, which prevented the irrigation solution from being extruded.[58] The amount of Apical Extrusion was observed to be higher when the group was applied with a standard needle irrigation method, particularly after traditional and ovarian preparation.[59]

On the other hand, there was no apical Extrusion observed in the group administered with the GW system, as compared to the groups administered with EndoVacs [56]. Furthermore, the literature has reported the efficacy of the GW system in the removal of Debris and Smeared Layer after Minimal Root Canal Preparation (MCP). However, in a Micro-Computured Tomography Study, 17% EdTA was used as the final Irrigation and Phorodynamic Therapy (PT) was used in conjunction with ER: YAG laser, demonstrating similar efficacy to that of the GW system [59].

Periapical NaOCl extrusion can cause complications such as pain, edema or ecchymosis after surgery [57]. When compared to standard needle irrigation, EndoVac, and other irrigation activation systems, the GW system generates negative apical pressure to prevent apical extrusion. The amount of periapical extrusion was higher in the group that received standard needle irrigation, particularly after traditional preparation, and ovarian preparation.

On the other hand, the group that received EndoVac and the GW system did not experience any apical extrusion [56]. Since bacterial invasion occurs in devital tooth tubules, it is important for irrigation solutions to act into dentinal tubules [60].

In the literature, the GW system has been reported to have a higher penetration of dentin tubule in the coronal root canal, middle root canal, and apical third root canal than other irrigation activation systems (see below). In some studies, the penetration of the dentin tubule of the irrigation solution is reported to be 4 times deeper than that of the irrigation system applied with an ultrasonic system (see below).

RESULTS AND DISCUSSION

No matter how effective it is, it is not possible to purify root canals 100% of microorganisms with any irrigation activation system. This is why RCTs are required to evaluate the disinfection effectiveness of multiple and diverse root canal irrigation techniques, the removal of the smear layer and the impact on clinical outcomes such as pain and recovery.

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Chapter 9

Sympathetic Skin Response in Dermatologic Diseases

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ABSTRACT

Sympathetic skin response (SSR) is sympathetic cholinergic eccrine sweat gland activation that causes changes in skin resistance or conductivity at rest or evoked conduction. The activity of the eccrine sweat glands causes emotional sweating. The sweating center starts from the hypothalamus and reaches the eccrine sweat glands by unmyelinated postganglionic sympathetic C fibers, where acetylcholine is secreted. SSR is a polysynaptic reflex and has the same mechanism as emotional sweating.

SSR is recorded with active and reference Ag/AgCl electrodes, usually from areas where eccrine sweat glands are dense, such as hands and feet. Deep inspiration, electrical, laser, or light stimuli are generally used to create SSR. The latency and amplitudes of the obtained response are analyzed.

In the literature, it is reported that SSR has been investigated in many autonomic function diseases and psychoneurological diseases affecting the emotional state. It is widely used in the peripheral nervous system (such as diabetic neuropathy), central nervous system diseases (such as multiple sclerosis, Parkinson's, and myelopathy), schizophrenia, depression, hypothyroidism, hyperthyroidism, and dermatological diseases. It is used in the diagnosis, prognosis, and treatment follow-up of the disease.

In this section, after the general knowledge about sweating and SSR, we mentioned information about the application of SSR in dermatological diseases such as hyperhidrosis, acne vulgaris, psoriasis, vitiligo, atopic dermatitis, and scleroderma. As seen in these studies, there is a need for more detailed studies on the age, gender, diagnosis stage, disease duration, treatment, and prognosis of patients with dermatological diseases.

Keywords: Sympathetic Skin Response**,** Hyperhydrosis**,** Acne Vulgaris, Psoriasis, Vitiligo, Atopic Dermatitis, Scleroderma

INTRODUCTION

The autonomic nervous system (ANS) shows a complex structure with specific effects on organs and systems. Diagnosis of ANS diseases depends on selecting the desired test and the accuracy of its interpretation. One of the measurement methods for the evaluation of sympathetic nerves is the sympathetic skin response (SSR). SSR reflects the sympathetic cholinergic sudomotor function that causes changes in skin resistance or conductivity to electrical conduction (Gutrecht, 1994: 520).

Sympathetic skin response is the most frequently used expression in the literature. Apart from this, different names such as electrodermal activity (EDA), electrodermal response (EDR), psychogalvanic reflex (PGR), galvanic skin response (GSR), peripheral autonomous surface response are used (Kucera et al., 2004: 109).

SSR was first described by Tarchanoff in 1890 as changes in skin potentials following stimulation of specific senses. With the development of the method, studies in the fields of physiology and psychology started (Verghese, 1968: 639). Shahani et al. By applying SSR for the first time in clinical neurophysiology, it has been shown that it is a sensitive index related to emotional senses, attention, and bodily arousal (Shahani et al., 1984: 536; Dawson et al., 2000: 201).

In this section, to better understand SSR activity, first of all, the basic mechanism of sweat production, and the functional mechanism of sweating will be mentioned, as the anatomical-physiological structure of the sympathetic skin response, SSR recording methods, different clinical applications of SRR and its use in the field of dermatology will be presented.

Basic Mechanism of Sweat Production

Sweat production takes place in sweat glands. Sweat glands are divided into apocrine and eccrine types, even if the sweat secretion mechanism is the same.

Apocrine glands originate from hair follicles and are mainly located in the armpits, nipples, and groin area. The secretory sections are wider and open to the skin surface after passing through the epidermis as a straight channel.

The eccrine glands consist of a secretory section that secretes an isotonic fluid and a duct that reabsorbs NaCl, producing a hypotonic sweat on the skin surface. They originate from the epidermis and are extensively distributed throughout the body (Vetrugno et al., 2003: 256).

Sweat gland secretion is activated by nerve impulses from the sympathetic nervous system, but their neurotransmitter is acetylcholine (Ach) at the neuroeffector junction. Efferent sweat fibers originate from the hypothalamic preoptic sweat center and descend along the ipsilateral brainstem and medulla to

synapse with neurons of the intermediolateral cell column (Langley, 1891: 348; Dale and Feldberg, 1934: 121). The preganglionic fibers emerge from the anterior roots and enter the sympathetic ganglia. Unmyelinated postganglionic sympathetic class C fibers arise from the sympathetic ganglia and join with the main peripheral nerves to reach the sweat glands and provide cholinergic innervation to them. Of the preganglionic nerve fibers, those arising from the 2nd and 9th thoracic segments innervate the skin of the upper extremities, those arising from the 1st to 4th thoracic segments innervate the face and eyelids, those arising from the 4th to 12th thoracic segments innervate the trunk, and those arising from the 10th thoracic and 3rd lumbar segments innervate the skin of the lower extremities (Figure 1).

The effect of Ach on sweat glands occurs by increasing intracellular Ca^{2+}. After Ach release and muscarinic receptor binding, there is an influx of Ca^{2+} from outside the cell into the cell by activation of receptor-bound Ca^{2+} channels, stimulating Cl$^-$ and K$^+$ channels, causing an outflow of potassium, chloride, and water. This produces cellular contraction by with the activation of cotransporters that return Na$^+$, K$^+$, and 2Cl$^-$ into the cell, which in turn stimulates Na$^+$K$^+$-ATPase in the sweat duct, creating an isotonic solution that results in a hypotonic sweat solution (Sato et al., 1993: 94).
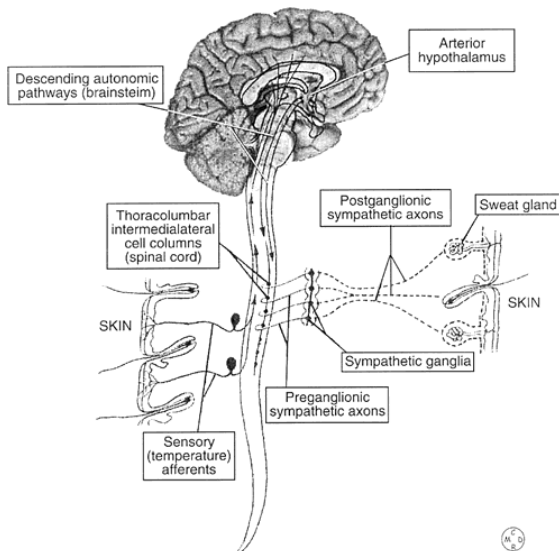

Figure 1 Functional anatomy of sudomotor pathways
(Vetrungo et al., 2003: 257)

Functional Regulation of Sweating

Sweating occurs in two types, thermoregulatory sweating and emotional sweating. Thermoregulatory sweating is the heat regulator that occurs throughout the body in response to changes in the environment. Emotional sweating (palmar and plantar) is emotional sweating limited to the palms, armpits, and soles of the feet. Due to the different formation mechanisms, they are carried out from different centers (Vetrugno et al., 2003: 258).

The activity of the eccrine sweat glands causes emotional sweating. Eccrine sweat glands are primarily thermoregulatory organs and are one of the most important effectors of the central autonomic network during spontaneous visceral changes associated with homeostatic adjustments. This pathway starts from the hypothalamus (preoptic area) and extends to the brain stem and spinal cord (Boulant, 1996: 105). The preoptic region receives afferent sensory information from thermoreceptors in the skin, spinal cord, trigeminal nucleus, thalamus, and midbrain (Kanosue, 1994: 284). Thus, preoptic neurons compare and integrate central and peripheral thermal information and regulate optimal thermoregulatory outputs. An increase in heat production and vasoconstriction occurs in vibratory thermogenesis caused by preoptic cooling (Vetrugno et al., 2003). Increased metabolic activity in brown adipose tissue and increased plasma levels of hormones such as thyroxine, catecholamines, and glucocorticoids cause preoptic cooling-induced non-shivering thermogenesis (Bruck and Wunnenberg: 561, 1970; Vetrugno et al., 2003: 259).

Emotional sweating is functionally different from thermoregulatory sweating. The emotional state is controlled by cognitive and neuroendocrine functions. The anterior cingulate cortex plays an important role in controlling emotional sweating (Neafsey, 1990: 148). It integrates instinctive and somatic responses necessary for both emotional and attentional arousal mechanisms. According to PET studies, the removal of the anterior cingulate cortex causes impairments in selective attention (Janer and Pardo, 1991: 233).

It has been shown that electrical stimulation of the amygdala, hippocampus, anterior cingulate, and frontal cortex modulates the SSR, and there is a positive correlation between neuronal activity in the cingulate cortex and SSR in subjects treated with emotional stimuli. Furthermore, the cingulate cortex can block attention to familiar, non-new stimuli, thereby mediating "habituation" in habitual stimuli and attention is paid to only important stimuli (Kwon et al., 1990: 3560).

Alertness and emotional state govern the orientation response. Orientation response includes rapid pupil movements to a new stimulus and autonomic responses such as tachycardia and mydriasis. Emotional sweating and SSR constitute important autonomic components of the orientation response that occur

at any time when attention is directed to a new and important stimulus (Vetrugno et al., 2003: 261).

Norepinephrine and serotonin systems are mediated in the thalamus, which participates in the sweating mechanism and orientation response (Steriade et al., 1997: 214). Therefore, thalamo-limbic circuits that control the degree of alertness, importance of stimuli, and habituation are involved in the control of emotional sweating and thus SSR.

Definition, Anatomical Structure and Physiology of Sympathetic Skin Response

SSR is an electrophysiological autonomic test reflecting autonomic peripheral sympathetic cholinergic function related to sudomotor activity and potential changes are recorded from the skin surface (Kucera and Kurca, 2004:109).

Endosomatic and exosomatic recording methods of this phenomenon were described in the 1970s. The endosomatic method is the recording of the electrical skin potential. In the exosomatic method, electrical skin resistance changes are recorded by external stimulation with an electrical current (Christie, 1981: 617).

SSR occurs as a result of polysynaptic reflex activation. The effectors of the reflex arc and the source of most potential changes are eccrine sweat glands activated by the cholinergic system (Elie and Guiheneuc, 1990: 259).

The efferent pathway of the SSR includes myelinated sympathetic fibers of neurons in the intermedia-lateral nuclei of the spinal cord T1-L2. Their axons are short and myelinated and terminate in the sympathetic paravertebral ganglia. Postganglionic fibers do not contain myelin (Type C) and innervate the eccrine sweat glands. For the upper extremity, the sympathetic fibers (sudomotor and vasomotor) leave the spinal cord at the T2-T6 level; fibers reaching the lower extremities leave the cord at the T12-L2 level (Zakrzewska-Pniewska et al., 1999: 474). The afferent pathway of SSR consists of large myelinated fibers.

Although the center of the reflex arc cannot be determined exactly, it is polysynaptic and is affected by various facilitating and inhibitory factors. Central control of sudomotor responses probably reaches cortical levels. The hypothalamus, ventrolateral part of the brainstem, midbrain, medial and basal parts of the frontal lobe, the medial part of the temporal lobe, and limbic structures are held responsible. (Sato and Schmidt, 1973: 917; Linden and Berlit, 1995: 373).

SSR can be created with many different alert types. It has been shown that mental stress and emotional arousal increase sympathetic activity and have a facilitating effect on SSR. The stimulation method determines the afferent path of the SSR reflex arc. The most commonly used method is electrical stimulation

of peripheral nerves in the extremity. The afferent pathway of this reflex includes thick myelinated sensory fibers (Type II) and sensory spinal cord pathways that terminate in the brainstem (Karl et al., 1975: 146; Nair et al., 2001: 78).

Sympathetic Skin Response Test Techniques

They are uncomplicated experiments. Standard Ag/AgCl electrodes are used for recording. Electrodes are placed in areas where eccrine sweat glands are dense. When the active electrode is placed on the finger, the reference electrode is on the back of the hand, and when the active electrode is on the sole of the foot, the reference electrode is on the back of the foot. Records can also be taken from the perineum, genital area, distal parts of the fingers, thumb, toes, and proximal parts of the extremities.

There are various stimulus methods to generate the SSR response. Shahani et al. (1984: 538) generally used deep inspiration in their studies. Single square wave electrical impulses with a magnitude of 10-30 mA and a duration of 01.-0.5 ms from peripheral nerves (especially median and tibial nerves) (Hanson et al., 1992: 556), 65-100 dB click sound stimuli given to both ears with over-ear headpohones (Guven et al., 2017: 3128; Dolu et al., 2013: 197), magnetic stimuli given from the C7 processus spinous region, laser stimuli applied to the skin, reflex hammer stimulus to the sternum, light stimuli are other stimulation methods used for SSR response (Kucera et al., 2004: 110).

