MULTIDISCIPLINARY APPROACH IN MEDICAL SCIENCE III

EDITOR
Assoc. Prof. Dr. Hüseyin KAFADAR

İKSAD
Publishing House

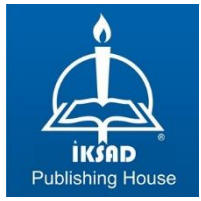
MULTIDISCIPLINARY APPROACH IN MEDICAL SCIENCE III

EDITOR

Assoc. Prof. Dr. Hüseyin KAFADAR

AUTHORS

Prof. Dr. Mehmet Nurullah KURUTKAN
Assoc. Prof. Dr. Güngör Çağdaş DİNÇEL
Assoc. Prof. Dr. Hüseyin Erdem AK.
Assoc. Prof. Dr. Latife Ceyda İRKİN
Assoc. Prof. Dr. Naci Ömer ALAYUNT
Assoc. Prof. Dr. Suat ÇAKINA
Asst. Prof. Şamil ÖZTÜRK
Asst. Prof. Şeref Buğra TUNÇER
Asst. Prof. Dr. Veysel TAHİROĞLU
Ayse KONAÇ , MD.
Alev GUNALDI, MD
Dr. Ayşegül HANİKOĞLU
Dr. Erkam COŞKUN
Dr. Elif UĞUR
Dr. Gülşah ZÖRGÖR
Hasan ÖKMEN,MD.
İshak YILDIZ,MD.
Ress. Ass. Elif DELEN
LecturerTuba ARSLAN
M. Sc. Merve Çiğdem ÖZGEL



(The Licence Number of Publicator: 2014/31220)
TURKEY TR: +90 342 606 06 75
USA: +1 631 685 0 853
E mail: iksadyayinevi@gmail.com
www.iksadyayinevi.com

ISBN: 978-625-367-137-2
Cover Design: İbrahim KAYA
June/ 2023
Ankara / Türkiye
Size = 16x24 cm

CONTENTS

PREFACE

Science is the lost property of humanity. Mankind has made great efforts to reach science and science since its existence. Today, research studies continue in order to reach science and produce knowledge. Very valuable scientists are in the race to take science to the next level by checking the existing information. In this way, in addition to coping with difficulties, it becomes possible to reach new information and make new discoveries in every field.

This book, which includes valuable chapters in the field of medicine and health sciences, consists of 10 chapters. We are happy to share our book with the scientific community and our readers. I heartily congratulate our esteemed writers, who put their valuable works into the service of humanity as a reward for a great effort.

We dedicate this book, which includes very valuable topics, to the doctors and their families who lost their lives in the 6 February 2023 earthquake. We commemorate our martyrs with mercy. Bless their souls.

I would like to thank the İKSAD Publishing family, scientific committee, authors and readers who contributed to the preparation, arrangement and publication of the book.

Assoc. Prof. Dr. Hüseyin KAFADAR[1]

[1] Harran University, Medical Faculty, Department of Forensic Medicine.
Email: dr.hkafadar@gmail.com
ORCID: 0000-0002-6844-7517

CHAPTER 1

GASTRIC CANCER AND *Helicobacter pylori*

M. Sc. Merve Çiğdem ÖZGEL[1]

Asst. Prof. Şeref Buğra TUNÇER[2]

[1] Istanbul University, Health Sciences Institute, Basic Oncology Departmant, Cancer Genetics Program, Istanbul, Turkey
E-mail: mervecigdemozgel@ogr.iu.edu.tr; ORCID ID: 0000-0002-3014-0843
[2] Istanbul University, Oncology Institute, Department of Cancer Genetics, Istanbul, Turkey
E-mail: seref.tuncer@istanbul.edu.tr; ORCID ID: 0000-0001-8023-3223

INTRODUCTION

Any sort of cell in the body that proliferates abnormally can develop into a malignancy (Peng & Croce, 2016). Good-natured or cancerous tumors are both possible. Unlike malignant growth, which is capable of spreading to various tissues and organs, a benign tumor does not penetrate or spread to nearby cells (Farhi L., 2017). There are numerous factors that can contribute to the development of malignancies, including chemicals, radiation, microbes, and viral organisms (Colditz et al., 2006; Elinav et al., 2013; Moore & Chang, 2010). The majority of cancer-causing agents, including radiation and chemical carcinogens, alter DNA and result in mutations in DNA (Basu, 2018). By promoting cell growth, tumor supporters accelerate the development of cancer (Alipour, 2021). Mutations result from regular DNA replication and are brought on by an increase in cells (Tomasetti et al., 2017). The estrogen hormone, pathogenic organisms like viruses and bacteria, and toxins like tobacco products are a few instances of tumor supporters (Vendramini-Costa & Carvalho, 2012). The most prevalent malignancies globally are lung cancer, which affects both sexes equally, and breast cancer in women (11.6% of all patients), subsequent to prostatic tumors (7.1%), colon carcinoma (6.1%), and non-melanoma derm (5.8%), gastric (5.7%), lip, and mouth gap (2%), incidences (Bray et al., 2018). Viral agents that cause cancer account for 15–20% of all human malignancies (Soto et al., 2017). Even though it is debatable whether or not bacteria play a part in the initiation of malignancies, studies have revealed that certain types of bacteria do (Mager, 2006). Researchers looked into the connection between being infected with *H. pylori* and the emergence of stomach tumors (Vogelmann & Amieva, 2007). Under the age of 10, 70–90% of people in underdeveloped nations have *H. pylori* on their bodies, whereas in industrialized countries, the infection rate ranges from 25–50% (Nezami et al., 2019).

Over 60% of stomach malignancies are caused by *H. pylori* (Alipour, 2021). Over 8.2% of all cancer-related deaths occur as a result of tumors in the stomach (Raza et al., 2020). Among all pathogens with infectious properties, *H. pylori* may be the most prevalent (Wang et al., 2014). Humans and Helicobacter evolved together for a minimum of 58,000 years, according to genetic sequencing studies (Linz et al., 2007). *H. pylori* is known to be intimately related to a number of digestive disorders ever since it was first discovered in 1982 (Marshall & Warren, 1984).

1. *Helicobacter pylori*

The leading cause of tumors in the stomach, which claim the lives of many thousands of humans every year, is *H. pylori* infection, which is a bacterial carcinogen (Hardbower et al., 2014). *H. pylori*-induced harm and inflammation are responsible for around 75% of the overall incidence of stomach cancer and 5.5% of all malignancies (Parkin et al., 2005), although the precise processes governing tumor formation as a consequence of this bacterium are unclear.

It is a microaerophilic, spiral-shaped, mobile, gram-negative microorganism called *H. pylori* (Matsunaga et al., 2018). Human stomachs are one of the known typical *H. pylori* reserves (Bachir et al., 2018). Infection with *H. pylori* typically emerges in juvenility and endures in the patient's body absent the use of antibiotics (Linz et al., 2007). The bacterium can spread between people through feces to mouth or oral to oral (Kayali et al., 2018). Around 15% of those who are infected with *H. pylori* go on to develop stomach ulcers, and it is thought that 50% of the population worldwide is regularly infected by this bacteria (Bravo et al., 2018). *H. pylori* infection can cause stomach cancer and peptic ulcers even if there are no symptoms (Khan, 2019). Persistent gastritis; although *H. pylori* is symptom-free, the first phase of the illness results in hypochlorhydria with severe gastritis, which can produce feeling sick, throwing up, and a painful abdomen that subsides in a couple of days (B., 2019).

A gram-negative bacterium called *H. pylori* preferentially settles in the stomach epithelium (Jr., 2016). Chronic *H. pylori* contamination is by far powerfully recognized reason for cancer in distal stomach adenocarcinoma, and in 1994, this microorganism was categorized in the class of Type I carcinogen by the WHO (Fox & Wang, 2007; Polk & Peek, 2010). Today, *H. pylori* can be detected via a quick urease test, a polymerase chain reaction method, histologic analysis of biopsies, and serology analysis (Mohammadian & Ganji, 2019).

In spite of the difficult gastric environment, *H. pylori* typically develops during childness and can survive into adulthood without combination antibiotic medication (Wroblewski et al., 2010). A fascinating conclusion from genomic investigations is that *H. pylori* has been present in humankind for a minimum of 58,000 years and that around 50% of people

worldwide are affected (Linz et al., 2007), prompting a number of hypotheses that *H. pylori* is an internal origin component of the stomach microbiome.

According to research on epidemiology, 0.1% of people who are diagnosed with mucosal-associated lymphoid tissue (MALT) lymphoma and 2-3% of those with *H. pylori* contamination establish stomach cancer (Bagheri et al., 2016; Diaz et al., 2018). With its flagella, *H. pylori* enters the mucosa of the stomach, where the mucus sheet shields the bacterium from the stomach's acidic environment (Ruch & Engel, 2017). Over 20% of *H. pylori* lineages cling to the stomach epithelium cells' membrane (Hessey et al., 1990).

Bacterial ingredients with a unique lineage, host genetic components, modifications in the stem cell niche, and effects of the environment, including the host microbiome and food, all have efficacy for the pathological result of illness caused by *H. pylori* (Wroblewski & Peek, 2013).

2. GASTRIC CANCER

With an estimated 723,000 fatalities from gastric adenocarcinoma in 2012 and a fewer than 15% overall survival rate after five years in the USA, it is the third majority fatality caused by carcinoma worldwide (de Martel et al., 2012; Ferlay et al., 2015; Parkin et al., 2005).

Adenocarcinoma is the most typical form of gastric malignancy; however, lymphoma and leiomyosarcoma are other possibilities (Jr., 2016). Histology shows that two separate forms of adenocarcinoma of the stomach may be characterized: diffuse type stomach carcinoma, which is composed of cancerous cells that are on their own entering but don't succeed in developing constructions that contain glands, and intestinal type carcinoma, which develops through a series of distinct histologic stages (Correa, 1992). There are four different subcategories of gastric cancer according to a molecular categorization that was suggested following the latest thorough molecular examination of about 300 primary stomach cancers (Cancer Genome Atlas Research, 2014). Gene expression information was utilized by Cristescu et al. to categorize tumors of the stomach into four molecular subgroups. The preliminary category consists of microsatellite instability-high tumors (MSI) that develop in the stomach gap and have the most available general disease assessment of the minimum relapse frequency. An average prognosis is given by tumor protein 53 (TP53) active and passive variants, with the inactive variants offering a poorer outcome than the active variant. The mesenchymal-

like kind, which makes up the fourth subcategory, has the poorest prognosis and maximum relapse frequency (Cristescu et al., 2015).

Over the last hundred years, there has been a dramatic reduction in the number of diagnoses of cancer of the stomach in industrialized nations, primarily as a result of a fall in intestinal-type adenocarcinomas in the distal part of the internal organ in which the major part of the digestion of food occurs (Fuchs & Mayer, 1995; Howson et al., 1986). On the other hand, proximal stomach adenocarcinomas, along with those originating at the junction between the stomach and esophagus, are becoming more common in Europe and the USA (Blot et al., 1991; Pera et al., 1993).

3. EPIDEMOLOGY OF *H. pylori* CONTAMINATION AND GASTRIC MALIGNANCIES

A major potential risk for stomach tumors, of which malignant tumors formed from glandular structures in the epithelial tissue of the stomach account for 90% of cases, is unquestionably *H. pylori* infection (Noto & Peek, 2012). In the latest research of 114 histology-confirmed patients with stomach cancer from Eastern Libya, the total frequency of contamination for *H. pylori* was 63.2%; transmission is increasingly prevalent in contrast to diffuse carcinoma (55.3%), intestinal type stomach carcinoma (71.7%), and malign lymphoma (66.6%), which are more common (Elzouki et al., 2012).

According to the position of the anatomical structure, the efficacy of *H. pylori* contamination on carcinomas of the stomach can differ (Wang et al., 2014). In high *H. pylori* endemic regions, patients rarely experience proximal gastric (cardia and gastroesophageal junction) tumors because they have distinct epidemiologic and pathophysiologic characteristics (Kamangar et al., 2006). For instance, *H. pylori* contamination or Barrett's esophagus may not be linked to adenocarcinoma of the gastroesophageal junction (Kamada, 2012).

The extranodal lymphoma known as stomach MALT lymphoma is primarily accomplished by tiny, anatomically diverse B cells (Wang et al., 2014). The connection between *H. pylori* contamination and the emergence of stomach MALT lymphomas is nowadays widely known (Wang et al., 2014). An exhaustive analysis of 1,844 patients who were eliminated from 38 research investigations found that the median frequency of *H. pylori* contamination in maltoma was 79%, with low-grade cases having a higher probability of becoming infected with it (79%) than advanced cases (60%) of

the disease (Asenjo & Gisbert, 2007). For 60-80% of MALT lymphoma patients, the removal of *H. pylori* brought about a full cure (Kusters et al., 2006; Zullo et al., 2010) and as many as 64% of individuals experienced a 10-year maintained cure (Wundisch et al., 2012). As a result, the norm of therapy for people with stomach MALT lymphoma now includes the elimination of *H. pylori* (Wang et al., 2014).

4. VIRULENCE FACTORS AFFECTING *H. pylori* GASTRIC PATHOGENESIS

The probability of being diagnosed with gastric adenocarcinoma after *H. pylori* infection is significantly affected by microbial virulence indicators (Jr., 2016). Numerous virulence factors made by *H. pylori* can disrupt intracellular communication networks in the host and reduce the threshold for neoplastic transformation (Wang et al., 2014). Three major pathogenic virulence indicators are VacA (vacuolation cytotoxin A), *CagA* (cytotoxin-associated gene A), and its pathogenicity island (Cag-PAI) (Wang et al., 2014).

One of the *H. pylori* pathogenicity indicators, Cag-PAI, a 40 kDa DNA insert component comprising nucleotide sequences encoding amino acid chains that constitute a type IV bacterial secretion system (T4SS), is indubitably connected to an increased danger of acquiring malignancy. Through its passage through microbial and epithelial barriers, Cag-T4SS delivers attached *H. pylori*, transferring *CagA* to host cells (Fischer et al., 2001; Kwok et al., 2007; Odenbreit et al., 2000; Shaffer et al., 2011).

4.1. The Role of *CagA* in Inflamed Stomach and Tumorigenesis

Another of the virulence indicators that lead to cancer of the gastric is the *H. pylori* Cag-PAI (Sgouras et al., 2015). Cag-PAI is a 40 kb DNA insert component that contains 27–31 genes that code the *CagA* and the various proteins that collectively constitute the Cag-T4SS (Backert et al., 2015). Cells of interest are able to be "given an injection" with CagA using the injector-like pilus structure that T4SS creates (Wang et al., 2014). CagA's movement inside the host cells involves connecting to the extracellular domain of the α5β1 integrin, which is a crucial step (Jimenez-Soto et al., 2009). When in the cytoplasm of the host tissue, CagA can attach to the inside layer of the cell barrier and be phosphorylated from tyrosine by Src family kinases to form

glutamic acid – proline – isoleucine - 4-hydroxyphenylalanine (also known as tyrosine) - 2-aminopropanoic acid (also known as alanine) (EPIYA) pattern (Wang et al., 2014). In order to stimulate downstream signaling networks like the MEK (mitogen-activated protein kinase kinase)/ERK (extracellular signal-regulated kinase) way, the nuclear factor κB (NF-κB) way, and the β-catenin way, phosphorylated and non-phosphorylated *CagA* communicates with a variety of host amino acid chains (Mueller et al., 2012; Xu et al., 2012). The capability of stomach epithelial cells to proliferate will be enhanced by these alterations (Wang et al., 2014).

In addition to serving as CagA's intracellular target, Src-homology protein tyrosine phosphatase 2 (SHP2) serves as an essential modulator of the downstream signaling that CagA causes (Wang et al., 2014). Tyrosine phosphorylated CagA may only attach to SHP2 and activate the SHP2-Ras-ERK signal in AGS cells, stomach cancer cells from primary culture, to cause Ras-addicted and unaddicted signaling (Wang et al., 2014). The "hummingbird phenotype", defined as lengthening of cells and dispersion, results from a breakdown of epithelial cell polarization caused by CagA-mediated SHP2 signaling (Wang et al., 2014). Focal adhesion kinase (FAK) is dephosphorylated and rendered inactive as a consequence of a connection between CagA and SHP2, which causes the lengthening of cells (Lee et al., 2012; Mueller et al., 2012).

There are numerous molecules that non-phosphorylated CagA can target (Wang et al., 2014). Research has recently found that CagA may, in a CagA-unaddicted way, stimulate the HGF (hepatocyte growth factor)/SF (scatter factor) c-Met receptor and adapter protein Grb2 (Mimuro, 2002), cause phospholipase C gamma (PLCγ) phosphorylation, and prevent the creation of the E-cadherin/β-catenin complex (Murata-Kamiya et al., 2007; Wroblewski et al., 2010). Furthermore, unphosphorylated CagA is acting like a suppression of PAR1b/MARK2 (PAR1b/MARK2) with kinase cleavage problems resulting in unusual signals of protein kinase C, which results in the breakdown of tight junctions and the loss of cell polarization (Kaplan-Turkoz, 2012).

The function of the C-terminal domain, which includes three EPIYA patterns and is tyrosine phosphorylated by the Abl and Src kinases in eukaryotic cells, has received a lot of interest (Wang et al., 2014). When the N-terminal of not-phosphorylated CagA interacts with several junctional proteins, such as E-cadherin, zonula occludens-1, and junctional adhesion

molecule A, it attacks the cell membrane, disrupts the epithelial cell's apical junctional complex, loses the polarization of cells, and triggers pro-inflammatory and mitogenic reactions (Wang et al., 2014). Malignant transformation and intestinal metaplasia are known to be facilitated by these mechanisms (Kaplan-Turkoz, 2012). Also, numerous intrinsic collaborators communicate with the CagA N-terminal domain (Wang et al., 2014). For instance, CagA changes the interaction between p53-2 (ASPP2) and p53 apoptosis-stimulating proteins to enhance proteasomal degradation of p53 (Buti et al., 2011), it deactivates the gastric tumor suppressor Runt-associated transcription factor 3 (RUNX3) (Tsang et al., 2010) and increases Lys 63-dependent ubiquitination of transforming growth factor-β (TGF-β)-activated kinase 1 (TAK1) through tumor necrosis factor receptor-associated factor 6 (TRAF6)-mediated (Lamb et al., 2009). Additionally, CagA is capable of translocating into host cells because its N-terminal domain has an attachment component for the ectodomain of the α5β1 integrin (Wang et al., 2014).

Intestinal and diffuse gastric cancer risk is 5.8-fold higher in people with *H. pylori* types expressing CagA than in people without the infection (Jr., 2016). The risk of being diagnosed with distal gastric cancer is only 2.2 times higher in *H. pylori* types without CagA than in individuals with no infection (Parsonnet et al., 1997). Based on an analysis that combines the results of multiple scientific investigations looking at the risks of developing malignancy, forms of *H. pylori* that include CagA are two times more likely than CagA-negative types to cause distal adenocarcinoma of the stomach (Huang et al., 2003).

4.2. The Role of VacA in Inflamed Stomach and Tumorigenesis

By means of a type V autotransport secretion mechanism, *H. pylori* releases the vacuolation cytotoxin (VacA) (Wang et al., 2014). A 88 kDa protein known as VacA is made up of the p33 and p55 subsections (Wang et al., 2014). Although p33 (33 kDa, N-terminal) is an internal duct for chlorine ion transportation, the p55 (55 kDa, C-terminal) sections are necessary for an antigenic poison, specifically one generated or reproduced by microbes that, if found in the body in nominal quantity, causes illness, to attach to host cells. There are numerous biologic functions for VacA (Wang et al., 2014). Although every type of *H. pylori* contains VacA, there are notable variations in VacA sequences (Jr., 2016). The most diverse parts are the 5' region of the

nucleotide sequence encoding the signal sequence and the NH_2- terminal of the released antigenic poison, specifically one generated or reproduced by microbes that, if found in the body in nominal quantity, causes illness (allele types s1a, s1b, s1c, or s2), an intermediate region (allele types i1 or i2), and an intermediate region (allele types m1 or m2) (Atherton et al., 1995; Rhead et al., 2007). Significant associations exist between stomach cancer and variants bearing the type s1, i1, or m1 alleles (Atherton et al., 1995; Atherton et al., 1997; Miehlke et al., 2000). It attaches to host cells and is taken up, causing a serious "vacuolation" that is marked by a mass of enormous vesicles that share characteristics with both late endosomes and early lysosomes (Wang et al., 2014). By inducing the secretion of cytochrome c, the movement of the mitochondrial transmembrane potential (ΔΨm), and the stimulation of the pro-apoptotic factor Bcl-2-associated X protein (Bax), VacA may be additionally transported to mitochondria, which can result in death (Rassow & Meinecke, 2012). Since inhibiting DRP1-addicted mitochondrial fission in VacA-toxicated cells suppresses Bax stimulation and mitochondrial outer membrane permeability (MOMP) and prevents the fatality of toxic cells, the stimulation of dynamin-associated protein 1 (DRP1) could have a crucial role throughout the VacA-induced disruption of mitochondria (Jain et al., 2011). Additionally, VacA may destroy epithelial cells' tight junctions and block T lymphocytes from proliferating and activating in the lamina propria (Wang et al., 2014). The other way that VacA causes inflammatory conditions in the stomach and aids in the initiation of stomach carcinoma is by interfering with autophagy (Palframan et al., 2012; Raju et al., 2012).

The carcinogenic capability of *H. pylori* may be influenced by VacA because it interferes with the β-catenin signal cascade (Jones et al., 2010). Through PI3K (phosphatidylinositol 3-kinase), which phosphorylates GSK3β (glycogen synthase kinase 3β), VacA stimulates Akt (commonly referred to as protein kinase B) (Nakayama et al., 2009). Two of the protein kinases known as PDK1 (3-phosphoinositide-dependent kinase 1) and mTORC2 (mammalian target of rapamycin complex 2) that connect to PIP3 phosphorylate and stimulate Akt (Yudushkin, 2019). GSK-3β controls cellular survival and growth, which Akt phosphorylation inhibits (Gao et al., 2019; Manning & Toker, 2017). GSK3 is structurally active at rest (Badimon et al., 2019). According to the condition of lack of ligand, β-catenin is phosphorylated by GSK3, which is a part of the cytoplasmic complex, which includes the adenomatous polyposis coli protein (APC), auxin, and β-catenin (Vallee &

Lecarpentier, 2016). Following that, phosphorylated β-catenin is ubiquitinated and degraded by the proteasome (Singh et al., 2018). When VacA is present, GSK3β is deactivated, resulting in a buildup of β-catenin in the plasm (Bowley et al., 2007). In order to trigger the transcription of β-catenin addicted genes like *cyclin D1*, β-catenin goes into the nucleus and then functions as a co-activator of TCF (T cell factor) and LEF (lymphoid enhancing factor) transcription factors (Lang et al., 2019; Li et al., 2019). Human malignancies, particularly *cyclin D1* overexpression, are related (Diehl, 2002).

Interesting novel theories propose that CagA and VacA can counter-regulate one another to control host cell reactions (Jr., 2016). In particular, CagA inhibits VacA's induction of programmed cell death and stimulates a cell survivability cascade that is controlled by MAPK and the anti-apoptotic protein MCL1 (Backert & Tegtmeyer, 2010). The opposite actions of VacA and CagA can be cell line-specific, according to a new investigation (Jr., 2016). *In vivo* creation monitoring of the stomach epithelial layer revealed that Lgr5 (leucine-rich repeat-containing G protein-coupled receptor 5)-positive cells are self-regenerating, multipotent stem cells in charge of the stomach epithelium's continuous regeneration (Barker et al., 2010). When compared to cancer patients who are not affected by *H. pylori*, the community of Lgr5+ epithelium is larger in people with cancer of the stomach who have this infection (Jr., 2016). In addition, evidence that Lgr5+ epithelium are a particular goal for *H. pylori* comes from the fact that these Lgr5+ epithelium are far more vulnerable to DNA disturbance caused by oxidation compared to Lgr5-deficient ones (Uehara, 2013).

Autophagy is initiated in differentiated gastric epithelial cells by digesting cytoplasmic CagA, and attachment of VacA to the epithelium receptor LRP1 causes a reduction of cytoplasmic glutathione and permits an overabundance of reactive oxygen species, which in turn triggers consumption of the body’s own tissue (Tsugawa et al., 2012). Contrary to expectations, CagA was discovered to build up in stomach epithelium that expresses CD44 variation 9, a stem cell indicator (Jr., 2016). Due to their capacity to resist reactive oxygen species, these cancer stem-like cells do not undergo autophagy, which prevents CagA from being degraded (Jr., 2016). These findings generally imply that the bacterial oncoprotein CagA can survive in a subset of host cells with progenitor-like characteristics that can impose long-

term harmful impacts on the host and possibly reduce the magnitude that must be exceeded for tumorigenesis (Tsugawa et al., 2012).

4.3. Stomach Carcinoma and Helicobacter Outer Membrane Proteins

Cancer of the stomach has been related to three proteins found in the outer membrane of the *H. pylori* bacteria: HomB, HopQ, and HopH (OipA) (Braga et al., 2019; Cover, 2016). There is no known external inflammatory protein antigen (OipA) receptor in particular (Posselt et al., 2013). The signal transducer and activator of transcription 1 (STAT-1) is phosphorylated as a result of *H. pylori* OipA (Alarcon-Millan et al., 2019). STAT is phosphorylated by a Janus kinase (JAK), a non-receptor tyrosine kinase linked with cytokine receptors (Alipour, 2021). The cytokine-excited JAK/STAT signaling pathway is the name given to this signaling network (Xin et al., 2020). The interferon γ-activated sequence (GAS) is bound by phosphorylated STAT1, which first forms a homodimer in the cytoplasm before moving to the nucleus to stimulate the production of interferon γ-induced genes (Alipour, 2021). Another effect of the interferon γ signal is the phosphorylation of STAT3, which connects to the GAS element and triggers the activation of genes relating to or causing inflammation in a part of the body (Ismael et al., 2018; Owen et al., 2019; Zhang et al., 2013). Reactive oxygen and nitrogen species are created during inflammation to combat disease-causing agents, but these agents also have the ability to damage DNA, which can lead to cancer-causing mutations (Kay et al., 2019). The transport of the CagA protein in the cell is made possible by the HopQ external membrane protein, which interacts with CEACAM on the outside tier of the gastric epithelial cell (Koniger et al., 2016). HopQ in *H. pylori* is an important hallmark of stomach cancer because it makes it easier for CagA protein to go within cells (Brush, 2019; Xia, 2019). HomB, a gastric tumor-associated external membrane protein, mediates the attachment of *H. pylori* to stomach epithelial cells (Oleastro & Menard, 2013; Talebi Bezmin Abadi et al., 2011). Inflammation probably results from HomB attaching to the stomach epithelium (Oleastro et al., 2008).

5. THE MANNER OF DEVELOPMENT OF STOMACH CANCERS IS CONTROLLED BY HOST AND PERIPHERAL AGENTS

Additionally, host polymorphisms affect the likelihood of developing cancer of the stomach (Jr., 2016). In those with *H. pylori* infection, there is a rise in the pro-inflammatory cytokine IL-1β, which limits the release of acids (Jr., 2016). Comparing people who have genotypes that limit IL-1β expression to those without it, we found that those with large grades of IL-1β polymorphism had a considerably higher risk of hypochlorhydria, stomach atrophy, and distal stomach carcinoma in the setting of being contaminated with *H. pylori* (El-Omar et al., 2000). A genetically predisposed person's chance of acquiring gastric cancer is further enhanced by the presence of an especially lethal strain of *H. pylor* (Jr., 2016). People with H. pylori VacA s1-allel or $CagA^{+}$ strain infections that contain strongly expressed IL-1β polymorphisms are at a 25-fold or 87-fold higher danger of getting stomach carcinoma than people without such infections (Figueiredo et al., 2002). TNF-α is a cytokine that relates to or causes inflammation of a part of the body that limits acid generation, much like IL-1β, and polymorphisms that enhance TNF-α expression are linked to an enhanced risk of getting carcinoma of the stomach and its precursors in an infection of *H. pylori* (El-Omar et al., 2003).

The possibility of growing a stomach tumor is enhanced by environmental variables, including nutrition (Jr., 2016). The foods that are most frequently connected to an enhanced danger of getting stomach carcinoma include those that are salty, pickled, smoke-dried, or badly stored, as well as diets that are high in meat and low in fruits and vegetables (Epplein et al., 2008; Gonzalez et al., 2006; Gonzalez et al., 2012; Kim et al., 2010; Kim et al., 2004; Ren et al., 2012; Tsugane & Sasazuki, 2007). The two factors most strongly connected to an enhanced danger of being diagnosed with a tumor of the gastric organ in the setting of an infection with *H. pylori* are iron deficiency and excessive salt consumption in the diet (Lee et al., 2003; Noto et al., 2013; Shikata et al., 2006).

Although human experiments have demonstrated that various elements of the stomach microbiome may affect the advancement of stomach disease, *H. pylori* infection remains the biggest accepted associated danger for the onset of stomach carcinoma (Jr., 2016). Thus, it was discovered that

antibiotic treatment for *H. pylori* dramatically decreased the risk of malignancies in the stomach in a 15-year follow-up investigation involving 3365 participants (Jr., 2016). The result of this investigation, that fewer than 50% of those who got antibiotics remained *H. pylori*-free after 15 years of follow-up, is especially intriguing (Ma et al., 2012). This shows that antibiotic treatment can change the non-*H. pylori* microbiome in a manner that lessens the occurrence of carcinoma of the stomach (Jr., 2016).

Fatness is widely recognized to increase the risk of over 20 varieties of cancer, such as gallbladder, hepatic, and stomach cancers (Li et al., 2012; Shen et al., 2012; Wang, 2012). Clinical experiments in epidemiology have shown that individuals with metabolic disorders and who are overweight have a higher incidence of infection with *H. pylori* (Albaker, 2011; Li et al., 2012; Marie, 2008). Increased glucose levels in the blood, known as insulin resistance, and infection with *H. pylori* are being shown to be directly related (Demir et al., 2008).

5.1. *H. pylori* and Iron

The connection among *H. pylori* contamination and iron deficiency anemia (IDA) is becoming more and more clear, especially in sporadic instances of people who appear with IDA who are resistant to iron supplements and in the majority of children with IDA (Queiroz, Harris, et al., 2013; Yamanouchi et al., 2014). Given that IDA affects 30% of people and is linked to mental and developmental disruption, *H. pylori* generally has considerable adverse effects on pediatric IDA in environments with poor supplies (Queiroz, Rocha, et al., 2013). Another finding is that indicators of a lack of iron are related to a higher danger of stomach carcinoma (Noto et al., 2013). As a result, *H. pylori* can lead to nominal iron rates, which may enhance the effects of *H. pylori* contamination (Amieva & Peek, 2016).

Due to iron restriction, an old congenital immune barrier against infection, iron is a crucial particle for nearly all life forms but a limiting supply for bacteria that infiltrate the human body (Amieva & Peek, 2016). The epithelium layer keeps germs from colonizing the mucosal layers away from interstitial and intracellular iron supplies, whereas high-affinity chelators like iron, ferritin, transfferin, and hemoglobin keep these resources in the body (Cassat & Skaar, 2013). Neutrophils release lactoferrin, which closely attaches independent iron to the mucosal superficies to famish the germs in the inflamed stomach mucosa (Choe et al., 2003). Additionally, inflammation

causes the main iron metabolism modulator hepcidin to be up-regulated, which initiates an iron reduction reaction against an infectious bacterium that can cause disease by obstructing iron absorption in the gut (Cassat & Skaar, 2013).