Characteristics of the Sympathetic Skin Response

The shape of the SSR wave can be biphasic, triphasic, or monophasic. The latency of the SSR wave is from the stimulus artifact to the onset of the positive wave response. The amplitude is measured from the beginning of the response to the peak (Figure 2).

Habituation is the decrease in SSR amplitude after repeated stimulation. Generally, a decrease in response occurs after 3 consecutive stimuli (Raszewa et al., 1991: 467; Dolu et al., 1999a: 79).
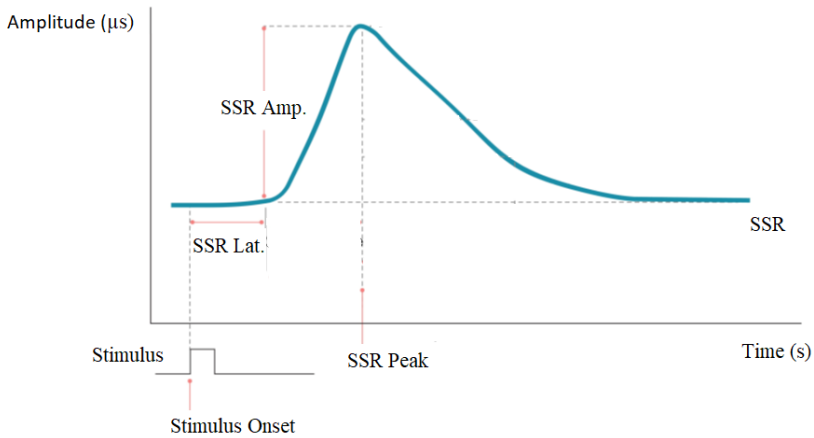
Figure 2 An illustrative curve of a SSR
(Modified from Ferreira et al., 2023: 620/3)

Investigation of Sympathetic Skin Response in Autonomic Function Diseases

a) Lesions of the Peripheral Nervous System and Nerve Roots: SSR is diagnosed clinically, in the diagnosis of autonomic diseases, by the analysis of the decrease in the amplitude of the reflex sympathetic reflex and the prolongation in latency. It is frequently used in the diagnosis of thin non-myelinated fiber lesions in patients with diabetic neuropathy (Bril et al., 2000: 1428). It has also been investigated in the diagnosis of familial amyloid neuropathy (Montagna et al., 1991: 679), alcoholic neuropathy (Miralles et al., 1995: 287), lepromatous neuropathy (Ulvi et al., 2003: 42), carpal tunnel syndrome (Verghese et al., 2000:1209).

b) Central Nervous System Diseases: SSR abnormalities have been found in more than 50% of patients with multiple sclerosis (Labuz-Roszak and Pierzchala, 2007: 375). A decrease in SSR amplitude and prolongation in latency was also detected in Parkinson's patients and Parkinsonian syndrome (Schestatsky et al., 2006: 486). SSR abnormalities have been observed in amyotrophic lateral sclerosis (absence of SSR response in 40% of patients) (Hu et al., 2016: 60), cervical myelopathy (Revanappa et al., 2017: 199), Huntington's disease (Sarilar, 2019: 3). SSR changes were found less frequently in epilepsy diseases (Nagai et al., 2019: 377).

c) Other diseases: SSR has been used in the investigation of many diseases such as schizophrenia (Xusan et al., 2021: 6211), erectile dysfunction (Chen et al., 2021: 277), hypothyroidism (Dolu et al., 1999a: 787), hyperthyroidism (Dolu et al., 1997: 1024; Dolu et al., 1999b: 79), depression (Whiston et al., 2022),

dermatological diseases and in evaluating the efficacy of treatment as in surgical-chemical sympathectomy (Lefaucheur et al, 1996: 581).

APPLICATION OF SYMPATHETIC SKIN RESPONSE IN DERMATOLOGIC DISEASES

Pathological changes involving autonomic nerves are involved in the etiopathogenesis of many skin diseases. The stress response plays an important role in symptoms, and ANS is known to have a close relationship with the efficacy of the stress response and the hypothalamic-pituitary-adrenal axis (HPA) (Shahani et al., 1984: 537). Therefore, studying sympathetic function using SSR gaining importance in clinical practice to assess some symptoms of skin diseases.

Hyperhidrosis

Hyperhidrosis is a dermatosis characterized by pathologically excessive focal or generalized sweating. It is associated with sympathetic cholinergic hyperactivity (Idiaquez et al., 2023: 2). Hyperhidrosis is divided into two as idiopathic primary form and secondary form. The idiopathic primary form typically begins during adolescence with localized sweating from the armpits, hands, face, or feet. The secondary form is the result of concomitant diseases or drug use and is often characterized by widespread sweating (Hashmonai et al., 2017: 379).

Although the pathophysiology of primary hyperhidrosis (PH) is not fully understood, it is believed to be a disease of ANS involving overstimulation of the sympathetic nervous system due to a defect in the hypothalamus. Patients feel embarrassment and anxiety because of excessive sweating, and their social lives are negatively affected (Henning et al., 2022: 635).

The sympathetic skin response is frequently used in the investigation of patients with hyperhidrosis. When SSR was measured in the upper extremities of people with and without palmar hyperhidrosis, it was shown that there was a significant difference between the latency and amplitude of the two groups. In addition, a direct relationship was observed between symptom severity and the degree of SSR abnormality, and it was concluded that the SSR changes in palmar hyperhidrosis were caused by the involvement of the sympathetic nervous system (Kazemi et al., 2004: 51).

Based on measurements of sympathetic skin response to excitatory stimuli in hyperhidrosis subjects before and after T2-T3 sympathectomy and in controls, Lin et al. suggested that PH may result from a regulatory dysfunction rather than over-function of sweat glands (Lin et al., 1995: 917). Iwase et al. (Iwase et al., 1997: 65) recorded simultaneous skin sympathetic nerve activity from the tibial

and peroneal nerves in ambulatory patients and controls in patients with primary palmoplantar hyperhidrosis. Compared with controls in hyperhidrosis patients, the sympathetic activity of the skin on the soles of the feet (tibial nerve) has been found to overreact to both mental and thermal stimuli. However, only slight changes were noted in the peroneal nerves that innervate the dorsum of the foot (not the hyperhidrotic region). It was concluded that both mental and thermal stimuli may be responsible for excessive sweating. In another study in patients with PH (Schestatsky et al, 2011: 92), it was shown that excessive sudomotor reactions occur, consistent with central sensitization of sympathetic circuits, to perceptual abnormalities and thermoalgesic stimuli. Sympathectomy was found to reduce sympathetic outflow and normalize sensory perception but did not alter the abnormal control of efferent sudomotor activity, so patients with PH may have central neurologic dysfunction. In Manca et al.'s (2000: 1767) study comparing the SSR recovery curves of patients with primary palmar hyperhidrosis and the control group, it was found that the SSR recovery curves of patients with primary palmar hyperhidrosis were higher than the control group. Overstimulation of the somato-sympathetic polysynaptic pathway involved in sweating was held responsible for this finding.

Acne Vulgaris

Acne vulgaris is a common pilosebaceous unit disease characterized by peripheral inflammation. The etiopathogenesis of acne vulgaris includes sebaceous gland hyperplasia, increased sebum production, follicular hyperkeratinization, and stress (Polat et al., 2017: 668).

The skin is a neuro-immuno-endocrine organ. The peripheral nervous system, cranial nervous system, and ANS are associated with the innervation of the skin and its appendages. In chronic stress, the HPA axis activates and stimulates the release of corticotropin-releasing hormone (CRH), adrenocorticotropin hormone (ACTH), alpha-melanocyte-stimulating hormone (α-MSH), and β-endorphins. They are excreted through the skin and central nervous system. Their increase causes an increase in the inflammatory response in pilosebaceous, which stimulates keratinocyte proliferation and differentiation.

Stress also activates the secretion of epinephrine and norepinephrine. These catecholamines are produced locally by keratinocytes and fibers of the sympathetic nervous system. The increase in catecholamines increases lymphocyte proliferation, cytokine release, and inflammation (Honeyman, 2016). In the study of Kaplan et al. (2014), in which they performed sympathetic nerve blockade, a significant decrease in acne coincidentally explains the relationship between skin and ANS (Kaplan et al., 2014: 264).

Despite this relationship between the sympathetic nervous system and the etiopathogenesis of acne vulgaris, Polat et al. (2017: 669) measured SSR by stimulating both median nerves from both wrists separately with 0.5-2000 Hz. and 10-second analysis time and found that SSR latencies and amplitudes of acne vulgaris and healthy control groups were not different. This indicates that further studies are needed.

Vitiligo

Vitiligo is a disease with multifactorial components. Although genetic components, metabolic factors due to cellular oxidative stress, melanocyte adhesion to the epithelium, and immune involvement resulting in autoimmune aggression against melanocytes play a role in its pathogenesis, the exact mechanisms are still not fully elucidated.

Autoimmune aggression against melanocytes causes hypochromic or acromic macules and patches on the skin and mucous membranes. Possible involvement of hair follicles in different extensions of the skin and systemic symptoms such as sensorineural deafness, uveitis, and thyroiditis are also possible (Marchioro et al., 2022: 478).

The has been reported that abnormal activation of the melatonin receptor may lead to increased release of catecholamines and other neurotransmitters (Dolu et al., 2005: 103). Temperature rise and acetylcholine activity, neuropeptide distributions, and catecholamine metabolism abnormalities have been demonstrated in depigmented skin. Depigmented areas tend to sweat less and have differential temperature regulation, electrical resistance, and other related neural dysfunctions in the skin (Al'Abadie et al., 1994: 160, Elwary et al., 1997: 81, Liu et al., 1996, Schallreuter et al., 1995: 954).

In the SSR records taken to investigate the effect of sympathetic activity on the physiopathogenesis of vitiligo, there was no difference in the SSR amplitude and latency of vitiligo patients and the control group (Bir and Aktan, 1999: 69; Dogramaci and Okuyucu, 2009: 58; Dikicier and Demiryürek (2019: 148) or found lower than normal amplitude and latency (Merello et al. 1993:72).

In the study of Dolu et al. (2005: 102), the electrodermal activity records of patients with generalized vitiligo before and after PUVA treatment were compared with the control group, and it was found that the level of skin conductivity was higher in the pre-treatment vitiligo group and the habituation status was delayed more than the control group. After the treatment, the level of skin conductivity and habituation in vitiligo patients decreased to approximate values in the control group. It was observed that the prevalence of

unresponsiveness before and after treatment in the vitiligo group was higher than in the controls.

Psoriasis

Psoriasis is a chronic, inflammatory autoimmune skin disease that is affected by genetics and various environmental factors. It affects men and women equally and is more common in adults than children. Although the mortality rate in psoriasis is low, patients experience a significant deterioration in quality of life and psychosocial burden. The disease is characterized by epidermal hyperplasia and dermal infiltration of immune cells. Its pathogenesis includes complex factors, including the interaction between keratinocytes, immune cells, and other skin-resident cells (Zhou et al. 2022: 81).

Plaque psoriasis is the most common type of psoriasis. It is characterized by erythematous scaly patches or plaques that usually occur on the extensor surfaces, but can also affect different areas such as the palms, soles, and nails. Its pathogenesis involves a feedforward inflammation mechanism primarily involving the T-helper cell type 17 (TH17) pathway. Genetic factors play a critical role in the development of the disease and the disease is exacerbated by environmental factors (Armstrong and Read, 2020:1947)

SSR has been studied to provide information about the brain-skin axis in patients with psoriasis or the basis of the local neuroimmunoendocrine circuit for the underlying cause and pathogenesis of stress-triggered allergic and inflammatory skin diseases such as psoriasis.

In this context, it has been reported that especially upper extremity SSR latency and amplitude values were prolonged in plaque-type psoriasis patients compared to the control group (Halıgür et al., 2012: 557; Sundareswaran et al., 2023: 195).

Atopic Dermatitis

Atopic dermatitis (AD) is a recurrent, chronic, non-infectious inflammatory dermatosis characterized by persistent itching of the skin. It is one of the most common skin diseases in childhood. The disease develops in the first year of life in 50-60% of cases, and 90% of patients are under the age of five. Adults also suffer from AD, mostly from childhood, and there are new adult cases as well. The clinical picture includes eczema-like rashes such as erythema, papules, and exudative lesions in a specific area, depending on the age of the patient (infant, childhood, and adulthood) and varying degrees of skin dryness. Due to the long-term course of the disease, chronic or recurrent inflammation and itching come to skin thickening and lichenification. The frequency of hyperhidrosis in atopic

patients is higher than in the control group. Constant itching of the skin causes insomnia and sleep disturbance. This significantly reduces the quality of life (Sroka-Tomaszewska and Trzeciak, 2021: 4130).

The results of many studies have revealed the role of ANS in mediating the immune system (Kim et al., 2020: 35) and it has been shown that atopic patients have a dysfunction in the sympathetic nervous system and sudomotor activity. There is a prolonged SSR latency in the atopic patient group, indicating an inadequate sympathetic innervation. It has been reported that insufficient innervation of sweat glands in atopic patients may lead to an increase in the development of Type IV allergy (Wruhs et al, 2017: 787).

Scleroderma

Scleroderma is an autoimmune rheumatic disease characterized by significant damage to the vascular system, tissue fibrosis, and collagen deposition in the skin. Hardening of the skin and connective tissue occurs locally or throughout the body. Scleroderma is divided into two types according to the level of formation localized and systemic. Localized scleroderma is limited to the skin and muscle levels, known as morphea and linear type. If it affects a wider skin and organ area, it is called systemic, including limited and diffuse forms (Romano et al., 2023: 513).

General immune activation, vascular damage, impaired angiogenesis, and excessive accumulation of the extracellular matrix with increased structurally normal collagen content play a role in the physiopathogenesis of scleroderma (Singh et al., 2019: 105; Germain et al., 2010: 246).

Patients with scleroderma have a sympathovagal imbalance of sympathetic dominance and vagal retraction both initially and over time (Rodrigues et al., 2022: 34).

Abnormalities have often been reported in the SSRs of scleroderma patients. In the study by Raszewa et al. (1991:468), 68.8% of patients with linear scleroderma had SSR abnormalities (delayed latency, decreased amplitude and/or asymmetry, no response) when they recorded SSR from the palms and soles of the feet by repeatedly stimulating the right and left median and tibial nerves. In particular, amplitude asymmetry of the upper extremity's incoming responses was reported as the most characteristic abnormality. No correlation was observed between SSR responses and the localization, degree, and character of skin changes (such as edema, atrophy, and sclerosis), duration of disease, ANS disorder symptoms (vasomotor and/or sudomotor), and changes in capillaroscopy (Raszewa et al, 1991:469). In the study of Badry et al. (2018: 2), the SSR potential

of patients with scleroderma was longer and their amplitudes decreased compared to the control.

In another study, it was reported that 77% of scleroderma patients had abnormal SSR, no response from the lower extremities, and normal responses from the upper extremities (Zakrzewska-Pniewska et al., 1999: 475).

CONCLUSION

SSR is an easy-to-apply, noninvasive method used today to investigate the etiopathogenesis of many diseases related to the sympathetic system. In this section, researches in the field of dermatology are presented. Although these studies usually have abnormal SSRs, unresponsiveness, decreased amplitude and delayed latency, further studies are needed to find definitive distinguishing features in each disease.

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Chapter 10

The Effectiveness of Dir/Floortime Therapy in a Child with Behavioral Problems: A Case Report[1]

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ABSTRACT

DIR Floortime is a Developmental, Individual Differences and Relationship-based intervention program commonly used for children with Autism Spectrum Disorder. Floortime is to enter the child's world by considering the child's differences while following the child's leadership.

Every child is different and special. For this reason, after interacting with an undiagnosed child and entering the child's world, the effectiveness of the Floortime method has been observed in the child's undesirable behavior, which is seen as a behavioral problem. A 3 year 2 month old boy who was previously observed by a child psychiatrist and clinical psychologist and directed to take floortime was included in the study. In order to determine the child's individual differences and sensory processing skills, Dunn's Sensory Profile was used, and the functional emotional development steps of the child which are Regulation, Engagement, Two-Way Communication, Social Problem Solving, Symbolic Play and Logical Thinking were evaluated with the observation technique. DIR Floortime was applied in a 4-month period (2 sessions*45 min/week), and at the end of the process, the developmental steps were observed again. According to the before-after evaluation results, improvements were observed in the child's skills and functional developmental stages. In addition, at the end of the sessions, it was stated by the family that there were improvements in the child-parent interaction and there were positive changes in the child's behavioral attitudes. The power of the play under the leadership of the child will be effective not only for the children with the diagnosis, but also for every child and will play a positive role in the development of the children.

Keywords: Floortime, Behavior Problems, Child-Parent Interaction

INTRODUCTION

Floortime was developed by child psychiatrist Stanley Greenspan and his colleagues in the United States in the 1980s. In floortime studies, the skills that are thought to be necessary to take necessary precautions in a healthy development process are taught. In this context, it is aimed that the child can establish purposeful and meaningful relationships with other people, establish closeness, communicate and maintain it, as well as develop creative and logical thinking skills (Greenspan and Wieder, 2006).

The Floortime model is an interdisciplinary framework that provides the ability to create a holistic assessment and intervention program for clinicians, parents and educators addressing the deficiencies in the developmental profile of the child and family (Greenspan and Wieder, 1999:147-161). Floortime, which means interactive play or time on the floor, is an interactive approach based on family structure and the strength of relationships and uses systematic relationships to assist children in their emotional developmental stages (Greenspan and Wieder, 2003:425-435). Floortime therapy which aims to support the emotional development of the child is also defined as play therapy which aims to develop the social relationship between the child and the adult (Eikeseth and Klintwall, 2014:2101-2123).

Play is the best way for children to express themselves and it also gives the play partner access to the child's own world (VanFleet et al., 2011). The majority of a child's actions or discourses in the play can be characterized as a symbolic and figurative description of the processes the child is in and the relationships child has established. The information obtained in this whole process also shows the way the child communicates (Kottman and Meany-Walen, 2016). If the child has the ability not to exhibit an undesirable behavior and child repeats this behavior despite being told not to do this behavior, this situation is seen as problematic behaviour (Birkan, 2022:18-20) When the child exhibits a problematic behavior, investigating when and under what conditions this behavior occurs, the reasons for its occurrence, the purpose of the behavior or the achievements of the child after performing this behavior will help to understand and solve the problem (Kaya, 2017). In other words, determining the child's weaknesses and strengths, social relations, situations that cause stress and family relations play an active role in the identification of behavioral problems and in the treatment process (Jongsma et al., 2014). In this context, Floortime emphasizes that each child is unique and each child has his/her own strengths and weaknesses and emphasizes that this model is made unique to each child and that family participation is also supported (Greenspan and Wieder, 1999:147-161).

Family participation is a very important aspect of the Floortime model. In addition, this model highlights the idea that real learning occurs in real contexts and not artificial ones, and generalizes acquired skills to various types of social interaction. The floortime model includes six developmental milestones of emotional functioning that allow professionals to assess children's intellectual and emotional maturity. The critical element of these six developmental milestones is mutual communication between the child and caregiver (Greenspan et al., 2001).

Functional Emotional Development Capacities

1. 0-3 months : Regulation and Attention
2. 2-7 months : Attachment and involvement in relationships, engagement
3. 3-10 months : Two-way purpose communication
4. 9-18 months : Complex social problem solving
5. 18-30 months : Symbolic play, representations of affects and ideas
6. 30-48 months: Logical thinking

In floortime therapy, sessions are held in an environment where the child feels comfortable and the play partner (clinician, parent, caregiver) works with the child sitting on the floor (Simpson et al., 2004)

The child is primarily observed, when the play partner seizes the appropriate moment for the child, she intends to approach the child and initiate a communication cycle. In Floortime, the leader is the child and all the work continues under the child's leadership. After the partnership starts, the play partner makes various moves using effects to develop this partnership, and then this communication cycle is expected to be closed with a verbal or non-verbal response of the child. During a session, the communication process can start and end many times. This whole process is considered the beginning of two-way communication (Greenspan and Wieder, 2006; Simpson et al., 2004).

Although Floortime has emerged as an intervention program for children with Autism Spectrum Disorder and it is seen as a therapy that effectively uses play for the development of developmental stages of children with ASD, the power of play can be used for the development of every child. In this study, it was aimed to examine the effect of Floortime therapy on the undesirable aspects of behavior seen in the child due to the problems in the parent-child relationship.

MATERIALS AND METHODS

In this study, a single-subject research design consisting of observation and intervention stages was used.

Case

3 year 2 month old boy who was previously observed by a child psychiatrist and clinical psychologist and directed to take floortime was included in the study. The study was conducted between November 2020 and February 2021. The reason for the mother's request for help was the behavior problems (yelling, biting, hitting, limitations in sharing plays and toys) and eating problems that her child showed. She stated that the child only ate the food in the form of slurry, and the mother even gave the bread by wetting it.

According to the development history taken from the mother and father, the motor development stages were completed within the expected periods, and it was stated that there was no eating problem in infancy. According to the information given by the family, the mother is a health worker and the child is taken care of by the grandparents at the caregiver's home while she is on duty. The father is self-employed, and he spends a limited amount of time with the child, as he has one day off at the weekend. While the mother has a miscarriage before this pregnancy, is very protective of her child, tends to do whatever the child wants, and is overly tolerant, the father may display a more inconsistent attitude in his relationship with the child. According to another information received from the parents during the interview, when the child behaves undesirably, he is left in his room and asked not to leave the room. When the child goes out, he is taken back to his room. Positive behaviors are only verbally rewarded with 'well done', and negative behaviors are punished. Forces made during the toilet training period (2.5 years old) and periods in which every caregiver in the family has been forced to eat and drink for a long time are seen as the beginning of undesirable behaviors.

At the end of the first meeting with the parents, detailed information about the DIR Floortime therapy was given to the family and an informed consent form was signed. In the consent form, it was stated that the mother's participation in this study was on a voluntary basis, that they would not participate in this study if they did not want to, and that their private information in this study would be kept confidential.

Scales

Dunn Sensory Profile: The scale was developed in 1999 by Occupational Therapist Winnie Dunn. There are evaluations for four different age groups: the early childhood sensory profile applied to babies aged 0-3, the sensory profile applied to children aged 3-10, the adult sensory profile applied to people over the age of 10, and the sensory profile for school.

The scale used in this study is the sensory profile applied to the 3-10 age group. The scale measures the child's responses to sensory events and is filled in by the caregiver. The sensory profile consists of 125 questions and 3 main headings: sensory processing, sensory modulation, and emotional and behavioral responses. In the 5-point Likert-type scale, the data is recorded by scoring from 1 to 5, with 1 point for the "always" response and 5 points for the "never" response. The Turkish validation of the sensory profile system was performed by Kayıhan et al., (2015) and it is a valid and reliable scale (Dunn, 1999).

The sensory profile scale was designed to reveal the individual differences of the child, and to direct him to receive sensory integration sessions if it is considered to be an issue that needs help (Kayihan et al., 2015:971-986).

The functional emotional development stages of the child were evaluated with the observation technique. DIR Floortime was applied in a 4-month period (2 sessions*45 minutes/week), and at the end of the process, the developmental steps were observed again.

Observation and Intervention Phases

The sessions were held in the family's home. In the first session, the mother and the child were taken together, and the interaction between the mother and the child was observed. The observation session lasted 50 minutes. The session started in the child's room, the child's constant wanting to take the mother out of the room, wanting to move the playground outside, and ignoring therapist were the first noticeable behaviors. The mother was always willing to intervene and presented many toys to the child as an option without waiting for the child to start the play. During the entire observation period, the child's hectic behavior, wanting to shout at the mother to make her requests, and hitting the mother when the mother objected were observed. After the observation session, the mother stated that she couldn't bear it anymore and stated that she was also angry and tried to make the child do her requests by shouting, albeit unintentionally.

After the first session, the child was taken to the observation session 2 more times separately from the mother. Having too many toys in the room caused the child to constantly switch from play to play. The desire to play by hitting the cars against each other and the desire to throw the toys in his hand were observed. It was determined that the child could rarely self-regulate and needed support for regulation. The child's strengths were determined as making eye contact, verbally stating his wishes and what he did not want, and having a strong receptive and expressive language. It has been determined that he wants

more active activities, likes fine motor activities, and if the child's instructions are followed in the play, a longer relationship is provided.

In the following sessions, with the child's acceptance of the therapist, the functional emotional development steps were reached. In the first month, the sessions progressed between the child and the therapist, and the mother was given suggestions about maintaining effective communication at home under the child's leadership. After the sessions, sensory activities were performed to support the oral sense, and the mother was offered activities that she could do at home. At the end of the sessions, food trials were conducted with the child. At the end of the second month, after 20-minute child-therapist sessions, the mother was also included in the sessions, communication circles were started and progressed. After the session, food trials continued and positive developments were recorded.

RESULTS

After calculating the Dunn sensory profile score, the child was evaluated according to the reference score table. In the Oral Sensory processing step, which is one of the sub-sections of the Sensory Processing section of the Dunn sensory profile, the child was found to be in the "more than others" range, while in the other subsections, the child was found to be in the "typical performance" range. The child, who was in the 'typical performance' range in the sub-sections of the modulation step, was found in the 'more than others' range in the emotional and social responses step, which is a sub-level of the behavior and emotional responses step. It was concluded that it showed 'typical performance' in other steps.

Depending on these results, after the sessions with the child, oral sensory exercises (massages to the cheek and chin muscles, stimulus with an intraoral vibrating brush, etc.) were made and suggestions were made to the family about what to do.

During the floortime sessions, it was seen that the child made progress. In the first sessions, it was not possible to reach the upper steps with the child who had adaptation problems, needed support in regulation and provided short-term coexistence. At the end of the four-month period, he was able to complete the Functional Emotional Development Steps specified in the Floortime Program.

1. Regulation: In the first sessions, it was observed that he could rarely regulate himself at the regulation stage, needed support and showed problem behaviors if regulation could not be achieved. At the end of the sessions, the child can now regulate himself without support, and it has been observed that he needs support from time to time.

2. Engagement: In the second step of establishing togetherness, short-term cooperation was provided in the first sessions, and it was observed that it often returned to the regulation step. During the next sessions, a relationship based on trust was established with the child who had difficulty in going up the next step, it was seen that the child was more compatible and could easily form the communication circle.

3. Two-way purpose communication: The child, who was able to initiate the communication circle even for a short time in the first sessions, could exhibit behaviors such as throwing toys, shouting, leaving the room when the play did not progress as he wanted, and our relationship could end by closing the communication ring abruptly by the child. After a month of therapy, the child was able to reach this step without negative behaviors. Although the duration of the communication cycle during the following sessions differed according to the activity, it was observed that the child was able to initiate the circle of communication, to continue the circle started by the therapist/parent, and to enjoy it.

4. Complex Social Problem Solving: In the first month, including the observation sessions, the step could not be reached. In the following sessions, it was observed that the child insisted on making his wishes because his sense of self was dominant. It has been stated that better results can be obtained if it is supported. As the sessions progressed, the child was able to show different emotions within the communication circle and expand the communication circles. At the end of the sessions, it was observed that when this step in the communication cycle was reached, the child's sequencing and planning skills were able to interact emotionally and socially with the therapist/parent with the intention of problem solving.

5. Representation of thoughts, symbolic play: It was noted that this step could not be passed due to the fact that the child remained at the lower levels in the first sessions and that the communication circle was closed by the child. As progress is made in the complex social problem solving step, it has been observed that the communication circles widen and expressions with more meaningful words begin. During the therapist/parent association, pretend plays started within the communication circle, and it was observed that the child was able to play interactive plays (arranging the toys in order, making the toys talk, feeding the babies, etc.).

6. Abstract thinking: It has been observed that during the interaction with the child in the play, the child can play symbolic plays containing logic and emotion, and the child can progress in the play by answering questions such as what, why, and how. It has also been observed that the child can attribute

meanings to the symbolic uses in the play. In the interviews with the family, it was stated that as the age of the child grows, the symbolic plays will become more diverse.