Numerous methods of capturing iron have been developed by *H. pylori*, and all of them can have consequences that lead to gastric disease (Amieva & Peek, 2016). For instance, *H. pylori* expresses a wide range of transporters in the membrane that are capable of absorbing solubility kinds of iron, like ferrous ferric citrate particles and ferrous ions (Velayudhan et al., 2000). This kind of iron is typically insoluble, but because of the acidic environment in the gastric lumen, nutritional ferric iron is soluble and is kept in solution in combination with ascorbic acid (Conrad & Schade, 1968). Thus, *H. pylori* may immediately utilize a supply of soluble iron found in acidic stomach juice (Amieva & Peek, 2016). Nonetheless, due to its inability to thrive in the acidic stomach lumen and preference for staying near the epithelium superficies, where it releases urease enzymes to buffer its local environment, *H. pylori* is able to obtain this supply of iron (Amieva & Peek, 2016). Long-term *H. pylori* infection frequently results in reduced stomach acid and ascorbic acid output, which lowers the amount of soluble iron available to *H. pylori* and leads to IDA (Annibale et al., 2003). Furthermore, lactoferrin also decreases the amount of free iron that is available close to the mucosa and can be a contributing cause of IDA (Choe et al., 2003).

Hepcidin up-regulation in reaction to *H. pylori* infection may potentially decrease the host's capacity to use iron and result in IDA (Amieva & Peek, 2016). For instance, iron taken by mouth is ineffective for treating iron insufficiency caused by *H. pylori* until antibiotics are used to completely destroy the bacterium (Amieva & Peek, 2016). Therapy of *H. pylori*-infected kids with IDA with iron via oral medication failed to decrease blood levels of hepcidin, indicating that full elimination of the bacterium is necessary to return healthy iron equilibrium (Azab & Esh, 2013). Mainly expressed in the parietal cells of the stomach glands, stomach hepcidin is enhanced by *H. pylori* contamination, but recovers to its baseline level following elimination (Schwarz, 2012).

It wouldn't be unexpected that *H. pylori* creates new ways of acquiring iron from the host, given that infection with the bacteria affects acid, hepcidin, and lactoferrin and causes a drop in free iron (Amieva & Peek, 2016). *H. pylori* is not creating siderophores, known to be tiny particles that

may snare iron from the host and other germs, in contrast to several other symbiotic and pathogenic microorganisms that reside on mucosal surfaces (Amieva & Peek, 2016). *H. pylori* may in fact utilize lactoferrin as a reservoir of iron, yet only when it is completely fed with iron, according to in vitro research with specified medium (Amieva & Peek, 2016). The identical research has demonstrated that *H. pylori* may draw iron from satiated hemoglobin and transferrin (Senkovich et al., 2010). As a result, *H. pylori* utilizes both iron from food as well as interior host iron stores that are stored beyond the epithelial layer (Amieva & Peek, 2016).

CagA and VacA have both been shown to be critical to their capacity to colonize the epithelial superficies in the presence of a reduced iron supply (Tan et al., 2011). Iron-satiated transferrin was induced to enter infected epithelial cells by the injection of CagA in the epithelium (Amieva & Peek, 2016). Additionally, it altered the polarization of cells to impair transferrin reuse and cause its transcytosis across the epithelial cells (Amieva & Peek, 2016). Additionally, VacA changed endosomal trafficking, which affected transferrin and its receptor's mislocalization (Amieva & Peek, 2016). Due to these cellular impacts, it has been postulated that *H. pylori* virulence indicators assist in the viability of bacteria *in vivo* in the presence of a reduced iron supply (Amieva & Peek, 2016). *H. pylori* variants obtained from individuals with minimal ferritin levels in humans at risk for cancer of the stomach induced the strongest inflammatory reactions when cultured together with stomach epithelial cells (Amieva & Peek, 2016).

5.2. *H. pylori* and Salt

Most human investigations have found a connection between excessive salt intake and a higher risk of stomach cancer (Lee et al., 2003; Tsugane, 2005). Salt can control gene expression in a number of microbial infections, including *H. pylori* (Cameron et al., 2012). It's intriguing to learn that only in specific types of *H. pylori* does *CagA* expression increase when exposed to high salinity terms (Loh et al., 2012; Loh et al., 2007), according to transcriptional and proteomic analyses. Using this information as a basis, in those with *H. pylori*'s clinical isolates, Loh et al. mapped the *CagA* promoter and found a specific DNA motif (TAATGA) in 1 or 2 duplicates (Amieva & Peek, 2016). Salt-excited up-regulation of *CagA* could usually be more extensively seen in types with 2 duplicates of the TAATGA pattern than in types with 1 copy, which provided further evidence in mutagenesis testing that both duplicates of the pattern are required (Amieva & Peek, 2016).

Utilizing 7.13, a particular carcinogenic variant of *H. pylori*, Gaddy et al. examined the impact of an overly salty food intake on germ-excited malignancy in rodents, especially gerbils (Gaddy et al., 2013). Compared to infected rodents on standard nutrition, gerbils fed a diet with excessive salt had a much greater risk of gastric adenocarcinoma detection (Gaddy et al., 2013). Infected gerbils on a diet containing a lot of salt additionally experienced increased gastric inflammation (Gaddy et al., 2013), and animals developing malignancy had parietal cell loss, elevated levels of stomach mucosal IL1B, and hypochlorhydria. Gerbils contaminated with an isogenic mutant type that is CagA-negative and whose nutrition is overly salty showed less stomach inflammation and neither hypochlorhydria nor stomach cancer (Amieva & Peek, 2016). The initiation of stomach cancer was not triggered by a salt-rich diet in gerbils that were not afflicted (Gaddy et al., 2013). These findings support the hypothesis that $CagA^+$ *H. pylori* variants have an enhanced ability to cause cancer (Amieva & Peek, 2016).

These findings suggest a number of possible approaches by which nutrition may promote the formation of stomach cancer (Amieva & Peek, 2016). Nutritional elements may harm the mucosa directly, which would then allow more carcinogens to enter the stomach tissue and cause cancer (Amieva & Peek, 2016). By communicating with intestinal immune receptors (Tilg, 2012), several food substances alter intestinal immunity, and comparable reactions can take place in the stomach. Dietary factors can influence the microbial community in the stomach or encourage the effuse of pathogenic *H. pylori* strains (Amieva & Peek, 2016). Nutritional variables, such as folic acid intake, may additionally impact epigenetic alterations by protecting against universal DNA methylation loss and reducing the initiation of an inflamed stomach and dysplasia in mice affected by bacteria (Gonda et al., 2012). As a result of raising the expression and functionality of the *CagA* gene in people who have *H. pylori* contamination, increased consumption of salt in food impacts the disease potential of *H. pylori*, as has recently been confirmed. (Amieva & Peek, 2016; Gaddy et al., 2013).

6. CONCLUSION

Knowing the risk indicators of gastric adenocarcinoma is essential to recognizing those who are most at risk of getting the illness, which accounts for a significant portion of fatalities caused by cancer globally. One of the most typical diseases in people that can lead to gastric carcinoma is *H. pylori* infection. Most *H. pylori*-affected people will never acquire stomach cancer,

despite the fact that around fifty percent of the global population has been infected with the bacteria. Through particular virulence indicators, including *H. pylori*, *CagA*, VagA, and outer membrane protein types, a number of variables, including host-specific and external influences, contribute to the development of cancer of the stomach. It opens up networks of signals that promote cellular growth, making it necessary to diagnose infected people in a lab. Programmed cell death, tumor suppressor genes, and modified cell growth are some examples of epigenetic alterations that can take place. Associated variables like host genetics, food, external variables, and alterations in the microbiota all affect the risk of acquiring cancer of the stomach, especially virulence characteristics unique to each type of *H. pylori*.

Further investigations may focus on inactivating *CagA* and VacA as potential targets for treatment since they promote cell proliferation and trigger cancer of the stomach. With a greater comprehension of the molecular processes behind *H. pylori*-induced ichor and stomach tumorigenesis, it will be feasible to develop more effective treatments for stomach cancer.

REFERENCES

Alarcon-Millan, J., Martinez-Carrillo, D. N., Peralta-Zaragoza, O., & Fernandez-Tilapa, G. (2019). Regulation of GKN1 expression in gastric carcinogenesis: A problem to resolve (Review). *Int J Oncol*, *55*(3), 555-569. https://doi.org/10.3892/ijo.2019.4843

Albaker, W. I. (2011). Helicobacter pylori infection and its relationship to metabolic syndrome: is it a myth or fact? *Saudi J Gastroenterol*, *17*(3), 165-169. https://doi.org/10.4103/1319-3767.80377

Alipour, M. (2021). Molecular Mechanism of Helicobacter pylori-Induced Gastric Cancer. *J Gastrointest Cancer*, *52*(1), 23-30. https://doi.org/10.1007/s12029-020-00518-5

Amieva, M., & Peek, R. M., Jr. (2016). Pathobiology of Helicobacter pylori-Induced Gastric Cancer. *Gastroenterology*, *150*(1), 64-78. https://doi.org/10.1053/j.gastro.2015.09.004

Annibale, B., Capurso, G., Lahner, E., Passi, S., Ricci, R., Maggio, F., & Delle Fave, G. (2003). Concomitant alterations in intragastric pH and ascorbic acid concentration in patients with Helicobacter pylori gastritis and associated iron deficiency anaemia. *Gut*, *52*(4), 496-501. https://doi.org/10.1136/gut.52.4.496

Asenjo, L. M., & Gisbert, J. P. (2007). [Prevalence of Helicobacter pylori infection in gastric MALT lymphoma: a systematic review]. *Rev Esp Enferm Dig*, *99*(7), 398-404. https://doi.org/10.4321/s1130-01082007000700006 (Prevalencia de la infeccion por Helicobacter pylori en el linfoma MALT gastrico: una revision sistematica.)

Atherton, J. C., Cao, P., Peek, R. M., Jr., Tummuru, M. K., Blaser, M. J., & Cover, T. L. (1995). Mosaicism in vacuolating cytotoxin alleles of Helicobacter pylori. Association of specific vacA types with cytotoxin production and peptic ulceration. *J Biol Chem*, *270*(30), 17771-17777. https://doi.org/10.1074/jbc.270.30.17771

Atherton, J. C., Peek, R. M., Jr., Tham, K. T., Cover, T. L., & Blaser, M. J. (1997). Clinical and pathological importance of heterogeneity in vacA, the vacuolating cytotoxin gene of Helicobacter pylori. *Gastroenterology*, *112*(1), 92-99. https://doi.org/10.1016/s0016-5085(97)70223-3

Azab, S. F., & Esh, A. M. (2013). Serum hepcidin levels in Helicobacter pylori-infected children with iron-deficiency anemia: a case-control

study. *Ann Hematol*, *92*(11), 1477-1483. https://doi.org/10.1007/s00277-013-1813-2

B., M. D. (2019). Helicobacter pylori infection and peptic ulcers. *Medicine*, *47*(5), 292-300.

Bachir, M., Allem, R., Benejat, L., Tifrit, A., Medjekane, M., Drici, A. E., Megraud, F., & Douidi, K. T. (2018). Molecular detection of mutations involved in Helicobacter pylori antibiotic resistance in Algeria. *J Antimicrob Chemother*, *73*(8), 2034-2038. https://doi.org/10.1093/jac/dky167

Backert, S., & Tegtmeyer, N. (2010). the versatility of the Helicobacter pylori vacuolating cytotoxin vacA in signal transduction and molecular crosstalk. *Toxins (Basel)*, *2*(1), 69-92. https://doi.org/10.3390/toxins2010069

Backert, S., Tegtmeyer, N., & Fischer, W. (2015). Composition, structure and function of the Helicobacter pylori cag pathogenicity island encoded type IV secretion system. *Future Microbiol*, *10*(6), 955-965. https://doi.org/10.2217/fmb.15.32

Badimon, L., Casani, L., Camino-Lopez, S., Juan-Babot, O., & Borrell-Pages, M. (2019). GSK3beta inhibition and canonical Wnt signaling in mice hearts after myocardial ischemic damage. *PLoS One*, *14*(6), e0218098. https://doi.org/10.1371/journal.pone.0218098

Bagheri, N., Azadegan-Dehkordi, F., Rafieian-Kopaei, M., Rahimian, G., Asadi-Samani, M., & Shirzad, H. (2016). Clinical relevance of Helicobacter pylori virulence factors in Iranian patients with gastrointestinal diseases. *Microb Pathog*, *100*, 154-162. https://doi.org/10.1016/j.micpath.2016.09.016

Barker, N., Huch, M., Kujala, P., van de Wetering, M., Snippert, H. J., van Es, J. H., Sato, T., Stange, D. E., Begthel, H., van den Born, M., Danenberg, E., van den Brink, S., Korving, J., Abo, A., Peters, P. J., Wright, N., Poulsom, R., & Clevers, H. (2010). Lgr5(+ve) stem cells drive self-renewal in the stomach and build long-lived gastric units in vitro. *Cell Stem Cell*, *6*(1), 25-36. https://doi.org/10.1016/j.stem.2009.11.013

Basu, A. K. (2018). DNA Damage, Mutagenesis and Cancer. *Int J Mol Sci*, *19*(4). https://doi.org/10.3390/ijms19040970

Blot, W. J., Devesa, S. S., Kneller, R. W., & Fraumeni, J. F., Jr. (1991). Rising incidence of adenocarcinoma of the esophagus and gastric

cardia. *JAMA*, *265*(10), 1287-1289. https://www.ncbi.nlm.nih.gov/pubmed/1995976

Bowley, E., O'Gorman, D. B., & Gan, B. S. (2007). Beta-catenin signaling in fibroproliferative disease. *J Surg Res*, *138*(1), 141-150. https://doi.org/10.1016/j.jss.2006.07.026

Braga, L., Batista, M. H. R., de Azevedo, O. G. R., da Silva Costa, K. C., Gomes, A. D., Rocha, G. A., & Queiroz, D. M. M. (2019). oipA "on" status of Helicobacter pylori is associated with gastric cancer in North-Eastern Brazil. *BMC Cancer*, *19*(1), 48. https://doi.org/10.1186/s12885-018-5249-x

Bravo, D., Hoare, A., Soto, C., Valenzuela, M. A., & Quest, A. F. (2018). Helicobacter pylori in human health and disease: Mechanisms for local gastric and systemic effects. *World J Gastroenterol*, *24*(28), 3071-3089. https://doi.org/10.3748/wjg.v24.i28.3071

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*, *68*(6), 394-424. https://doi.org/10.3322/caac.21492

Brush, E. R. (2019). Host-microbe evolutionary conflict: investigating the host specificity of Helicobacter pylori adhesin HopQ via its engagement with primate CEACAM1 University of Oregon.

Buti, L., Spooner, E., Van der Veen, A. G., Rappuoli, R., Covacci, A., & Ploegh, H. L. (2011). Helicobacter pylori cytotoxin-associated gene A (CagA) subverts the apoptosis-stimulating protein of p53 (ASPP2) tumor suppressor pathway of the host. *Proc Natl Acad Sci U S A*, *108*(22), 9238-9243. https://doi.org/10.1073/pnas.1106200108

Cameron, A., Frirdich, E., Huynh, S., Parker, C. T., & Gaynor, E. C. (2012). Hyperosmotic stress response of Campylobacter jejuni. *J Bacteriol*, *194*(22), 6116-6130. https://doi.org/10.1128/JB.01409-12

Cancer Genome Atlas Research, N. (2014). Comprehensive molecular characterization of gastric adenocarcinoma. *Nature*, *513*(7517), 202-209. https://doi.org/10.1038/nature13480

Cassat, J. E., & Skaar, E. P. (2013). Iron in infection and immunity. *Cell Host Microbe*, *13*(5), 509-519. https://doi.org/10.1016/j.chom.2013.04.010

Choe, Y. H., Oh, Y. J., Lee, N. G., Imoto, I., Adachi, Y., Toyoda, N., & Gabazza, E. C. (2003). Lactoferrin sequestration and its contribution to iron-deficiency anemia in Helicobacter pylori-infected gastric

mucosa. *J Gastroenterol Hepatol*, *18*(8), 980-985. https://doi.org/10.1046/j.1440-1746.2003.03098.x

Colditz, G. A., Sellers, T. A., & Trapido, E. (2006). Epidemiology - identifying the causes and preventability of cancer? *Nat Rev Cancer*, *6*(1), 75-83. https://doi.org/10.1038/nrc1784

Conrad, M. E., & Schade, S. G. (1968). Ascorbic acid chelates in iron absorption: a role for hydrochloric acid and bile. *Gastroenterology*, *55*(1), 35-45. https://www.ncbi.nlm.nih.gov/pubmed/5663503

Correa, P. (1992). Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. *Cancer Res*, *52*(24), 6735-6740. https://www.ncbi.nlm.nih.gov/pubmed/1458460

Cover, T. L. (2016). Helicobacter pylori Diversity and Gastric Cancer Risk. *mBio*, *7*(1), e01869-01815. https://doi.org/10.1128/mBio.01869-15

Cristescu, R., Lee, J., Nebozhyn, M., Kim, K. M., Ting, J. C., Wong, S. S., Liu, J., Yue, Y. G., Wang, J., Yu, K., Ye, X. S., Do, I. G., Liu, S., Gong, L., Fu, J., Jin, J. G., Choi, M. G., Sohn, T. S., Lee, J. H., . . . Aggarwal, A. (2015). Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes. *Nat Med*, *21*(5), 449-456. https://doi.org/10.1038/nm.3850

de Martel, C., Ferlay, J., Franceschi, S., Vignat, J., Bray, F., Forman, D., & Plummer, M. (2012). Global burden of cancers attributable to infections in 2008: a review and synthetic analysis. *Lancet Oncol*, *13*(6), 607-615. https://doi.org/10.1016/S1470-2045(12)70137-7

Demir, M., Gokturk, H. S., Ozturk, N. A., Kulaksizoglu, M., Serin, E., & Yilmaz, U. (2008). Helicobacter pylori prevalence in diabetes mellitus patients with dyspeptic symptoms and its relationship to glycemic control and late complications. *Dig Dis Sci*, *53*(10), 2646-2649. https://doi.org/10.1007/s10620-007-0185-7

Diaz, P., Valenzuela Valderrama, M., Bravo, J., & Quest, A. F. G. (2018). Helicobacter pylori and Gastric Cancer: Adaptive Cellular Mechanisms Involved in Disease Progression. *Front Microbiol*, *9*, 5. https://doi.org/10.3389/fmicb.2018.00005

Diehl, J. A. (2002). Cycling to cancer with cyclin D1. *Cancer Biol Ther*, *1*(3), 226-231. https://doi.org/10.4161/cbt.72

El-Omar, E. M., Carrington, M., Chow, W. H., McColl, K. E., Bream, J. H., Young, H. A., Herrera, J., Lissowska, J., Yuan, C. C., Rothman, N., Lanyon, G., Martin, M., Fraumeni, J. F., Jr., & Rabkin, C. S. (2000).

Interleukin-1 polymorphisms associated with increased risk of gastric cancer. *Nature*, *404*(6776), 398-402. https://doi.org/10.1038/35006081

El-Omar, E. M., Rabkin, C. S., Gammon, M. D., Vaughan, T. L., Risch, H. A., Schoenberg, J. B., Stanford, J. L., Mayne, S. T., Goedert, J., Blot, W. J., Fraumeni, J. F., Jr., & Chow, W. H. (2003). Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. *Gastroenterology*, *124*(5), 1193-1201. https://doi.org/10.1016/s0016-5085(03)00157-4

Elinav, E., Nowarski, R., Thaiss, C. A., Hu, B., Jin, C., & Flavell, R. A. (2013). Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. *Nat Rev Cancer*, *13*(11), 759-771. https://doi.org/10.1038/nrc3611

Elzouki, A. N., Buhjab, S. I., Alkialani, A., Habel, S., & Sasco, A. J. (2012). Gastric cancer and Helicobacter pylori infection in the eastern Libya: a descriptive epidemiological study. *Arab J Gastroenterol*, *13*(2), 85-88. https://doi.org/10.1016/j.ajg.2012.06.002

Epplein, M., Nomura, A. M., Hankin, J. H., Blaser, M. J., Perez-Perez, G., Stemmermann, G. N., Wilkens, L. R., & Kolonel, L. N. (2008). Association of Helicobacter pylori infection and diet on the risk of gastric cancer: a case-control study in Hawaii. *Cancer Causes Control*, *19*(8), 869-877. https://doi.org/10.1007/s10552-008-9149-2

Farhi L., Y. A. (2017). Comparison of brain tumor MRI classification methods using probabilistic features. 13th IASTED International Conference on Biomedical Engineering,

Ferlay, J., Soerjomataram, I., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D. M., Forman, D., & Bray, F. (2015). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*, *136*(5), E359-386. https://doi.org/10.1002/ijc.29210

Figueiredo, C., Machado, J. C., Pharoah, P., Seruca, R., Sousa, S., Carvalho, R., Capelinha, A. F., Quint, W., Caldas, C., van Doorn, L. J., Carneiro, F., & Sobrinho-Simoes, M. (2002). Helicobacter pylori and interleukin 1 genotyping: an opportunity to identify high-risk individuals for gastric carcinoma. *J Natl Cancer Inst*, *94*(22), 1680-1687. https://doi.org/10.1093/jnci/94.22.1680

Fischer, W., Puls, J., Buhrdorf, R., Gebert, B., Odenbreit, S., & Haas, R. (2001). Systematic mutagenesis of the Helicobacter pylori cag

pathogenicity island: essential genes for CagA translocation in host cells and induction of interleukin-8. *Mol Microbiol*, *42*(5), 1337-1348. https://doi.org/10.1046/j.1365-2958.2001.02714.x

Fox, J. G., & Wang, T. C. (2007). Inflammation, atrophy, and gastric cancer. *J Clin Invest*, *117*(1), 60-69. https://doi.org/10.1172/JCI30111

Fuchs, C. S., & Mayer, R. J. (1995). Gastric carcinoma. *N Engl J Med*, *333*(1), 32-41. https://doi.org/10.1056/NEJM199507063330107

Gaddy, J. A., Radin, J. N., Loh, J. T., Zhang, F., Washington, M. K., Peek, R. M., Jr., Algood, H. M., & Cover, T. L. (2013). High dietary salt intake exacerbates Helicobacter pylori-induced gastric carcinogenesis. *Infect Immun*, *81*(6), 2258-2267. https://doi.org/10.1128/IAI.01271-12

Gao, C., Yuan, X., Jiang, Z., Gan, D., Ding, L., Sun, Y., Zhou, J., Xu, L., Liu, Y., & Wang, G. (2019). Regulation of AKT phosphorylation by GSK3beta and PTEN to control chemoresistance in breast cancer. *Breast Cancer Res Treat*, *176*(2), 291-301. https://doi.org/10.1007/s10549-019-05239-3

Gonda, T. A., Kim, Y. I., Salas, M. C., Gamble, M. V., Shibata, W., Muthupalani, S., Sohn, K. J., Abrams, J. A., Fox, J. G., Wang, T. C., & Tycko, B. (2012). Folic acid increases global DNA methylation and reduces inflammation to prevent Helicobacter-associated gastric cancer in mice. *Gastroenterology*, *142*(4), 824-833 e827. https://doi.org/10.1053/j.gastro.2011.12.058

Gonzalez, C. A., Jakszyn, P., Pera, G., Agudo, A., Bingham, S., Palli, D., Ferrari, P., Boeing, H., del Giudice, G., Plebani, M., Carneiro, F., Nesi, G., Berrino, F., Sacerdote, C., Tumino, R., Panico, S., Berglund, G., Siman, H., Nyren, O., . . . Riboli, E. (2006). Meat intake and risk of stomach and esophageal adenocarcinoma within the European Prospective Investigation Into Cancer and Nutrition (EPIC). *J Natl Cancer Inst*, *98*(5), 345-354. https://doi.org/10.1093/jnci/djj071

Gonzalez, C. A., Lujan-Barroso, L., Bueno-de-Mesquita, H. B., Jenab, M., Duell, E. J., Agudo, A., Tjonneland, A., Boutron-Ruault, M. C., Clavel-Chapelon, F., Touillaud, M., Teucher, B., Kaaks, R., Boeing, H., Steffen, A., Trichopoulou, A., Roukos, D., Karapetyan, T., Palli, D., Tagliabue, G., . . . Riboli, E. (2012). Fruit and vegetable intake and the risk of gastric adenocarcinoma: a reanalysis of the European Prospective Investigation into Cancer and Nutrition (EPIC-

EURGAST) study after a longer follow-up. *Int J Cancer*, *131*(12), 2910-2919. https://doi.org/10.1002/ijc.27565

Hardbower, D. M., Peek, R. M., Jr., & Wilson, K. T. (2014). At the Bench: Helicobacter pylori, dysregulated host responses, DNA damage, and gastric cancer. *J Leukoc Biol*, *96*(2), 201-212. https://doi.org/10.1189/jlb.4BT0214-099R

Hessey, S. J., Spencer, J., Wyatt, J. I., Sobala, G., Rathbone, B. J., Axon, A. T., & Dixon, M. F. (1990). Bacterial adhesion and disease activity in Helicobacter associated chronic gastritis. *Gut*, *31*(2), 134-138. https://doi.org/10.1136/gut.31.2.134

Howson, C. P., Hiyama, T., & Wynder, E. L. (1986). The decline in gastric cancer: epidemiology of an unplanned triumph. *Epidemiol Rev*, *8*, 1-27. https://doi.org/10.1093/oxfordjournals.epirev.a036288

Huang, J. Q., Zheng, G. F., Sumanac, K., Irvine, E. J., & Hunt, R. H. (2003). Meta-analysis of the relationship between cagA seropositivity and gastric cancer. *Gastroenterology*, *125*(6), 1636-1644. https://doi.org/10.1053/j.gastro.2003.08.033

Ismael, A. B., Mergani, A., Salim, A., Mostafa, S., & Alkafaween, I. (2018). Interferon-gamma receptor-1 gene promoter polymorphisms and susceptibility for brucellosis in Makkah region. *Afr Health Sci*, *18*(4), 1157-1165. https://doi.org/10.4314/ahs.v18i4.36

Jain, P., Luo, Z. Q., & Blanke, S. R. (2011). Helicobacter pylori vacuolating cytotoxin A (VacA) engages the mitochondrial fission machinery to induce host cell death. *Proc Natl Acad Sci U S A*, *108*(38), 16032-16037. https://doi.org/10.1073/pnas.1105175108

Jimenez-Soto, L. F., Kutter, S., Sewald, X., Ertl, C., Weiss, E., Kapp, U., Rohde, M., Pirch, T., Jung, K., Retta, S. F., Terradot, L., Fischer, W., & Haas, R. (2009). Helicobacter pylori type IV secretion apparatus exploits beta1 integrin in a novel RGD-independent manner. *PLoS Pathog*, *5*(12), e1000684. https://doi.org/10.1371/journal.ppat.1000684

Jones, K. R., Whitmire, J. M., & Merrell, D. S. (2010). A Tale of Two Toxins: Helicobacter Pylori CagA and VacA Modulate Host Pathways that Impact Disease. *Front Microbiol*, *1*, 115. https://doi.org/10.3389/fmicb.2010.00115

Jr., L. E. W. a. R. M. P. (2016). Helicobacter pylori , Cancer, and the Gastric Microbiota In *Advances in Experimental Medicine and Biology* (Vol. 908, pp. 393-408). Springer.

Kamada, T., Kurose, H., Yamanaka, Y., Manabe, N., Kusunoki, H., Shiotani, A., Inoue, K., Hata, J., Matsumoto, H., Akiyama, T., Hirai, T., Sadahira, Y., Haruma, K. (2012). Relationship between gastroesophageal junction adenocarcinoma and Helicobacter pylori infection in Japan. *Digestion, 85*, 256-260.

Kamangar, F., Dawsey, S. M., Blaser, M. J., Perez-Perez, G. I., Pietinen, P., Newschaffer, C. J., Abnet, C. C., Albanes, D., Virtamo, J., & Taylor, P. R. (2006). Opposing risks of gastric cardia and noncardia gastric adenocarcinomas associated with Helicobacter pylori seropositivity. *J Natl Cancer Inst*, *98*(20), 1445-1452. https://doi.org/10.1093/jnci/djj393

Kaplan-Turkoz, B., Jimenez-Soto, L.F., Dian, C., Ertl, C., Remaut, H., Louche, A., Tosi, T., Haas, R., Terradot, L. (2012). Structural insights into Helicobacter pylori oncoprotein CagA interaction with beta1 integrin. *Proc. Natl. Acad. Sci 109*, 14640-14645.

Kay, J., Thadhani, E., Samson, L., & Engelward, B. (2019). Inflammation-induced DNA damage, mutations and cancer. *DNA Repair (Amst)*, *83*, 102673. https://doi.org/10.1016/j.dnarep.2019.102673

Kayali, S., Manfredi, M., Gaiani, F., Bianchi, L., Bizzarri, B., Leandro, G., Di Mario, F., & De' Angelis, G. L. (2018). Helicobacter pylori, transmission routes and recurrence of infection: state of the art. *Acta Biomed*, *89*(8-S), 72-76. https://doi.org/10.23750/abm.v89i8-S.7947

Khan, M. A., Howden, C.W. (2019). Helicobacter pylori and related diseases, in Essential Medical Disorders of the Stomach and Small Intestine. *Springer*, 141-154.