Effective communication with the child is established at the end of the first month. The child-therapist relationship was based on trust and progressed in the form of playmate, the therapist and parents accepted the child's leadership in the play and progressed by following the child. The family has given more opportunities for the child to initiate and maintain communication. At the end of the sessions, various foods were offered to the child, and food was included in the play in the following sessions. It was stated by the family that the child is now open to new tastes and eats solid foods. The mother stated that she changed her food attitudes towards the child, did not turn every meal into a slurry for fear of not eating it, offered the food they ate to the child as an option, and mostly received positive feedback. The approach to the child has completely changed by the family, and the mother has stated that she is much happier and calmer depending on the child's progress. The father stated that he was more willing towards the child because they could spend quality time with the child. In addition, it was said by the family that the child's undesirable behaviors such as hitting and biting ended. It was stated that as the family sees the child's strengths and accepts the self that the child wants to show, their relations with the child are affected positively.

DISCUSSION

The aim of this study is to examine the effectiveness of the Floortime approach in a child with behavioral problems. In this study, where the floortime approach was applied in the cooperation of parents and families, it was concluded that the interaction between the child and the family increased and the child's adaptive behavior improved.

The floortime approach is relationship-based, so the child's needs are tried to be met through social interaction. These interactions can occur in any environment and at any time during spontaneous playtime (Greenspan and Wieder, 2003:425-435). In this context, it has been reported that the Floortime approach has positive effects on the child's adaptive behavior, verbal communication, peer relations, imitation skills, symbolic play skills and academic skills (Solomon et al., 2007:205-224).

A review of the literature highlights that there is evidence that emotional processes such as participation, joint attention, emotional reciprocity, and creative play are associated with healthy social, language, and intellectual

functioning (Siller and Sigman, 2022:77-89; Mundy et al., 1990:115-128; Mundy, 1993:381-384; Greenspan, 2004).

The floortime model focuses on the child's constant interaction flow, symbolic play and high-level thinking throughout the daily sessions, and also supports the child's problem solving, reality-based logical conversations, effective communication and friendship. In addition, the necessity of the play is emphasized in the Floortime model (Greenspan and Wieder, 2005:39-61).

Play is an activity that takes place in most of the child's life and has positive effects on social emotional, psychomotor, cognitive, language and personal development, which are among the developmental areas of the child (Akandere, 2002; Sel, 1984). Children can show all their emotions through play and express themselves through play. Children can easily learn to communicate effectively with people, to establish relationships, to empathize and to tolerate limits, thanks to play. All these achievements can be counted as the effects of play on the child's social and emotional development (Seyrek and Sun, 2003). At the same time, the play materials used by the child during the play period are an indicator of the child's wishes. The child who reflects his skills to the play can also show his personality in the play, so the child's self-confidence develops (Koçyiğit, 2007:324-342).

According to studies in the literature, behavioral problems in children are based on various reasons. Among the most frequently encountered factors are the characteristics of the parents and their willingness to participate in the trainings. Dunlap et al.,(2001:215-221) in their study, stated that family involvement plays an important role in the positive behavior of children. The result of a study by McCormick et al., it was concluded that as family involvement increases, behavioral problems in children decrease (McCormick, 2013:277-300). It has been stated that with the mutual emotional transfers provided in child-parent interactive plays, children gain behavioral flexibility and existing behavioral problems are reduce (Cohen and Shulman, 2019:131-140). With the observations made within the scope of this study and the feedback received from the family, it is possible to say that the child-parent association is ensured and the behavior problems seen in the child come to an end after the relationship-based progress.

In addition, it has been stated that child-parent joint interactive plays have a positive effect on children's eating disorders (Butcher et al., 2013). In this study, positive developments were observed in the behavior of the child with the participation of the family, by using the floortime principles, and eating problems were eliminated to a great extent.

CONCLUSION

As a result, Floortime activity has an important place in children who convey their expectations, feelings and thoughts through play. With the participation of the parents, the effectiveness of the play reaches higher levels. Thanks to Floortime activities, children express their feelings without leaving their own world. It can be commented that understanding these feelings well and producing solutions is the main purpose of this activity. At the same time, although Floortime is a model developed for children with autism, it can be applied anywhere, in any area where children and play are included.

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Chapter 11

Genital Self-Image:
Body Image and Sexual Health Areas

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ABSTRACT

Genital self-image refers to the emotional/psychological perception and awareness of individuals about their sexual organs. Body image dissatisfaction is related to the negative perception of one's physical appearance. An individual's body image evaluative thoughts, beliefs, feelings and behaviors can vary in different dimensions. Among women, negative body image is associated with low self-esteem, depression, and anxiety and has a negative effect on sexual pleasure. Women are also prone to develop distorted views of their genitals due to several phenomena. Dissatisfaction creates a growing tendency among some women to have surgery to improve the external physical appearance of their genitals. The lower the satisfaction of women with their genitals, the higher their interest and desire for genital plastic surgery. Negative genital self-image and genital-focused anxieties may decrease women's self-esteem, increase sexual performance anxiety and hinder sexual satisfaction. The relationship between genital self-image and two areas of body image (specific to emotional and sexual encounters) is valuable. Genital self-image is significantly associated with women's experiences of sexual desire, sexual arousal, vaginal lubrication, orgasm, and sexual pain. Professional interventions and treatments should specifically target negative body cognitions that arise during a sexual encounter to help increase their sexual satisfaction and function. Sexual satisfaction and sexual problems can affect experiences with partners. Relationships between genital self-image and various taboos and acceptances regarding sexuality in women continue to be evaluated. It is multifactorial, such as sexual experience, age, and religiousness. Genital self-image is known to be a separate but independent predictor of sexual satisfaction and sexual functioning among women. Experiences of negative body image specific to sexual encounters may result from poor genital self-image and include negative aspects of sexual life. Research in this area can inform future clinical interventions regarding sexual function. Body image in general and genital self-image in particular are important factors in sexual experiences. To grasp the diversity of sexual organs beyond what is presented in the national and international media; It will help young women to normalize genital diversity. It will be through education that women serve to increase self-acceptance despite differences. Increasing the level of knowledge and awareness; will positively affect sexual experiences for women.

Keywords: Genital self-image, sexual satisfaction, sexual life, women's health, sexual problems

GENITAL SELF IMAGINE

Genital self-image refers to the emotional/psychological perception and awareness of individuals about their sexual organs. Body image dissatisfaction is related to the negative perception of one's physical appearance [1]. An individual's body image evaluative thoughts, beliefs, feelings and behaviors can vary in different dimensions.

Women's negative self-perceptions and emotional states negatively affect women's quality of life. The thought that women's bodies are unhealthy will then lead to the emergence of negative behaviors and motivations about women themselves.

Negative Genital Self-Image

The harmful consequences of negative body image include eating disorders, depression, low self-esteem, reduced self-care, concerns about physical appearance, and decreased enjoyment in daily activities [2]. It was also found that women who reported lower body image, lower degree of body attractiveness, and greater body dissatisfaction had more body shame and less pleasure during sexual activity.

Among women, negative body image is associated with low self-esteem, depression, and anxiety and has a negative effect on sexual pleasure.

Unfortunately, body image concerns among women have become common psychological experiences.

More recently, definitions of body image concerns have expanded to include genital self-image concerns in women. While body satisfaction is only one aspect of women's genital self-perception, much research has focused on this aspect (eg – genital image).

Although both women and men report negative genital self-images, research has shown that they tend to have more negative genital self-images than women [3]. This difference may be the result of several different parameters. Studies on female genital self-perception; examined perceptions of both appearance and function.

Women are also prone to develop distorted views of their genitals due to several phenomena. First, images of female genitals in pornography and other media can contribute to societal prejudices about "how" female genitalia should look [4]. Also, women's genitals are often less visible and traditionally unspeakable has been more taboo. For this reason, they may appear more 'unknowable' to women. The researches also; In this study, the attitudes of women towards their sexual organs were analyzed qualitatively.

Women; they tend to focus their concerns about their sexuality and body on their genitals [5]. If women feel that they do not meet perfection for their functions and/or appearance; dissatisfaction with their genitals will increase. Dissatisfaction creates a growing tendency among some women to have surgery to improve the external physical appearance of their genitals.

The lower the satisfaction of women with their genitals, the higher their interest and desire for genital plastic surgery [6].

Negative genital self-image is also associated with other areas of body image.

More studies are needed to investigate the relationships between body image and genital self-image in women. However, it should be noted that; the relationship between more positive genital self-perceptions and positive self-perceptions of the woman's body; ensures healthy sexual activity [7]. Indeed, studies indicate that negative genital self-image affects sexual function as well as sexual satisfaction.

Women's concerns about their genitals and/or sexual performance may stem from women's negative views of their genitals and/or concerns about their partner's evaluation of their genitals. As a result, negative genital self-image and genital-focused anxieties may decrease women's self-esteem, increase sexual performance anxiety and hinder sexual satisfaction.

Body Image and Sexual Health

Poor genital self-image among young women is reported to predict orgasmic difficulties through sexual anxiety. Women are distracted during sexual intercourse due to sexual anxiety. They may experience difficulties in sexual functions with the realization of the opposite sex.

Poor genital self-image and knowledge and awareness of their genitals also affect women's experiences during coitus. Women who are concerned about their partner's perceptions of their genitals will experience decreased sexual satisfaction and decreased pleasure from sexual activity [8].

Women with increased self-esteem during sexual activity will experience increased sexual satisfaction and pleasure from sexual activity. Women are also more likely to report increased genital self-awareness. It has been found that sexual pleasure is facilitated among women with a more positive attitude towards the genitals. For women, the relationship between genital self-image and two areas of body image (specific to emotional and sexual encounters) is valuable.

Genital self-image is a predictor of sexual satisfaction and sexual function. Among women, positive genital self-image is associated with positive feelings

about one's body in general and with reduced body-related anxieties during sexual intercourse. For women, genital body image; It is strongly associated with emotional body image and related body image concerns during sexual encounters.

Women with more genital satisfaction are less worried about exposing their bodies during sexual activity [7]. Women who are more aware of their genitals report that they feel more sexually attractive. Interventions aimed at improving genital self-image among women; It will also have a positive effect on body self-image.

Genital self-image is significantly associated with women's experiences of sexual desire, sexual arousal, vaginal lubrication, orgasm, and sexual pain. More positive genital self-image is associated with reduced sexual dysfunction. Therefore, women having negative attitudes about their genitals can lead to a decrease in desire and arousal.

Negative information and assumptions; can potentially negatively affect orgasm and sexual functioning. Although genital self-image and overall body image each have independent effects on sexual experience, genital self-image has a more pronounced effect. After controlling for general body self-image and sexual encounter-specific body anxieties, genital self-image is an independent predictor of sexual satisfaction among women.

Positive genital self-image

Positive genital self-image is associated with increased sexual satisfaction among women.

The five sexual dysfunctions in women (desire, arousal, lubrication, orgasm, and satisfaction) are significantly related to genital image [9]. More positive genital self-image is associated with higher sexual functioning among women. Therefore, more positive genital self-image is associated with higher sexual functioning among women.

Positive genital self-image is positively associated with sexual desire and positive body image [9]. Positive genital self-image, sexual distress during sex is negatively associated with depression. It shows that women who have a more positive view of their genital appearance and function experience higher sexual esteem and greater perceived sexual attraction. Improving the genital self-image will help improve or preserve sexual function as well as affirming women's self-conscious experiences about their bodies.

Professional interventions and treatments should specifically target negative body cognitions that arise during a sexual encounter to help increase their sexual satisfaction and function.

Genital Body Image and Sexual Satisfaction

To make a significant contribution to the field of body image and sexual experience, genital self-image must be moved beyond the person's general feelings about their body to a positive level.

Sexual satisfaction and sexual problems can affect experiences with partners. Relationships between genital self-image and various taboos and acceptances regarding sexuality in women continue to be evaluated. Genital self-image influences relationships between other areas of body image and a range of sexual experiences. The rate of variance explained in sexual dysfunction experiences generally ranges from 12-1.6% [2, 10]. It is multifactorial, such as sexual experience, age, and religiousness.

Sexual dysfunction in women; associated with negative emotions and stress-related problems. Future research should continue to examine the wide variety of factors that may be associated with sexual dysfunction in women.

Suggestions

Genital self-image is known to be a separate but independent predictor of sexual satisfaction and sexual functioning among women.

Experiences of negative body image specific to sexual encounters may result from poor genital self-image and include negative aspects of sexual life. Research in this area can inform future clinical interventions regarding sexual function. What is most likely from the literature is that body image in general and genital self-image in particular are important factors in sexual experiences. Also, future interventions to improve body image should also include genital areas, especially for women. Recent studies have shown that in young women; The positive effects of raising awareness about the various healthy appearances of female genitals are reported. In order to improve genital self-images, the level of knowledge about sexual health should be increased.

To grasp the diversity of sexual organs beyond what is presented in the national and international media; It will help young women to normalize genital diversity. It will be through education that women serve to increase self-acceptance despite differences. Increasing the level of knowledge and awareness; will positively affect sexual experiences for women.

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Chapter 12

A Clinician's Perspective on The Diagnosis and Treatment of Hyperprolactinaemia

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ABSTRACT

INTRODUCTION

Prolactin synthesis and secretion

Prolactin (PRL), known as the lactation hormone, is synthesised as an amino acid by lactotrophic cells in the pituitary gland and has a pulsatile and circadian release (Freeman et al, 2000:1523). When synthesised by the pituitary gland, PRL weighs 199 kilodaltons (kDa); it then undergoes proteolysis and is split into units of 16 kDa and 23.5 kDa (Bachelot et al, 2007:361, Piwnica et al, 2006:3263). PRL has a circadian rhythm and is higher during non rapid eye movement (REM) sleep period, but this variation is less marked than for cortisol (Mancini et al, 2008:67). PRL is also secreted by the central nervous system, immune system, placenta, breasts and uterus (Bachelot et al, 2007:361).

Factors that stimulate and inhibit prolactin secretion

There are several factors that control PRL release. The controlling factors are divided into two main groups as stimulatory (suction, estrogen increase and stress) and inhibitory (dopamine) (Mancini et al, 2008:67). Increased dopamine levels in the pituitary portal system suppress PRL synthesis via dopamine 2 receptors (DPR2) (Freeman et al, 2000:1523, Mancini et al, 2008:67). This effect is also important in mediating the hyperprolactinemic (HP) effect of some drugs (Bargiota et al, 2013, Knegtering et al, 2003:109, Canuso et al, 2002:11). The most important drug group with anti-dopaminergic effects are anti-psychotic drugs (APDs) (Bargiota vd, 2013). APDs constitute an important part of referrals due to drug induced HP (DIHP) (Bargiota vd, 2013, Knegtering vd, 2003:109, Canuso vd, 2002:11). Typical APDs (1st generation APDs) block DPR2 in all regions of the brain without any selectivity (Canuso vd, 2002:11) and provide control of schizophrenic symptoms in this way (Canuso vd, 2002:11). On the other hand, 2nd generation (atypical APDs) bind to serotonin 2 receptor (5HTR2) at a higher rate and DPR2 at a lower rate, and this effect significantly reduces the HP-inducing effects of atypical APDs (Canuso et al, 2002:11). In addition, somatostatin and corticosteroid hormones have inhibitory effects on PRL release (Mancini et al, 2008:67). There is also a PRL feedback mechanism (Mancini et al, 2008:67). This mechanism works as follows: increased PRL secretion in the pituitary increases dopamine production in the hypothalamus and suppresses PRL release (Mancini et al, 2008:67). A schematic view of the factors that influence PRL secretion and synthesis is shown in Figure 1.
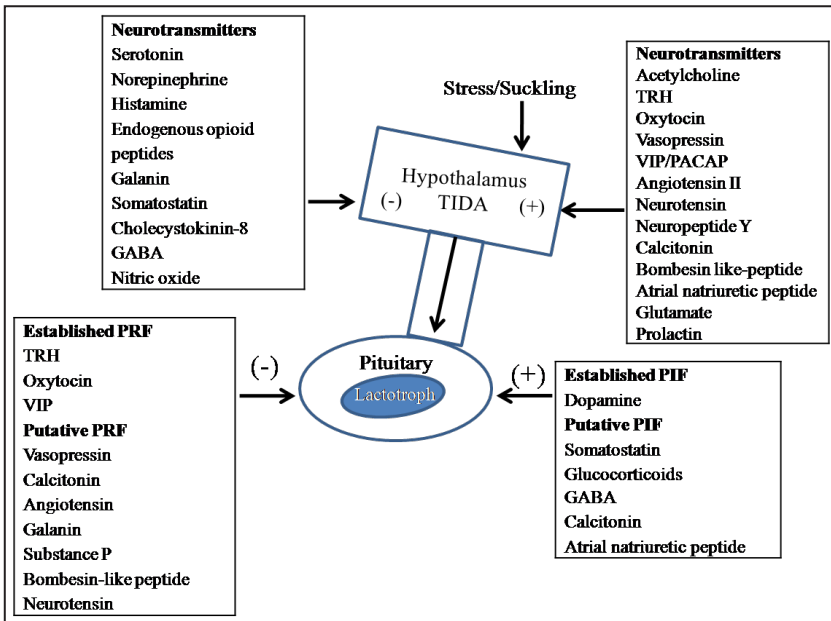
Figure 1. Schematic view of factors affecting prolactin secretion and synthesis. TIDA: tuberoinfundibular dopaminergic activity. Modified from T. Mancini (Mancini et al, 2008:67).

CLINICAL MANIFESTATIONS OF HYPERPROLACTINAEMIA

The emergence of clinical findings in HP; PRL increase occurs by disrupting the pulsatile release of gonadotropins from the pituitary or by reducing the release of gonadotropins (Yarman, S. TEMS Pituitary guide 2019:1). The onset of clinical findings may differ according to gender. In women, HP affects the pulsatility of gonadotropins, which results in more rapid symptoms (oligomenorrhoea or dysmenorrhoea), whereas in men, the process of referral to a doctor is slower than in women. One of the main reasons for this is that menstrual irregularity in women does not produce symptoms as rapidly as menstrual irregularity, in other words, the onset of symptoms is slower in men. This, combined with the patient's inability to accept the diagnosis of the condition, prolongs the process of seeking medical help. In addition, while HP causes galactorrhoea in women, there is almost no evidence of galactorrhoea in men. Table 1 shows the distribution of clinical findings by gender.

While HP causes its clinical findings in women as a result of its hormonal action, in men it is mostly caused by compression findings of the tumour (Sibal et al, 2002:243, Colao et al, 2004:1704). As a result of oligomenorrhoea and anovulatory cycles, approximately 25% bone loss is observed in the vertebrae

due to hypogonadism (Klibanski et al, 1994:24), and similarly vertebral bone loss is observed in men due to hypogonadism (Schlechte et al, 1992:698).

Table 1: Frequency and distribution of clinical findings in hyperprolactinaemia according to gender

Female	Male
Amenorrhoea/oligomenorrhoea	Compression signs of adenoma
Galactorrhoea	Impotence, loss of libido
Infertility	Infertility
Sexual dysfunction, vaginal dryness	Gynaecomastia
Hirsutism	Osteopenia/osteoporosis
Osteopenia/osteoporosis	Galactorrhoea (rare)
Compression signs of adenoma	

DIAGNOSTIC APPROACH IN HYPERPROLACTINAEMIA
Biochemical diagnosis of hyperprolactinaemia

Before starting to diagnose HP, physiological causes such as pregnancy and drugs that can increase PRL levels (especially APDs), systemic diseases such as hypothyroidism, chronic renal failure, chronic liver disease and pituitary stalk incision or damage should be excluded. Once these have been ruled out, current guidelines consider a single morning fasting measurement to be sufficient for the diagnosis of HP (Melmed et al, 2011:213, Auriemma et al, 2023). An elevated PRL level in the presence of clinical findings makes the diagnosis (Melmed et al, 2011:213, Auriemma et al, 2023). Normal levels of PRL:

In women:

Median10.29 ng/mL (5.18-26.53) ng/mL, covering 90% of normal values.

In men:

Median 6.99 ng/ml (3.46-19.40) ng/mL, 100% of normal values.

In the case of inconsistent clinical findings, some guidelines recommend measuring PRL by taking 2-3 samples from the venous cannula at 15-20 minute (min) intervals using a venous catheter placed in the venous line (Mancini et al, 2008:67, Melmed et al, 2011:213). On the other hand, the guidelines of the Turkish Endocrinology and Metabolism Society (TEMS) state that a single sample taken at any time of day is sufficient, provided that it is taken in the morning hours of another day, 2 hours after waking up (Yarman, S. TEMS Pituitary Guideline 2019:1). On the other hand, some studies have reported stress-related HP with a frequency ranging from 9.0% (Whyte, M.B. et al, 2015:319)-28.6% (Cidade-Rodrigues et al, 2021:e133), which decreases to normal levels as a result of serial PRL measurements. The author's own observation is that there is approximately 15-20% stress-related HP in daily

practice, especially in patients with mild HP. Therefore, in patients with mild HP (PRL level 25-150 ng/mL), serial PRL measurement in the setting of discordant clinical findings may reduce unnecessary further investigations and treatment. The clinical approach to HP is summarised in Figure 2.
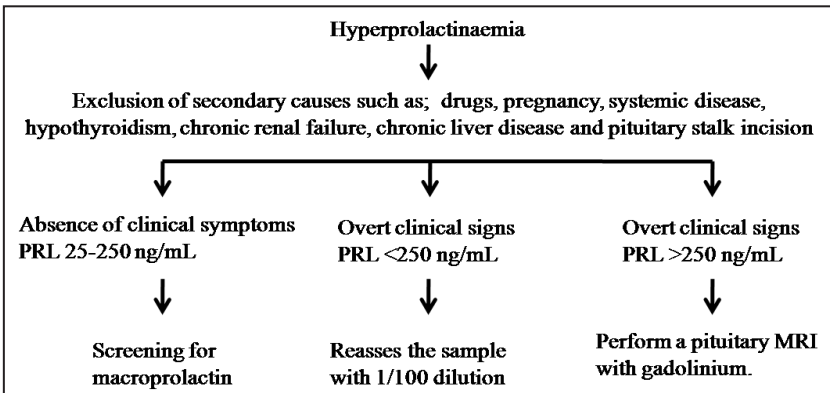

Figure 2. Diagnostic approach in hyperprolactinaemia. PRL: prolactin, MRI: magnetic resonance imaging, modified from Auriemma, R.S. (Auriemma et al, 2023)

In patients with mild HP without obvious clinical findings, macroprolactin (mPRL) should be analysed to demonstrate the absence of mPRL. Large complexes of PRL with antibodies, mostly in the immunoglobulin (Ig) G structure, are called mPRL (Donadio et al, 2007:552). Studies have reported the incidence of mPRL to be around 40%. In addition, mPRL causes a decrease in clearance due to its large structure, but its biological activity is negligible (Donadio et al, 2007:552). Polyethylene glycol (PEG) is the cheapest and most effective method of measuring mPRL. The measurement is performed as follows; first serum PRL is measured (PRLa), then PEG is added to the serum and serum PRL is measured again (PRLb), if the PRLb/PRLa ratio is <40% it means that there is mPRL, if >60% there is no mPRL, values between 40-60% are considered a grey area, it is necessary to decide according to the patient and clinical situation (Auriemma et al, 2023).

In patients with PRL levels <250 ng/mL despite significant clinical findings, PRL should be measured again after dilution of 1/100 since there may be a "Hook effect" (Melmed et al, 2011:213).

Drug-associated hyperprolactinaemia

Drugs are one of the most common causes of HP after mPRL and prolactinoma. Generally, PRL levels ranging from 25 to 100 ng/mL are seen (Melmed et al, 2011:213). Metoclopramide, risperidone and phenothiazines may cause PRL levels exceeding 200 ng/mL (Melmed et al, 2011:213). Some drugs and HP frequencies are as follows; Risperidone (81%), typical antipsychotics (38%), olanzepine (35%), ziprasidone (29%) and verapamil (8.5%) (Melmed et al, 2011:213). Generally, PRL levels return to normal limits three days after drug discontinuation (Melmed et al, 2011:213). Oral contraceptive drugs (OCS) containing high estrogen cause mild HP with rates ranging from 12-30%, but usually do not cause clinical signs and do not require treatment (Melmed et al, 2011:213).

Detection of the etiological cause in the patient with hyperprolactinemia

Once the diagnosis of HP has been confirmed biochemically, the aetiological cause should be determined. This requires gadolinium magnetic resonance imaging (MRI). The imaging technique should be high-resolution (e.g. 16 cm field of view; 192 × 256 matrix size), in thin slices of 2-3 mm thickness. First T1-weighted imaging in the coronal and sagittal planes, and after intravenous gadolinium (0.05 mmol/kg) administration, T1-weighted imaging in the axial plane before and after contrast. T2-weighted images are also obtained to evaluate the fluid content.

The aetiological cause is pituitary microadenoma or hyperplasia in 90% and pituitary macroadenoma in 10% (Auriemma et al, 2023). As with other pituitary adenomas, those smaller than 10 mm are classified as microadenomas (Figure 3) and those 10 mm or larger as macroadenomas (Figure 4).
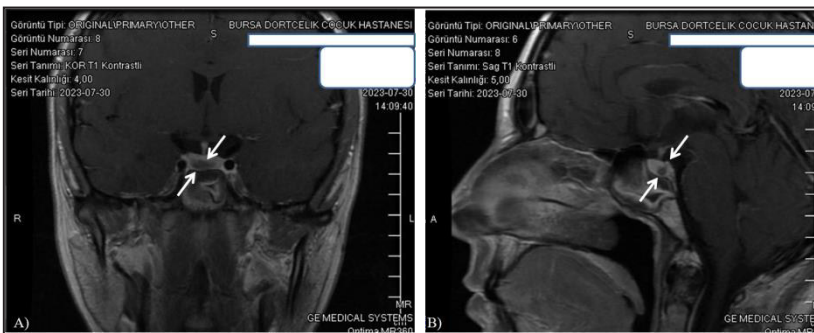

Figure 3. The appearance of microadenoma in coronal (A) and sagittal sections (B) on magnetic resonance imaging with contrast in a patient with elevated prolactin.
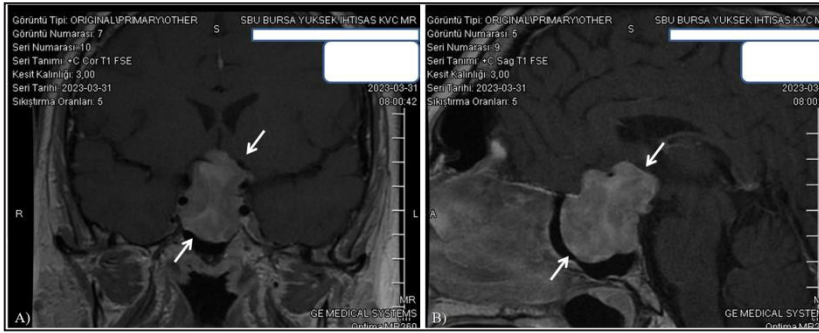
Figure 4. The appearance of macroadenoma in coronal (A) and sagittal sections (B) on magnetic resonance imaging with contrast in a patient with elevated prolactin levels.

MANAGEMENT OF PATIENTS WITH HYPERPROLACTINEMIA
Management of the hyperprolactinemia patient with microadenoma

Treatment is not recommended for asymptomatic microadenomas (Melmed et al, 2011:213, Auriemma et al, 2023). OCS or testosterone replacement is recommended for those with hypogonadism (Melmed et al, 2011:213, Auriemma et al, 2023). Spontaneous remission in idiopathic HP is 30% (Schlechte et al, 1989:412), and the likelihood of conversion of untreated microadenomas to macroadenomas is very low at 2-5% (Schlechte et al, 1989:412). Treatment with dopamine agonists (DA) is recommended for patients with symptomatic microadenomas (Melmed et al, 2011:213, Auriemma et al, 2023).