Kim, H. J., Lim, S. Y., Lee, J. S., Park, S., Shin, A., Choi, B. Y., Shimazu, T., Inoue, M., Tsugane, S., & Kim, J. (2010). Fresh and pickled vegetable consumption and gastric cancer in Japanese and Korean populations: a meta-analysis of observational studies. *Cancer Sci*, *101*(2), 508-516. https://doi.org/10.1111/j.1349-7006.2009.01374.x

Kim, M. K., Sasaki, S., Sasazuki, S., Tsugane, S., & Japan Public Health Center-based Prospective Study, G. (2004). Prospective study of three major dietary patterns and risk of gastric cancer in Japan. *Int J Cancer*, *110*(3), 435-442. https://doi.org/10.1002/ijc.20132

Koniger, V., Holsten, L., Harrison, U., Busch, B., Loell, E., Zhao, Q., Bonsor, D. A., Roth, A., Kengmo-Tchoupa, A., Smith, S. I., Mueller, S., Sundberg, E. J., Zimmermann, W., Fischer, W., Hauck, C. R., & Haas, R. (2016). Helicobacter pylori exploits human CEACAMs via

HopQ for adherence and translocation of CagA. *Nat Microbiol*, *2*, 16188. https://doi.org/10.1038/nmicrobiol.2016.188

Kusters, J. G., van Vliet, A. H., & Kuipers, E. J. (2006). Pathogenesis of Helicobacter pylori infection. *Clin Microbiol Rev*, *19*(3), 449-490. https://doi.org/10.1128/CMR.00054-05

Kwok, T., Zabler, D., Urman, S., Rohde, M., Hartig, R., Wessler, S., Misselwitz, R., Berger, J., Sewald, N., Konig, W., & Backert, S. (2007). Helicobacter exploits integrin for type IV secretion and kinase activation. *Nature*, *449*(7164), 862-866. https://doi.org/10.1038/nature06187

Lamb, A., Yang, X. D., Tsang, Y. H., Li, J. D., Higashi, H., Hatakeyama, M., Peek, R. M., Blanke, S. R., & Chen, L. F. (2009). Helicobacter pylori CagA activates NF-kappaB by targeting TAK1 for TRAF6-mediated Lys 63 ubiquitination. *EMBO Rep*, *10*(11), 1242-1249. https://doi.org/10.1038/embor.2009.210

Lang, C. M. R., Chan, C. K., Veltri, A., & Lien, W. H. (2019). Wnt Signaling Pathways in Keratinocyte Carcinomas. *Cancers (Basel)*, *11*(9). https://doi.org/10.3390/cancers11091216

Lee, K. S., Kalantzis, A., Jackson, C. B., O'Connor, L., Murata-Kamiya, N., Hatakeyama, M., Judd, L. M., Giraud, A. S., & Menheniott, T. R. (2012). Helicobacter pylori CagA triggers expression of the bactericidal lectin REG3gamma via gastric STAT3 activation. *PLoS One*, *7*(2), e30786. https://doi.org/10.1371/journal.pone.0030786

Lee, S. A., Kang, D., Shim, K. N., Choe, J. W., Hong, W. S., & Choi, H. (2003). Effect of diet and Helicobacter pylori infection to the risk of early gastric cancer. *J Epidemiol*, *13*(3), 162-168. https://doi.org/10.2188/jea.13.162

Li, M., Chen, T., Wang, R., Luo, J. Y., He, J. J., Ye, R. S., Xie, M. Y., Xi, Q. Y., Jiang, Q. Y., Sun, J. J., & Zhang, Y. L. (2019). Plant MIR156 regulates intestinal growth in mammals by targeting the Wnt/beta-catenin pathway. *Am J Physiol Cell Physiol*, *317*(3), C434-C448. https://doi.org/10.1152/ajpcell.00030.2019

Li, Q., Zhang, J., Zhou, Y., & Qiao, L. (2012). Obesity and gastric cancer. *Front Biosci (Landmark Ed)*, *17*(7), 2383-2390. https://doi.org/10.2741/4059

Linz, B., Balloux, F., Moodley, Y., Manica, A., Liu, H., Roumagnac, P., Falush, D., Stamer, C., Prugnolle, F., van der Merwe, S. W., Yamaoka, Y., Graham, D. Y., Perez-Trallero, E., Wadstrom, T.,

Suerbaum, S., & Achtman, M. (2007). An African origin for the intimate association between humans and Helicobacter pylori. *Nature*, *445*(7130), 915-918. https://doi.org/10.1038/nature05562

Loh, J. T., Friedman, D. B., Piazuelo, M. B., Bravo, L. E., Wilson, K. T., Peek, R. M., Jr., Correa, P., & Cover, T. L. (2012). Analysis of Helicobacter pylori cagA promoter elements required for salt-induced upregulation of CagA expression. *Infect Immun*, *80*(9), 3094-3106. https://doi.org/10.1128/IAI.00232-12

Loh, J. T., Torres, V. J., & Cover, T. L. (2007). Regulation of Helicobacter pylori cagA expression in response to salt. *Cancer Res*, *67*(10), 4709-4715. https://doi.org/10.1158/0008-5472.CAN-06-4746

Ma, J. L., Zhang, L., Brown, L. M., Li, J. Y., Shen, L., Pan, K. F., Liu, W. D., Hu, Y., Han, Z. X., Crystal-Mansour, S., Pee, D., Blot, W. J., Fraumeni, J. F., Jr., You, W. C., & Gail, M. H. (2012). Fifteen-year effects of Helicobacter pylori, garlic, and vitamin treatments on gastric cancer incidence and mortality. *J Natl Cancer Inst*, *104*(6), 488-492. https://doi.org/10.1093/jnci/djs003

Mager, D. L. (2006). Bacteria and cancer: cause, coincidence or cure? A review. *J Transl Med*, *4*, 14. https://doi.org/10.1186/1479-5876-4-14

Manning, B. D., & Toker, A. (2017). AKT/PKB Signaling: Navigating the Network. *Cell*, *169*(3), 381-405. https://doi.org/10.1016/j.cell.2017.04.001

Marie, M. A. (2008). Seroprevalence of Helicobacter pylori Infection in Large Series of Patients in an Urban Area of Saudi Arabia. *Korean J Gastroenterol*, *52*(4), 226-229. https://www.ncbi.nlm.nih.gov/pubmed/19077524

Marshall, B. J., & Warren, J. R. (1984). Unidentified curved bacilli in the stomach of patients with gastritis and peptic ulceration. *Lancet*, *1*(8390), 1311-1315. https://doi.org/10.1016/s0140-6736(84)91816-6

Matsunaga, S., Nishiumi, S., Tagawa, R., & Yoshida, M. (2018). Alterations in metabolic pathways in gastric epithelial cells infected with Helicobacter pylori. *Microb Pathog*, *124*, 122-129. https://doi.org/10.1016/j.micpath.2018.08.033

Miehlke, S., Kirsch, C., Agha-Amiri, K., Gunther, T., Lehn, N., Malfertheiner, P., Stolte, M., Ehninger, G., & Bayerdorffer, E. (2000). The Helicobacter pylori vacA s1, m1 genotype and cagA is associated with gastric carcinoma in Germany. *Int J Cancer*, *87*(3), 322-327. https://www.ncbi.nlm.nih.gov/pubmed/10897035

Mimuro, H., Suzuki, T., Tanaka, J., Asahi, M., Haas, R., Sasakawa, C. (2002). Grb2 is a key mediator of Helicobacter pylori CagA protein activities. *Mol. Cell*, *10*, 745-755.

Mohammadian, T., & Ganji, L. (2019). The Diagnostic Tests for Detection of Helicobacter pylori Infection. *Monoclon Antib Immunodiagn Immunother*, *38*(1), 1-7. https://doi.org/10.1089/mab.2018.0032

Moore, P. S., & Chang, Y. (2010). Why do viruses cause cancer? Highlights of the first century of human tumour virology. *Nat Rev Cancer*, *10*(12), 878-889. https://doi.org/10.1038/nrc2961

Mueller, D., Tegtmeyer, N., Brandt, S., Yamaoka, Y., De Poire, E., Sgouras, D., Wessler, S., Torres, J., Smolka, A., & Backert, S. (2012). c-Src and c-Abl kinases control hierarchic phosphorylation and function of the CagA effector protein in Western and East Asian Helicobacter pylori strains. *J Clin Invest*, *122*(4), 1553-1566. https://doi.org/10.1172/JCI61143

Murata-Kamiya, N., Kurashima, Y., Teishikata, Y., Yamahashi, Y., Saito, Y., Higashi, H., Aburatani, H., Akiyama, T., Peek, R. M., Jr., Azuma, T., & Hatakeyama, M. (2007). Helicobacter pylori CagA interacts with E-cadherin and deregulates the beta-catenin signal that promotes intestinal transdifferentiation in gastric epithelial cells. *Oncogene*, *26*(32), 4617-4626. https://doi.org/10.1038/sj.onc.1210251

Nakayama, M., Hisatsune, J., Yamasaki, E., Isomoto, H., Kurazono, H., Hatakeyama, M., Azuma, T., Yamaoka, Y., Yahiro, K., Moss, J., & Hirayama, T. (2009). Helicobacter pylori VacA-induced inhibition of GSK3 through the PI3K/Akt signaling pathway. *J Biol Chem*, *284*(3), 1612-1619. https://doi.org/10.1074/jbc.M806981200

Nezami, B. G., Jani, M., Alouani, D., Rhoads, D. D., & Sadri, N. (2019). Helicobacter pylori Mutations Detected by Next-Generation Sequencing in Formalin-Fixed, Paraffin-Embedded Gastric Biopsy Specimens Are Associated with Treatment Failure. *J Clin Microbiol*, *57*(7). https://doi.org/10.1128/JCM.01834-18

Noto, J. M., Gaddy, J. A., Lee, J. Y., Piazuelo, M. B., Friedman, D. B., Colvin, D. C., Romero-Gallo, J., Suarez, G., Loh, J., Slaughter, J. C., Tan, S., Morgan, D. R., Wilson, K. T., Bravo, L. E., Correa, P., Cover, T. L., Amieva, M. R., & Peek, R. M., Jr. (2013). Iron deficiency accelerates Helicobacter pylori-induced carcinogenesis in rodents and humans. *J Clin Invest*, *123*(1), 479-492. https://doi.org/10.1172/JCI64373

Noto, J. M., & Peek, R. M., Jr. (2012). Helicobacter pylori: an overview. *Methods Mol Biol*, *921*, 7-10. https://doi.org/10.1007/978-1-62703-005-2_2

Odenbreit, S., Puls, J., Sedlmaier, B., Gerland, E., Fischer, W., & Haas, R. (2000). Translocation of Helicobacter pylori CagA into gastric epithelial cells by type IV secretion. *Science*, *287*(5457), 1497-1500. https://doi.org/10.1126/science.287.5457.1497

Oleastro, M., Cordeiro, R., Ferrand, J., Nunes, B., Lehours, P., Carvalho-Oliveira, I., Mendes, A. I., Penque, D., Monteiro, L., Megraud, F., & Menard, A. (2008). Evaluation of the clinical significance of homB, a novel candidate marker of Helicobacter pylori strains associated with peptic ulcer disease. *J Infect Dis*, *198*(9), 1379-1387. https://doi.org/10.1086/592166

Oleastro, M., & Menard, A. (2013). The Role of Helicobacter pylori Outer Membrane Proteins in Adherence and Pathogenesis. *Biology (Basel)*, *2*(3), 1110-1134. https://doi.org/10.3390/biology2031110

Owen, K. L., Brockwell, N. K., & Parker, B. S. (2019). JAK-STAT Signaling: A Double-Edged Sword of Immune Regulation and Cancer Progression. *Cancers (Basel)*, *11*(12). https://doi.org/10.3390/cancers11122002

Palframan, S. L., Kwok, T., & Gabriel, K. (2012). Vacuolating cytotoxin A (VacA), a key toxin for Helicobacter pylori pathogenesis. *Front Cell Infect Microbiol*, *2*, 92. https://doi.org/10.3389/fcimb.2012.00092

Parkin, D. M., Bray, F., Ferlay, J., & Pisani, P. (2005). Global cancer statistics, 2002. *CA Cancer J Clin*, *55*(2), 74-108. https://doi.org/10.3322/canjclin.55.2.74

Parsonnet, J., Friedman, G. D., Orentreich, N., & Vogelman, H. (1997). Risk for gastric cancer in people with CagA positive or CagA negative Helicobacter pylori infection. *Gut*, *40*(3), 297-301. https://doi.org/10.1136/gut.40.3.297

Peng, Y., & Croce, C. M. (2016). The role of MicroRNAs in human cancer. *Signal Transduct Target Ther*, *1*, 15004. https://doi.org/10.1038/sigtrans.2015.4

Pera, M., Cameron, A. J., Trastek, V. F., Carpenter, H. A., & Zinsmeister, A. R. (1993). Increasing incidence of adenocarcinoma of the esophagus and esophagogastric junction. *Gastroenterology*, *104*(2), 510-513. https://doi.org/10.1016/0016-5085(93)90420-h

Polk, D. B., & Peek, R. M., Jr. (2010). Helicobacter pylori: gastric cancer and beyond. *Nat Rev Cancer*, *10*(6), 403-414. https://doi.org/10.1038/nrc2857

Posselt, G., Backert, S., & Wessler, S. (2013). The functional interplay of Helicobacter pylori factors with gastric epithelial cells induces a multi-step process in pathogenesis. *Cell Commun Signal*, *11*, 77. https://doi.org/10.1186/1478-811X-11-77

Queiroz, D. M., Harris, P. R., Sanderson, I. R., Windle, H. J., Walker, M. M., Rocha, A. M., Rocha, G. A., Carvalho, S. D., Bittencourt, P. F., de Castro, L. P., Villagran, A., Serrano, C., Kelleher, D., & Crabtree, J. E. (2013). Iron status and Helicobacter pylori infection in symptomatic children: an international multi-centered study. *PLoS One*, *8*(7), e68833. https://doi.org/10.1371/journal.pone.0068833

Queiroz, D. M., Rocha, A. M., & Crabtree, J. E. (2013). Unintended consequences of Helicobacter pylori infection in children in developing countries: iron deficiency, diarrhea, and growth retardation. *Gut Microbes*, *4*(6), 494-504. https://doi.org/10.4161/gmic.26277

Raju, D., Hussey, S., Ang, M., Terebiznik, M. R., Sibony, M., Galindo-Mata, E., Gupta, V., Blanke, S. R., Delgado, A., Romero-Gallo, J., Ramjeet, M. S., Mascarenhas, H., Peek, R. M., Correa, P., Streutker, C., Hold, G., Kunstmann, E., Yoshimori, T., Silverberg, M. S., . . . Jones, N. L. (2012). Vacuolating cytotoxin and variants in Atg16L1 that disrupt autophagy promote Helicobacter pylori infection in humans. *Gastroenterology*, *142*(5), 1160-1171. https://doi.org/10.1053/j.gastro.2012.01.043

Rassow, J., & Meinecke, M. (2012). Helicobacter pylori VacA: a new perspective on an invasive chloride channel. *Microbes Infect*, *14*(12), 1026-1033. https://doi.org/10.1016/j.micinf.2012.07.002

Raza, Y., Ahmed, A., Khan, A., Chishti, A. A., Akhter, S. S., Mubarak, M., Bernstein, C., Zaitlin, B., & Kazmi, S. U. (2020). Helicobacter pylori severely reduces expression of DNA repair proteins PMS2 and ERCC1 in gastritis and gastric cancer. *DNA Repair (Amst)*, *89*, 102836. https://doi.org/10.1016/j.dnarep.2020.102836

Ren, J. S., Kamangar, F., Forman, D., & Islami, F. (2012). Pickled food and risk of gastric cancer--a systematic review and meta-analysis of English and Chinese literature. *Cancer Epidemiol Biomarkers Prev*, *21*(6), 905-915. https://doi.org/10.1158/1055-9965.EPI-12-0202

Rhead, J. L., Letley, D. P., Mohammadi, M., Hussein, N., Mohagheghi, M. A., Eshagh Hosseini, M., & Atherton, J. C. (2007). A new Helicobacter pylori vacuolating cytotoxin determinant, the intermediate region, is associated with gastric cancer. *Gastroenterology*, *133*(3), 926-936. https://doi.org/10.1053/j.gastro.2007.06.056

Ruch, T. R., & Engel, J. N. (2017). Targeting the Mucosal Barrier: How Pathogens Modulate the Cellular Polarity Network. *Cold Spring Harb Perspect Biol*, *9*(6). https://doi.org/10.1101/cshperspect.a027953

Schwarz, P. K., J.A. Strnad, P. et al. (2012). Hepcidin is localised in gastric parietal cells, regulates acid secretion and is induced by Helicobacter pylori infection. *Gut, 61*, 193-201.

Senkovich, O., Ceaser, S., McGee, D. J., & Testerman, T. L. (2010). Unique host iron utilization mechanisms of Helicobacter pylori revealed with iron-deficient chemically defined media. *Infect Immun*, *78*(5), 1841-1849. https://doi.org/10.1128/IAI.01258-09

Sgouras, D. N., Trang, T. T., & Yamaoka, Y. (2015). Pathogenesis of Helicobacter pylori Infection. *Helicobacter, 20 Suppl 1*(0 1), 8-16. https://doi.org/10.1111/hel.12251

Shaffer, C. L., Gaddy, J. A., Loh, J. T., Johnson, E. M., Hill, S., Hennig, E. E., McClain, M. S., McDonald, W. H., & Cover, T. L. (2011). Helicobacter pylori exploits a unique repertoire of type IV secretion system components for pilus assembly at the bacteria-host cell interface. *PLoS Pathog*, *7*(9), e1002237. https://doi.org/10.1371/journal.ppat.1002237

Shen, C., Zhao, C. Y., Zhang, R., & Qiao, L. (2012). Obesity-related hepatocellular carcinoma: roles of risk factors altered in obesity. *Front Biosci (Landmark Ed)*, *17*(6), 2356-2370. https://doi.org/10.2741/4057

Shikata, K., Kiyohara, Y., Kubo, M., Yonemoto, K., Ninomiya, T., Shirota, T., Tanizaki, Y., Doi, Y., Tanaka, K., Oishi, Y., Matsumoto, T., & Iida, M. (2006). A prospective study of dietary salt intake and gastric cancer incidence in a defined Japanese population: the Hisayama study. *Int J Cancer*, *119*(1), 196-201. https://doi.org/10.1002/ijc.21822

Singh, S., Mishra, A., Mohanbhai, S. J., Tiwari, V., Chaturvedi, R. K., Khurana, S., & Shukla, S. (2018). Axin-2 knockdown promote mitochondrial biogenesis and dopaminergic neurogenesis by

regulating Wnt/beta-catenin signaling in rat model of Parkinson's disease. *Free Radic Biol Med*, *129*, 73-87. https://doi.org/10.1016/j.freeradbiomed.2018.08.033

Soto, D., Song, C., & McLaughlin-Drubin, M. E. (2017). Epigenetic Alterations in Human Papillomavirus-Associated Cancers. *Viruses*, *9*(9). https://doi.org/10.3390/v9090248

Talebi Bezmin Abadi, A., Rafiei, A., Ajami, A., Hosseini, V., Taghvaei, T., Jones, K. R., & Merrell, D. S. (2011). Helicobacter pylori homB, but not cagA, is associated with gastric cancer in Iran. *J Clin Microbiol*, *49*(9), 3191-3197. https://doi.org/10.1128/JCM.00947-11

Tan, S., Noto, J. M., Romero-Gallo, J., Peek, R. M., Jr., & Amieva, M. R. (2011). Helicobacter pylori perturbs iron trafficking in the epithelium to grow on the cell surface. *PLoS Pathog*, *7*(5), e1002050. https://doi.org/10.1371/journal.ppat.1002050

Tilg, H. (2012). Diet and intestinal immunity. *N Engl J Med*, *366*(2), 181-183. https://doi.org/10.1056/NEJMcibr1113158

Tomasetti, C., Li, L., & Vogelstein, B. (2017). Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. *Science*, *355*(6331), 1330-1334. https://doi.org/10.1126/science.aaf9011

Tsang, Y. H., Lamb, A., Romero-Gallo, J., Huang, B., Ito, K., Peek, R. M., Jr., Ito, Y., & Chen, L. F. (2010). Helicobacter pylori CagA targets gastric tumor suppressor RUNX3 for proteasome-mediated degradation. *Oncogene*, *29*(41), 5643-5650. https://doi.org/10.1038/onc.2010.304

Tsugane, S. (2005). Salt, salted food intake, and risk of gastric cancer: epidemiologic evidence. *Cancer Sci*, *96*(1), 1-6. https://doi.org/10.1111/j.1349-7006.2005.00006.x

Tsugane, S., & Sasazuki, S. (2007). Diet and the risk of gastric cancer: review of epidemiological evidence. *Gastric Cancer*, *10*(2), 75-83. https://doi.org/10.1007/s10120-007-0420-0

Tsugawa, H., Suzuki, H., Saya, H., Hatakeyama, M., Hirayama, T., Hirata, K., Nagano, O., Matsuzaki, J., & Hibi, T. (2012). Reactive oxygen species-induced autophagic degradation of Helicobacter pylori CagA is specifically suppressed in cancer stem-like cells. *Cell Host Microbe*, *12*(6), 764-777. https://doi.org/10.1016/j.chom.2012.10.014

Uehara, T. (2013). H. pylori infection is associated with DNA damage of Lgr5-positive epithelial stem cells in the stomach of patients with gastric cancer. *Dig Dis Sci*, *58*(1), 140-149.

Vallee, A., & Lecarpentier, Y. (2016). Alzheimer Disease: Crosstalk between the Canonical Wnt/Beta-Catenin Pathway and PPARs Alpha and Gamma. *Front Neurosci*, *10*, 459. https://doi.org/10.3389/fnins.2016.00459

Velayudhan, J., Hughes, N. J., McColm, A. A., Bagshaw, J., Clayton, C. L., Andrews, S. C., & Kelly, D. J. (2000). Iron acquisition and virulence in Helicobacter pylori: a major role for FeoB, a high-affinity ferrous iron transporter. *Mol Microbiol*, *37*(2), 274-286. https://doi.org/10.1046/j.1365-2958.2000.01987.x

Vendramini-Costa, D. B., & Carvalho, J. E. (2012). Molecular link mechanisms between inflammation and cancer. *Curr Pharm Des*, *18*(26), 3831-3852. https://doi.org/10.2174/138161212802083707

Vogelmann, R., & Amieva, M. R. (2007). The role of bacterial pathogens in cancer. *Curr Opin Microbiol*, *10*(1), 76-81. https://doi.org/10.1016/j.mib.2006.12.004

Wang, F., Meng, W., Wang, B., & Qiao, L. (2014). Helicobacter pylori-induced gastric inflammation and gastric cancer. *Cancer Lett*, *345*(2), 196-202. https://doi.org/10.1016/j.canlet.2013.08.016

Wang, F., Wang, B., Qiao, L. (2012). Association between obesity and gallbladder cancer. *Front Biosci.*, *17*, 2550-2558.

Wroblewski, L. E., & Peek, R. M., Jr. (2013). Helicobacter pylori in gastric carcinogenesis: mechanisms. *Gastroenterol Clin North Am*, *42*(2), 285-298. https://doi.org/10.1016/j.gtc.2013.01.006

Wroblewski, L. E., Peek, R. M., Jr., & Wilson, K. T. (2010). Helicobacter pylori and gastric cancer: factors that modulate disease risk. *Clin Microbiol Rev*, *23*(4), 713-739. https://doi.org/10.1128/CMR.00011-10

Wundisch, T., Dieckhoff, P., Greene, B., Thiede, C., Wilhelm, C., Stolte, M., & Neubauer, A. (2012). Second cancers and residual disease in patients treated for gastric mucosa-associated lymphoid tissue lymphoma by Helicobacter pylori eradication and followed for 10 years. *Gastroenterology*, *143*(4), 936-942; quiz e913-934. https://doi.org/10.1053/j.gastro.2012.06.035

Xia, R., Zhang, B., Wang, X., Jia, Q. . (2019). Pathogenic interactions between Helicobacter pylori adhesion protein HopQ and human cell surface adhesion molecules CEACAMs in gastric epithelial cells. *Iran J Basic Med Sci*, *22*(7), 710-715.

Xin, P., Xu, X., Deng, C., Liu, S., Wang, Y., Zhou, X., Ma, H., Wei, D., & Sun, S. (2020). The role of JAK/STAT signaling pathway and its inhibitors in diseases. *Int Immunopharmacol*, *80*, 106210. https://doi.org/10.1016/j.intimp.2020.106210

Xu, X., Liu, Z., Fang, M., Yu, H., Liang, X., Li, X., Liu, X., Chen, C., & Jia, J. (2012). Helicobacter pylori CagA induces ornithine decarboxylase upregulation via Src/MEK/ERK/c-Myc pathway: implication for progression of gastric diseases. *Exp Biol Med (Maywood)*, *237*(4), 435-441. https://doi.org/10.1258/ebm.2011.011199

Yamanouchi, J., Azuma, T., Yakushijin, Y., Hato, T., & Yasukawa, M. (2014). Dramatic and prompt efficacy of Helicobacter pylori eradication in the treatment of severe refractory iron deficiency anemia in adults. *Ann Hematol*, *93*(10), 1779-1780. https://doi.org/10.1007/s00277-014-2052-x

Yudushkin, I. (2019). Getting the Akt Together: Guiding Intracellular Akt Activity by PI3K. *Biomolecules*, *9*(2). https://doi.org/10.3390/biom9020067

Zhang, P., Jiang, G., Gao, J., Li, L., Du, J., & Jiao, X. (2013). SAHA down-regulates the expression of indoleamine 2,3-dioxygenase via inhibition of the JAK/STAT1 signaling pathway in gallbladder carcinoma cells. *Oncol Rep*, *29*(1), 269-275. https://doi.org/10.3892/or.2012.2073

Zullo, A., Hassan, C., Cristofari, F., Andriani, A., De Francesco, V., Ierardi, E., Tomao, S., Stolte, M., Morini, S., & Vaira, D. (2010). Effects of Helicobacter pylori eradication on early stage gastric mucosa-associated lymphoid tissue lymphoma. *Clin Gastroenterol Hepatol*, *8*(2), 105-110. https://doi.org/10.1016/j.cgh.2009.07.017

CHAPTER 2

THE PROTECTIVE EFFECTS OF CURCUMIN AND RESVERATROL ON KIDNEY TISSUE AGAINST CADMIUM-INDUCED OXIDATIVE STRESS IN RATS

Assoc. Prof. Dr. Suat ÇAKINA[1]
Assoc. Prof. Dr. Latife Ceyda İRKİN[2]
Asst. Prof. Şamil ÖZTÜRK[3]

[1] Canakkale Onsekiz Mart University, Health Service Vocational College, Canakkale, Turkey. suatcakina@comu.edu.tr, Orcid ID: 0000-0002-3990-7641
[2] Canakkale Onsekiz Mart University, Canakkale Faculty of Applied Sciences, Department of Fisheries Technology, Canakkale, Turkey . latifeirkin@gmail.com, Orcid ID: 0000-0001-6603-8413
[3] Canakkale Onsekiz Mart University, Health Service Vocational College, Canakkale, Turkey. samilozturk16@hotmail.com, Orcid ID: 0000-0002-9435-8139

1. INTRODUCTION

Cadmium (Cd) is known to cause oxidative stress and tissue damage. Exposure sources for living things are water, air, and soil. The sources of inhalation exposure are industrial activities, the burning of fossil fuels, and smoking.(Patrick, 2003; Rani, Kumar, Lal, & Pant, 2014; Yan & Allen, 2021) Cd is highly accumulated in the kidney, liver, pancreas, and lung. Cd indirectly produces superoxide, hydroxyl and nitric oxide radicals. This metal displaces iron and copper in proteins in the cytoplasm and membrane, leading to free radical formation. The free and weakly bound copper and iron ion levels increase for the Fenton reaction. Copper causes oxidative stress leading to pathological disorders in the liver, kidney and brain. Lipid peroxidation is the primary mechanism in Cd poisoning resulting from oxidative stress. Lipid peroxidation is a chain reaction. Free radicals damage the cell membrane and disrupt its structure as a result of lipid peroxidation.(Gong et al., 2021; Ingawale, Mandlik, & Naik, 2014; Jomova & Valko, 2011; Wiwanitkit, 2008) The mechanisms of acute poisoning with Cd include decreased glutathione, formation of superoxide ions. Cd-mediated augmented free oxygen groups cause lipid peroxidation and subsequent DNA destruction. Cd is not rapidly excreted by the kidneys, it accumulates and causes kidney damage. It also increases the tendency of kidney stone formation. There is a defense mechanism called antioxidant to prevent the harmful effects of ROS.(Jie Liu et al., 2008; J. Liu, Qu, & Kadiiska, 2009; Wang et al., 2019; Wu et al., 2016)

Curcumin is obtained from turmeric (Indian saffron), which is a yellow color spice. Curcumin has anti-inflammatory, antioxidant, anticarcinogenic, antidiabetic, antiviral and neuroprotective effects. It facilitates the removal of many reactive oxygen radicals, especially superoxide anions. It has also been reported that it protects cellular macromolecules by scavenging ROS against oxidative damage and inhibiting lipid peroxidation.(Kotha & Luthria, 2019; Naik, Thakare, & Patil, 2011; Zia, Farkhondeh, Pourbagher-Shahri, & Samarghandian, 2021) It has also been reported that curcumin administration decreased glutathione (GSH) levels in Cd-induced nephrotoxicity in rats.(Tarasub, Tarasub, & Devakul Na Ayutthaya, 2011)

Resveratrol has been described for its effect as a powerful antioxidant. Resveratrol prevents the formation of free radicals. Resveratrol is one of the most researched polyphenols for its ability to scavenge free radicals. Its antioxidant activity is attributed to the ribonucleotide, its

reductase inhibition ability, and the cyclooxygenase transcription ability in DNA polymerase activity. Scavenges free radicals, prevents DNA damage and LDL oxidation by inhibiting lipid peroxidation caused by these free radicals. Resveratrol plays a regulatory role in inflammatory events, atherosclerosis, and carcinogenesis. In addition, antioxidant, anticyclooxygenase, lipid, and lipoprotein metabolism-regulating effects of resveratrol have also been demonstrated.(Galiniak, Aebisher, & Bartusik-Aebisher, 2019; Malaguarnera, 2019; Shaito et al., 2020) Cirmi et al. reported that oxidative stress increased in Cd-exposed mice and that the levels of antioxidant enzymes increased significantly when Curcumin, Resveratrol and Bergamot Juice were administered to mice alone or in combination.(Cirmi et al., 2021)

In recent years, the effects of antioxidant products have been investigated by genetic, biochemical and histopathologic methods to prevent the damage caused by Cd exposure. In these studies, some results have been obtained by using genetic, biochemical and histopathological methods. In recent years, current studies include the research and development of new drugs with antioxidant properties against Cd toxicity. We aimed to determine the effects of Curcumin and Resveratrol against Cd-induced oxidative stress in rat kidney tissue.

2. MATERIALS AND METHODS

2.1. Ethical Statement

Study procedures were conducted within the framework of guidelines approved by the local ethics committee for animal experiments at Çanakkale Onsekiz Mart University Faculty of Medicine (2021/02-07; 05.03.2021).

2.2. Study design and animals

This work was supported by Çanakkale Onsekiz Mart University The Scientific Research Coordination Unit (Project number: THD-2021-3626). Female Wistar rats weighing (200±25) g were housed in clean plastic cages under standard temperature and humidity conditions. The animals were fed on a standard laboratory pellet diet and sterile water. Inclusion criteria in this study are (a) healthy rats and no abnormalities, (b) four-month-old-female, (c) weight 250-300 grams. Exclusion criteria are, (a) disability or disorder rats, (b) the dead rats after treatment.

There were randomized design into five groups as follows (six rats in each group):

- Group 1: control
- Group 2: CdCl2 (1 mg/kg, I.P. (Dkhil et al., 2020)) for 10 days
- Group 3: Curcumin (200 mg/kg/day gavage) for 4 weeks(Takhtfooladi & Takhtfooladi, 2019)
- Group 4: CdCl2 (1 mg/kg, I.P.) 10 days + Curcumin (200 mg/kg/day gavage) for 4 weeks (from the day of Cd administration)
- Group 5: Resveratrol (10 mg/kg/day gavage) for 4 weeks(Grujić-Milanović et al., 2022)
- Group 6: CdCl2 (1 mg/kg, I.P.) 10 days + Resveratrol (10 mg/kg/day gavage) for 4 weeks (from the day of Cd administration).

The experimental and sacrificial procedures of our study were performed under ketamine/xylazine anesthesia.(Cosar et al., 2012) No animal died due to drug treatment.

2.3. Spectrophotometric Analysis

The kidney was washed in ice-cold 1.15% KCl and homogenized. It was then centrifuged at 14,000 rpm for 30 minutes and experiments were performed on the supernatant obtained. Tissue samples taken for malondialdehyde measurement were first homogenized and then subjected to the specified procedures.(Ohkawa, Ohishi, & Yagi, 1979) TAC and TOC levels were measured by spectrophotometric method in accordance with the protocols of the commercial company (Rel Assay Diagnostics, Turkey). OSI was calculated as the ratio of TAC to TOC level.

2.4. Statistical analysis

The values are given as mean ± standard deviation (SD). Statistical analysis was performed using SPSS, version 19.0 (SPSS, IBM Company). Biochemical levels of the groups were compared by Kruskal-Wallis test. The subgroups were compared among themselves by Mann-Whitney U test. $P<0.05$ was considered statistically significant.

3. RESULTS

In CdCl2-exposed rats, a significant ($p < 0.05$) decrease in TAC plasma levels and a significant ($p < 0.05$) increase in TOC, OSI and MDA values were observed compared to the control group. TAC, TOC and MDA levels were significantly lower in the kidney tissue of rats treated with curcumin alone ($p > 0.05$) compared to the control group ($p < 0.05$). In the Curcumin group given together with CdCl2 (group 4), OSI and MDA levels remained significantly ($p < 0.05$) lower than in group 2. A decrease in plasma MDA levels and a significant ($p < 0.05$) increase in TOC values were observed in rats given resveratrol in group 5, compared to the control group. In group 6 treated with resveratrol concomitantly with CdCl2, TOC, OSI and MDA levels remain significantly ($p < 0.05$) lower than in group 2. (Table 1).

Table 1: Spectrophotometric analysis results

Group	TAC (µmole H_2O_2 Equiv./gram protein)	TOC (µmole H_2O_2 Equiv./gram protein)	OSI	MDA (nmol/g)
1	3.52±0.59	10.88±0.41	0.31±0.05	1.63±0.47
2	2.68±0.48§p	13.48±1.10§p	0.51±0.09§p	3.16±0.41§p
3	3.30±0.67	12.43±0.54¶p	0.38±0.07	1.48±0.22
4	3.68±0.98♯p	12.66±1.56	0.37±0.09♯p	2.55±0.28♯p
5	4.07±0.33	13.27±0.53 ‡p	0.32±0.03	1.51±0.24
6	3.89±0.30*	12.02±1.53	0.30±0.06*	2.52±0.16*

Group 1: Control group; Group 2: CdCl2; Group 3: Curcumin; Group 4: CdCl2 + Curcumin; Group 5: Resveratrol; Group 6: CdCl2 + Resveratrol. OSI = ((TOC, µmole H_2O_2 Equiv./gram protein)/(TAC, µmole H_2O_2 Equiv./gram protein) × 100. Group Comparisons: §p= grup1 and grup 2; ¶p= grup 1 and grup 3; ‡p= grup1 and grup 5; ♯p= grup 2 and grup 4; * grup 2 and grup 6.