Cabergolin (CAB)

DA, ergo derivative. As its half-life is longer, it is sufficient to take it 1-2 times a week. The starting dose is 0.25 mg 1-2 times a week or a single dose of 0.5 mg (Yarman, S. TEMS Pituitary guide 2019:5). Its hypotensive effect is less, but it would be better to take it in the evening before going to bed as a precaution. The dose is gradually increased according to the PRL level checked after 4-6 weeks and until the PRL level returns to normal (Yarman, S. TEMS Pituitary guidelines 2019:5). In general, the average treatment dose is 0.25-3 mg/week, with doses of up to 11 mg/week rarely required (Yarman, S. TEMS Pituitary guidelines 2019:5).

Bromocriptine (BCR)

DA, ergo derivative. Short-acting forms (2.5 mg tablets) and slow-release forms (2.5 and 5 mg SR tablets) are available. Due to its short plasma half-life,

it should be taken 2-3 times daily (Yarman, S. TEMS Pituitary guidance 2019:5). Due to its hypotensive effect, it is recommended to take a dose of 1.25 mg at night before going to bed, and to increase the dose by 1.25 mg once a week, usually to 5-7.5 mg/day, until a clinical response is achieved (Yarman, S. TEMS Pituitary Guideline 2019:5).

Quinagolid

DA, a non-Ergo derivative. It binds specifically to the dopamine receptor. Unlike Ergo-derived DAs, it does not bind to the 5-hydroxytryptamine receptor, so it does not carry the risk of heart valve fibrosis and pulmonary hypertension in long-term use (Yarman, S. TEMS Pituitary guide 2019:5). The starting dose is 0.075 mg and is given twice daily (Yarman, S. TEMS Pituitary guidance 2019:5). The dose is increased until the effect is seen, the maximum dose is 0.9 mg/day (Yarman, S. TEMS Pituitary guide 2019:5).

In the final report of "A systematic review of the literature" of the Endocrine Society Commission "Evaluation of the treatment effects of dopamine agonists in patients with hyperprolactinaemia"; it is recommended that CAB be preferred to DA in treatment. Reduction in tumour size (62%; 20-100%), improvement in visual field defects (67%; 33-100%), improvement in amenorrhoea (78%; 40-100%), improvement in infertility (53%; 10-100%), improvement in male sexual function (67%; 40-100%) were reported.

Follow-up for microadenomas: PRL measurement every 1-2 months until desired PRL level is reached, then every 6 months. MRI assessment should be performed after 1 year.

Management of hyperprolactinemia patients with macroadenoma
Follow-up in macroadenomas:

PRL measurement: 1 month after initiation of treatment, every 2 months until PRL normalisation. One of the most important points to be considered here is that in macroadenomas (especially in tumours >4 cm), the drug dose should be started at 0.25 mg/week and gradually increased. Because these tumours are very sensitive to the drug and sudden and rapid shrinkage may cause bleeding into the tumour and pituitary apoplexy.

MRI evaluation:
After 2 months, then every 6 months.

Visual field:

At diagnosis, 2 months after treatment in patients with signs of compression. Later in conjunction with MRI.

Side effects of medication

Nausea or vomiting, headache and dizziness, dry mouth, constipation, nasal congestion. Orthostatic hypotension and associated dizziness. Psychiatric changes: depression, psychosis, alcohol intolerance, hypersexuality and personality changes, impulse control disorder. In addition, at high doses, vasospasm of the finger, valve (mitral, aortic and tricuspid) insufficiency.

Definition of a patient resistant to medical treatment

Failure to normalise PRL levels or significant tumour reduction (less than 50% shrinkage) in symptomatic patients on treatment with standard doses of DA. "Failure to normalise PRL levels" is defined as resistance even though BRC 15 mg/day, CAB 3 mg/week and quinagolide 300 µg/day are used for at least 3 months (Yarman, S. TEMS Pituitary Guideline 2019:5). It is observed in 10-15% of patients (Yarman, S. TEMS Pituitary guidelines 2019:5).

Surgical treatment

DA resistance or intolerance occurs. If optic nerve compression persists at 3 months. Usually transsphenoidal, rarely craniotomy is recommended.

Radiotherapy

In resistant cases, when other treatments do not yield results and in malignant cases.

CONCLUSION

PRL increase is caused by disruption of the pulsatile release of gonadotropins from the pituitary gland or by a decrease in the release of gonadotropins. Clinical findings may vary according to gender. While HP causes clinical findings in women as a result of the chemical action of the hormones, men are more likely to have compression findings related to the tumour. Before starting to diagnose HP, physiological causes such as pregnancy and drugs that can increase PRL levels (especially APDs), systemic diseases such as hypothyroidism, chronic renal failure, chronic liver disease and pituitary stalk incision or damage should be excluded. Patients with mild HP (PRL level 25-150 ng/mL) should be screened with mPRL and serial PRL measurement in the presence of discordant clinical findings, which may reduce unnecessary

further investigation and treatment. Dilution of PRL should be investigated in patients with macroadenomas but mildly elevated PRL levels. Symptomatic microadenomas and macroadenomas should be treated with DA regardless of symptoms. The first-line treatment is CAB. In giant adenomas, treatment should be started gradually because of the risk of of pituitary apoplexy. Asymptomatic microadenomas can be watched. Surgery and radiotherapy may be considered in cases of treatment resistance and malignancy.

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Chapter 13

Management of Neglected Achilles Tendon Ruptures in Children

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ABSTRACT

Neglected Achilles tendon rupture is an injury that leaves patients with functional fragility, a significant risk of complications, and generally poor clinical results. A neglected achilles tendon rupture in children is an extremely unusual occurrence. This chapter aims to analyse neglected achilles tendon ruptures in children. A comprehensive and meticulous physical examination is necessary to determine whether the Achilles tendon is intact after any skin wound on the back of the leg. The primary repair and plantaris augmentation approach is associated with favorable clinical and functional outcomes for neglected achilles tendon ruptures in children. Considering that complicated ruptures have not been observed in this age range as they have in adults, a new classification and management procedure that is exclusive to this age group may be devised.

Keywords: Achilles tendon, rupture, neglected, children

INTRODUCTION

Anatomy

The largest tendon in the human body, the Achilles tendon, is formed by the union of the gastrocnemius and soleus tendons. As the surface area of the Achilles tendon advances distally, it becomes rounded proximally and then flattens as it approaches the superior calcaneal tuberosity. The region where the tendon attaches to the heel bone is highly specialized; it is distal to the tendon, has a junction with hyaline cartilage at its distal end, and is not covered with periosteum (Rufai et al. , 1995). Similar to other tendons, the vascularity of the Achilles tendon is maintained in three distinct locations: the muscle-tendinous junction, the surrounding connective tissue, and the bone-tendon junction (Maffuli, 1999).

Tendons are structures that transfer force between muscle and bone while maintaining balance. Collagen comprises the majority of the tendon's dried weight. Approximately 95% of the collagen in the structure of the tendon is type-I collagen. This collagen tissue combines with some elasatin, and its fascicles form the principal architectural framework of the tendon, which is surrounded by the epitenon through fascicle-based fusion. In this structure, the epitenon and tendon are separated by a thin layer that provides lubrication and are surrounded by the paratenon.

Biomechanics

Achilles tendon, gastrocnemius and soleus (Triceps surae) muscles, It acts as a structure that transmits the tension in the body to the calcaneus. The triceps surae muscles are active during complex posture control, standing, walking, and sprinting and jumping activities. During Achilles' gait cycle, The force within the tendon increases just before the heel touches the ground and then suddenly drops. Then, until you reach the top at the end of the "push off" phase. once again it rises rapidly. (Komi etal. , 1992) Tendons must be able to resist these forces in order to function effectively. While resisting this force, the tendons must also lengthen, shorten and deform. During this cycle, collagen fibers may undergo deformation. This results in the development of high stress concentrations in the Achilles tendon. The region between 2 and 5 centimeters proximal to the tendon's attachment to the calcaneus is characterized by the highest incidence of tendon injury. (Barfred, 1973)

Achilles tendon rupture
Epidemiology

Although Achilles tendon rupture is quite common, its incidence in the general population has not been established. However, most of the studies in the literature concern the adult population, and studies in the pediatric population are usually case reports (Tudisco and Bisicchia, 2012; Vasileff and Moutzouros, 2014; Andaloussi, 2021). Achilles tendon tears are mostly (44-83%) occurs during sportive activities (Cardden et al. , 1987; ,Cetti et al. , 1993). It is more common in men than women (1.7:1-12:1) (Hattrup and Johnson, 1985). Left Achilles tendon ruptured to the right more common; this is probably due to the high prevalence of right-sided dominant individuals and thus being "pushed" with the left lower extremity. In a recent pediatric study by Ashebo et al. on this subject, 43.6% of the patients were female in a study conducted with thirty-nine patients. 25 patients (64.1%) presented with traumatic injury; among them, 48.0% (n=12/25) were ≤12 years old. All patients aged ≤12 years had a traumatic injury. The most common traumatic mechanism was open laceration due to penetrating trauma (68.0%), followed by closed tears (32.0%) due to blunt trauma. Fourteen patients (35.9%) presented with a closed tear due to muscle contraction.(Ashebo et al. , 2023)

Clinical presentation and diagnosis

The story is quite typical in many cases. The patient usually has no previous complaints about the Achilles tendon. Adult patients usually have sudden onset pain in the affected leg.

they describe a sharp pain, a feeling as if the back of the leg has been hit. (Kauwe, 2017) Some of them explode on the back of the leg. They can express that they have heard a sound around achilles tendon. The most obvious clinical finding after a tear is pain that becomes evident after a load on the leg. In pediatric cases, such symptoms may appear more subtle. Pediatric cases usually present with limping when walking, weakness in plantar flexion, and heel paresthesia (Tudisco and Bisicchia, 2012; Vasileff and Moutzouros, 2014).

Under normal circumstances, a clinical examination of an adult patient is sufficient for diagnosis. Due to the effect of other muscles, such as the tibialis posterior, which plantar flexes the foot, the diagnosis of non-full-thickness injuries may be delayed. When examining pediatric patients, more precision is required. Although MRI and somnographic evaluation are used in the follow-up of patients, we believe it is advantageous to use MRI (Figure1) and ultrasound for diagnostic purposes in suspected pediatric patients (Tudisco and Bisicchia, 2012; Vasileff and Moutzouros, 2014).
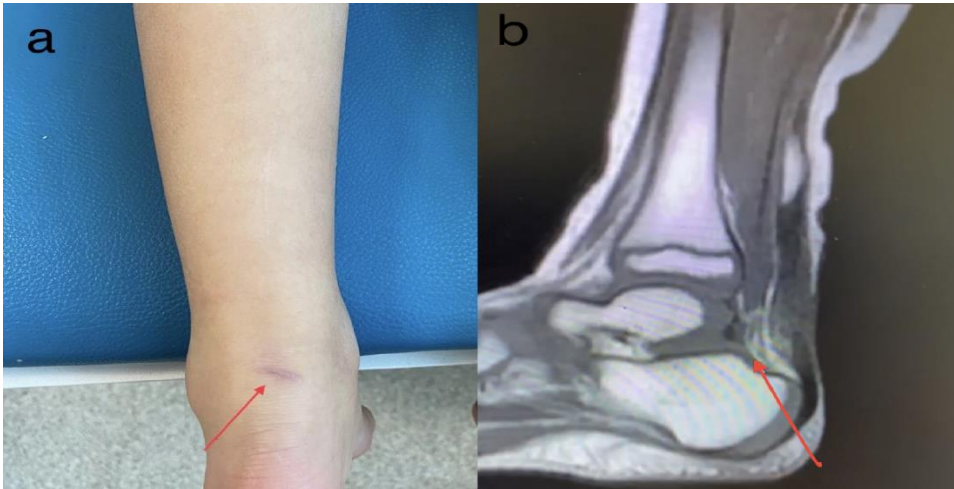
Figure 1. The red arrows show the level of the ruptured Achilles tendon clinically (a) and radiologically (b) (MRI), respectively.

Treatment of acute achilles tendon rupture

Various techniques and procedures for treating acute Achilles tendon ruptures have been described. Regarding the total, the treatment may differ based on age, gender, comorbidities, and the duration of the diagnosis. Conservative treatment, percutaneous repair, and open surgical repair are among these options (Park et al. , 2020; Myhrvold et al. , 2022.). Although there are still some who prefer conservative treatment, in the last two decades, particularly among athletes, young adults, and patients with neglected achilles tendon rupture, operative methods have been favored.

Treatment of neglected achilles tendon rupture

There are many different techniques used for Achilles tendon repair.

For the diagnosis and treatment of Achilles tendon tears, Kuwada classification

It is widely used and useful in deciding which strategy to use based on the size of the tear.

(Table 1) (Kuwada, 1990).

Table1. Kuwada classification for Achilles tendon ruptures

Defect size	Surgical procedure
Partial, 50% tear	Immobilization
< 3 cm	End-to-end anastomosis
3-6 cm	V-Y lengthening ± tendon transfer
> 6 cm	Tendon transfer with V-Y advancement or turndown flap

Kuwada classification is for adult patients. It is obvious that this classification is not sufficient for the pediatric population and a new classification is required. When we look at the literature, there is no classification made for the pediatric population and there is a deficiency in the literature on this subject. Due to the lack of conclusive evidence in this case, especially in order to guide treatment options. Treatment decision in skeletally undeveloped patients at the discretion of the provider and the patient's family, should be determined. For this special condition, it is necessary to evaluate on a patient basis and decide accordingly. However, when we look at the literature, the treatment of delayed rupture in children, whether primary repair or reinforcement with additional tendons (Figure 2), is surgery(Tudisco and Bisicchia, 2012; Vasileff and Moutzouros, 2014; Andaloussi, 2021).
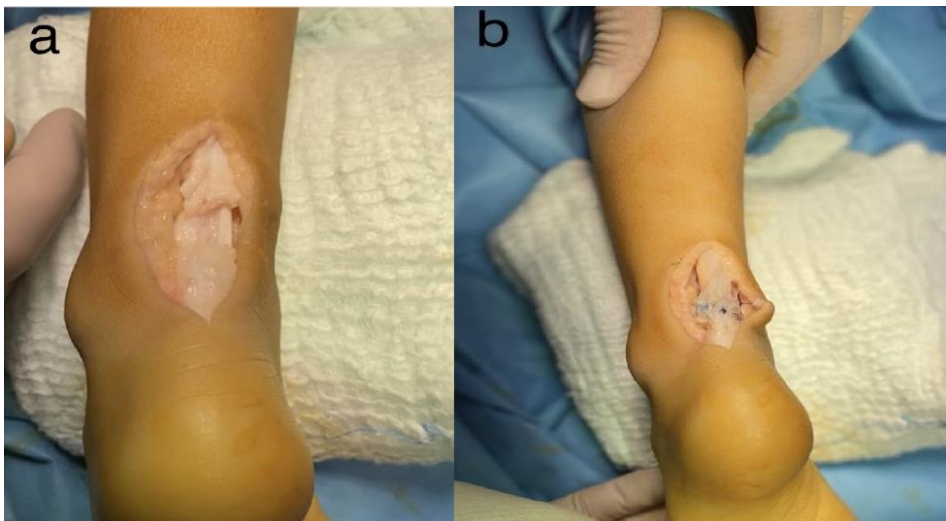

Figure 2. a. Clinical view of 4 cm gap in a 9-year-old patient with neglected Achilles tendon rupture, b. Clinical appearance, primer repair and plantaris tendon augmentation

Postoperative follow-up

If there is no additional problem on the 1st postoperative day, the patient is discharged with a long leg cast. In the follow-ups, the plaster is removed in the 6th week and passive dorsiflexion exercises are started first, followed by active dorsiflexion 1 week later.