4. DISCUSSION

Cd is a heavy metal that is associated with pathological changes in target organs, including the lung, liver and kidney, and causes serious health problems, even at low exposure levels. In many studies, the toxic effects of Cd on human health have been investigated. Heavy metals such as Cd+2 cause oxidative stress by disrupting the redox balance in cells. Many studies

have reported that Cd+2 toxicity damages biological components of the cell in humans and animals. In other studies have reported that Cd causes an increase in malondialdehyde levels, which is an indicator of lipid peroxidation, and a decrease in antioxidant enzymes in various organs (lung, liver...).(Anetor, 2012; Genchi, Sinicropi, Lauria, Carocci, & Catalano, 2020; Koons & Rajasurya, 2022; Lee, Son, Pratheeshkumar, & Shi, 2012; Jie Liu et al., 2008; J. Liu et al., 2009) In our study, TOC, OSI and MDA levels increased, while TAC value decreased in the Cd+2-treated group compared to the control group. This situation explains the inadequacy of the antioxidant defense system despite the increase in ROS in the toxic effect of Cd+2.

In recent studies, curcumin has attracted attention for its potential antioxidant or anti-apoptotic properties. Curcumin has many beneficial properties, among them antioxidant and anti-inflammatory effects.(Corona-Rivera et al., 2007; Menon & Sudheer, 2007; Park, Lee, & Kim, 2021) In our study, it was observed that the TAC level increased and the MDA level and OSI value decreased in the group given curcumin together with Cd. Based on our results, we can say that curcumin may benefit kidney tissue in Cd-induced oxidative stress.

It has been obtained as a result of studies that resveratrol prevents oxidative stress-induced tissue damage by preventing oxidation of membrane lipids and increasing antioxidant capacity. It has been reported that ROS scavenges free radicals (O2.-, OH.) in the cell culture medium and prevents peroxidation of membrane lipids, which develops due to increased radical production with chromium exposure.(Gerogiannaki-Christopoulou, Athanasopoulos, Kyriakidis, Gerogiannaki, & Spanos, 2006; Signorelli & Ghidoni, 2005; Soleas, Diamandis, & Goldberg, 1997) In this study, it was observed that the TAC level increased and the MDA level and OSI value decreased in the group given resveratrol together with Cd. Because of the hydroxyl groups it has, resveratrol donates a hydrogen electron and becomes OH. and prevents peroxidation of cell membranes by scavenging O2.- radicals. According to our results, resveratrol contributes to the defense system of the cell by both reducing the oxidative stress caused by Cd and increasing antioxidant enzymes.

5. CONCLUSION

As a result, it shows that both resveratrol and curcumin support the defense system of cells by scavenging free radicals that increase oxidative damage caused by Cd in the kidneys. More extensive studies are needed on this subject.

REFERENCES

Anetor, J. (2012). Rising Environmental Cadmium Levels in Developing Countries: Threat to Genome Stability and Health. Nigerian journal of physiological sciences : official publication of the Physiological Society of Nigeria, 27, 103-115. doi:10.4172/2161-0525.1000140

Cirmi, S., Maugeri, A., Micali, A., Marini, H. R., Puzzolo, D., Santoro, G., . . . Minutoli, L. (2021). Cadmium-Induced Kidney Injury in Mice Is Counteracted by a Flavonoid-Rich Extract of Bergamot Juice, Alone or in Association with Curcumin and Resveratrol, via the Enhancement of Different Defense Mechanisms. Biomedicines, 9(12). doi:10.3390/biomedicines9121797

Corona-Rivera, A., Urbina-Cano, P., Bobadilla-Morales, L., Vargas-Lares, J. d. J., Ramírez-Herrera, M. A., Mendoza-Magaña, M. L., . . . Corona-Rivera, J. R. (2007). Protectivein vivo effect of curcumin on copper genotoxicity evaluated by comet and micronucleus assays. Journal of Applied Genetics, 48(4), 389-396. doi:10.1007/BF03195238

Cosar, R., Yurut-Caloglu, V., Eskiocak, S., Ozen, A., Altaner, S., Ibis, K., . . . Kocak, Z. (2012). Radiation-induced chronic oxidative renal damage can be reduced by amifostine. Med Oncol, 29(2), 768-775. doi:10.1007/s12032-011-9870-7

Dkhil, M. A., Diab, M. S. M., Lokman, M. S., El-Sayed, H., Bauomy, A. A., Al-Shaebi, E. M., & Al-Quraishy, S. (2020). Nephroprotective effect of Pleurotus ostreatus extract against cadmium chloride toxicity in rats. An Acad Bras Cienc, 92(1), e20191121. doi:10.1590/0001-3765202020191121

Galiniak, S., Aebisher, D., & Bartusik-Aebisher, D. (2019). Health benefits of resveratrol administration. Acta Biochim Pol, 66(1), 13-21. doi:10.18388/abp.2018_2749

Genchi, G., Sinicropi, M. S., Lauria, G., Carocci, A., & Catalano, A. (2020). The Effects of Cadmium Toxicity. Int J Environ Res Public Health, 17(11). doi:10.3390/ijerph17113782

Gerogiannaki-Christopoulou, M., Athanasopoulos, P., Kyriakidis, N., Gerogiannaki, I. A., & Spanos, M. (2006). trans-Resveratrol in wines from the major Greek red and white grape varieties. Food Control, 17(9), 700-706. doi:https://doi.org/10.1016/j.foodcont.2005.04.006

Gong, P., Wang, M., Yang, W., Chang, X., Wang, L., & Chen, F. (2021). Integrated metabolomics coupled with pattern recognition and

pathway analysis to reveal molecular mechanism of cadmium-induced diabetic nephropathy. Toxicology Research, 10(4), 777-791. doi:10.1093/toxres/tfab059 %J Toxicology Research

Grujić-Milanović, J., Jaćević, V., Miloradović, Z., Milanović, S. D., Jovović, D., Ivanov, M., . . . Mihailović-Stanojević, N. (2022). Resveratrol improved kidney function and structure in malignantly hypertensive rats by restoration of antioxidant capacity and nitric oxide bioavailability. Biomedicine & Pharmacotherapy, 154, 113642. doi:https://doi.org/10.1016/j.biopha.2022.113642

Ingawale, D. K., Mandlik, S. K., & Naik, S. R. (2014). Models of hepatotoxicity and the underlying cellular, biochemical and immunological mechanism(s): a critical discussion. Environ Toxicol Pharmacol, 37(1), 118-133. doi:10.1016/j.etap.2013.08.015

Jomova, K., & Valko, M. (2011). Advances in metal-induced oxidative stress and human disease. Toxicology, 283(2-3), 65-87. doi:10.1016/j.tox.2011.03.001

Koons, A. L., & Rajasurya, V. (2022). Cadmium Toxicity. In StatPearls. Treasure Island (FL): StatPearls Publishing

Copyright © 2022, StatPearls Publishing LLC.

Kotha, R. R., & Luthria, D. L. (2019). Curcumin: Biological, Pharmaceutical, Nutraceutical, and Analytical Aspects. Molecules, 24(16). doi:10.3390/molecules24162930

Lee, J. C., Son, Y. O., Pratheeshkumar, P., & Shi, X. (2012). Oxidative stress and metal carcinogenesis. Free radical biology & medicine, 53(4), 742-757. doi:10.1016/j.freeradbiomed.2012.06.002

Liu, J., Qian, S. Y., Guo, Q., Jiang, J., Waalkes, M. P., Mason, R. P., & Kadiiska, M. B. (2008). Cadmium generates reactive oxygen- and carbon-centered radical species in rats: insights from in vivo spin-trapping studies. Free radical biology & medicine, 45(4), 475-481. doi:10.1016/j.freeradbiomed.2008.04.041

Liu, J., Qu, W., & Kadiiska, M. B. (2009). Role of oxidative stress in cadmium toxicity and carcinogenesis. Toxicol Appl Pharmacol, 238(3), 209-214. doi:10.1016/j.taap.2009.01.029

Malaguarnera, L. (2019). Influence of Resveratrol on the Immune Response. Nutrients, 11(5). doi:10.3390/nu11050946

Menon, V. P., & Sudheer, A. R. (2007). Antioxidant and anti-inflammatory properties of curcumin. Adv Exp Med Biol, 595, 105-125. doi:10.1007/978-0-387-46401-5_3

Naik, S. R., Thakare, V. N., & Patil, S. R. (2011). Protective effect of curcumin on experimentally induced inflammation, hepatotoxicity and cardiotoxicity in rats: evidence of its antioxidant property. Exp Toxicol Pathol, 63(5), 419-431. doi:10.1016/j.etp.2010.03.001

Ohkawa, H., Ohishi, N., & Yagi, K. (1979). Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. Anal Biochem, 95(2), 351-358. doi:10.1016/0003-2697(79)90738-3

Park, J. H., Lee, B. M., & Kim, H. S. (2021). Potential protective roles of curcumin against cadmium-induced toxicity and oxidative stress. J Toxicol Environ Health B Crit Rev, 24(3), 95-118. doi:10.1080/10937404.2020.1860842

Patrick, L. (2003). Toxic metals and antioxidants: Part II. The role of antioxidants in arsenic and cadmium toxicity. Altern Med Rev, 8(2), 106-128.

Rani, A., Kumar, A., Lal, A., & Pant, M. (2014). Cellular mechanisms of cadmium-induced toxicity: a review. Int J Environ Health Res, 24(4), 378-399. doi:10.1080/09603123.2013.835032

Shaito, A., Posadino, A. M., Younes, N., Hasan, H., Halabi, S., Alhababi, D., . . . Pintus, G. (2020). Potential Adverse Effects of Resveratrol: A Literature Review. Int J Mol Sci, 21(6). doi:10.3390/ijms21062084

Signorelli, P., & Ghidoni, R. (2005). Resveratrol as an anticancer nutrient: molecular basis, open questions and promises. J Nutr Biochem, 16(8), 449-466. doi:10.1016/j.jnutbio.2005.01.017

Soleas, G. J., Diamandis, E. P., & Goldberg, D. M. (1997). Resveratrol: a molecule whose time has come? And gone? Clin Biochem, 30(2), 91-113. doi:10.1016/s0009-9120(96)00155-5

Takhtfooladi, H. A., & Takhtfooladi, M. A. (2019). Effect of curcumin on lung injury induced by skeletal muscle ischemia/reperfusion in rats. Ulus Travma Acil Cerrahi Derg, 25(1), 7-11. doi:10.5505/tjtes.2018.83616

Tarasub, N., Tarasub, C., & Devakul Na Ayutthaya, W. (2011). Protective role of curcumin on cadmium-induced nephrotoxicity in rats. J. Environ. Chem. Ecotoxicol, 3, 17-24.

Wang, J., Zhang, Y., Fang, Z., Sun, L., Wang, Y., Liu, Y.,. Gooneratne, R. (2019). Oleic Acid Alleviates Cadmium-Induced Oxidative Damage in Rat by Its Radicals Scavenging Activity. Biol Trace Elem Res, 190(1), 95-100. doi:10.1007/s12011-018-1526-4

Wiwanitkit, V. (2008). Minor heavy metal: A review on occupational and environmental intoxication. Indian J Occup Environ Med, 12(3), 116-121. doi:10.4103/0019-5278.44692

Wu, X., Cobbina, S. J., Mao, G., Xu, H., Zhang, Z., & Yang, L. (2016). A review of toxicity and mechanisms of individual and mixtures of heavy metals in the environment. Environ Sci Pollut Res Int, 23(9), 8244-8259. doi:10.1007/s11356-016-6333-x

Yan, L. J., & Allen, D. C. (2021). Cadmium-Induced Kidney Injury: Oxidative Damage as a Unifying Mechanism. Biomolecules, 11(11). doi:10.3390/biom11111575

Zia, A., Farkhondeh, T., Pourbagher-Shahri, A. M., & Samarghandian, S. (2021). The role of curcumin in aging and senescence: Molecular mechanisms. Biomed Pharmacother, 134, 111119. doi:10.1016/j.biopha.2020.111119

CHAPTER 3

A HOLISTIC VIEW OF STUDIES CONDUCTED ON AESTHETIC VAGINAL PLASTIC SURGERY WITH THE SCIENCE MAPPING METHOD

MD. Ayse KONAÇ[1]

[1] Institution Information: Gelişim Üniversitesi, Sağlık Bilimleri Fakültesi, İstanbul/TÜRKİYE
ORCID: 0000-0002-9119-3332
Mail: akonac@gelisim.edu.tr

INTRODUCTION

Today, the appearance of the vagina, which is one of the aesthetic concerns of women, can be corrected with surgical procedures called vaginoplasty. In recent years, vaginoplasty has become increasingly popular and has become a common treatment option among women with sexual dysfunction. Studies on this subject are generally addressed in the medical field as well as in gender studies (Laub et al., 1988; Jiang et al., 2018; Selvaggi et al., 2005; Salim and Poh, 2018).

Vaginoplasty is a surgical method frequently used in the treatment of a rare condition called Mayer-Rokitansky-Küster-Hauser (MRKH) syndrome, which is a congenital disorder caused by vaginal agenesis or atresia. In most patients, primary vaginal extension is performed with vaginal dilation as the first-line treatment, while surgery may be required for patients who fail dilation therapy or prefer surgical intervention (Shao et al., 2022).

High-quality and robust research focusing on long-term outcomes, quality of life, sexual function, and patient-centered outcomes is needed for all aesthetic gynecological procedures (Renganahthan et al., 2009). Therefore, more research is needed in this area. Additional research is considered helpful in obtaining a more precise idea about the safety, efficacy, and patient satisfaction related to aesthetic gynecological procedures.

In this study, a bibliometric analysis was conducted on the scientific research conducted in this area by taking a holistic perspective on the topic of vaginoplasty. Bibliometrics is a method that enables the numerical analysis of publications on a topic and can be expressed with methods that provide clues about scientific disciplines, related topics or titles, institutions, countries, and collaborations between authors (Kurutkan and Orhan, 2018).

As a result of these analyses, a more comprehensive idea about the progress and future directions of studies on vaginoplasty will be obtained. Additionally, this study aims to provide medical researchers, surgeons, and other relevant experts with a current perspective on vaginoplasty.

VAGINOPLASTY

Vaginoplasty is a surgical procedure that has gained significant interest among women in recent years due to technological and medical advancements in the field of aesthetic surgery. Women are now placing more emphasis on genital aesthetics in addition to facial and body features. This has

led to an increase in the demand for genital aesthetic operations by plastic surgeons.

The decrease in the number and function of collagen cells in the body as a person ages reduces tissue elasticity and leads to unwanted sagging, loosening, and shape irregularities in the genital area, among many women. Additionally, factors such as difficult childbirth, high number of births, type of delivery, and genetic structure contribute to this condition. This leads to a decrease in self-confidence among women, especially embarrassment in front of their partners during sexual intercourse, leading to unhappiness and even relationship breakdowns.

The increase in self-confidence and sexual satisfaction observed among women after genital cosmetic surgery has led to an increase in demand for these types of surgical procedures, especially among women (Kloer et al., 2023).

Genital cosmetic and vaginal plastic surgery is a growing and increasingly popular field that has seen an increase of around 220% in the last five years. Currently, more than 25% of plastic surgeons perform these procedures (Placik and Devgan, 2019). Both invasive and non-invasive methods are determined and applied according to the patient's needs. The development of laser technology has increased the demand for non-invasive cosmetic preferences.

Female genital cosmetic surgery (FGCS) procedures are new but their popularity is increasing (Braun, 2005). FGCS is a medical procedure that aims to change the aesthetics or functionality of female genital organs, which is not necessarily a medical requirement, and vaginoplasty is one such procedure. Many procedures, such as labiaplasty, have seen an increase in global demand and popularity (Yoon and Pather, 2022).

In recent years, the frequency and variety of female genital aesthetic surgeries and laser procedures have increased. The Aesthetic Society reported a 29.7% increase in labiaplasty surgeries between 2015 and 2019, with 47.9% of these surgeries being performed on women between the ages of 18 and 34 (Shaw et al., 2022).

Female genital aesthetic surgery is considered a safe surgical treatment that can improve the quality of life for women (Chen, 2022). It is a known fact that there is an increase in self-confidence and improvement in

sexual life in women after improvement in their genital areas. Therefore, the demand for vaginal surgery, especially by women, is increasing.

Female genital cosmetic surgery (FGCS) refers to a group of procedures designed to change the aesthetics or "function" of female genital anatomy (Rodrigues, 2012). Aesthetic and functional procedures involving female genital cosmetic surgery (FGCS) include traditional vaginal prolapse procedures, as well as cosmetic vulvar and labial procedures (Iglesia et al., 2013).

Studies have shown that women's experiences with FGCS are positive and result in increased sexual satisfaction and quality of life. However, an informed decision-making process about the risks and complications of FGCS is also necessary, and therefore, it is important for women to have complete information about all possible outcomes of the procedure (Nezhad et al., 2023). In addition, as the demand for FGCS increases among women, the medical community and regulatory agencies should conduct more research and update standards and guidelines for FGCS.

The findings show that female genital aesthetic surgery improves women's body image and sexual function, and can lead to a more enjoyable and healthy marriage relationship (Eftekhar et al., 2021).

Female genital cosmetic surgery (FGCS) includes numerous surgical procedures, including hymenoplasty, labioplasty, 'G-spot' enlargement, and vaginal 'rejuvenation' (Liao et al., 2012).

Vaginoplasty is the most commonly performed gender-confirming genital surgery for individuals with gender dysphoria. The procedure is done to create an aesthetic and functional vulva and vaginal canal that facilitates receptive intercourse, erogenous clitoral sensation, and downward urine flow (Morrison et al., 2023).

Vaginoplasty is currently one of the most performed surgeries, including repair of birth tears, vaginal tightening, Labioplasty (Minora, Majora), Clitoral hood reduction, Kliteropeksy, Majora fillings, Majora reduction, Hymenoplasty, and Perineoplasty.

Vaginoplasty is a surgical procedure that addresses aesthetic and functional problems in female genital organs. While interest in these types of

surgeries is increasing among women, there is insufficient data on long-term results and complications (Wilkie and Bartz, 2018).

Vaginoplasty is the most commonly performed gender-affirming surgical procedure for individuals with gender dysphoria. The goal is to create an aesthetic and functional vulva and vaginal canal and provide receptive intercourse, erogenous clitoral sensation, and downward urine flow. Usually, neovagina is created using tissues taken from the patient's own body, and this procedure improves quality of life by reducing the risk of urinary tract infections and other complications (Morrison et al., 2023).

In addition, education and counseling should be a priority to ensure that women have reliable information about normal variations and physiological changes in the vagina and vulva throughout their lives, as well as the potential unwanted outcomes of cosmetic surgery in the genital area (Shaw et al., 2013).

Bibliometrics

Visualizing and analyzing information about documents, authors, publishing sources, and more from scientific articles published in different fields is important for academics in today's world where scientific publications are increasing. Bibliometric analysis methods, such as Bibliometrix, allow for the collection, analysis, and visualization of information from scientific articles published in various disciplines (Akyüz, 2021; Kurutkan & Orhan, 2018). Bibliometric analyses can be used for performance analysis and scientific mapping. Performance analysis aims to measure the performance of authors and institutions, while scientific mapping focuses on the structure and dynamics of scientific fields. In bibliometric analysis, the first step is to identify the research area, collect data related to the identified area, compile the collected data, analyze it with one or more bibliometric analysis tools, and visualize the results (Aria & Cuccurullo, 2017; Tsay & Li, 2017; Zupic & Čater, 2014). The main goal of bibliometric analysis is to provide a general overview of academic research in a certain field by analyzing and visualizing information about publications, authors, fields, keywords, etc. in order to measure the impact and relationships of scientific studies. This allows for the identification of major trends supported in articles, citations, keywords, and institutions (Rodríguez et al., 2022).

Data Collection and Analysis Method

Research and review articles in the field of vaginoplasty were selected as the study area. For this purpose, the Web of Science "WoS" database was chosen, which contains high-quality and comprehensive scientific studies with a high impact (Li & Hale, 2016; WoS, y.y.). The search term "vaginoplasty" was searched as a "Topic" in the WoS database. The Topic search covers the article title, keywords, and abstract sections. Studies published in 2023 were not included in the search. Article and Review Article document types and English language articles from the Web of Science indexes SCI-EXPANDED, ESCI, and SSCI were selected. As a result of the search, 1061 articles were reached. The Web of Science scanning criteria and the interface showing the results are shown in Figure 1.

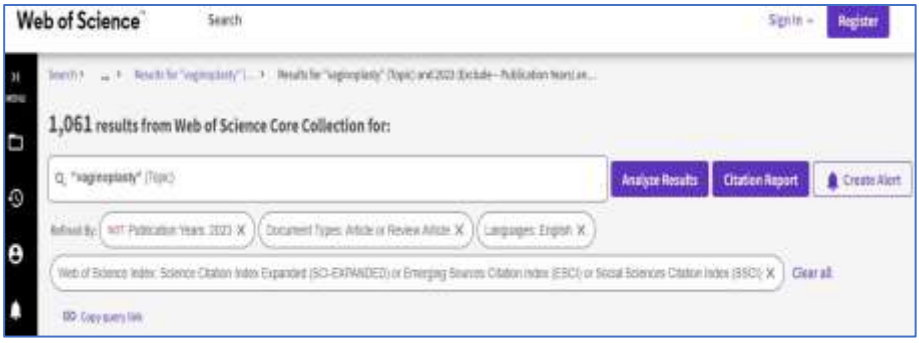


Figure 1. Web of Science search results screen capture

The obtained data was downloaded in plain text format. The downloaded articles were analyzed and visualized using Biblioshiny, an R-based bibliometric analysis and visualization program. Biblioshiny program, developed by Massimo Aria, uses the bibliometrix library and is written in Java. It allows for analysis without the need for coding thanks to its user interface (Huang et al., 2021; Xie et al., 2020). Some of the visuals were generated using the Tableau program, based on the data obtained from the analysis. The flowchart showing the process from data acquisition to visualization is presented in Figure 2.

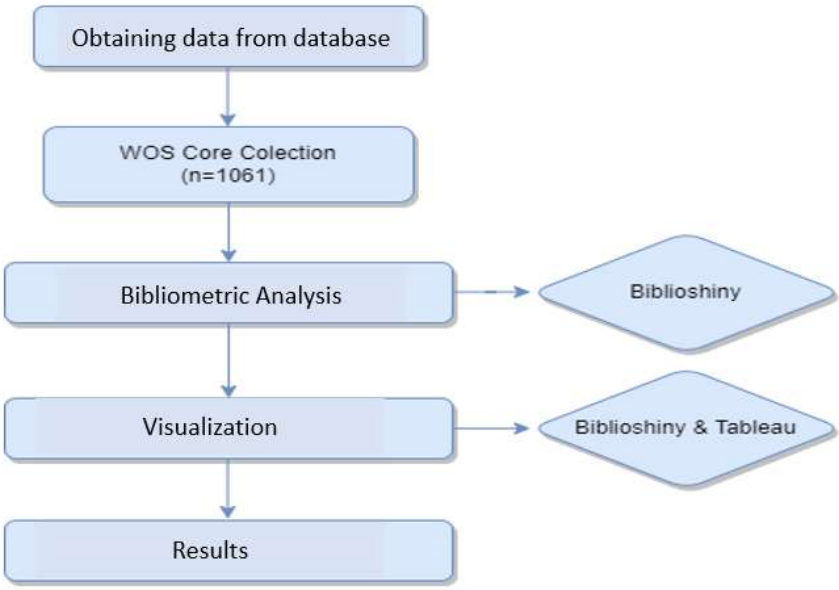


Figure 2: Flow Chart

RESULTS

General Information

General information about academic studies related to vaginoplasty is provided in Table 1. According to the search results, the first article was published in 1980. From 1980 to 2022, 1061 studies were published from 307 sources. Of these, 909 were research articles and 152 were review articles. The annual growth rate is 10.45%. The number of citations per document is 15.18. Of the total 4058 authors, 57 conducted single-author studies, and the number of single-authored documents is 66.

Table 1: General information about vaginoplasty studies

Description	**Value**
Time Period	1980:2022
Sources (Journals, Books, etc.)	307
Documents	1061
Research Articles	909
Review Articles	152
Annual Growth Rate %	11.45

Average Age of Documents	10.2
Average Number of Citations per Document	15.18
References	13079
Keywords	1189
Author Keywords	3994
Authors	4058
Authors of Single-Author Documents	57
Single-Author Documents	66
Average Collaborating Authors per Document	5.06
International Collaboration %	10.93

The production of academic studies in the field of vaginoplasty over the years and the average citation rates per year are shown in Figure 3. The first article was published in 1980. There has been an increasing trend in the number of articles since 1990, especially after 2016. The average total citation rate per year is calculated by dividing the total number of citations by the number of years elapsed since the article was published. The highest citation rate belongs to the articles published in 2018 (2.83). However, there has been a decrease in the total citation rate after 2018. Although only one article was produced in 1996, the total citation rate is quite high.

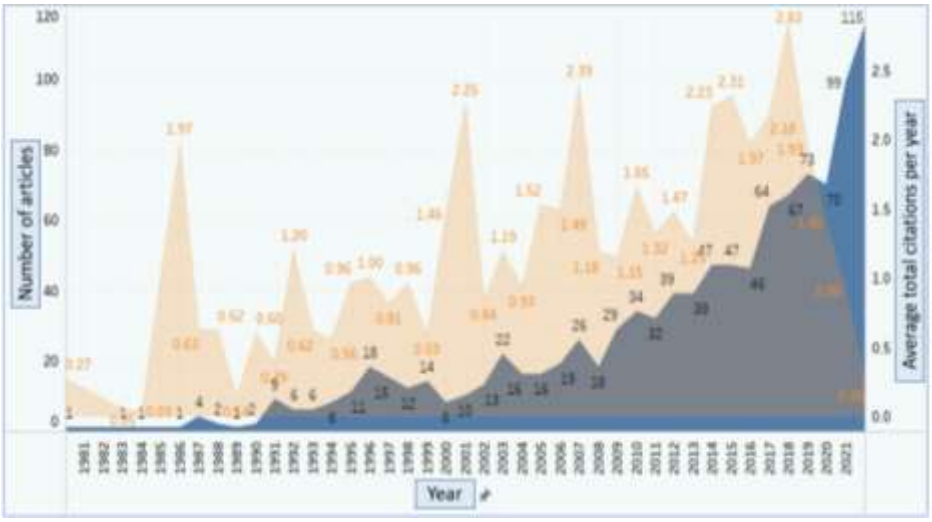


Figure 3. The production of academic studies in the field of vaginoplasty over the years and the average citation rates per year

Source Analysis

To measure the interest and impact of the sources (journals, etc.) publishing academic studies in the field of vaginoplasty, h-index, g-index, and m-index values of the top 10 sources according to h-index ranking, along with some publication information, are presented in Table 2. It can be easily stated that the most relevant and influential source to the research field is the Journal of Sexual Medicine. The journal, which first published in the field in 2007, has received a total of 1575 citations for its 44 studies published until today. The journal has the highest h-index (25), g-index (39), and m-index (1.471) values.

Source Name	h-index	g-index	m-index	TC	NP	FPY
JOURNAL OF SEXUAL MEDICINE	25	39	1.471	1575	44	2007
JOURNAL OF UROLOGY	24	32	0.774	1079	38	1993
FERTILITY AND STERILITY	18	27	0.783	907	27	2001
PLASTIC AND RECONSTRUCTIVE SURGERY	18	31	0.581	970	35	1993
JOURNAL OF PEDIATRIC SURGERY	16	25	0.432	677	32	1987
HUMAN REPRODUCTION	14	15	0.5	674	15	1996
ANNALS OF PLASTIC SURGERY	13	23	0.448	530	24	1995
OBSTETRICS AND GYNECOLOGY	12	17	0.316	348	17	1986
BJU INTERNATIONAL	10	15	0.4	626	15	1999
INTERNATIONAL UROGYNECOLOGY JOURNAL	10	18	0.556	338	26	2006
TC: Total Citations, NP: Number of Publications, FPY: First Publication Year						

Table 2: Sources publishing academic studies in the field of vaginoplasty

The source clustering analysis was conducted using Bradford's law, and the results are presented in Figure 4. According to the law, named after S.C. Bradford in 1934, only a few sources contain the largest share of works in a given field, while the remaining ones have one or two works only. The sources with the highest share of works are considered core sources and are located in Zone 1. This means that the core sources are the most productive

and efficient sources in the field (Tsay & Li, 2017). In the studied field, 14 source journals producing articles have become core sources by being located in Zone 1. 52 sources are located in Zone 2 and 241 sources are in Zone 3. The Journal of Sexual Medicine is located at the center.

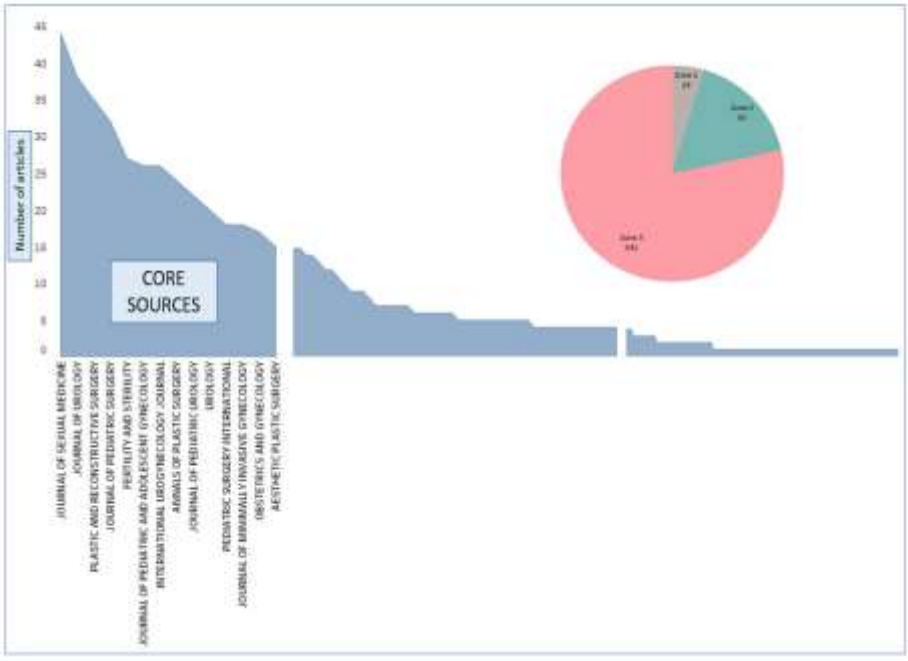


Figure 4. Resource cluster analysis with Bradford's law

Author Analysis

In order to measure the interest and impact of authors who have academic studies in the field of vaginoplasty, the h-index, g-index and m-index of the top 10 authors according to the h-index ranking, along with some publication information, are given in Table 3. The most relevant and effective author in the field of study is Bouman MB. The author, who published their first work in 2014, has received a total of 881 citations for the 31 works they have published to date. The author has an h-index of 16, a g-index of 29, and an m-index of 1.6. Information on the other top 10 authors is shown in the table.

Table 3: Authors with academic studies in the field of vaginoplasty.

Author	**h-index**	**g-index**	**m-index**	**TC**	**NP**	**FPY**
BOUMAN MB	16	29	1.6	881	31	2014
MULLENDER MG	14	18	1.4	772	18	2014
MONSTREY S	13	17	0.619	769	17	2003
BUNCAMPER ME	12	15	1.2	727	15	2014
HAGE JJ	11	16	0.367	416	16	1994
VAN DER SLUIS WB	11	22	1.222	490	25	2015
CREIGHTON SM	10	12	0.526	407	12	2005
KARIM RB	10	13	0.333	353	13	1994
DE CUYPERE G	9	9	0.474	535	9	2005
OZER M	9	13	1	470	13	2015
TC: Total Citations, NP: Number of Publications, FPY: First Publication Year						

The graph showing the production of authors over time and their average total citations per year is presented in Figure 5. The size of the circles in the graph is proportional to the number of articles, and the color intensity is proportional to the average citations per year. Bouman MB, the most relevant and effective author in the field, published articles every year between 2014 and 2022, with the highest number of publications in 2016 (n=12). Among the top 10 authors, Hage JJ and Karim RB did not have any publications after 2007. The year 2016 had the highest number of article publications (n=45).