In the fourth or sixth month following surgery, patients resume to sports activities (Tudisco and Bisicchia, 2012; Vasileff and Moutzouros, 2014; Andaloussi, 2021).

CONCLUSION

A comprehensive and meticulous physical examination is necessary to determine whether the Achilles tendon is intact after any skin wound on the back of the leg. The primary repair and plantaris augmentation approach is associated with favorable clinical and functional outcomes for neglected achilles tendon ruptures in children. Considering that complicated ruptures have not been observed in this age range as they have in adults, a new classification and management procedure that is exclusive to this age group may be devised.

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Chapter 14

The Relationship of Depression Level and Sexual Satisfaction in Women Aged 18-60

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Abstract

Backround: Female sexuality is a hidden and ignored concept. Sexual satisfaction, which is the last stage of the sexual response cycle and a sexual right, is a component of sexuality. Depression is a mood disorder that brings with it many problems, including sexual problems. **Aims:** This study was planned to examine the relationship between depression levels and sexual satisfaction levels in women with active sexual life.

Methodology: 481 women were included in the study, which was planned in a descriptive and relationship-seeking manner, using the snowball sampling method. Participants accessed the research online. In the study conducted by using Descriptive Information Form, Beck Depression Scale and New Sexual Satisfaction Scale; Pearson analysis was used to determine whether there was a significant relationship between the Beck Depression Scale total scores of women and the New Sexual Satisfaction Scale (NSSS) sub-dimensions.

Results: It was concluded that as the level of depression increases, sexual satisfaction decreases, and factors such as education level, income level, and antidepressant use have an effect on sexual satisfaction. When the results of the study were examined, it was revealed that depression is an important factor affecting the level of sexual satisfaction.

Conclusions: Results; discussed in the light of the relevant literature and suggestions were made. We think that this study will bring a novelty to the literature in terms of examining only the relationship between sexual satisfaction and depression level, since it is different from examining the relationship between sexual dysfunctions and depression level in women.

Key Words: Women, depression, sexual satisfaction, psychiatric nursing

1. INTRODUCTION

Sexual satisfaction, considered as the final stage of the sexual response cycle and a sexual right, is a component of sexuality [1]. Sexual satisfaction is easily affected by the individual's life and changes in her life, on the other hand, changes in sexual satisfaction affect the individual physiologically, biologically, sociologically and psychologically [2]. Studies that draw attention to the importance of sexual satisfaction in women and the inadequacy of studies in this field state that the factors affecting sexual satisfaction and sexual satisfaction should be examined and diagnosed appropriately [1,3].

Depression is a psychological mood disorder that is defined as the deterioration of individuals' emotional states in a way that negatively affects their functionality [4]. According to the data prepared by the Health Metrics and Evaluation Institute, 3.76% of people in the world were diagnosed with depression in 2019. According to the same report, while the prevalence of depression is 4.54% in women, it is 2.96% in men [5]. Depression, which is almost twice as common in women as in men, is increasingly becoming a public concern [6,7]. There is an increased risk of depression in women during a woman's life cycle [8]. In addition, it is thought that self-neglect due to the multiple roles and responsibilities imposed on women also triggers depression [4].

Depression affects the mood of individuals and as a result, many problems are encountered. One of these problems is the effect of depression on sexual health [8,9]. The World Health Organization defines sexual health as a state of complete sexual well-being and not merely the absence of sexual dysfunction or infirmity [10]. Along with depression, symptoms that negatively affect sexual health such as a decrease in libido, a lack of sexual desire, a lack of interest in activities that they used to enjoy, and a decrease in obtaining sexual satisfaction occur [8,9,11]. In addition, it is stated in the literature that some drugs used in the treatment of increasing age and depression also cause sexual dysfunction [12,13].

Although depression and sexual dysfunctions are frequently seen together, the unclear relationship between them is explained by putting forward 5 models [14].

1. Psychosocial stress factors that can be seen in sexual dysfunctions may initiate depression in susceptible individuals.

2. Sexual dysfunction can be a symptom of depression.

3. Antidepressant drugs used can cause sexual dysfunction.

4. A common cause such as alcohol use, cardiovascular disease, hypogonadism may play a role in the etiology of depression and sexual dysfunction.

5. Since depression and sexual dysfunction are very common, they can develop independently of each other etiologically and only comorbidity can be seen.

In the light of all this information, this study was conducted to determine the relationship between depression levels and sexual satisfaction in women between the ages of 18-60.

2. METHODOLOGY
2.1. Research Design

In the research, mainly descriptive and relation-seeking research models were used. The main purpose of descriptive research is; The aim is to reveal the characteristics of the main mass with tools such as survey, observation, interview and sampling. In this type of design, the purpose is to define and decipher the relationship between variables. In the research, it was tried to determine whether the relationship between the variables is in a positive or negative direction.

2.2. Research Sample

The population of the study consisted of women between the ages of 18-60 and active sexual life throughout Turkey. The sample of the study consisted of women who were able to reach throughout the country with the personal connections of the researchers and who met the inclusion criteria of the study. In this study, in which the snowball sampling method was used, the participants were asked to invite women who met the inclusion criteria to the study. The data were collected online on 09.11.2022-09.01.2022. The sample number consists of 481 women.

2.3. Prosedues and Data Collection

Descriptive Information Form, Beck Depression Scale and New Sexual Satisfaction Scale were chosen as data collection tools. Data were collected by sharing the link address of the data collection form created via Google Forms with the participants. The forms were filled in by the participants who volunteered to participate in the research, and it took an average of 5-10 minutes for each participant to fill out the form. The data are presented in the supplementary material

2.4. Measurement

2.4.1. Descriptive Information Form In the form prepared by the participants in line with the literatüre [4,11], there are 9 questions in total, including 7 sociodemographic information, 2 of which were diagnosed with depression before and currently using antidepressants.

2.4.2. Beck Depression Scale It was developed by Beck in 1961 to measure the risk of depression and severity of symptoms in adolescents and adults. As a result of the clinical findings and the data obtained as a result of the research; 21 questions can be answered with scores ranging from 0 to 3 points and a maximum of 63 points is reached in total [15]. In 1978, the entire scale was revised, duplications describing the severity were eliminated, and patients were asked to mark their status for the last week, including today [16]. The Turkish validity and reliability of the scale was established [17].

2.4.3. New Sexual Satisfaction Scale The New Sexual Satisfaction Scale is a valid and reliable scale by Stulhofer et al. The validity and reliability study of the original scale was applied to volunteers in the 18-55 age group. It was found that the item total score reliability coefficient of the scale ranged between r=.57-.61 and the Cronbach's alpha coefficient for internal consistency was. 94. The scale developed to measure sexual satisfaction in clinical and field studies is a 5-point Likert-type (1-5) measurement tool. The lowest score that can be obtained from the scale is 20, and the highest score is 100. The scale consists of self-centered sub-dimension and co-partner/sexual activity-centered sub-dimension. A high score from the scale indicates good sexual satisfaction [18]. The Turkish validity and reliability of the scale was established [19].

2.5. Ethical Considerations

Approval was obtained from the ethics committee of Istanbul Gedik University to conduct the study. It is essential that the participants participate in the research voluntarily, of their own free will, without any coercion or obligation. Before data collection, participants were informed and all participants were asked to approve the informed consent form online. All information obtained in connection with the study and identified with the participant was kept confidential, not shared with third parties, and used only with the consent of the participant. They were not required to share their identity information on the forms used. One participant was allowed to access the form only once. Necessary permissions were obtained in order to use the scales.

2.6. Data Analysis

Statistical analysis of the data was evaluated with SPSS 22 version package program. Parametric analyzes were preferred for hypothesis testing. Independent groups t-test was used for descriptive statistics. One-way analysis of variance (ANOVA) was applied to determine whether the sub-dimensions of the scale showed a significant difference according to the variables. Then, Tamhane's T2 analysis and Scheffe analysis were used to determine which groups caused the difference

determined for this sub-dimension. In the research, it was tried to determine whether the relationship between the variables is in a positive or negative direction.

3. RESULTS

Demographic data of women participating in the study are shown in the table below. Of these women, 214 (22.2%) had previously been diagnosed with depression, 748 (77.8%) had not been diagnosed with depression before; 96 (10.0%) currently use antidepressants, 866 (90.0%) do not (Table 1).

Table 1. Demographic Characteristics of Women

Variable	Groups	f	%	Variable	Groups	f	%
	18-30	176	36.6		Rural areas	20	4.2
	31-40	151	31.4	**Residence**	Other cities	96	20.0
Age	41-50	87	18.1		Metropolitan cities	365	75.9
	51 and above	67	13.9	**Family structure**	Nuclear family	430	89.4
Marital Status	Living alone	115	23.9		Extended family	51	10.6
	Living with spouse	366	76.1	**Depression Diagnosis**	Yes	107	22.2
	Elementary school	46	9.6		No	374	77.8
	High school	89	18.5	**Anti Depressant**	Yes	48	10.0
Education Level	Vocational school	87	18.1		No	433	90.0
	University	143	29.7		Income < Expense	102	21.2
	Master and PHD	116	24.1	**Income Rate**	Income = Expense	290	60.3
					Income > Expense	89	18.5

Mean Beck depression scale scores of women in the sample group $\bar{x}$=15.15 standard deviation sd=11.44 skewness value S=1.27 kurtosis value K=1.87; New Sexual Satisfaction Inventory (NSSS) self-centered sexuality sub-dimension scores mean $\bar{x}$=32.93 standard deviation sd=12.00 skewness value S=-.35 kurtosis value

K=-.95; The mean x̄=35.10 standard deviation sd=11.39 skewness value of NSSS partner-centered sexuality sub-dimension scores was calculated as S=-.55 kurtosis value K=-.63. George and Mallery (2019) state that the normality of the distribution can be accepted if the skewness and kurtosis values are between ±2.00. In this context, the shape of the distributions was accepted as normal and parametric analyzes were preferred for hypothesis testing (Table 2).

Table 2. Descriptive Values of Women's Scale Scores

Points	N	$\bar{x}$	ss	*Skewness*	*Kurtosis*
Beck Depression Scores	481	15.15	11.44	1.27	1.87
NSSS Self-Centered Sexuality Sub-Dimension	481	32.93	12.00	-.35	-.95
NSSS Partner-Centered Sexuality Sub-Dimension	481	35.10	11.39	-.55	-.63

Pearson analysis was used to determine whether there was a significant relationship between the women's Beck Depression Scale total scores and the New Sexual Satisfaction Scale (NSSS) sub-dimensions. As a result of the analysis, the relationships between Depression scores and self-centered sub-dimension scores of NSSS (r=-.624; p=.000) and partner-centered sub-dimension scores (r=-.547; p=.000) were found to be negative and significant. As the depression scores increase, the self-centered and partner-centered sub-dimensions of NSSS decrease significantly (Table 3).

Tablo 3. Relationships Between Women's New Sexual Satisfaction Scale Sub-Dimensions and Beck Depression Scale Scores

NSSS	Beck Depression Scale Scores		
	N	r	p
Self-Centered Sexuality Sub-Dimension	481	-.624	**.000**
Partner-Centered Sexuality Sub-Dimension	481	-.547	**.000**

Simple standard regression analyzes were performed to determine whether the Beck Depression Scale scores of women significantly predicted their NSSS sub-dimension scores. As a result of the analysis, regression models were found suitable for the self-centered sub-dimension (F=305.49; p=.000) and the partner-centered sub-dimension scores (F=204.63; p=.000). Beck Depression Scale scores significantly predict both e self-centered sub-dimension (t=-17.48; p=.000) scores and partner-centered sub-dimension (t=-14.31; p=.000) scores. Depression scale scores accounted for approximately 39% of the variance in the self-centered sub-dimension scores; explains approximately 30% of the variance in the partner-centered sub-dimension scores of NSSS. When the depression scale scores increase by one unit,

the self-centered sub-dimension scores are approximately .65 units; The partner-centered sub-dimension scores decrease by .54 units. In the light of these values, the regression equations were formed as follows:

Self-centered = 42.84 + (-.654 x Depression)
Partner-centered = 43.35 + (-.544 x Depression) (Table 4).

Tablo 4. Regression Analysis Between Beck Depression Scale Scores and Sub-Dimensions of NSSS

Independent Variable	Dependent Variable	F	p	R	DR^2	β	t	p
Beck Depression Scale	Self-Centered Sexuality Sub-Dimension	305.49	.000	.624	.388	-.654	-17.48	.000
	Partner-Centered Sexuality Sub-Dimension	204.63	.000	.547	.298	-.544	-14.31	.000

The difference between the arithmetic means of the groups was found to be significant as a result of the independent groups t-test performed to determine whether the Beck Depression Scale scores showed a significant difference according to the variable of employment status of women (t=-2.21; p=.028). The depression mean of the non-working group was found to be significantly higher than the mean of the working group (Table 5).