Figure 5. Yearly production graph of authors

The author collaboration network analysis, which aims to show the collaboration status among the authors, is presented in Figure 6. Collaboration analysis reveals the relationships between authors based on the articles they published together, using social network analysis. The size of the circle in the graph is proportional to the number of articles, and the thickness of the lines between the circles is proportional to the intensity of the relationship, i.e., the number of articles they co-authored. When determining the analysis parameters, the node count was set to 50, and the minimum relationship count was set to 1. Louvain Algorithm was chosen as the clustering algorithm. As a result of the analysis, 10 clusters were formed. 6 clusters consist of only 2 authors, and these authors have no relationship with other authors outside of the cluster. The most intense relationship is in the red-colored cluster. "Bouman mb" (Closeness centrality value= 133.85) is at the center of the cluster. The author with whom "Bouman mb" has the most intense relationship is "van der sluis wb". The highest number of relationships between clusters is between the yellow and red clusters. "De cuypere g" (Closeness centrality value= 37.09) is at the center of the blue cluster, "zhao lc" (Closeness centrality value= 35.19) is at the center of the lilac-colored cluster, and "bizic mr" (Closeness centrality value= 7.05) is at the center of the yellow-colored cluster.

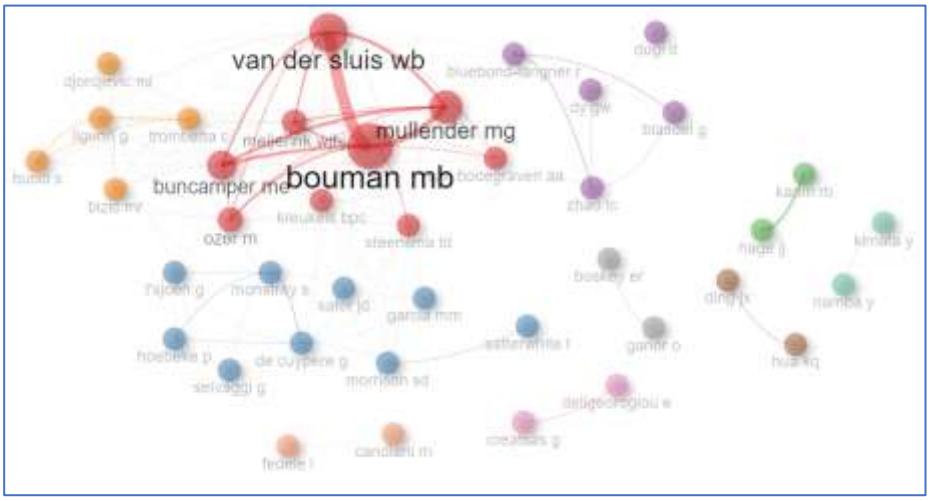


Figure 6: Author co-citation network

Author co-citation network analysis is a social network analysis that reveals when two authors are cited together by a third author. The analysis conducted for this purpose is shown in Figure 7. The size of the circles is proportional to the number of citations, and the thickness of the lines between circles is proportional to the number of co-citations. When setting the parameters, a node count of 50 and a minimum co-citation count of 2 were selected. The Louvain algorithm was used as the clustering algorithm. As a result of the analysis, 2 clusters were formed. The red cluster is centered on "anonymous" authors (Closeness centrality=195.59). The blue cluster is centered on "kim sk" (Closeness centrality=150.24). Although the citation counts of both authors are low, the number of co-citations they received is higher than others. In the blue cluster, the author "hage jj" received a high number of co-citations with "perovic sv", "karim rb", and "selvaggi g". In the red cluster, it can be seen that "frank rt" received a high number of co-citations with "mcindoe ah" and "fedele l".

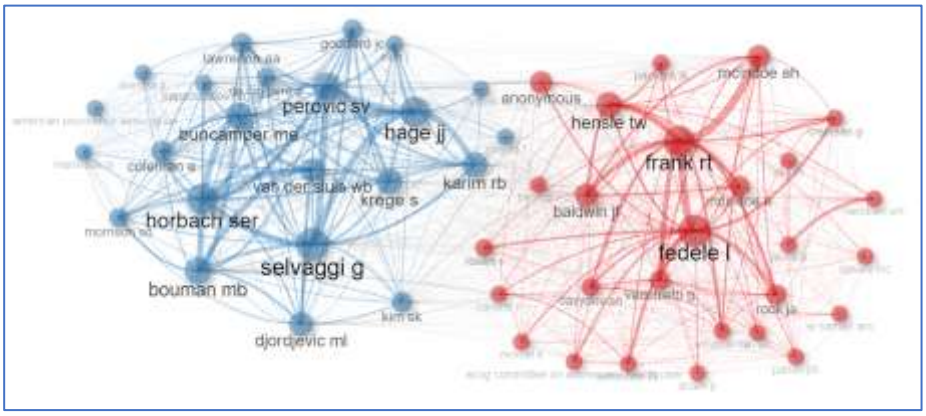


Figure 7: Author co-citation network analysis

Analysis of Countries of the Authors

The graph showing the top 5 countries with the highest number of published articles over time, calculated according to the countries of the article authors, is presented in Figure 8. When examining the graph, it can be seen that the USA is significantly ahead of the other countries. The USA has shown an increasing trend in article production since 1996, and particularly since 2016, there has been a significant upward trend. The number of articles produced by the other four countries, including Turkey, is close to each other. These countries have also shown an increasing trend in article production since 2006.

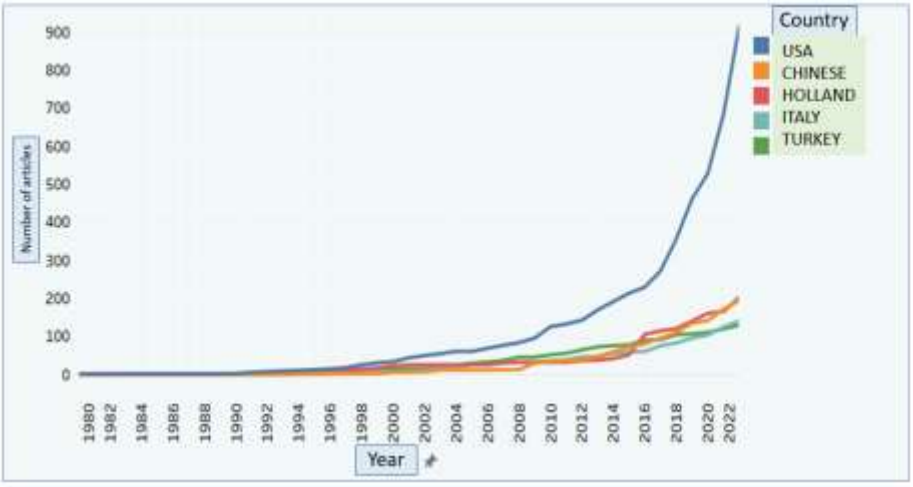


Figure 8. Country production over time

Figure 9 shows the country collaboration graph of the top 10 countries that published the most articles. The United States, which published the most articles, collaborated with other country authors on 28 out of 287 articles. Japan did not collaborate with authors from other countries on any of their published articles. Germany, which collaborated with authors from other countries on 10 out of 34 published articles, was the country that collaborated the most.

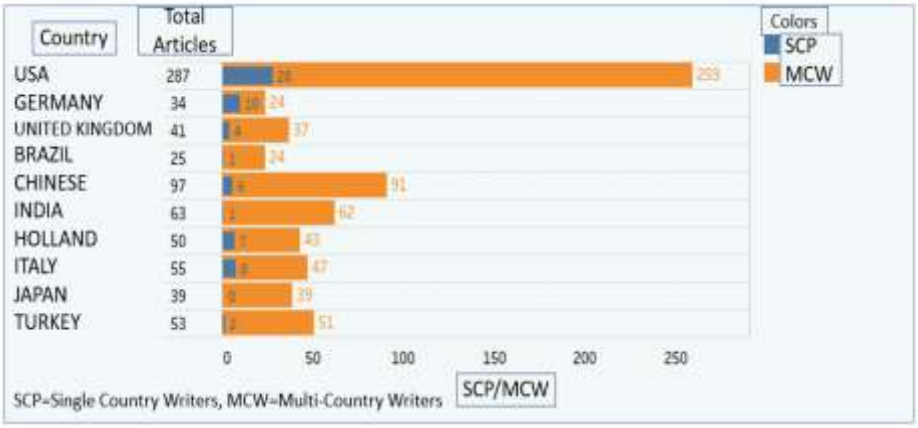


Figure 9. Country article production and collaboration

To see the collaboration status among countries, a collaboration network analysis was conducted (Figure 10). Collaboration analysis reveals the relationships between countries based on their co-published articles using social network analysis method. Node number was set to 30 and minimum relationship number was set to 1. Louvain Algorithm was chosen as the clustering algorithm. As a result of the analysis, 4 different clusters were identified. The center of the red cluster is occupied by the United States (betweenness value= 112.65). It has relations with all the countries in the cluster and many countries outside the cluster. Its most intense relationship is with Canada. The center of the blue cluster is occupied by the United Kingdom (betweenness value= 55.58). Its most intense relationship is with the United States. The center of the green cluster is occupied by Austria (betweenness value= 1.98). The center of the yellow cluster is occupied by Germany (betweenness value= 7.76). Indonesia, Japan, and Nigeria are not included in any of the clusters.

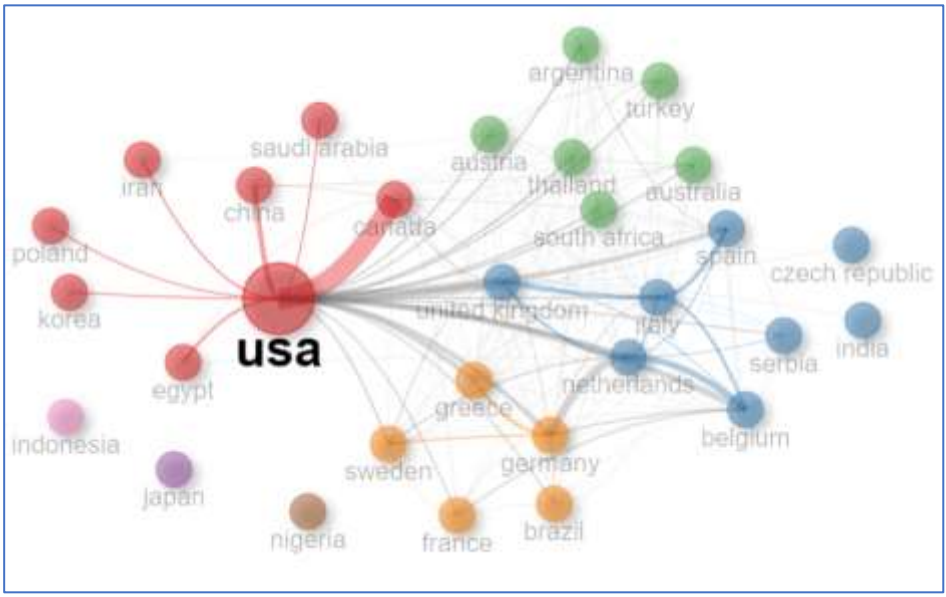


Figure 10: Country collaboration network

Document Analysis

Figure 11 shows the top 10 studies based on the total citations, indicating both local and global citations for articles published in the research area. Local citations represent the references made by 1,061 documents included in the dataset. Global citations represent the references made by all documents registered in the Web of Science database, which is the data source used. The article with the highest number of citations (319 in total) is the one with the DOI number 10.1111/jsm.12868, titled "Horbach, 2015, J SEX MED". This article has 131 local and 188 global citations.

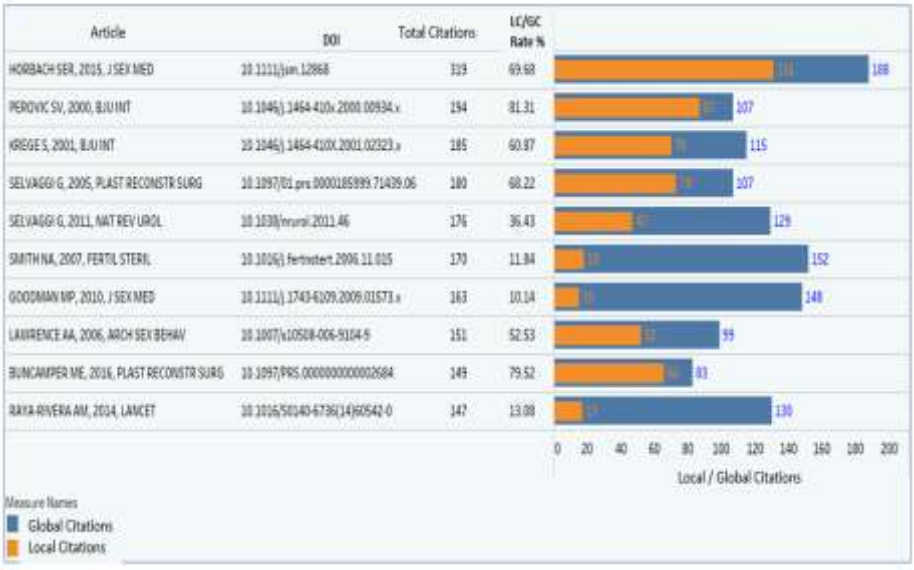


Figure 11. Article local and global citations

The word cloud and the top 10 most frequently used keywords, generated from author keywords, are shown in Figure 12. The search term "vaginoplasty" was not included in the word cloud, which was used to obtain the data. The term "vaginoplasty" was used 354 times, and the term "vaginal agenesis" was the second most frequently used keyword, used 116 times.

Figure 12. Keyword word cloud

To analyze the co-occurrence of author keywords, a Keyword Co-occurrence Network Analysis was performed and presented in Figure 13. The size of the circles represents the frequency of keyword usage, and the thickness of the lines represents the frequency of co-occurrence. The parameters used were 50 nodes and a minimum co-occurrence of 2. The Louvain algorithm was used for clustering. The analysis resulted in four clusters. The center of the red cluster is the keyword "vaginoplasty" (Closeness centrality=835.16). The term "vaginoplasty" is frequently used with "transgender" from its own cluster and "vaginal agenesis" from the blue cluster. It is also frequently used in combination with other clusters. The center of the blue cluster is the keyword "neovagina" (Closeness centrality=43.80). The center of the green cluster is the keyword "vagina" (Closeness centrality=46.50). The center of the purple cluster is the keyword "congenital adrenal hyperplasia" (Closeness centrality=1.84).

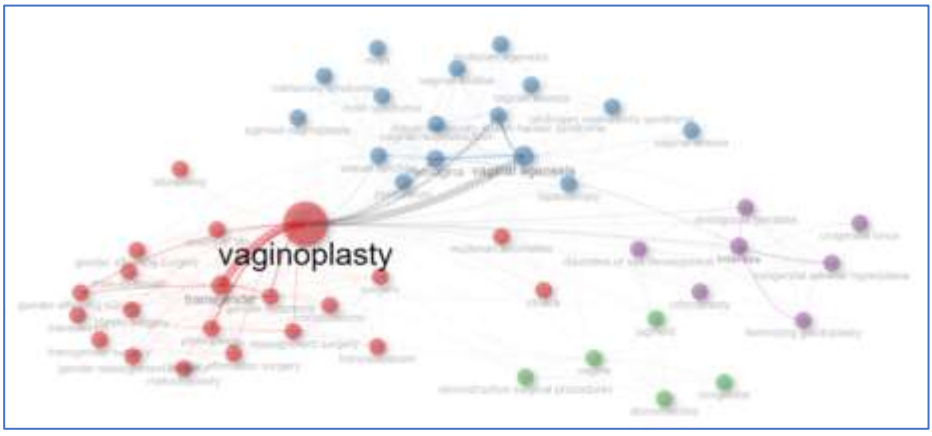


Figure 13. Keyword co-occurrence network

A thematic map was used to analyze the importance and development of the themes in studies conducted in the field of vaginoplasty (Figure 14). The thematic map consists of a two-dimensional axis where centrality is represented on the x-axis and density is represented on the y-axis, dividing the map into four quadrants. Related keywords are clustered together to form a theme set, and the clustered keywords are placed in one of the four quadrants based on their density and centrality (Callon et al., 1991).

Highly centralized and dense Motor themes are located in the upper right corner of the thematic map. They have intensive relationships with both

their own cluster elements and other cluster elements outside their own. Their locations are strategic and they usually consist of key words that are systematically taken for a long time. On the left upper part of the map, there are niche themes with high density but low centrality. Although the elements in this theme are developed, they are considered isolated. Their relationships with other cluster elements are weak despite strong intra-cluster relationships. Simple Themes with high centrality but low density are located in the lower right section. Although their relationships with intra-cluster elements are low, they have strong relationships with other cluster elements. They are strategically important for the study area but can also be part of other related study areas. They have sufficient centrality and are in the maturation stage. In the lower left section, there are newly emerged or declining themes with both low centrality and density. These clusters contain elements that have just emerged or are no longer used in the study area (Callon et al., 1991; Cobo et al., 2011; Nasir et al., 2020).

Each cluster is shown as a circle on the map. Each cluster represents the most frequently used keyword within that cluster. Other keywords within the cluster are listed next to each cluster circle. The parameters were set as 250 words and a minimum frequency of 5. The Louvain algorithm was selected as the clustering algorithm.

As a result of the analysis, there were 1 cluster in Motor theme, 2 clusters in Niche theme, 2 clusters in Simple theme, and 1 cluster in newly emerged or declining theme. "Vaginoplasty" is located at the center of the cluster in the Motor theme. There are a total of 10 keywords as cluster elements. Although this cluster is in the Motor theme, it is close to the center of the map, indicating that it is not highly centralized and dense. However, these are still the most strategically important keywords for the study area. The cluster represented by "Congenital adrenal hyperplasia" is located in the Simple theme and has a high centrality but low density. Its relationships with other cluster elements are strong but its intra-cluster relationships are low. This cluster also consists of 10 keywords. Another cluster in the Basic theme is represented by the keyword "vaginal agenesis" and has a very low density. In the Niche theme, there are two clusters represented by the keywords "vagina" and "labiaplasty". The centrality of the "vagina" theme is higher than the other. In the newly emerged or declining theme, the cluster represented by the keyword "vaginal atresia" has a higher density than its centrality. The

keywords in this cluster may include newly emerged or declining ones in the field.

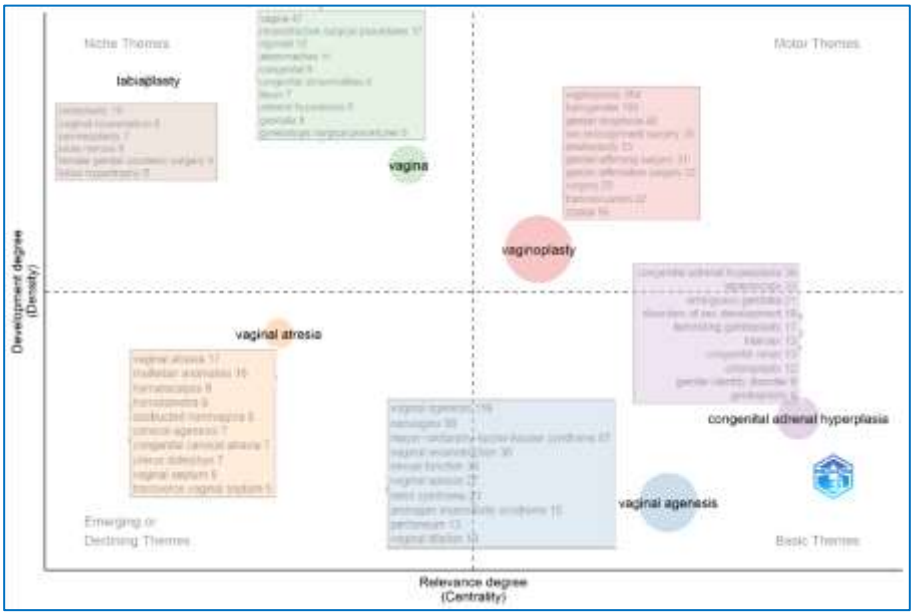


Figure 14. Thematic map

CONCLUSIONS

It is observed that academic studies in the field of vaginoplasty have rapidly increased in the last 40 years, and a significant portion of these studies are research articles. When the number of articles is examined according to the years, an increasing trend has been observed since 1990, and the studies with the highest citation rate were produced in 2018. Journal of Sexual Medicine has the highest h-index, g-index, and m-index values, and is considered as the most effective source.

Bouman MB was identified as the most effective author, and author collaboration network analysis and co-citation network analysis were conducted among the authors. In addition, cooperation between countries was also examined, and it was seen that the USA had the most cooperation with other countries.

This study describes a study on research trends and themes in the field of vaginoplasty. Based on a dataset of 1061 articles, this study analyzed the citation patterns, keywords, and themes of the articles, identifying the most

effective articles, the most commonly used keywords, and the main themes in the field.

The study found that the article with the highest citation count was published in the Journal of Sexual Medicine in 2015, with a total of 319 citations. The most commonly used keyword was "vaginal agenesis", followed by "vaginoplasty". The study also used keyword co-occurrence network analysis to determine the clustering of related keyword sets and found that "vaginoplasty" was a central node that was frequently used with other clusters. The study also identified the main themes, including surgical techniques, outcomes and complications, patient experiences, and ethical issues, using thematic mapping. Overall, this study provides information about research trends and themes in the field of vaginoplasty and emphasizes the importance of interdisciplinary research to advance the field.

As a result of the analyses, it is noted that "vaginoplasty" is the most commonly used keyword, and "vaginal agenesis" is the second most commonly used keyword. Using keyword co-occurrence network analysis, it was found that there were four clusters, and "vaginoplasty" was the most frequently used keyword. Using thematic mapping, it was seen that "vaginoplasty" was in the Motor theme and was one of the most strategically important keywords. While the "Congenital adrenal hyperplasia" keyword was in the Simple theme, the "vagina" and "labiaplasty" keywords were in the Niche theme. Additionally, it was noted that the intensity of the "vaginal atresia" keyword was higher in the new emerging or declining theme, compared to its centrality.

In conclusion, it is observed that publications related to vaginoplasty have increased in recent years, and most of these publications have been conducted in the fields of female genital aesthetics and gynecology. Furthermore, it was seen that most of the studies related to this topic were conducted in Western countries.

The results of this study can be used to evaluate the development of research in the field of vaginoplasty and the impact of authors. It is expected that the studies in this field will continue to increase and cooperation between different countries will increase. These studies can contribute to the development of new surgical techniques and technologies, and to the improvement of patient outcomes and experiences.

REFERENCES

Akyüz, S. (2021). Sağlık Okuryazarlığı Araştırmalarının Bibliyometrik Analizi. *Genel Tıp Dergisi*, *31*(4), 402–416. https://doi.org/10.54005/geneltip.975248

Aria, M., & Cuccurullo, C. (2017). bibliometrix: An R-tool for comprehensive science mapping analysis. *Journal of Informetrics*, *11*(4), 959–975. https://doi.org/https://doi.org/10.1016/j.joi.2017.08.007

Braun, V. (2005). In search of (better) sexual pleasure: female genital 'cosmetic'surgery. Sexualities, 8(4), 407-424.

Callon, M., Courtial, J. P., & Laville, F. (1991). Co-word analysis as a tool for describing the network of interactions between basic and technological research: The case of polymer chemsitry. *Scientometrics*, *22*(1), 155–205. https://doi.org/10.1007/BF02019280

Chen, S. (2022). Female Genital Mutilation and Female Genital Cosmetic Surgery. 2021 International Conference on Social Development and Media Communication (SDMC 2021)

Cobo, M. J., López-Herrera, A. G., Herrera-Viedma, E., & Herrera, F. (2011). Science mapping software tools: Review, analysis, and cooperative study among tools. *Journal of the American Society for Information Science and Technology*, *62*(7), 1382–1402. https://doi.org/10.1002/asi.21525

Eftekhar, T., Hajibabaei, M., Veisi, F., Ghanbari, Z., & Montazeri, A. (2021). Body image, sexual function, and sexual satisfaction among couples before and after gynecologic cosmetic surgery. Journal of Family & Reproductive Health, 15(4), 252.

Huang, J.-H., Duan, X.-Y., He, F.-F., Wang, G.-J., & Hu, X.-Y. (2021). A historical review and Bibliometric analysis of research on Weak measurement research over the past decades based on Biblioshiny. *CoRR, abs/2108.1*.

Iglesia, C. B., Yurteri-Kaplan, L., & Alinsod, R. (2013). Female genital cosmetic surgery: a review of techniques and outcomes. International urogynecology journal, 24, 1997-2009.

Jiang, D., Witten, J., Berli, J., & Dugi III, D. (2018). Does depth matter? Factors affecting choice of vulvoplasty over vaginoplasty as gender-affirming genital surgery for transgender women. *The Journal of Sexual Medicine*, *15*(6), 902-906.

Kloer, C., Blasdel, G., Shakir, N. A., Parker, A., Itzel Gómez, A., Zhao, L. C.,

& Bluebond-Langner, R. (2023). Does Genital Self-image Correspond with Sexual Health before and after Vaginoplasty?. Plast Reconstr Surg Glob Open, 11(2), 4806.

Kurutkan, M. N., & Orhan, F. (2018). *Kalite Prensiplerinin Görsel Haritalama Tekniğine Göre Bibliyometrik Analizi*.

Laub, D. R., Laub 2nd, D. R., & Biber, S. (1988). Vaginoplasty for gender confirmation. Clinics in Plastic Surgery, 15(3), 463-470.

Li, J., & Hale, A. (2016). Output distributions and topic maps of safety related journals. *Safety Science*, *82*, 236–244. https://doi.org/https://doi.org/10.1016/j.ssci.2015.09.004

Liao, L.-M., Taghinejadi, N., & Creighton, S. M. (2012). An analysis of the content and clinical implications of online advertisements for female genital cosmetic surgery. BMJ open, 2(6), e001908.

Morrison, S. D., Claes, K., Morris, M. P., Monstrey, S., Hoebeke, P., & Buncamper, M. (2023). Principles and outcomes of gender-affirming vaginoplasty. Nature Reviews Urology, 1-15.

Nasir, A., Shaukat, K., Hameed, I. A., Luo, S., Alam, T. M., & Iqbal, F. (2020). A Bibliometric Analysis of Corona Pandemic in Social Sciences: A Review of Influential Aspects and Conceptual Structure. *IEEE Access*, *8*, 133377–133402. https://doi.org/10.1109/ACCESS.2020.3008733

Nezhad, F. T., Jalali, R., Karimi, F., & Menati, L. (2023). Exploration of Women's Experiences of Sexual Function after Female Genital Cosmetic Surgery: A Phenomenological Descriptive Study. Current Women's Health Reviews, 19(1), 77-82.

Niang, O., & Ginny Moore. (2022). D. Cultural parallels between female genital cosmetic surgery and female genital mutilation.

Placik, O. J., & Devgan, L. L. (2019). Female genital and vaginal plastic surgery: an overview. Plastic and Reconstructive Surgery, 144(2), 284e-297e.

Renganathan, A., Cartwright, R., & Cardozo, L. (2009). Gynecological cosmetic surgery. Expert Review of Obstetrics & Gynecology, 4(2), 101-104.

Rodrigues, S. (2012). From vaginal exception to exceptional vagina: The biopolitics of female genital cosmetic surgery. Sexualities, 15(7), 778-794.

Rodríguez, M. S., Ortega Alvarez, A. M., & Arango-Vasquez, L. (2022). Worldwide trends in the scientific production on soccer players

market value, a bibliometric analysis using bibliometrix R-tool. *Team Performance Management: An International Journal*, *28*(5/6), 415–440. https://doi.org/10.1108/TPM-02-2022-0015.

Salim, A., & Poh, M. (2018). Gender-affirming penile inversion vaginoplasty. Clinics in Plastic Surgery, 45(3), 343-350.

Selvaggi, G., Ceulemans, P., De Cuypere, G., VanLanduyt, K., Blondeel, P., Hamdi, M., ... & Monstrey, S. (2005). Gender identity disorder: general overview and surgical treatment for vaginoplasty in male-to-female transsexuals. Plastic and Reconstructive Surgery, 116(6), 135e-145e.

Shao, S., Wang, X., Lei, X., Hua, K., & Zhang, Y. (2022). Psychological intervention in women with Mayer-Rokitansky-Küster-Hauser syndrome after artificial vaginoplasty: a prospective study. International Urogynecology Journal, 33(3), 723-729.

Shaw, D., Lefebvre, G., Bouchard, C., Shapiro, J., Blake, J., Allen, L., Cassell, K., Leyland, N., Wolfman, W., & Allaire, C. (2013). Female genital cosmetic surgery. Journal of Obstetrics and Gynaecology Canada, 35(12), 1108-1112.

Shaw, D., Allen, L., Chan, C., Kives, S., Popadiuk, C., Robertson, D., & Shapiro, J. (2022). Guideline No. 423: Female genital cosmetic surgery and procedures. Journal of Obstetrics and Gynaecology Canada, 44(2), 204-214. e201.

Tsay, M. yueh, & Li, C. ning. (2017). Bibliometric analysis of the journal literature on women's studies. *Scientometrics*, *113*(2), 705–734. https://doi.org/10.1007/s11192-017-2493-9.

Wilkie, G., & Bartz, D. (2018). Vaginal rejuvenation: a review of female genital cosmetic surgery. Obstetrical & gynecological survey, 73(5), 287-292.

WoS. (y.y.). *No Title*. https://www.webofscience.com

Xie, H., Zhang, Y., Wu, Z., & Lv, T. (2020). A Bibliometric Analysis on Land Degradation: Current Status, Development, and Future Directions. Içinde *LAND* (C. 9, Sayı 1). https://doi.org/10.3390/land9010028

Yoon, J., & Pather, N. (2022). Female genital cosmetic surgery: the role of anatomical knowledge in decision making. Anatomy: International Journal of Experimental & Clinical Anatomy, 16.

Zupic, I., & Čater, T. (2014). Bibliometric Methods in Management and Organization. *Organizational Research Methods*, *18*(3), 429–472.

https://doi.org/10.1177/1094428114562629

CHAPTER 4

NEW DEVELOPMENTS IN IMAGING OF BREAST CANCER

Alev GUNALDI, MD[1]

[1]MD, Maltepe University, Department of Radiology, Istanbul, Turkey. e-mail: mdalevgunaldi@gmail.com
ORCID: 0000-0003-3142-823x

INTRODUCTION

Breast cancer is one of the most commonly seen cancers in women. It is the leading health related concern among women because of its high rates of morbidity and mortality. Among women, more new cases of breast cancers are seen compared to other cancer types. There is a great difference in breast cancer survival rates worldwide with an estimated rate of survival 80% in the developed countries and 40 % for developing countries. There is a great difference in breast cancer survival rates worldwide with an estimated rate of survival 80% in the developed countries and 40 % for developing countries. Breast cancer is a metastatic cancer and commonly spread to distant organs such as liver, lung, brain and bone that mainly accounts for its incuratibility. Imaging is a crucial part of the management of patients with breast cancer. There are plenty of imaging modalities used for both diagnostic and therapeutic purposes as well as the assessment of response to treatment. Imaging methods for cancer screening are being developed every passing day. In this chapter, novel methods used in the management of breast cancer are discussed in line with the current literature.