Table 5. Comparison of Beck Depression Scale Scores by Employment Status of Women

Points	Working status	N	$\overline{x}$	Sd	t Test		
					t	Sd	p
Beck Depression Scale	Working	305	14.28	11.11			
	Non-working	176	16.66	11.87	-2.21	479	.028

One-way analysis of variance (ANOVA) was applied in order to determine whether the scores of the women's NSSS sub-dimensions showed a significant difference according to the education level variable. While the variances for the self-centered sexuality sub-dimension were homogeneous (=1.36; p=.247), the variances were not found for the partner-centered sexuality sub-dimension (=3.20, p=.013). For this reason, the significance of ANOVA for the partner-centered sexuality sub-dimension was evaluated over the Welch value. As a result of ANOVA, the difference between the arithmetic means of the groups for the sub-dimension scores

of self-centered sexuality (F=15.16; p=.000) and partner-centered sexuality (F=10.23; p=.000) was found to be significant (Table 6). After this result, Scheffe for self-centered sexuality and Tamhane's T2 test for partner-centered sexuality were applied in order to determine the sources of the differences and are presented in Table 7.

Table 6. Comparison of Women's NSSS Sub-Dimensional Scores by Education Level

	f , $\bar{\text{X}}$ ve SS Values				ANOVA Results					
Point	**Groups**	**n**	**$\bar{x}$**	**Sd**	**V.S.**	**KT**	**Sd**	**KO**	**F_{Welch}**	**p**
	Elementary school	46	21.65	11.89	**Intergroup**	7807.828	4	1951.957		
	High school	89	31.97	11.11	**In-Group**	61284.625	476	128.749		
Self-Centered Sexuality Sub-Dimension	Vocational school	87	32.57	12.50	**Total**	69092.453	480		15.161	.000
	University	143	34.39	10.67						
	Master	116	36.59	11.21						
	Total	481	32.93	12.00						
	Elementary school	46	26.59	12.45	**ntergroup**	4924.261	4	1231.065		
	High school	89	33.69	11.59	**In-Group**	57310.542	476	120.400		
Partner-Centered Sexuality Sub-Dimension	Vocational school	87	34.89	12.16	**Total**	62234.802	480		10.225	.000
	University	143	36.22	9.98						
	Master	116	38.35	10.07						
	Total	481	35.10	11.39						

Tablo 7. Tamhane's T2 Test ans Scheffe Results According to Education Level for NSSS Sub-Dimensional Scores

Points	(**I**) Education Level	(**J**) Education Groups	$\bar{x_i} - \bar{x_j}$	***Sh***	***p***
Self-Centered Sexuality Sub-Dimension (Scheffe)	Elementary school	Highschool	-10.31	2.06	.000
		Vocational school	-10.92	2.07	.000
		University	-12.74	1.92	.000
		Master	-14.94	1.98	.000
	Highschool	Elementary school	10.1	2.06	.000
		Vocational school	-.61	1.71	.998
		University	-2.43	1.53	.644
		Master	-4.63	1.60	.080
	Vocational school	Elementary school	10,92	2.07	.000
		Highschool	.61	1.71	.998
		University	-1.82	1.54	.846
		Master	-4.02	1.61	.184
	University	Elementary school	12.74	1.92	.000
		Highschool	2.43	1.53	.644
		Vocational school	1.82	1.54	.846
		Master	-2.20	1.42	.660
	Master	Elementary school	14.94	1.98	.000
		Highschool	4.63	1.60	.080
		Vocational school	4.02	1.61	.184
		University	2.20	1.42	.660
Partner-Centered Sexuality Sub-Dimension (Tamhane T2)	Elementary school	Highschool	-7.10	2.21	.018
		Vocational school	-8.30	2.25	.004
		University	-9.64	2.02	.000
		Master	-11.77	2.06	.000
	Highschool	Elementary school	7.10	2.21	.018
		Vocational school	-1.20	1.79	.999
		University	-2.54	1.49	.608
		Master	-4.67	1.54	.028
	Vocational school	Elementary school	8.30	2.25	.004
		Highschool	1.20	1.79	.999
		University	-1.34	1.55	.993
		Master	-3.47	1.60	.278
	University	Elementary school	9.64	2.02	.000
		Highschool	2.54	1.49	.608

	Vocational school	1.34	1.55	.993
	Master	-2.13	1.25	.613
Master	Elementary school	11.77	2.06	.000
	Highschool	4.67	1.54	.028
	Vocational school	3.47	1.60	.278
	University	2.13	1.25	.613

As can be seen in Table 7, Scheffe analysis was performed to determine from which groups the difference determined for the self-centered sexuality sub-dimension was caused. As a result of the analysis, the average of elementary school graduates was found to be significantly lower than the averages of all other education level groups. On the other hand, Tamhane's T2 analysis was conducted to determine which groups caused the difference determined for the partner-centered sexuality sub-dimension. As a result of the analysis, the average of elementary school graduates is from all other education groups; the mean of the high school graduates group was found to be significantly lower than the mean of the university graduates group. The differences between the mean of the other groups were not significant (Table 7).

The difference between the arithmetic means of the groups as a result of the independent groups t-test, which was conducted to determine whether the sub-dimension scores of the Women's New Sexual Satisfaction Scale (NSSS) differ significantly according to the variable of using antidepressants, self-centered sexuality (t=-5.41; p=.000)) and partner-centered sexuality (t=-4.67; p=.000) sub-dimensions. The mean of the group not using antidepressants was found to be significantly higher than the mean of the group using antidepressants (Table 8).

Table 8. Comparison of NSSS Sub-Dimensional Scores According to Antidepressant Use

Point	Use Status	N	$\overline{X}$	Sd	*t* Test		
					t	*Sd*	*p*
Self-Centered Sexuality Sub-Dimension	Yes	48	24.29	12.649	-5.408	479	.000
	No	433	33.88	11.547			
Partner-Centered Sexuality Sub-Dimension	Yes	48	27.98	12.576	-4.667	479	.000
	No	433	35.89	10.981			

4.   DISCUSSION

In this section, in line with the goal of the research, the relationship between sexual satisfaction and depression level and the relationships between sexual satisfaction, depression level and demographic variables were examined; the findings of the study were discussed in the light of the relevant literature.

According to the results of the research; as women's depression levels increase, their sexual satisfaction levels decrease. The Third National Survey of Sexual Attitudes and Lifestyles (NATSAL-3) of more than 15,000 people aged 16 to 74 reported that 41.6% of men and 51.2% of women reported problems with sexual response.   d In addition, it was stated in the same report that the existence of depressive symptoms is the only special health status associated with low sexual satisfaction [20,21]. It has been noted by clinicians and researchers that both emotional and sexual disorders in the relationship between depression and sexual function are quite common, are considered comorbid, and may even share a common etiology. When the literature was examined, it was seen that studies were generally planned to examine the relationship between depression and sexual dysfunctions. In a study planned to examine the relationship between sexual satisfaction and depression and anxiety in adolescents and young adults; It was concluded that among adolescents, those who do not have a romantic relationship have lower levels of sexual satisfaction, and that anxiety and depression levels are higher in young women [22]. According to the findings of the research conducted with women who applied to the sexual dysfunctions outpatient clinic in Turkey, one of the most common psychiatric disorders in addition to sexual dysfunctions is depression [22]. In another study, it was aimed to investigate the personality traits, sexual satisfaction and body perceptions of individuals diagnosed with erectile dysfunction and their spouses by comparing them with depressed individuals. Men with erectile dysfunction were found to be similar to depressed men in terms of sexual dissatisfaction, except for neurotic features and specific problems in general [15]. In an epidemiological study, it was reported that the prevalence of sexual problems in depressed individuals was approximately twice the prevalence in controls [23]. In another study planned to examine the relationship between depression and sexual quality of life in postmenopausal women, a statistically significant and moderately negative correlation was found between the Beck Depression Inventory and Sexual Quality of Life Questionnaire mean scores of women [24]. In a study conducted in the USA to determine the lifetime sexual satisfaction status of adults and related factors, it was observed that individuals with depression reported significantly lower levels of sexual satisfaction [25]. Our study is similar to the studies in the literature. Considering that depression is a disorder that reduces the desire and pleasure of the individual in most areas, it can also be considered that it is a condition that causes a

decrease in sexual desire and sexual satisfaction. The result of the research is in the expected direction.

According to the results of the research, the depression level of non-working women was found to be significantly higher than the average of working women. When examined in terms of depression risk factors, studies show that; men report more work-related factors, while women report more interpersonal problems [26]. In a study in which only women participated in Korea, it was reported that the rate of depression non-working women was higher than in working women, but there was no statistical difference [27]. In another study, it was reported that the working status of women had no effect on depression and anxiety levels [28]. In a study in Bangladesh, it was shown that the prevalence of moderate and severe depression among working women is quite high. But the thing is, studies show that people with depression, anxiety, or other mental disorders have higher unemployment rates, less productivity, and more absenteeism [29]. The question that comes to mind here is: Is not working a risk factor for depression, or is having depression a risk factor for not working? This is actually a vicious circle.

According to the results of the study, as the education level of women increases, the level of sexual satisfaction also increases. A study was planned to describe sexual activity and sexual satisfaction with and without partners, and to identify sociodemographic factors in older men and women from Norway, Denmark, Belgium and Portugal. In Belgium, the level of being sexually active was found to be 3.6 times higher for women with higher education than for women with elementary education. This ratio was 2.6 in Norway and 5.9 in Portugal. In Portugal, women who retire from a job have 60% higher sexual satisfaction than non-retired women and 4.3 times higher sexual satisfaction among women with tertiary education compared to women with primary education [30]. In a study conducted in the USA to determine the life-long sexual satisfaction status of adults and related factors, it was reported that as the level of education increases, sexual satisfaction increases [25]. In a study planned to determine sexual satisfaction and frequency of sexual intercourse in early marriage; it has been reported that receiving higher education in couples increases sexual satisfaction and frequency of sexual intercourse [31]. According to another study, it was concluded that women with high education levels had higher sexual satisfaction levels than women with low education levels [32]. Our study is similar to the studies in the literature. As the awareness of individuals increases, their level of sexual satisfaction also increases. Because it is thought that having the right information about sexuality positively affects sexual satisfaction. People with higher education and income levels are more inclined to get support and information about sexuality [33]. In another study, it was concluded that there was no significant relationship between education level and sexual satisfaction [33]. For this reason, it

is expected that people with higher education levels have higher sexual satisfaction. Contrary to our study; in a master's thesis study in Turkey, no relationship was found between education level and sexual satisfaction. However, this result was attributed to the fact that 83% of the study group of the research consisted of people with higher education and high or middle income level. The fact that some of the studies identified in the literature are in this direction, the level of education at the level of sexual satisfaction variable does not play an active role, it is insufficient to explain sexual satisfaction, sexual satisfaction should be examined from the window of different variables.

According to the results of the study, the sexual satisfaction levels of women who do not use antidepressants were found to be significantly higher than women who use antidepressants. When the literature is examined; it is seen that the use of antidepressants has negative effects on sexual functions. In a meta-analysis study planned to investigate sexual dysfunction, libido, arousal and orgasmic dysfunction after antidepressant treatment; sexual dysfunction has been reported in 25.8% to 80.3% of patients taking sertraline, venlafaxine, citalopram, paroxetine, fluoxetine, imipramine, phenelzine, duloxetine, escitalopram, and fluvoxamine [34]. In a systematic review, genital anesthesia causing decreased sexual satisfaction, unpleasant or weak orgasm, erectile dysfunction and premature ejaculation problems were reported among the common symptoms of SSRI (Selective serotonin reuptake inhibitor) use [35]. In an fMRI study, the association between the use of the antidepressant paroxetine and sexual dysfunction in healthy male volunteers was associated with functional connectivity between the anterior cingulate cortex, midbrain and insula, and the sublenticular enlarged amygdala [36]. In another study, sexual functionality was evaluated separately for both sexes in patients receiving antidepressant treatment, and it was concluded that antidepressant use was associated with both sexes, especially in terms of sexual satisfaction [37]. In another study, sexual satisfaction and quality of life were evaluated in major depressive disorder before and after SSRI treatment, and low sexual satisfaction was found in 64.3% of patients with major depressive disorder [38]. This result of the research is in the expected direction. Because, especially when neurobiological studies are examined, it is seen that antidepressant group drugs cause sexual dysfunction side effects. Therefore, evaluation of sexual function before and after antidepressant prescription is very important for patient satisfaction and drug compliance.

5. IMPLICATIONS FOR PRACTICE

When the results of the study were examined, it was revealed that depression, which affects sexual satisfaction, has an important place. For this reason, it is very important to examine other psychological factors in terms of women's sexual lives

and individual mental health. In women, sexual satisfaction of receiving premarital counseling found to increase. Psychiatric nurses, on the other hand, can assume the role of providing sexual safety for patients and counseling about sexuality. Providing information, counseling and rehabilitation is an important aspect of ensuring quality of life and psychiatric nurses play a key role in providing this situation. Giving such a key role to psychiatric nurses, who are an integral part of the mental health team, the acceptance of sexuality as an integral part of psychiatric nursing care, and the inclusion of sexual dysfunctions in nursing diagnoses reveal the importance of research on sexuality in the field of psychiatric nursing. We think that our study will bring a novelty to the literature in terms of examining only the relationship between sexual satisfaction and depression level in women. Because when the literature is examined, it is seen that the sexual satisfaction of women is less discussed in studies conducted in Turkey and in the world, which makes us think that women's sexual satisfaction is not considered important. It is thought that this study will reveal the current situation regarding female sexuality, be a guide for future research on sexuality in the field of psychiatry nursing, and contribute to the determination of priorities and needs in this field.

6. CONCLUSION

The study group of this research is not evenly distributed in terms of age, education and income level. In order to increase the generalizability of future studies, it may be recommended to include individuals from lower and upper socioeconomic levels, from different age and education groups, into the study groups. The fact that the research was conducted on the internet may have caused the questions not to be clearly understood or answered carefully. Conducting the study face to face can also contribute to the literature with different results. In addition, due to the fact that the research was conducted on the internet, the requested information could not be obtained from the female participants above a certain age limit. It is recommended to carry out a face-to-face study with a wider age range.

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