1. Breast Cancer

Breast cancer is one of the most common cancers in women worldwide with 685,000 deaths in 2020. In 2020, an estimated 2.26 million breast cancer cases were recorded (Sung et al., 2021). Breast cancer is the leading health related concern among women because of its high rates of morbidity and mortality (Riggio, Varley and Welm, 2021). Among women in the USA, more new cases of breast cancers are seen compared to other cancer types. The incidence of breast cancer shows variability according to geographical factors with the incidence rate being highest in the developed countries and the lowest in the developing countries in Asia, Africa and Middle East (Parkin et al., 2002). There is a great difference in breast cancer survival rates worldwide with an estimated rate of survival 80% in the developed countries and 40 % for developing countries (Coleman et al., 2008). Breast cancer is a metastatic cancer and commonly spread to distant organs such as liver, lung, brain and bone that mainly accounts for its incuratibility. Early diagnosis and treatment of breast cancer can result in a good prognosis and a high rate of survivals (Sun et al., 2017). However, despite significant advances in the diagnosis and treatment of breast cancer, several major unsolved scientific and clinical issues remain. These issues

involve prevention, diagnosis, tumor recurrence and progression, treatment and therapeutic resistance (Polyak, 2007).

The exact etiology of breast cancer is unclear, although family history is one of the strongest determinants of risk for developing cancer, suggesting hereditary factors. It is considered that the majority of hereditary breast cancer cases are associated with BRCA1 and BRCA2 mutation (Park et al., 2011). According to the recently published GLOBOCAN 2018 data published by International Agency for Research on Cancer (IARC) from 185 countries there were 2.3 million new cases of breast cancer and mortality rate of 6.9% (Bray et al., 2018). The incidence of age-specific breast cancer rapidly increases from the age of 40 (Berg, 2009) and its incidence increases faster before 50 years old. Risk factors associated with developing breast cancer include age at first birth, number of births, age of menopause, smoking, breastfeeding, radiation exposure, postmenopausal hormone use, oral contraceptive use, fatty diet and obesity (Ozsoy et al., 2017).

Early detection and monitoring patients are the main aspects of breast cancer therapy. Breast cancer can be detected through imaging methods and especially mammography, pain and paşpabşe mass. Imaging modalities have emerged as powerful tools for detection and monitoring response to treatment in patients with breast cancer. Several techniques have been developed for this purpose such as mammography, ultrasound, magnetic resonance imaging (MRI), positron emission tomography (PET) and single-photon emission computerized tomography (SPECT). However, the utility of imaging techniques is limited due to costs, lack of sensitivity and specificity and thus, it seems that introducing novel biomarkers for diagnosis of breast cancer could overcome imaging limitations (Jafari et al., 2018). Improvements in multimodal therapy have resulted in increasing change for cure in approximately 70-80% of patients (Ginsburg et al., 2017).

2. New Developments in imaging modalities in breast cancer

There have been continuous advances and new developments in the diagnosis and treatment of breast cancer, which remains a great concern among the public due to its high rates of morbidity, mortality and recurrence. Imaging is the mainstay in the diagnosis of breast cancer in addition to pain and palpation. New developments and improvements in imaging modalities in breast cancer are discussed below in line with the current literature.

2.1. Molecular Imaging of Breast Cancer

Molecular imaging is a technique providing information about what is occurring in the human body at both cellular and molecular levels. Molecular imaging can play a major role as it allows early recognition of modifications that develop in tissue and changes in management of patients in real time. Molecular imaging can be used as a non-invasive diagnostic tool (Schillaci and Urbano, 2017). The introduction of positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) has revolutionized the imaging examination of patients with breast cancer (Rinzivillo et al., 2018). Today, all PET scans are combined with computed tomography (CT), making ^{18}FDG-PET-CT imaging the most commonly used modality for different stages of the treatment including guided biopsy, diagnosis, initial staging and planning of the treatment. However, ^{18}FDG-PET-CT has a limited role when it comes to management of patients with breast cancer. Nowadays it is used in distant metastasis, recurrent tumors and therapeutic response (Groheux et al., 2013).

2.2. Artificial Intelligence for detection of breast cancer in mammography

Screening for breast cancer has been performed differently in different countries. In many healthcare centers around the world screening is institution-based. Depending on the healthcare facility, the obtained images may be interpreted while the woman waits and additional imaging can be performed meanwhile at the same visit. Screening for breast cancer is performed by the government in many countries. After screening, when a woman is recalled or referred, she undergoes diagnostic investigations consisting of digital mammography (DM) and/or digital breast tomosynthesis (DBT).

2.2.1. Digital mammography

Digital mammography (DM) was developed and introduced in clinical practice with the development of affordable large-area digital detectors in the early 2000s. DM uses a digital X-ray detector, which results in a digital image, enabling interpretation by a radiologist. An alternative modality is the use of CT-based mammography for the breast screening process. However, since the performance of this technique is poor, its use has been reduced (Bosmans et al., 2013; Thomassin et al., 2019).

DM includes the acquisition of a single 2D image of the breast. This image results in tissue superposition and different tissues in the breast are projected onto the same location in the 2D mammography image. To overcome this issue, screening mammography is performed by acquisition of two views of each breast involving cranio-caudal and medio-lateral oblique views. In conclusion, interpretation of mammograms includes review and comparison features of the views of the same breast and between the two breasts.

2.2.2. Digital breast tomosynthesis

Digital breast tomosynthesis (DBT) was developed and introduced in clinical practice owing to the 2D nature of digital mammography (Sechopoulos, Teuwen and Mann, 2021). DBT is a pseudo-tomographic imaging modality that provides a stack of 2D images with vertical resolution. This partial tomographic effect decreases the masking impact of superimposed tissues. Studies with DBT have reported an increase in detection of breast cancer (Zackrisson et al., 2018; Bernardi et al., 2016, Hofvind, et al. 2018).

Although studies have reported promising results in terms of the detection of breast cancer, DBT has a major disadvantage of increased time of interpretation compared to DM. Interpretation time of DBT images has been reported to be two folds higher than that of DM (Skaane et al., 2013). Automated interpretation methods will have an impact in the potential of DBT to be introduced in daily practice.

2.2.3. Artificial intelligence (AI) algorithms for detected of breast cancer in DM and DBT

First of all, algorithms for detection of breast cancer in DM and DBT need to search for both calcification and soft tissue lesions. In general, different detection algorithms are used for each of these lesion times and the results are combined in the final analysis. The algorithms should determine the location of suspicious findings and not only determine whether an image contains a suspicious lesion. The development of such algorithms has involved the combination of the information from analyzing patches via featıres used in conventional computer-aided detection CAD with the deep learning convolutional neural networks (CNN) analysis, which has resulted in increased quality at the patch level (Kooi et al., 2017). Samala et al. used CNN algorithm as a pre-screening tool to identify suspicious areas of

classifications, and then designed a deep learning CNN to differentiate false calcifications from true ones, and obtained improved performance compared to using only deep learning CNN (Samala et al., 2016).

It is important to remember that these methods that include analysis at pixel or patch level usually need annotated training sets, on which malignant lesions are displayed on the images or the images consist of only the patches where the lesion is located. Additional improvements have been suggested to analyze DM and DBT images across the breasts and finally to compare the results with prior examinations. For this purpose, Kim et al. developed a deep learning CNN-based technique to analyze bilateral images in DBT for detection of masses and the result was improved performance compared to the use of hand-crafted features (Kim et al., 2016). Kooi and Karssemeijer also developed a new technique to detect asymmetries through comparison of images acquired across breast, and methods to compare current examinations to prior ones (Kooi et al., 2017).

2.3. ^{99}mTC-sestamibi breast imaging

Molecular classification of paraffin embedded tissues, based on immunohistochemical analysis is considered the best predictor of the behaviour of breast cancer (Viale et al., 2018). This classification is based on the analysis of main predictive and prognostic biomarkers of the breast including epidermal growth factor receptor 2 (HER2), estrogen receptor (ER), progesterone receptor (PR) and Ki67 (Viale et al., 2018).

According to the American College of Radiology, the clinical parameters such as Breast Specific Gamma Imaging (BSGI) and molecular breast imaging (MBI) have been defined especially for patients who are not suitable for MRI investigation. Studies have confirmed high sensitivity and specificity of BSGI in detection of cancerous lesions of the breast. In a study by Conners et al., 286 women who underwent MBI were injected with 8−33 mCi of ^{99}mTc-sestamibi and the exact lesion was detected in more than 80% of the patients (Conners et al., 2015). Despite these promising data, a better insight into the biological mechanisms regarding uptake of radiotracers used for both MBI and BSGI can pave the way for new scenarios in the management of patients with breast cancers. Particularly the use of BSGI with ^{99}mTc-sestamibi can provide early identification of breast lesions with high propensity to form bone metastasis. Most studies that have been performed with BSGI and MBI have used ^{99}mTc-sestamibi as the radiopharmacological

component (Ma, et al., 2014). ^{99}mTc-sestamibi was found to have accumulated in breast cancer tissues. Despite low uptake, ^{99}mTc-sestamibi is preferred in MBI due to its high sensitivity in diagnosing breast cancer (Hruska, 2017).

2.4. New Tracers for PET Imaging and Theranostic Concepts

Various new tracers are used for PET imaging of patients with breast cancer. Among these tracers, [^{18}F]Fluoroestradiol has attracted interest because it was approved by the Food and Drug Administration (FDA) in 2021 (FDA, 2020). FAPI (fibroblast-activation-protein inhibitor) is a promising novel theranostic ligand in breast cancer patients and is currently in the stage of early clinical development.

2.4.1. [^{18}F]Fluoroestradiol ([^{18}F] FES)

Assessment of hormone receptor status is an integral part of making decisions for subsequent treatment. For example, estrogen receptors are expressed in about 2/3 of patients with invasive breast cancer (Carlson et al., 2007). [^{18}F]Fluoroestradiol can visualize expression of estrogen receptors by showing a very similar behaviour to estrogen in a noninvasive way, but being bound to a radioactive marker isotope (Venema et al., 2016). In current clinical practice, estrogen receptor status is determined mainly by invasive biopsy followed by immunohistochemical examination. However, especially in patients with metastasis, some lesions are challenging or impossible for biopsy because of their location. Whereas, [^{18}F]Fluoroestradiol PET/CT is an excellent noninvasive tool to evaluate the estrogen status of all metastases throughout the entire body in a single exam (Kurland et al., 2020). Liu et al. reported that the use of [^{18}F]Fluoroestradiol PET/CT changed management of breast cancer in 26.3% of patients (Liu et al., 2019). Particularly bone metastases can be better identified by [^{18}F]Fluoroestradiol PET/CT. Further comprehensive studies are warranted in order to verify whether [^{18}F]Fluoroestradiol improves outcomes of patients with metastatic breast cancer based on the changes in treatment.

[^{18}F]Fluoroestradiol PET/CT seems to predict the extent of response to endocrine treatment (Ulaner et al., 2021). In conclusion, patients who are likely to benefit from endocrine treatment can be determined beforehand. This provides a unique treatment advantage, since an optimized regime can be selected before therapy failure occurs. Based on these features and potential

clinical benefit, [^{18}F]Fluoroestradiol PET/CT was approved in May 2021 by the FDA in patients with recurrent and öetastatic breast cancer.

2.4.2. FAPI: A new tracer for theranostic concepts

Fibroblast-activation-protein (FAP) seems to be a promising target for future theranostic strategies. FAP is primarily expressed by cancer-related fibroblasts and was detected in more than 90% of human epithelial cancers (Lindner et al., 2018). Several FAPI PET tracers including [^{68}Ga]Ga-FAPI-04 and [^{68}Ga]Ga-FAPI-46 are currently assessed for the diagnostic imaging process (Dendl et al., 2021). Kratochwil et al. showed that breast cancer has a high FAPI uptake (Kratochwil et al., 2019). FAPI PET/CT was superior over [^{18}F]Fluoroestradiol PET/CT in identification of the primary tumor in addition to various metastases because of its high SUV_{max}.

FAPI also enables to be used as a theranostic ligand in conjunction with Yttrium-90 or Lutetium-177. Both variants have been used as a therapeutic radionuclide in patients with end stage breast cancers (Ballal et al., 2021). Early findings suggest that a significant decrease can be achieved in pain medication through FAPI therapy. In addition FAPI has not shown toxicity, and particularly hematotoxicity.

2.3. Future perspective for using contrast-enhanced MRI for breast cancer screening

The use of shorter and less expensive MRI protocol is necessary in order to enable wider use of breast MRI and cost-effectiveness. The concept of abbreviated breast MRI was introduced for this purpose. Abbreviated breast MRI reduces the acquisition time to three minutes and enables much faster reading (Kuhl et al., 2014). Studies conducted on this subject have shown that abbreviated protocols provide equal cancer detection performance compared with more extended breast MRI protocols (Lithner et al., 2018). Assessment of only these ultrafast acquisitions was recently shown to provide similar results as reading a full protocol including diffusion-weighted imaging (DWI) (van Zelst et al., 2018). Unfortunately, MRI method requires the use of an intravenous contrast agent. MRI methods that do not require contrast administration such as DWI are under evaluation. Therefore, currently MRI techniques without i.v. contrast agent administration can not compete with contrast-enhanced MRI for breast screening.

CONCLUSION

As in other fields of medicine, the development of new imaging modalities for detection of breast cancer, prognosis and response to treatment, metastases and recurrence is continuing. With the integration of artificial intelligence with these modalities will provide a higher performance, reducing screening time and costs. 3D imaging using neural networks seems promising in facilitating the management of breast cancer. Further comprehensive studies are needed to evaluate performance of novel imaging modalities.

REFERENCES

Ballal, S., Yadav, M. P., Kramer, V., Moon, E. S., Roesch, F., Tripathi, M., Mallick, S., ArunRaj, S. T., & Bal, C. (2021). A theranostic approach of [68Ga]Ga-DOTA.SA.FAPi PET/CT-guided [177Lu]Lu-DOTA.SA.FAPi radionuclide therapy in an end-stage breast cancer patient: new frontier in targeted radionuclide therapy. European journal of nuclear medicine and molecular imaging, 48(3), 942–944.

Berg W. A. (2009). Tailored supplemental screening for breast cancer: what now and what next?. AJR. American journal of roentgenology, 192(2), 390–399.

Bernardi, D., Macaskill, P., Pellegrini, M., Valentini, M., Fantò, C., Ostillio, L., Tuttobene, P., Luparia, A., & Houssami, N. (2016). Breast cancer screening with tomosynthesis (3D mammography) with acquired or synthetic 2D mammography compared with 2D mammography alone (STORM-2): a population-based prospective study. The Lancet. Oncology, 17(8), 1105–1113.

Bosmans, H., De Hauwere, A., Lemmens, K., Zanca, F., Thierens, H., Van Ongeval, C., Van Herck, K., Van Steen, A., Martens, P., Bleyen, L., Vande Putte, G., Kellen, E., Mortier, G., & Van Limbergen, E. (2013). Technical and clinical breast cancer screening performance indicators for computed radiography versus direct digital radiography. European radiology, 23(10), 2891–2898.

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians, 68(6), 394–424.

Carlson, R. W., Anderson, B. O., Burstein, H. J., Carter, W. B., Edge, S. B., Farrar, W. B., Goldstein, L. J., Gradishar, W. J., Hayes, D. F., Hudis, C. A., Jahanzeb, M., Ljung, B. M., Kiel, K., Marks, L. B., McCormick, B., Nabell, L. M., Pierce, L. J., Reed, E. C., Silver, S. M., Smith, M. L., … Wolff, A. C. (2007). Invasive breast cancer. Journal of the National Comprehensive Cancer Network : JNCCN, 5(3), 246–312.

Coleman, M. P., Quaresma, M., Berrino, F., Lutz, J. M., De Angelis, R., Capocaccia, R., Baili, P., Rachet, B., Gatta, G., Hakulinen, T., Micheli, A., Sant, M., Weir, H. K., Elwood, J. M., Tsukuma, H., Koifman, S., E Silva, G. A., Francisci, S., Santaquilani, M.,

Verdecchia, A., … CONCORD Working Group (2008). Cancer survival in five continents: a worldwide population-based study (CONCORD). The Lancet. Oncology, 9(8), 730–756.

Conners, A. L., Jones, K. N., Hruska, C. B., Geske, J. R., Boughey, J. C., & Rhodes, D. J. (2015). Direct-Conversion Molecular Breast Imaging of Invasive Breast Cancer: Imaging Features, Extent of Invasive Disease, and Comparison Between Invasive Ductal and Lobular Histology. AJR. American journal of roentgenology, 205(3), W374–W381.

Dendl, K., Koerber, S. A., Finck, R., Mokoala, K. M. G., Staudinger, F., Schillings, L., Heger, U., Röhrich, M., Kratochwil, C., Sathekge, M., Jäger, D., Debus, J., Haberkorn, U., & Giesel, F. L. (2021). 68Ga-FAPI-PET/CT in patients with various gynecological malignancies. European journal of nuclear medicine and molecular imaging, 48(12), 4089–4100.

Ginsburg, O., Bray, F., Coleman, M. P., Vanderpuye, V., Eniu, A., Kotha, S. R., Sarker, M., Huong, T. T., Allemani, C., Dvaladze, A., Gralow, J., Yeates, K., Taylor, C., Oomman, N., Krishnan, S., Sullivan, R.,

Groheux, D., Espié, M., Giacchetti, S., & Hindié, E. (2013). Performance of FDG PET/CT in the clinical management of breast cancer. Radiology, 266(2), 388–405.

Hofvind, S., Hovda, T., Holen, Å. S., Lee, C. I., Albertsen, J., Bjørndal, H., Brandal, S. H. B., Gullien, R., Lømo, J., Park, D., Romundstad, L., Suhrke, P., Vigeland, E., & Skaane, P. (2018). Digital Breast Tomosynthesis and Synthetic 2D Mammography versus Digital Mammography: Evaluation in a Population-based Screening Program. Radiology, 287(3), 787–794.

Jafari, S. H., Saadatpour, Z., Salmaninejad, A., Momeni, F., Mokhtari, M., Nahand, J. S., Rahmati, M., Mirzaei, H., & Kianmehr, M. (2018). Breast cancer diagnosis: Imaging techniques and biochemical markers. Journal of cellular physiology, 233(7), 5200–5213.

Kim, D.H., Kim, S.T., Ro, Y.M. (2016). Latent feature representation with 3-D multi-view deep convolutional neural network for bilateral analysis in digital breast tomosynthesis, 2016 IEEE International Conference on Acoustics, Speech and Signal Processing (ICASSP) 927–931.

Kooi, T., Litjens, G., van Ginneken, B., Gubern-Mérida, A., Sánchez, C. I., Mann, R., den Heeten, A., & Karssemeijer, N. (2017). Large scale

deep learning for computer aided detection of mammographic lesions. Medical image analysis, 35, 303–312.

Kombe, D., Blas, M. M., Parham, G., Kassami, N., … Conteh, L. (2017). The global burden of women's cancers: a grand challenge in global health. Lancet (London, England), 389(10071), 847–860.

Kratochwil, C., Flechsig, P., Lindner, T., Abderrahim, L., Altmann, A., Mier, W., Adeberg, S., Rathke, H., Röhrich, M., Winter, H., Plinkert, P. K., Marme, F., Lang, M., Kauczor, H. U., Jäger, D., Debus, J., Haberkorn, U., & Giesel, F. L. (2019). 68Ga-FAPI PET/CT: Tracer Uptake in 28 Different Kinds of Cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 60(6), 801–805.

Kurland, B. F., Wiggins, J. R., Coche, A., Fontan, C., Bouvet, Y., Webner, P., Divgi, C., & Linden, H. M. (2020). Whole-Body Characterization of Estrogen Receptor Status in Metastatic Breast Cancer with 16α-18F-Fluoro-17β-Estradiol Positron Emission Tomography: Meta-Analysis and Recommendations for Integration into Clinical Applications. The oncologist, 25(10), 835–844.

Kuhl, C. K., Schrading, S., Strobel, K., Schild, H. H., Hilgers, R. D., & Bieling, H. B. (2014). Abbreviated breast magnetic resonance imaging (MRI): first postcontrast subtracted images and maximum-intensity projection-a novel approach to breast cancer screening with MRI. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 32(22), 2304–2310.

Leithner, D., Moy, L., Morris, E. A., Marino, M. A., Helbich, T. H., & Pinker, K. (2019). Abbreviated MRI of the Breast: Does It Provide Value?. Journal of magnetic resonance imaging : JMRI, 49(7), e85–e100.

Lindner, T., Loktev, A., Altmann, A., Giesel, F., Kratochwil, C., Debus, J., Jäger, D., Mier, W., & Haberkorn, U. (2018). Development of Quinoline-Based Theranostic Ligands for the Targeting of Fibroblast Activation Protein. Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 59(9), 1415–1422.

Liu, C., Gong, C., Liu, S., Zhang, Y., Zhang, Y., Xu, X., Yuan, H., Wang, B., & Yang, Z. (2019). 18F-FES PET/CT Influences the Staging and Management of Patients with Newly Diagnosed Estrogen Receptor-Positive Breast Cancer: A Retrospective Comparative Study with 18F-FDG PET/CT. The oncologist, 24(12), e1277–e1285.

Ma, Q., Chen, B., Gao, S., Ji, T., Wen, Q., Song, Y., Zhu, L., Xu, Z., & Liu, L. (2014). 99mTc-3P4-RGD2 scintimammography in the assessment

of breast lesions: comparative study with 99mTc-MIBI. PloS one, 9(9), e108349.

Ozsoy, A., Barca, N., Dolek, B. A., Aktaş, H., Elverici, E., Araz, L., & Ozkaraoğlu, O. (2017). The Relationship Between Breast Cancer and Risk Factors: A Single-Center Study. European journal of breast health, 13(3), 145–149.

Park, M. J., Park, E. C., Choi, K. S., Jun, J. K., & Lee, H. Y. (2011). Sociodemographic gradients in breast and cervical cancer screening in Korea: the Korean National Cancer Screening Survey (KNCSS) 2005-2009. BMC cancer, 11, 257.

Parkin, D. M., Bray, F., Ferlay, J., & Pisani, P. (2005). Global cancer statistics, 2002. CA: a cancer journal for clinicians, 55(2), 74–108.

Polyak K. (2007). Breast cancer: origins and evolution. The Journal of clinical investigation, 117(11), 3155–3163.

Riggio, A.I., Varley, K.E. and Welm, A.L. (2021) "The lingering mysteries of metastatic recurrence in breast cancer," https://www.nature.com/articles/s41416-020-01161-4.

Rinzivillo, M., Partelli, S., Prosperi, D., Capurso, G., Pizzichini, P., Iannicelli, E., Merola, E., Muffatti, F., Scopinaro, F., Schillaci, O., Salgarello, M., Falconi, M., Delle Fave, G., & Panzuto, F. (2018). Clinical Usefulness of 18F-Fluorodeoxyglucose Positron Emission Tomography in the Diagnostic Algorithm of Advanced Entero-Pancreatic Neuroendocrine Neoplasms. The oncologist, 23(2), 186–192.

Sechopoulos, I., Teuwen, J., & Mann, R. (2021). Artificial intelligence for breast cancer detection in mammography and digital breast tomosynthesis: State of the art. Seminars in cancer biology, 72, 214–225.

Skaane, P., Bandos, A. I., Gullien, R., Eben, E. B., Ekseth, U., Haakenaasen, U., Izadi, M., Jebsen, I. N., Jahr, G., Krager, M., Niklason, L. T., Hofvind, S., & Gur, D. (2013). Comparison of digital mammography alone and digital mammography plus tomosynthesis in a population-based screening program. Radiology, 267(1), 47–56.

Sun, Y. S., Zhao, Z., Yang, Z. N., Xu, F., Lu, H. J., Zhu, Z. Y., Shi, W., Jiang, J., Yao, P. P., & Zhu, H. P. (2017). Risk Factors and Preventions of Breast Cancer. International journal of biological sciences, 13(11), 1387–1397.

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA: a cancer journal for clinicians, 71(3), 209–249.

Schillaci, O., & Urbano, N. (2017). Personalized medicine: a new option for nuclear medicine and molecular imaging in the third millennium. European journal of nuclear medicine and molecular imaging, 44(4), 563–566.

Thomassin-Naggara, I., Balleyguier, C., Ceugnart, L., Heid, P., Lenczner, G., Maire, A., Séradour, B., Verzaux, L., Taourel, P., & Conseil national professionnel de la radiologie et imagerie médicale (G4) (2019). Artificial intelligence and breast screening: French Radiology Community position paper. Diagnostic and interventional imaging, 100(10), 553–566.

Ulaner, G. A., Jhaveri, K., Chandarlapaty, S., Hatzoglou, V., Riedl, C. C., Lewis, J. S., & Mauguen, A. (2021). Head-to-Head Evaluation of 18F-FES and 18F-FDG PET/CT in Metastatic Invasive Lobular Breast Cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine, 62(3), 326–331.

United States Food and Drug Administration. Novel drug approvals for 2020. Available from: www.fda.gov2021, https://www. fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2020.

van Zelst, J. C. M., Vreemann, S., Witt, H. J., Gubern-Merida, A., Dorrius, M. D., Duvivier, K., Lardenoije-Broker, S., Lobbes, M. B. I., Loo, C., Veldhuis, W., Veltman, J., Drieling, D., Karssemeijer, N., & Mann, R. M. (2018). Multireader Study on the Diagnostic Accuracy of Ultrafast Breast Magnetic Resonance Imaging for Breast Cancer Screening. Investigative radiology, 53(10), 579–586.

Venema, C. M., Apollonio, G., Hospers, G. A., Schröder, C. P., Dierckx, R. A., de Vries, E. F., & Glaudemans, A. W. (2016). Recommendations and Technical Aspects of 16α-[18F]Fluoro-17β-Estradiol PET to Image the Estrogen Receptor In Vivo: The Groningen Experience. Clinical nuclear medicine, 41(11), 844–851.

Viale, G., de Snoo, F. A., Slaets, L., Bogaerts, J., van 't Veer, L., Rutgers, E. J., Piccart-Gebhart, M. J., Stork-Sloots, L., Glas, A., Russo, L., Dell'Orto, P., Tryfonidis, K., Litière, S., Cardoso, F., & MINDACT investigators (2018). Immunohistochemical versus molecular

(BluePrint and MammaPrint) subtyping of breast carcinoma. Outcome results from the EORTC 10041/BIG 3-04 MINDACT trial. Breast cancer research and treatment, 167(1), 123–131.

Zackrisson, S., Lång, K., Rosso, A., Johnson, K., Dustler, M., Förnvik, D., Förnvik, H., Sartor, H., Timberg, P., Tingberg, A., & Andersson, I. (2018). One-view breast tomosynthesis versus two-view mammography in the Malmö Breast Tomosynthesis Screening Trial (MBTST): a prospective, population-based, diagnostic accuracy study. The Lancet. Oncology, 19(11), 1493–1503.

CHAPTER 5

THE ROLES OF SERINE/THREONINE KINASE CK2 AND INTERLEUKIN-7/ INTERLEUKIN-7 RECEPTOR IN CANCER PATHOPHYSIOLOGY

Assoc. Prof. Dr. Güngör Çağdaş DİNÇEL[1]

[1] Aksaray University, Eskil Vocational High School, Aksaray/TURKEY
E-mail: gcdincel@yahoo.com.tr
ORCID ID: 0000-0002-6985-3197

INTRODUCTION

Primary cancer cells have high metabolic demands, particularly for proliferation and subsequent invasion of new tissues. They also metabolically differentiate in order to evade the body's defence systems and survive (Galluzzi et al., 2013; Cairns et al., 2011). Studies of cancer cells have a long history. First observed by Otto Warburg in 1924, he showed that many cancer cells metabolise glucose via aerobic glycolysis, a different pathway to the oxidative phosphorylation of glucose in healthy cells, prioritising biosynthesis over energy production. Subsequent studies have shown that rapidly proliferating cancer cells actively use pentose phosphate metabolism, lipid biosynthesis, high glucose/glutamine consumption and autophagy (Galluzzi et al., 2013; Kroemer & Pouyssegur, 2008).

This chapter reviews the results of in vivo/in vitro studies of protein kinase CK2 (Ser/Thr CK2) and interleukin-7 (IL-7)/interleukin-7 receptor (IL-7R) expression and activity levels in cancer cells. In addition, the complex consequences of these important markers in cancer pathogenesis are interpreted in detail and important points are highlighted.

1. Pathophysiology of Ser/Thr CK2 in Cancer

Ser/Thr CK2 is a serine/threonine kinase with numerous protein substrates and is one of the key cellular signals for cell survival, growth and proliferation (St-Denis & Litchfield, 2009; Strum et al., 2022). This enzyme is at a critical juncture for the continuation of life. Not only is it involved in all stages of the cell cycle, but it also plays a crucial role in the decision-making process of controlled cell death (apoptosis) (St-Denis & Litchfield, 2009; Strum et al., 2022).

When we look at the important role of Ser/Thr CK2 in cancer, some points cannot be ignored. It was found that Ser/Thr CK2 alpha, a subunit of Ser/Thr CK2, was localised in the perinuclear region, whereas alpha was localised in the intranuclear region within 2 to 6 hours after exposure of HeLa human cervical carcinoma cells to ionising radiation (IR). Therefore, the dynamic relocalisation of Ser/Thr CK2 subunits after IR is quite remarkable. However, it was shown that apoptosis was increased with the decrease of Ser/Thr CK2 alpha and alphaI subunits. In addition, this study suggests that Ser/Thr CK2 also acts through caspases after treatment with z-VAD, a pan-caspase inhibitor. This study shows that the Ser/Thr CK2 alpha and alphaI subunits contribute to the inhibition of caspase-mediated apoptosis and play

an active role in the cancer process (Yamane & Kinsella, 2005). Therefore, it is clear that the association of Ser/Thr CK2 with apoptosis in the pathogenesis of cervical carcinoma affects the prognosis of the disease.

A very strong negative correlation was found between Ser/Thr CK2 and miR-532-5p expressions in ovarian cancer. In human ovarian cancer cell lines, Ser/Thr CK2A2 expression was significantly down-regulated in response to overexpression of miR-532-5p over a 96 hour period. Thus, miR-532-5p negatively regulated the master gene controlling the Wnt pathway. Furthermore, the results obtained by suppressing Ser/Thr CK2A2 showed that Ser/Thr CK2A2 is indispensable for the proliferation of human ovarian cancer cells, suggesting that miR-532-5p plays an important role in the regulation of Ser/Thr CK2A2 (Wang, et al., 2016). Therefore, this strong negative correlation between Ser/Thr CK2 and miR-532-5p expressions is an important finding for determining treatment processes.

The role of Ser/Thr CK2 was investigated in experimentally developed T-cell lymphoma in adult transgenic mice, and it was observed that neonatal leukaemia occurred with co-expression of the c-myc transgene. These findings demonstrated that the Ser/Thr CK2 gene can act as an oncogene and that pathological expression of c-myc in lymphocytes can induce T-cell lymphoma (Seldin & Leder, 1995). Ser/Thr CK2 alpha transgenic mice, in which the p53 gene is partially or completely suppressed, were found to develop thymic lymphoma significantly faster than p53-deficient mice lacking the Ser/Thr CK2 alpha transgene. It was explained that the p53 gene is heterozygous in Ser/Thr CK2 alpha transgenic mice and that the loss of the p53 allele leads to progressive tumour development in lymphoma cases. This indicates that loss of the p53 gene plays an important role in tumour development. Importantly, it was also reported that in transgenic mice null for p53, thymic lymphoma appeared as early as three weeks of age, but p53 was still monoclonal (Landesman-Bollag et al., 1998). This finding clearly indicates that additional stochastic mutations are indeed involved in the development of lymphoma. Ser/Thr CK2 appears to contribute to the development of thymic lymphoma.

Using antisense oligodeoxynucleotides (ODNs) against the alpha and beta subunits of Ser/Thr CK2, important findings were obtained in a study investigating the potential effects of increasing or decreasing Ser/Thr CK2 signalling in cancer cell lines. Antisense Ser/Thr CK2-alpha was shown to be more effective than antisense Ser/Thr CK2-beta in cancer cell lines. In

addition, antisense ODN was found to significantly induce strong apoptosis in all cases. When the effect of antisense ODN on Ser/Thr CK2 activity in the nuclear matrix was examined, it was found to be less effective than its strong role in apoptosis. Consequently, these findings suggest that down-regulation of Ser/Thr CK2 can strongly induce an apoptotic response in cancer cells (Wang et al, 2001). Indeed, these findings suggest that Ser/Thr CK2 plays an important role in the apoptosis induction phase in cancer cells. Therapeutically, the development of Ser/Thr CK2 inhibition therapies may shed light on how to defeat cancer.

Comparative studies in human and rat models of breast cancer have suggested that Ser/Thr CK2 may be associated with tumour development. Ser/Thr CK2 has been shown to be highly expressed at pathological levels in human and rat mammary tumours. Furthermore, transgenic mice with dysregulated overexpression of Ser/Thr CK2 alpha in the mammary gland showed hyperplasia and dysplasia in the mammary gland. In addition to increased beta-catenin protein expression in these mice, mammary adenocarcinoma was found to be associated with activation of the Wnt pathway. The activation of NF-kappaB and the high expression of c-Myc are considered remarkable findings. The decrease in NF-kappaB expression with inhibition of Ser/Thr CK2 is a remarkable finding (Landesman-Bollag et al., 2001; Landesman-Bollag et al., 2001). In conclusion, dysregulated expression of Ser/Thr CK2 is closely associated with breast tumour development and its inhibition may be one of the treatment strategies.

In recent years, studies have been carried out to gain a better understanding of the pathogenesis of multiple myeloma (MM). Studies investigating the role of Ser/Thr CK2 in the pathogenesis of MM are some of them. High Ser/Thr CK2 expression has been found at pathological levels in MM cell lines and highly purified malignant plasma cells from patients with MM compared to normal polyclonal plasma cells and B lymphocytes. Inhibition of Ser/Thr CK2 in MM plasma cells was also developed in this study and the elimination of both extrinsic and intrinsic caspase cascades was induced with a cytotoxic effect on cancer cells. Furthermore, this Ser/Thr CK2 inhibition resulted in an impairment of IL-6-dependent STAT3 activation and a decrease in NF-kappaB-driven transcription (Piazza et al., 2006). Ser/Thr CK2 has been shown to localise to the endoplasmic reticulum (ER) in myeloma cells in vitro and in vivo, and ER stress triggers kinase activity. Again, Ser/Thr CK2 inhibition decreased the levels of IRE1α and

BIP/GRP78, which are important markers of ER stress. In addition, PERK and EIF2α phosphorylation increased and ER stress-induced apoptosis developed (Manni et al., 2012). These results clearly demonstrate that Ser/Thr CK2 is involved in the pathophysiology of MM and suggest that it plays an important role in the survival of malignant plasma cells. Inhibition of Ser/Thr CK2, impaired STAT3 activation, decreased NF-kappaB-driven transcription and positive correlation between Ser/Thr CK2 and ER stress are important points to consider in the development of therapeutic strategies.

Ser/Thr CK2 has been reported to play an important role in the development of lung cancer. Ser/Thr CK2 alpha was shown to be a positive regulator of Notch1 signalling in A549 and H1299 lung cancer cell lines. When Ser/Thr CK2 alpha expression was inhibited, Notch1 protein levels were significantly reduced in lung cancer cells. However, the expected result was obtained. That is, as a result of forced overexpression of Ser/Thr CK2 alpha, an increase in Notch1 transcriptional activity was observed. In addition to these findings, inhibition of Ser/Thr CK2 alpha resulted in a decrease in the ratio of the CD44+/CD24- cell population. In short, Ser/Thr CK2 alpha inhibition was found to reduce Notch1 expression and cancer stem-like cell population in lung cancer cells (Zhang et al., 2013). Indeed, this study shows that there is a positive correlation between Ser/Thr CK2 alpha and Notch1 expression. In another study in the same lung cancer cell lines, Ser/Thr CK2 was positively correlated with Hh/Gli signalling. In one hundred primary lung cancer tissues, a strong correlation was found between Ser/Thr CK2 alpha and Gli1 mRNA levels. In addition to this finding, the expression of markers indicative of the Hedgehog (Hh) signalling pathway involved in stem cell production was shown to be reduced. In contrast to Ser/Thr CK2 alpha inhibition, forced overexpression of Ser/Thr CK2 alpha resulted in a significant increase in both Gli1 expression and transcriptional activity in lung cancer A549 cell lines (Zhang et al., 2012). These findings clearly indicate that Ser/Thr CK2 is involved in the pathogenesis of lung cancer with a positive correlation in the Hh/Gli signalling pathway.

In general, all these studies show that there is a similarity in the pathogenesis of cancer, regardless of the type of cancer. This similarity is mainly the role of Ser/Thr CK2. It is clear that Ser/Thr CK2 does indeed play a role in the development of cancer cells and at all stages from the development to the feeding of the stem cell. Therefore, it is believed that this is a point that should not be ignored in the fight against cancer. At this point,

it is important to fully understand the role of Ser/Thr CK2 and to develop methods to inhibit it.

2. Pathophysiology of IL-7/IL-7R in Cancer

Interleukin-7 (IL-7), a well-defined lymphopoietic cytokine, is produced by resting stromal cells in lymphoid tissues (Wang et al., 2001; Mazzucchelli & Durum, 2007). IL-7 is essential for the development and survival of T lymphocytes and has been described to play a critical role in peripheral T cell homeostasis (Fry & Mackall, 2005). It is also an essential cytokine for the adaptive immune system and has been shown to play an important role in B cell development (Parrish et al., 2009). Studies have shown that IL-7 regulates itself in a very delicate balance. IL-7 has the ability to adapt to environmental conditions by down-regulating its receptor, the IL-7 receptor (IL-7R), which is found on most T cells (Barata et al., 2019). In this case, it is clear that the biological functions of IL-7 are mainly mediated by IL-7R activation. In addition, IL-7 contributes to the memory and maintenance of naive T cell populations. In cases of lymphopenia, IL-7 levels are significantly increased and contribute to the restoration of peripheral T cell homeostasis (Fry & Mackall, 2005; Barata et al., 2019). IL-7 is expressed through the equilibrium within the Bcl-2 family members. In fact, Bcl-2 itself and Mcl-1 on the positive side and Bax, Bad and Bim expression on the negative side adapt to the requirements of IL-7 (Jiang et al., 2005).

It has been suggested that IL-7, a potent growth factor, may be responsible for lymphoid tumour formation. Rich et al 1993 showed that IL-7 expression leads to a prolonged preneoplastic pilonidal lymphoproliferative state followed by the development of lymphoma. They explained that lymphomas and thymomas are of both B and T cell origin. As a result, long-term IL-7 expression in vivo largely promotes the development of monoclonal tumours (Rich et al., 1993).

Gamma-cytokines have been shown to play a role in the pathophysiology of T-cell acute lymphoblastic leukaemia (T-ALL). The role of all gamma-cytokines in the proliferation of primary T-ALL cells has been clearly demonstrated. Most importantly, IL-7 is the cytokine that most frequently induces leukaemic cell proliferation and promotes the strongest responses (Barata et al, 2004). These results clearly indicate that IL-7 may act as a critical regulator of T-ALL and contribute to cancer development.

Studies show that IL-7, acting through IL-7R, is closely associated with poor prognosis in prostate cancer. Both IL-7 and IL-7R expressions have been shown to be significantly up-regulated in prostate cancer cells. In fact, IL-7 has been reported to promote the invasion and migration of prostate cancer cells. In the molecular pathogenesis, IL-7 and IL-7R trigger AKT and nuclear factor kappa B (NF-κB) activation, while blocking AKT was shown to suppress IL-7-mediated NF-κB activity. Furthermore, IL-7 and IL-7R increased matrix metalloproteinase (MMP)-3 and MMP-7 expression in prostate cancer cells, while inhibition of MMP activity significantly suppressed IL-7-mediated cell invasion and migration (Qu ve ark., 2016; Alshyarba ve ark., 2021). It is clear that IL-7 and IL-7R contribute to prostate cancer cell invasion and migration as they are responsible for the increase in AKT/NF-κB and MMP-3 and MMP-7 expression. Therefore, the complete elucidation of the links between these pathways, primarily with IL-7 and IL-7R, will be an important step in determining the pathogenesis of the disease.

A study on the role and regulatory mechanisms of IL-7R in hepatitis B virus (HBV)-associated hepatocellular carcinoma (HCC) has been published. HBV was shown to induce a significant increase in IL-7R expression in hepatoma cells via the multifunctional non-structural protein X (HBX). HBX was shown to be responsible for HBV-mediated upstream expression of IL-7R. That is, HBX and IL-7R expression were highly expressed in HBV-associated HCC tissues. Furthermore, IL-7R was described to be primarily responsible for HBX-induced proliferation and migration of hepatoma cells. It was clearly demonstrated that HBX contributes to the proliferation and migration of hepatoma cells by causing an increase in IL-7R expression (Kong et al., 2016). This study demonstrates that IL-7R is significantly involved in the molecular pathogenesis of HCC. Importantly, the fact that the IL-7R gene is one of the genes likely to be associated with the dedifferentiation of HCC (Midorikawa et al., 2002) shows that it is at a point that cannot be ignored in this cancer.

IL-7R expression has been shown to play an important role in the poor prognosis of esophageal squamous cell carcinoma (ESCC). IL-7R expression was shown to be significantly increased in ESCC cells cultured directly with macrophages. It was clearly demonstrated that this high IL-7R expression contributes to the survival and growth of cancer cells through the activation of AKT and Erk1/2 signalling pathways. Furthermore, the migratory ability of ESCC cells was also found to be enhanced by IL-7/IL-

7R-induced activation of the AKT and Erk1/2 pathways. In addition to these findings, increased numbers of cancer-associated fibroblasts (CAFs) and tumour-associated macrophages were positively correlated with high levels of IL-7R expression, which was associated with poor prognosis in ESCC patients (Kitamura et al., 2023). In light of these findings, it should be considered that increased expression of IL-7R may promote the development of malignancy in cancer cells. Therefore, these findings suggest that IL-7R may be a novel therapeutic target for ESCC.

IL-7-expressing CAFs were shown to promote the development of breast cancer cells by maintaining tumour cell stem cells. Under the control of IL-7, fibroblasts, which act as key modulators of cancer progression, were found to straddle the boundary where they physically interact with tumour cells and were highly expressed in these regions. Removal of IL-7-expressing fibroblasts from the centre of the tumour was also shown to disrupt breast tumour growth and reduce the clonogenic potential of cancer cells. In particular, CXCL12 expression was found to be strongly increased in IL-7-expressing CAFs (Boesch et al., 2018). This suggests that CXCL12 expression and IL-7 expression are linked in the development of breast cancer cells. In short, it is quite clear that IL-7-expressing CAFs play a role in the promotion of tumour cell stem cells and the proliferation of breast cancer cells.

There is strong evidence that IL-7 and IL-7R play an important role in the pathogenesis of lung cancer. In lung cancer cell lines and nude mice, three key points in the development of cancer cells have been demonstrated. IL-7 and IL-7R were found to 1) increase cyclin D1 expression, a regulator of the cell cycle, 2) increase c-Fos/c-Jun phosphorylation and 3) significantly induce c-Fos and c-Jun heterodimer formation. It has also been shown to increase c-Fos/c-Jun DNA binding activity to regulate cyclin D1. In lung cancer, inhibition of IL-7R to reduce cell proliferation has also been shown to be beneficial for disease prognosis (Ming et al., 2012). IL-7 and IL-7R appear to induce upregulation of cyclin D1 via the c-Fos/c-Jun pathway to promote cell proliferation in lung cancer. In a similar study, IL-7 and IL-7R were shown to induce a significant increase in the expression of vascular endothelial growth factor (VEGF)-D. It was also shown that VEGF-D was upregulated via the same c-Fos/c-Jun signalling pathway, thereby increasing lymphangiogenesis (Ming et al., 2009; Ming et al., 2012). These findings clearly indicate that IL-7 and IL-7R play an important role in the poor prognosis of lung cancer.

In a study linking IL-7 to autophagy in non-small cell lung cancer, three different IL-7-mediated pathogenesis were identified. 1) IL-7 induces translocation of the anti-apoptotic marker p53 from the nucleus to the cytoplasm, 2) it induces inhibition of AMP-activated protein kinase (AMPK) phosphorylation and vice versa, 3) it was shown to induce mammalian target of rapamycin (mTOR) phosphorylation. The mechanism by which IL-7 inhibits autophagy is precisely through the AMPK/mTOR pathway regulated by p53 (Zhu et al, 2022). These findings suggest that AMPK and p53 expression act in concert with IL-7/IL-7R and mTOR expression. Therefore, these signalling pathways are important in the pathogenesis of NSCLC.

These studies show that IL-7 and its receptor IL-7R play a very important role in cancer pathogenesis, although they do not differ according to the type of cancer. IL-7/IL-7R, which is very important for life, seriously threatens life in cancer processes. It is therefore crucial to identify the right stage at which to intervene. Although the studies on IL-7/IL-7R are extensive, there are still many unanswered questions.

CONCLUSION

In conclusion, although much work has been done on the complex networks involved in cancer pathogenesis, a fully elucidated map is still lacking. The main point highlighted in this chapter is the importance of identifying specific targets of pathways in cancer pathogenesis for therapeutic intervention. Therefore, Ser/Thr CK2 and IL-7/IL-7R expressions, which have clearly been shown to play an important role in the development of cancer cells, are considered priority targets. In light of the studies discussed in this chapter, it is not difficult to conclude that targeted combination trials in cancer therapy will continue to develop over the next few years.

REFERENCES

Alshyarba, M., Otifi, H., Al Fayi, M., A Dera, A., & Rajagopalan, P. (2021). Thymoquinone inhibits IL-7-induced tumor progression and metastatic invasion in prostate cancer cells by attenuating matrix metalloproteinase activity and Akt/NF-κB signaling. *Biotechnology and applied biochemistry*, *68*(6),1403–1411.

Barata, J. T., Durum, S. K., & Seddon, B. (2019). Flip the coin: IL-7 and IL-7R in health and disease. *Nature immunology*, *20*(12),1584–1593.

Barata, J. T., Keenan, T. D., Silva, A., Nadler, L. M., Boussiotis, V. A., & Cardoso, A. A. (2004). Common gamma chain-signaling cytokines promote proliferation of T-cell acute lymphoblastic leukemia. *Haematologica*, *89*(12), 1459–1467.

Boesch, M., Onder, L., Cheng, H. W., Novkovic, M., Mörbe, U., Sopper, S., Gastl, G., Jochum, W., Ruhstaller, T., Knauer, M., & Ludewig, B. (2018). Interleukin 7-expressing fibroblasts promote breast cancer growth through sustenance of tumor cell stemness. *Oncoimmunology*, *7*(4), e1414129.

Cairns, R. A., Harris, I. S., & Mak, T. W. (2011). Regulation of cancer cell metabolism. *Nature reviews. Cancer*, *11*(2), 85–95.

Fry, T. J., & Mackall, C. L. (2005). The many faces of IL-7: from lymphopoiesis to peripheral T cell maintenance. *Journal of immunology (Baltimore, Md. : 1950)*, *174*(11), 6571–6576.

Galluzzi L, Kepp O, Vander Heiden MG, Kroemer G. Metabolic targets for cancer therapy. Nat Rev Drug Discov. 2013 Nov;12(11):829-46. doi: 10.1038/nrd4145.

Jiang, Q., Li, W. Q., Aiello, F. B., Mazzucchelli, R., Asefa, B., Khaled, A. R., & Durum, S. K. (2005). Cell biology of IL-7, a key lymphotrophin. *Cytokine & growth factor reviews*, *16*(4-5),513–533.

Kitamura, Y., Koma, Y. I., Tanigawa, K., Tsukamoto, S., Azumi, Y., Miyako, S., Urakami, S., Kodama, T., Nishio, M., Shigeoka, M., Kakeji, Y., & Yokozaki, H. (2023). Roles of IL-7R Induced by Interactions between Cancer Cells and Macrophages in the Progression of Esophageal Squamous Cell Carcinoma. *Cancers*, *15*(2),394.

Kong, F., Hu, W., Zhou, K., Wei, X., Kou, Y., You, H., Zheng, K., & Tang, R. (2016). Hepatitis B virus X protein promotes interleukin-7 receptor expression via NF-κB and Notch1 pathway to facilitate proliferation

and migration of hepatitis B virus-related hepatoma cells. *Journal of experimental & clinical cancer research : CR*, *35*(1), 172.

Kroemer, G., & Pouyssegur, J. (2008). Tumor cell metabolism: cancer's Achilles' heel. *Cancer cell*, *13*(6), 472–482.

Landesman-Bollag, E., Channavajhala, P. L., Cardiff, R. D., & Seldin, D. C. (1998). p53 deficiency and misexpression of protein kinase CK2alpha collaborate in the development of thymic lymphomas in mice. *Oncogene*, *16*(23), 2965–2974.

Landesman-Bollag, E., Romieu-Mourez, R., Song, D. H., Sonenshein, G. E., Cardiff, R. D., & Seldin, D. C. (2001). Protein kinase CK2 in mammary gland tumorigenesis. *Oncogene*, *20*(25), 3247–3257.

Landesman-Bollag, E., Song, D. H., Romieu-Mourez, R., Sussman, D. J., Cardiff, R. D., Sonenshein, G. E., & Seldin, D. C. (2001). Protein kinase CK2: signaling and tumorigenesis in the mammary gland. *Molecular and cellular biochemistry*, *227*(1-2), 153–165.

Manni, S., Brancalion, A., Tubi, L. Q., Colpo, A., Pavan, L., Cabrelle, A., Ave, E., Zaffino, F., Di Maira, G., Ruzzene, M., Adami, F., Zambello, R., Pitari, M. R., Tassone, P., Pinna, L. A., Gurrieri, C., Semenzato, G., & Piazza, F. (2012). Protein kinase CK2 protects multiple myeloma cells from ER stress-induced apoptosis and from the cytotoxic effect of HSP90 inhibition through regulation of the unfolded protein response. *Clinical cancer research : an official journal of the American Association for Cancer Research*, *18*(7), 1888–1900.

Mazzucchelli, R., & Durum, S. K. (2007). Interleukin-7 receptor expression: intelligent design. *Nature reviews. Immunology*, *7*(2), 144–154.

Midorikawa, Y., Tsutsumi, S., Taniguchi, H., Ishii, M., Kobune, Y., Kodama, T., Makuuchi, M., & Aburatani, H. (2002). Identification of genes associated with dedifferentiation of hepatocellular carcinoma with expression profiling analysis. *Japanese journal of cancer research : Gann*, *93*(6), 636–643.

Ming, J., Jiang, G., Zhang, Q., Qiu, X., & Wang, E. (2012). Interleukin-7 up-regulates cyclin D1 via activator protein-1 to promote proliferation of cell in lung cancer. *Cancer immunology, immunotherapy : CII*, *61*(1), 79–88.

Ming, J., Zhang, Q. F., Jiang, Y. D., Jiang, G. C., & Qiu, X. S. (2012). *Zhonghua bing li xue za zhi = Chinese journal of pathology*, *41*(8), 511–518.

Ming, J., Zhang, Q., Qiu, X., & Wang, E. (2009). Interleukin 7/interleukin 7 receptor induce c-Fos/c-Jun-dependent vascular endothelial growth factor-D up-regulation: a mechanism of lymphangiogenesis in lung cancer. *European journal of cancer (Oxford, England : 1990)*, *45*(5), 866–873.

Parrish, Y. K., Baez, I., Milford, T. A., Benitez, A., Galloway, N., Rogerio, J. W., Sahakian, E., Kagoda, M., Huang, G., Hao, Q. L., Sevilla, Y., Barsky, L. W., Zielinska, E., Price, M. A., Wall, N. R., Dovat, S., & Payne, K. J. (2009). IL-7 Dependence in human B lymphopoiesis increases during progression of ontogeny from cord blood to bone marrow. *Journal of immunology (Baltimore, Md. : 1950)*, *182*(7), 4255–4266.

Piazza, F. A., Ruzzene, M., Gurrieri, C., Montini, B., Bonanni, L., Chioetto, G., Di Maira, G., Barbon, F., Cabrelle, A., Zambello, R., Adami, F., Trentin, L., Pinna, L. A., & Semenzato, G. (2006). Multiple myeloma cell survival relies on high activity of protein kinase CK2. *Blood*, *108*(5), 1698–1707.

Qu, H., Zou, Z., Pan, Z., Zhang, T., Deng, N., Chen, G., & Wang, Z. (2016). IL-7/IL-7 receptor axis stimulates prostate cancer cell invasion and migration via AKT/NF-κB pathway. *International immunopharmacology*, *40*, 203–210.

Rich, B. E., Campos-Torres, J., Tepper, R. I., Moreadith, R. W., & Leder, P. (1993). Cutaneous lymphoproliferation and lymphomas in interleukin 7 transgenic mice. *The Journal of experimental medicine*, *177*(2), 305–316.

Seldin, D. C., & Leder, P. (1995). Casein kinase II alpha transgene-induced murine lymphoma: relation to theileriosis in cattle. *Science (New York, N.Y.)*, *267*(5199), 894–897.

St-Denis, N. A., & Litchfield, D. W. (2009). Protein kinase CK2 in health and disease: From birth to death: the role of protein kinase CK2 in the regulation of cell proliferation and survival. Cellular and molecular life sciences : CMLS, 66(11-12), 1817–1829.

Strum, S. W., Gyenis, L., & Litchfield, D. W. (2022). CSNK2 in cancer: pathophysiology and translational applications. *British journal of cancer*, *126*(7), 994–1003.

Wang, F., Chang, J. T., Kao, C. J., & Huang, R. S. (2016). High Expression of miR-532-5p, a Tumor Suppressor, Leads to Better Prognosis in

Ovarian Cancer Both In Vivo and In Vitro. *Molecular cancer therapeutics*, *15*(5), 1123–1131.

Wang, H., Davis, A., Yu, S., & Ahmed, K. (2001). Response of cancer cells to molecular interruption of the CK2 signal. *Molecular and cellular biochemistry*, *227*(1-2), 167–174.

Yamane, K., & Kinsella, T. J. (2005). CK2 inhibits apoptosis and changes its cellular localization following ionizing radiation. *Cancer research*, *65*(10), 4362–4367.

Zhang, S., Long, H., Yang, Y. L., Wang, Y., Hsieh, D., Li, W., Au, A., Stoppler, H. J., Xu, Z., Jablons, D. M., & You, L. (2013). Inhibition of CK2α down-regulates Notch1 signalling in lung cancer cells. *Journal of cellular and molecular medicine*, *17*(7), 854–862.

Zhang, S., Wang, Y., Mao, J. H., Hsieh, D., Kim, I. J., Hu, L. M., Xu, Z., Long, H., Jablons, D. M., & You, L. (2012). Inhibition of CK2α down-regulates Hedgehog/Gli signaling leading to a reduction of a stem-like side population in human lung cancer cells. *PloS one*, *7*(6), e38996.

Zhu, Y., Jiang, X., Ding, Z., & Ming, J. (2022). Interleukin 7 inhibit autophagy via P53 regulated AMPK/mTOR signaling pathway in non-small cell lung cancer. *Scientific reports*, *12*(1), 11208.

CHAPTER 6

BIOCHEMICAL PERSPECTIVE ON PARKINSON'S DISEASE

Dr. Ayşegül HANİKOĞLU[1]

Ress. Ass. Elif DELEN[2]

[1] Dr. Ayşegül Hanikoğlu, Istanbul Health and Technology University, Medical Biochemistry (ORCİD:0000-0003-1086 2184)
[2] Ress. Ass. Elif Delen, Istanbul Health and Technology University, Medical Biochemistry (ORCİD: 0000-0002-2913-0728)

1. PARKINSON'S DISEASE - DEFINITION

Parkinson's disease (PD) is a chronic and progressive neurodegenerative disorder that affects the nervous system and primarily affects movement. It is characterized by the degeneration and loss of dopamine-producing neurons in a part of the brain called the substantia nigra. The resulting dopamine deficiency in the brain leads to a range of motor symptoms, including tremors, rigidity, bradykinesia (slowness of movement), and postural instability. Parkinson's disease can also cause non-motor symptoms, such as depression, anxiety, sleep disturbances, and cognitive impairment. Parkinson's disease is typically diagnosed in people over the age of 60, but it can also affect younger people. Although there is currently no cure for Parkinson's disease, treatments are available to help manage the symptoms and improve quality of life (Ciofalo et al., 2019).

Parkinson's disease is named after James Parkinson, an English physician who first described the condition in 1817. His work, titled "An Essay on the Shaking Palsy," provided a detailed clinical description of the motor symptoms associated with the disease.In the late 19th and early 20th centuries, several researchers made significant contributions to the understanding of Parkinson's disease. Jean-Martin Charcot, a French neurologist, further expanded on the clinical description and classification of the disease, emphasizing the characteristic tremors and rigidity (Goetz, 2011).

2. THE REASONS OF PARKINSON'S DISEASE

The exact causes of Parkinson's disease are not yet fully understood, but it is believed to be a combination of genetic and environmental factors. Here are some of the possible reasons for Parkinson's disease:

Genetics: In some cases, Parkinson's disease may be inherited. Researchers have identified several genetic mutations that are associated with the development of the disease. Most Common genes related to Parkinson's Diseases are VPS35, LRRK2, PARK7, PINK1,PARK2,SNCA (Cherian & Divya, 2020).

Environmental factors: Exposure to certain toxins, such as pesticides, herbicides, and industrial chemicals, has been linked to an increased risk of Parkinson's disease (Goldman, 2014).

Age: Parkinson's disease is more common in older adults, and the risk of developing the disease increases with age (Emami Kazemabad et al., 2022).

Gender: Men are more likely to develop Parkinson's disease than women (Cerri, Mus, & Blandini, 2019) .

Head trauma: People who have experienced head injuries may have a higher risk of developing Parkinson's disease (Bower et al., 2003).

Inflammation: Chronic inflammation in the brain may contribute to the development of Parkinson's disease (Pajares, A, Manda, Bosca, & Cuadrado, 2020).

Oxidative stress: This is a process that occurs when there is an imbalance between free radicals and antioxidants in the body. Oxidative stress can damage cells in the brain and contribute to the development of Parkinson's disease (Subramaniam & Chesselet, 2013).

It is important to note that having one or more of these risk factors does not necessarily mean that a person will develop Parkinson's disease. The disease is complex, and more research is needed to fully understand the causes and contributing factors.

3. PARKINSON'S DISEASE SYMPTOMS

The symptoms of Parkinson's disease can vary from person to person, and may include both motor and non-motor symptoms (Sveinbjornsdottir, 2016). Some of the common symptoms of Parkinson's disease include:

Tremors: Tremors or shaking, typically in the hands, fingers, arms, or legs, are a hallmark symptom of Parkinson's disease.

Rigidity: Stiffness or rigidity in the muscles, which can make it difficult to move and may cause pain.

Bradykinesia: Slowness of movement, which can make simple tasks such as buttoning a shirt or walking difficult.

Postural instability: Impaired balance and coordination, which can increase the risk of falls.

Non-motor symptoms: Parkinson's disease can also cause non-motor symptoms such as depression, anxiety, sleep disturbances, cognitive impairment, and autonomic dysfunction (problems with blood pressure, heart rate, and digestion).

Micrographia: Small handwriting

Masked face: Reduced facial expression or a "mask-like" appearance.

It is important to note that not all people with Parkinson's disease will experience all of these symptoms, and the severity of symptoms can vary depending on the individual. In addition, some symptoms may worsen over time as the disease progresses. If you are experiencing any of these symptoms, it is important to see a healthcare provider for an evaluation (Eklund et al., 2022).

4. NEUROPATHOLOGY OF PARKINSON'S DISEASE

The neuropathology of Parkinson's disease involves the progressive degeneration of specific regions in the brain, particularly in the midbrain, where the substantia nigra is located. This leads to the loss of dopamine-producing neurons, which are critical for the regulation of movement and motor function. One of the hallmark neuropathological features of Parkinson's disease is the accumulation of a protein called alpha-synuclein in the brain. Alpha-synuclein is normally present in the brain and is involved in the regulation of synaptic function, but in Parkinson's disease, it forms abnormal clumps called Lewy bodies, which are found in the neurons of affected brain regions. The loss of dopamine-producing neurons and the accumulation of Lewy bodies in the brain are believed to disrupt the normal functioning of brain circuits that regulate movement, leading to the motor symptoms of Parkinson's disease such as tremors, rigidity, and bradykinesia. In addition to the loss of dopamine-producing neurons and the accumulation of Lewy bodies, other neuropathological features of Parkinson's disease include inflammation and oxidative stress, which can contribute to the degeneration of neurons (Dickson, 2018).

Another neuropathological changes in dopaminergic neurons includes degeneration of dopaminergic neurons,loss of dopaminergic transporters and changes in neurotransmitters.

Degeneration of Dopaminergic Neurons: Parkinson's disease is characterized by the selective degeneration of dopaminergic neurons in the substantia nigra. These neurons produce dopamine, a neurotransmitter critical for motor control. As the disease progresses, there is a progressive loss of these neurons, resulting in a significant reduction in dopamine levels in affected brain regions (Ikeda, Ebina, Kawabe, & Iwasaki, 2019).

Loss of Dopamine Transporters: Dopamine transporters are proteins responsible for reuptake of dopamine from the synaptic cleft. In Parkinson's disease, there is a significant loss of dopamine transporters, which can be visualized using imaging techniques like single-photon emission computed tomography (SPECT) or positron emission tomography (PET) scans. This loss reflects the degeneration of dopaminergic neurons (Ikeda et al., 2019).

Changes in Another Neurotransmitter Levels

Acetylcholine: Acetylcholine is another neurotransmitter involved in motor control. In Parkinson's disease, there is an imbalance between dopamine and acetylcholine levels, with an increase in acetylcholine activity due to the loss of dopaminergic inhibition. This imbalance contributes to the motor symptoms and disrupts the delicate balance necessary for smooth motor function (Bono et al., 2021).

Serotonin: Serotonin is a neurotransmitter that plays a role in mood regulation and other functions. Changes in serotonin levels have been observed in Parkinson's disease and may contribute to non-motor symptoms such as depression, anxiety, and sleep disturbances (Suratos, Del Rosario, & Jamora, 2020).

Noradrenaline (Norepinephrine): Noradrenaline is involved in regulating attention, arousal, and blood pressure. It has been found that there is a loss of noradrenaline-producing neurons in certain brain regions in Parkinson's disease. These changes may contribute to non-motor symptoms such as orthostatic hypotension (low blood pressure upon standing) and fatigue (Cacabelos et al., 2021).

Glutamate: Glutamate is the primary excitatory neurotransmitter in the brain. In Parkinson's disease, there are changes in glutamate levels and signaling, including increased glutamate release and altered glutamate receptor activity. These changes can contribute to excitotoxicity, a process that leads to neuronal damage and death, further exacerbating the neurodegenerative process (Lyu et al., 2021).

The interplay and imbalance between these neurotransmitters, particularly the dopamine-acetylcholine system, play a significant role in the motor symptoms of Parkinson's disease. Other neurotransmitters, such as serotonin, noradrenaline, and glutamate, contribute to non-motor symptoms

and the overall pathophysiology of the disease. Understanding these neurotransmitter changes is important for developing therapeutic strategies aimed at restoring neurotransmitter balance and managing the symptoms of Parkinson's disease**.**

Overall, the neuropathology of Parkinson's disease is complex and involves a combination of genetic and environmental factors, as well as changes in brain chemistry and the accumulation of abnormal proteins. Understanding the neuropathology of Parkinson's disease is important for the development of new treatments and therapies that can slow or halt the progression of the disease.

5.PATHOGENESIS OF PARKINSON'S DISEASE

5.1 Oxidative Stress -Inflammation and Mitochondrial Dysfunction

Oxidative stress, inflammation, and mitochondrial dysfunction are interconnected processes that can influence and exacerbate each other, contributing to various diseases, including neurodegenerative disorders like Parkinson's disease. Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's ability to neutralize and repair their damaging effects. ROS, such as free radicals, can cause cellular damage and trigger inflammation. In the context of Parkinson's disease, oxidative stress plays a significant role in the progressive degeneration of dopamine-producing neurons. The high energy demands of neurons make them particularly vulnerable to oxidative damage. Inflammation is the body's response to injury, infection, or other harmful stimuli. In the case of Parkinson's disease, chronic inflammation is believed to contribute to neurodegeneration. Activated immune cells release pro-inflammatory molecules, such as cytokines and chemokines, which can further induce oxidative stress. The inflammatory response in the brain can also activate microglia, the immune cells of the central nervous system, which can produce toxic substances that damage neurons. Mitochondrial dysfunction refers to abnormalities in the function and structure of mitochondria, the powerhouses of the cells responsible for energy production. Mitochondria are crucial for neuronal health, and any disruption in their function can lead to energy deficits, increased ROS production, and impaired cellular processes. In Parkinson's disease, dysfunctional mitochondria have been observed in affected brain regions and are thought to contribute to the degeneration of

dopamine neurons.The relationship between these processes is complex and interconnected. Oxidative stress can induce mitochondrial dysfunction by impairing mitochondrial DNA, enzymes, and membrane integrity, leading to reduced energy production and increased ROS generation. Mitochondrial dysfunction, in turn, can lead to increased oxidative stress as a result of impaired electron transport chain function. Both oxidative stress and mitochondrial dysfunction can trigger inflammatory responses, while inflammation, through the release of pro-inflammatory molecules, can exacerbate oxidative stress and further impair mitochondrial function. These processes create a vicious cycle, where oxidative stress, inflammation, and mitochondrial dysfunction reinforce and amplify each other, ultimately leading to progressive neuronal damage and the development and progression of diseases like Parkinson's disease. Understanding and targeting these interconnected processes may hold promise for developing therapeutic strategies to mitigate the progression of neurodegenerative disorders (Wang, Wang, Gao, & Sun, 2022).

5.2 Excitotoxicity

Excitotoxicity is a phenomenon that involves excessive activation of excitatory neurotransmitters, particularly glutamate, leading to neuronal damage or death. While excitotoxicity is primarily associated with conditions like stroke and neurodegenerative diseases, emerging evidence suggests its involvement in Parkinson's disease as well. In Parkinson's disease, excitotoxicity is believed to play a role in the degeneration of dopamine-producing neurons in the substantia nigra, a brain region involved in motor control. The imbalance between excitatory and inhibitory neurotransmission, with excessive glutamate signaling, can result in prolonged and excessive activation of glutamate receptors, particularly N-methyl-D-aspartate (NMDA) receptors. Several factors contribute to excitotoxicity in Parkinson's disease. One of the key factors is the dysfunction of the glutamate transporters responsible for removing excess glutamate from the synaptic cleft. Impaired glutamate reuptake can lead to an accumulation of glutamate, which further enhances excitotoxicity. Additionally, the loss of dopamine, a neurotransmitter that helps regulate glutamate release and excitatory signaling, can disrupt the balance of excitatory and inhibitory neurotransmission. Excitotoxicity triggers a cascade of events within neurons, including calcium influx and activation of various enzymes and pathways, ultimately leading to neuronal dysfunction and death. The excessive calcium influx activates enzymes such as

phospholipases, proteases, and nitric oxide synthase, which can damage cellular components, disrupt energy metabolism, and generate ROS. These processes contribute to oxidative stress and further neuronal damage. Furthermore, excitotoxicity can induce mitochondrial dysfunction, impairing the ability of mitochondria to produce ATP and regulate calcium homeostasis. Dysfunctional mitochondria produce more ROS, contributing to oxidative stress and exacerbating neuronal damage.To counteract excitotoxicity, the brain employs various protective mechanisms, including the release of inhibitory neurotransmitters like gamma-aminobutyric acid (GABA) and the activation of anti-excitotoxic pathways. However, in Parkinson's disease, these compensatory mechanisms may be overwhelmed or impaired, leading to a heightened susceptibility to excitotoxicity. Targeting excitotoxicity is an area of active research for potential therapeutic interventions in Parkinson's disease. Strategies include developing drugs that modulate glutamate receptors, enhancing glutamate clearance mechanisms, and promoting the activation of neuroprotective pathways to mitigate the damaging effects of excessive glutamate signaling. Overall, while excitotoxicity's role in Parkinson's disease is still being elucidated, evidence suggests that it contributes to the degeneration of dopamine neurons and may represent a potential target for therapeutic interventions (Iovino, Tremblay, & Civiero, 2020).

6. Diagnosing Parkinson’s Disease and Treatment Guidelines

Diagnosis of Parkinson's disease usually involves a combination of clinical evaluation, medical history, and physical examination. There is no specific test for Parkinson's disease, but healthcare providers may use certain tests, such as imaging studies like MRI or DaTscan, to rule out other conditions that may cause similar symptoms. Diagnosis of Parkinson's disease is usually made based on the presence of two or more of the hallmark motor symptoms, such as tremors, rigidity, bradykinesia, and postural instability. Treatment of Parkinson's disease is focused on managing symptoms and improving quality of life. There are several medications that can help increase dopamine levels in the brain and improve motor symptoms, such as levodopa and dopamine agonists. In addition to medications, physical therapy and exercise can also be beneficial for improving mobility and reducing stiffness and rigidity. For more advanced cases, deep brain stimulation (DBS) surgery may be an option. DBS involves implanting a small electrode into the brain that delivers electrical impulses to targeted areas, which can help alleviate

symptoms such as tremors, rigidity, and dyskinesia (involuntary movements). It is important to note that there is currently no cure for Parkinson's disease, and treatments are focused on managing symptoms and improving quality of life. In addition to medical treatments, support groups, counseling, and lifestyle modifications such as a healthy diet and regular exercise may also be helpful for people with Parkinson's disease (Rizek, Kumar, & Jog, 2016).

REFERENCES

Bono, F., Mutti, V., Devoto, P., Bolognin, S., Schwamborn, J. C., Missale, C., & Fiorentini, C. (2021). Impaired dopamine D3 and nicotinic acetylcholine receptor membrane localization in iPSCs-derived dopaminergic neurons from two Parkinson's disease patients carrying the LRRK2 G2019S mutation. *Neurobiol Aging, 99*, 65-78. doi: 10.1016/j.neurobiolaging.2020.12.001

Bower, J. H., Maraganore, D. M., Peterson, B. J., McDonnell, S. K., Ahlskog, J. E., & Rocca, W. A. (2003). Head trauma preceding PD: a case-control study. *Neurology, 60*(10), 1610-1615. doi: 10.1212/01.wnl.0000068008.78394.2c

Cacabelos, R., Carrera, I., Martinez, O., Naidoo, V., Cacabelos, N., Aliev, G., & Carril, J. C. (2021). Influence of dopamine, noradrenaline, and serotonin transporters on the pharmacogenetics of Atremorine in Parkinson's disease. *Drug Dev Res, 82*(5), 695-706. doi: 10.1002/ddr.21784

Cerri, S., Mus, L., & Blandini, F. (2019). Parkinson's Disease in Women and Men: What's the Difference? *J Parkinsons Dis, 9*(3), 501-515. doi: 10.3233/JPD-191683

Cherian, A., & Divya, K. P. (2020). Genetics of Parkinson's disease. *Acta Neurol Belg, 120*(6), 1297-1305. doi: 10.1007/s13760-020-01473-5

Ciofalo, A., Gulotta, G., Iannella, G., Pasquariello, B., Manno, A., Angeletti, D., . . . Magliulo, G. (2019). Giant Cell Arteritis (GCA): Pathogenesis, Clinical Aspects and Treatment Approaches. *Curr Rheumatol Rev, 15*(4), 259-268. doi: 10.2174/1573397115666190227194014

Dickson, D. W. (2018). Neuropathology of Parkinson disease. *Parkinsonism Relat Disord, 46 Suppl 1*(Suppl 1), S30-S33. doi: 10.1016/j.parkreldis.2017.07.033

Eklund, M., Nuuttila, S., Joutsa, J., Jaakkola, E., Makinen, E., Honkanen, E. A., . . . Kaasinen, V. (2022). Diagnostic value of micrographia in Parkinson's disease: a study with [(123)I]FP-CIT SPECT. *J Neural Transm (Vienna), 129*(7), 895-904. doi: 10.1007/s00702-022-02517-1

Emami Kazemabad, M. J., Asgari Toni, S., Tizro, N., Dadkhah, P. A., Amani, H., Akhavan Rezayat, S., . . . Deravi, N. (2022). Pharmacotherapeutic potential of pomegranate in age-related neurological disorders. *Front Aging Neurosci, 14*, 955735. doi: 10.3389/fnagi.2022.955735

Goetz, C. G. (2011). The history of Parkinson's disease: early clinical descriptions and neurological therapies. *Cold Spring Harb Perspect Med, 1*(1), a008862. doi: 10.1101/cshperspect.a008862

Goldman, S. M. (2014). Environmental toxins and Parkinson's disease. *Annu Rev Pharmacol Toxicol, 54*, 141-164. doi: 10.1146/annurev-pharmtox-011613-135937

Ikeda, K., Ebina, J., Kawabe, K., & Iwasaki, Y. (2019). Dopamine Transporter Imaging in Parkinson Disease: Progressive Changes and Therapeutic Modification after Anti-parkinsonian Medications. *Intern Med, 58*(12), 1665-1672. doi: 10.2169/internalmedicine.2489-18

Iovino, L., Tremblay, M. E., & Civiero, L. (2020). Glutamate-induced excitotoxicity in Parkinson's disease: The role of glial cells. *J Pharmacol Sci, 144*(3), 151-164. doi: 10.1016/j.jphs.2020.07.011

Lyu, S., Guo, Y., Zhang, L., Tang, G., Li, R., Yang, J., Liu, J. (2021). Downregulation of astroglial glutamate transporter GLT-1 in the lateral habenula is associated with depressive-like behaviors in a rat model of Parkinson's disease. *Neuropharmacology, 196*, 108691. doi: 10.1016/j.neuropharm.2021.108691

Pajares, M., A, I. R., Manda, G., Bosca, L., & Cuadrado, A. (2020). Inflammation in Parkinson's Disease: Mechanisms and Therapeutic Implications. *Cells, 9*(7). doi: 10.3390/cells9071687

Rizek, P., Kumar, N., & Jog, M. S. (2016). An update on the diagnosis and treatment of Parkinson disease. *CMAJ, 188*(16), 1157-1165. doi: 10.1503/cmaj.151179

Subramaniam, S. R., & Chesselet, M. F. (2013). Mitochondrial dysfunction and oxidative stress in Parkinson's disease. *Prog Neurobiol, 106-107*, 17-32. doi: 10.1016/j.pneurobio.2013.04.004

Suratos, C. T. R., Del Rosario, M. M., & Jamora, R. D. G. (2020). Serotonin syndrome in a Parkinson disease patient after intake of an ethanol-containing homeopathic medication. *Neurodegener Dis Manag, 10*(4), 219-222. doi: 10.2217/nmt-2020-0006

Sveinbjornsdottir, S. (2016). The clinical symptoms of Parkinson's disease. *J Neurochem, 139 Suppl 1*, 318-324. doi: 10.1111/jnc.13691

Wang, Y. F., Wang, Y. D., Gao, S., & Sun, W. (2022). Implications of p53 in mitochondrial dysfunction and Parkinson's disease. *Int J Neurosci*, 1-12. doi: 10.1080/00207454.2022.2158824

CHAPTER 7

BIBLIOMETRIC ANALYSIS OF ADVERSE DRUG ERRORS

Lecturer Tuba ARSLAN[1]

Prof. Dr. Mehmet Nurullah KURUTKAN[2]

[1] Kilis 7 Aralık University, Vocational School of Health Services, Department of Medical Services and Techniques, Kilis, Turkey. tubaarslan@kilis.edu.tr ,
Orcid ID: 0000-0001-6183-9262
[2] Düzce University, Faculty of Business Administration, Department of Health Management, Düzce, Turkey. nurullahkurutkan@duzce.edu.tr , Orcid ID: 0000-0002-3740-4231

INTRODUCTION

People take medications to protect themselves from the disease, use diagnostic or therapeutic services, or physiologically recover. The harmful and unintended effect of drugs used in normal doses is called adverse drug reaction (ADR). Adverse drug reaction has a high potential to occur in almost all patients depending on the dose and characteristics of the drug used (Göksel Ülker, 2012). In the studies conducted on the subject, it was determined that adverse drug reactions occur in patients with heart disease (Bankes et. al., 2020; Fabretti et. al., 2018; Al-Hashar et. al., 2018; Girgin, 2012), infectious disease (Al-Hashar et. al., 2018), lung disease (Baker et. al., 2020; Al-Hashar et. al., 2018; Girgin, 2012), anxiety (Baker et. al., 2020), kidney disease (Baker et. al., 2020; Al-Hashar et. al., 2018), neurological disease (Baker et. al., 2020; Al-Hashar et. al., 2018; Girgin, 2012), malnutrition (Baker et. al., 2020), allergy (Girgin, 2012), pneumonia (Baker et. al., 2020; Fabretti et. al., 2018), hypertension (Bankes et. al., 2020; Fabretti et. al., 2018), diabetes (Bankes et. al., 2020), thyroid (Bankes et. al., 2020; Girgin, 2012), behavioral disorder (Bankes et. al., 2020) and hearing impairment (Evans et. al., 2001).

In numerous studies, drug-related problems and ADR results have been studied in a systematic review (Kefale et. al., 2020; Vaismoradi et. al., 2019). There are studies that focus on a country, as well as studies that examine it by the age variable. Kenya (Kefale et. al., 2020), Norway (Vaismoradi et. al., 2019) and Italy studies (Sessa et. al., 2018) are examples of country-based studies. The concept of ADR was examined in reviews based on pediatrics (Khan et., al., 2020; Yu et. al., 2019; Col et. al., 1990) and geriatric population (Sakiris et., al., 2020). However, systematic review articles cannot fully explain the details of research trends and the invisible relationships between ADR and adverse events. Bibliometric analyses are one of the analyses developed to explain the relationship between ADR and adverse events with raw data that covers both the entire population (pediatrics, geriatric and other) and where the results of all countries can be found.

Thanks to bibliometric methods, the direction of research, its value and the development process of subjects can be evaluated (Rodríguez-Soler et. al., 2020; Derviş, 2019). Because bibliometry is the intersection or combination of linguistics, information and statistics on a particular subject (He at. al., 2017). 5 stages are required to use the bibliometric analysis process in studies. These are study design, data collection, data analysis, data visualization, and data interpretation (Zupic and Čater, 2015). In the design

of the study, the research questions are defined and appropriate bibliometric methods are chosen to answer the questions. The aim of the research questions is to get information about the following topics (Aria and Cuccurullo, 2017);

- Determining the knowledge base and intellectual structure of a topic or field of research;

- To be able to examine the research-based conceptual structure of a topic or field of research;

- To create the social network structure of a particular scientific community.

In the study design, one of the most important choices for scholars is the time span. Bibliometric analysis can keep the time interval wide to capture the development of the subject related to the research field over time (Aria and Cuccurullo, 2017). In data collection, the database containing the bibliometric data is selected, the data set is filtered and the data is exported from the selected database (Waltman, 2016). In data analysis, one or more bibliometric or statistical software tools are used. The fourth stage is the visualization of the data. Visualization is a technique used for bibliometric analysis. Researchers can visualize the study area, structure or trend of a subject with bibliometric analysis (Cobo et. al., 2012). The bibliometrix analysis technique can be used for this (Rodríguez-Soler et. al., 2020; Jalal, 2019; Aria and Cuccurullo, 2017). The bibliometrix analysis technique, which is a quantitative approach used to analyze the academic literature, is used to identify publications, citations and sources of information in the field ((Rodríguez-Soler et. al., 2020). Bibliometrix analysis can be evaluated with some generally accepted bibliometric indicators, such as the total number of publications performed on the subject, the number of citations, the average number of citations, indexes (h, g, m), researchers/experts, countries and words used in studies (Jalal, 2019). The last stage is the stage of interpreting the data. It is the part where the researchers interpret and explain the findings they obtained from the data (Aria and Cuccurullo, 2017).

The results of science mapping techniques can help academics in the healthcare industry understand the evolution of the ADR and Adverse event

relationship and provide a valuable tool to quickly access literature in this area.

METHOD

In this study, R based bibliometrix (Biblioshiny) and VOSviwer software were used. The raw data required for the software were downloaded and analyzed in the Web of Science database with a certain search strategy. The Web of Science database is one of the world's leading databases covering more than 20,300 journals. It also aims to assist in the analytical analysis (Dabbagh et. al., 2019). Therefore, the research was conducted on adverse drug errors using the Web of Science database in this study. Keywords in the study were "adverse drug reactions", "ADRs", "adverse drug reaction", "drug-induced reaction", "pharmacovigilance", "incident reporting", global trigger tool "," Harvard medical practice study ". In the Web Of Science Core Collection: Citation Indexes section, journals with SCI-EXPANDED, SSCI and ESCI were searched. 8,762 studies were reached and publications between 2020 and 2021 (since these years were not completed) were excluded from the research. The number of publications falling to 8,136 was reduced to 5,099 by limiting it to "article" and "review". In the final stage, it was refined again using the keyword "adverse event" and 2,009 studies were reached.

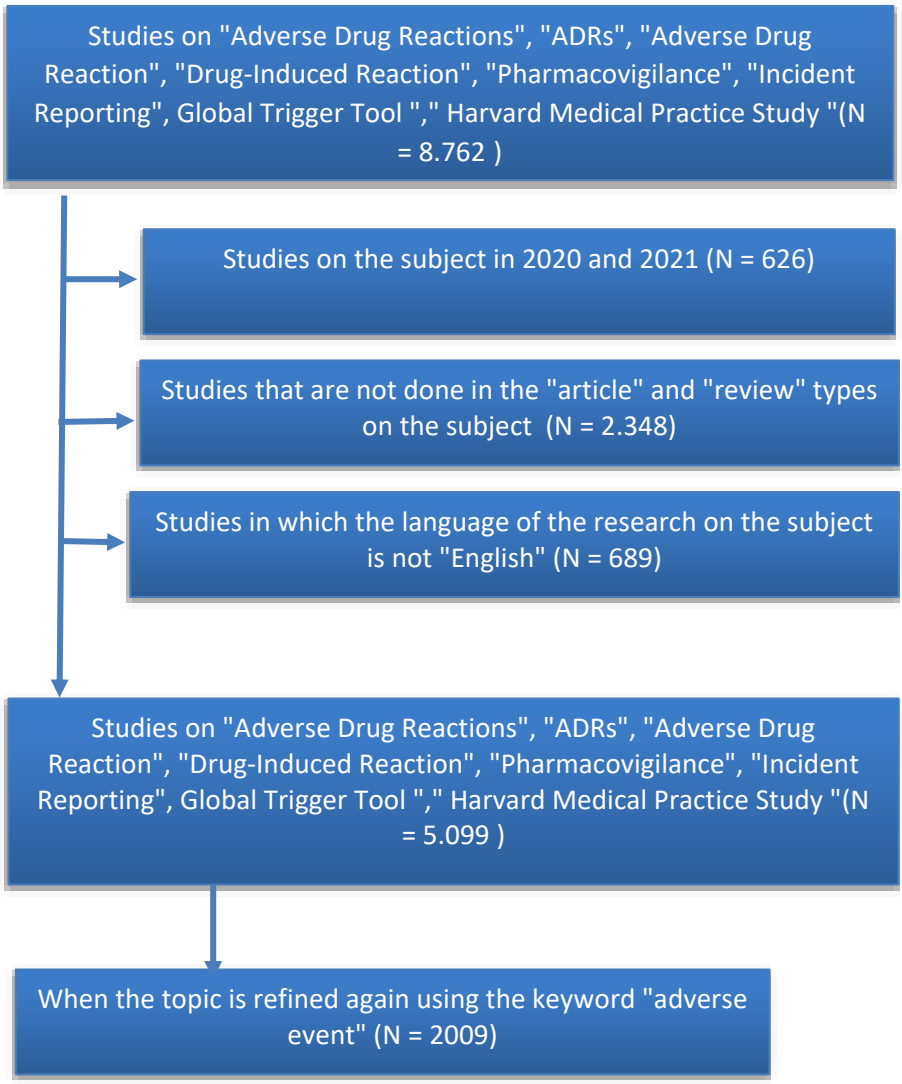


Figure 1. Tree Diagram

Bibliometrix, which has a library, was used to conduct research through the R statistics tool. Bibliometrix helps various analysis with its web-based interface Biblioshiny (Dadkhah et. al., 2020).

RESULTS

Between 1991 and 2020, 2009 documents were published in 29 years. These documents include a total of 1,712 articles and 297 reviews. The total number of authors is 8,266. The number of studies with single authors is 103 and the number of studies with multiple authors is 8,163. The ratio of the number of studies with a single author to total authors is 0.012. The ratio of the number of studies with multiple authors to total authors is 0.987. The cooperation index rate in the publications is 4.31, and all other data are given below (Table 1).

Table 1. Main Statistics About The 1991–2020

Main Information About Data			
Description	Results	Description	Results
Timespan	1991:2020	Docüment Contents	
Sources (Journals, Books, etc)	670	Keywords Plus (ID)	3627
Documents	2009	Author's Keywords (DE)	3542
Average years from publication	7,94	AUTHORS	
Average citations per documents	24,64	Authors	8266
Average citations per year per doc	2,357	Author Appearances	11738
Docüment Types		Authors of single-authored documents	103
article	1657	Authors of multi-authored documents	8163
article; data paper	1	Authors Collaboration	

article; early access	3	Single-authored documents	117
article; proceedings paper	51	Documents per Author	0,243
review	295	Authors per Document	4,11
review; book chapter	1	Co-Authors per Documents	5,84
review; early access	1	Collaboration Index	4,31

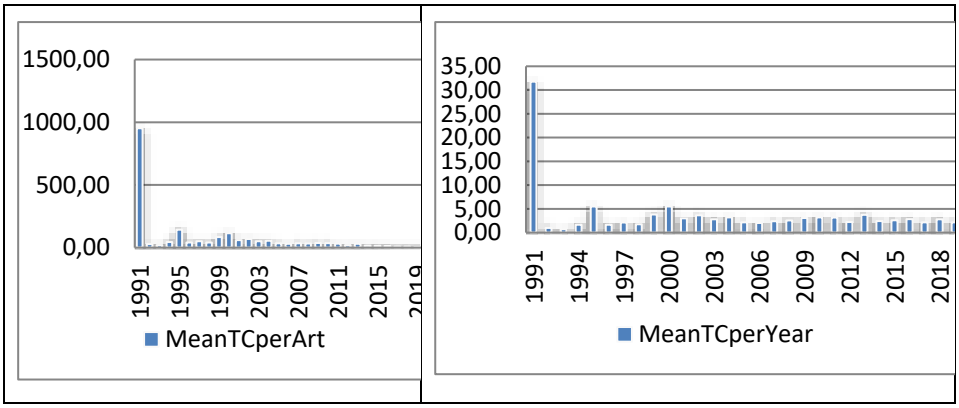


Figure 2. Annual Scientific Production

According to Figure 2, the number of published articles increased steadily from 1995 to 2018. There was a slight decrease in 2019. The increase in the number of studies conducted in this case indicates the existence of problems that require further discussion on the issue. (Figure 2).

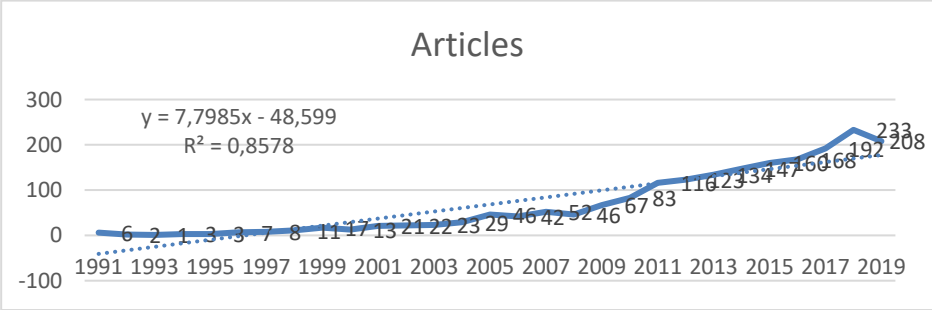


Figure 3. Average Article Citations Per Year

Figure 3 shows the average citation numbers of articles published in a given year. According to the figure, there was a sudden decline in the average number of citations of articles published after 1991. But it is possible to say that the average number of citations of articles published annually after 1993 tends to rise by 2018 (Figure 3).

Table 2. Most Relevant Sources

Sources	**Articles**
Drug Safety	196
Pharmacoepıdemıology And Drug Safety	129
Expert Opınıon On Drug Safety	60
European Journal Of Clınıcal Pharmacology	46
Brıtısh Journal Of Clınıcal Pharmacology	45
Plos One	37
Vaccıne	34
Internatıonal Journal Of Clınıcal Pharmacy	24
Clınıcal Pharmacology & Therapeutıcs	22
Bmj Open	20
Drug Informatıon Journal	20
Annals Of Pharmacotherapy	19

Frontıers In Pharmacology	19
Malarıa Journal	18
Journal Of The Amerıcan Medıcal Informatıcs Assocıatıon	17
Journal Of Clınıcal Pharmacy And Therapeutıcs	16
Indıan Journal Of Pharmacology	14
Clınıcal Drug Investıgatıon	13
Internatıonal Journal Of Medıcal Scıences	13
Journal Of Bıomedıcal Informatıcs	13

Table 2 shows the sources used in relation to the subject. According to the figure, it is possible to say that the sources most related to the subject are "Drug Safety (n = 196), Farmacoepidemiology and Drug Safety (n = 129), Expert Opinion On Drug Safety (n = 60), European Journal Of Clinical Pharmacology (n = 46) and British Journal of Clinical Pharmacology (n = 45)".

Figure 4. Bradford's Law

In the analysis made according to Bradford law, the journal "Drug Safety" published 196 articles and the journal "Pharmacoepidemiology And Drug Safety" published 129 articles regarding the term "adverse drug errors" and these two journals are in the core magazine (Zone 1) zone and it can be said that they are the most efficient resources in this field (Figure 4).

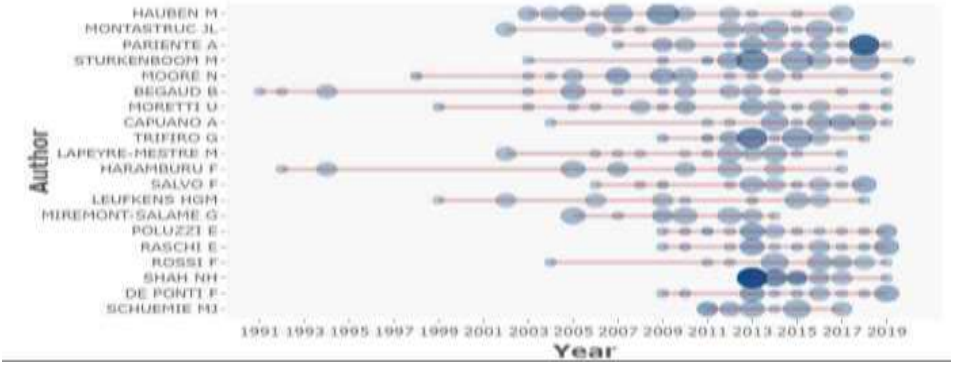


Figure 5. Top-Authors' Production Over Time

The horizontal line shows the time period between the author's first publication and his/her last publication in the relevant period. The size of the small bubbles indicates the abundance of publications. The darkness of the colors in the bubbles gets darker in proportion to the number of citations received. From this point of view, when we look at the figure above, the authors who have been publishing for many years are Begaud, Moore, Hauben, Pariente, Lapeyre-Mestre and Poluzzi. The most published and cited authors in a very short period of time are Pariente and Shah (Figure 5). When the authors' fields of study are examined in terms of their subjects, it is seen that Begaud comes to the fore with his studies on “underreporting of adverse drug reactions and causality of adverse drug reactions”. Moore, on the other hand, seems to focus more on studies related to “errors in reporting of adverse drugs, their cost, and errors caused by drug-drug interaction". Hauben appears to come to the fore with his studies on “data mining for the identification of adverse drugs and detection of adverse drug reactions”. Pariente is at the forefront with his work on the use of compounding systems in adverse drug reactions. Lapeyre-Mestre stands out with studies such as “adverse reactions in patients admitted to pediatrics and emergency services, gender differences in adverse reactions, drug-drug interaction and pharmacovigilance”. Poluzzi appears to have carried out more studies on "reporting of adverse drugs and adverse reactions in the treatment of certain diseases (cancer, migraine, liver, etc.)". Shah emerges from studies of “drug safety, reporting of adverse drugs, the relationship of adverse drugs with composition systems and data mining in determining adverse drugs”.

Table 3. Most Relevant Affiliations

Item	University	Publications
1	HARVARD UNIV	59
2	UNIV PITTSBURGH	53
3	NORTHWESTERN UNIV	46
4	SEOUL NATL UNIV	45
5	COLUMBIA UNIV	44
6	ERASMUS UNIV	38
7	STANFORD UNIV	38
8	UNIV WASHINGTON	38
9	NOTREPORTED	37
10	UNIV UTRECHT	36

The top five universities with the highest contribution in the table of publication numbers of universities are Harvard University (n = 59), University of Pittsburgh (n = 53), Northwestern University (n = 46), Seoul Natl University (n = 45) and Columbia University (n = 44) (Table 3).

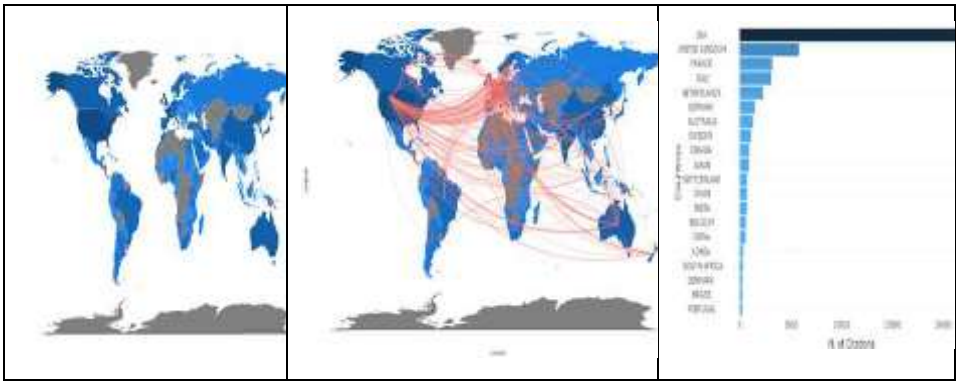


Figure 6. Country Scientific Production, Country Collaboration, and Most Cited Countries

The countries marked as dark blue in the figures above are the countries that have produced more articles, have more collaborated and are most cited. Countries with the most scientific studies and citations are shown in bold in Figure 6. These countries are respectively USA (n = 1.963), France (n = 752), United Kingdom (n = 541), Italy (n = 517) and Netherlands (n = 336). Figure 7 shows the total number of citations of the countries that have researched the subject in the world. Accordingly, the countries with the highest total number of citations are respectively USA (n = 21.979), United Kingdom (n = 5.834), France (n = 3.204), Italy (n = 3.088) and Netherlands (n = 2.294). Figure 8 shows the cooperation between different countries. According to the figure, it is possible to say that China, New Zealand, Canada, France, Denmark, Germany, India, Malaysia and Singapore are mostly linked with other countries to do research on the subject.

Word Analysis

Word analysis was carried out with the help of bibliometrix analysis. Bibliometrix software analyzes words by using the title of the article, keywords, abstract and the bibliography of the article. The analysis obtained using the article's references is called keyword plus (a feature not found in other software). In the words derived from the article title, the words with the highest frequency are adverse, drug, reactions, reporting, pharmacovigilance, and events. In other words, the authors mostly preferred these words in the title of the article. In the abstracts, words such as adverse, events, drugs, patients, reporting, adrs, safety, data, reports and methods were used more. The word "study" should be excluded from these words. Because such words are used in the abstract of each article by their nature (Figure 7).

10-a) Words by Article title

10-b) Words by abstract

10-c) Keyword plus

10-d) Words by keywords

Figure 7. Article Title, Keywords, Abstract and Keyword Plus Word Trees

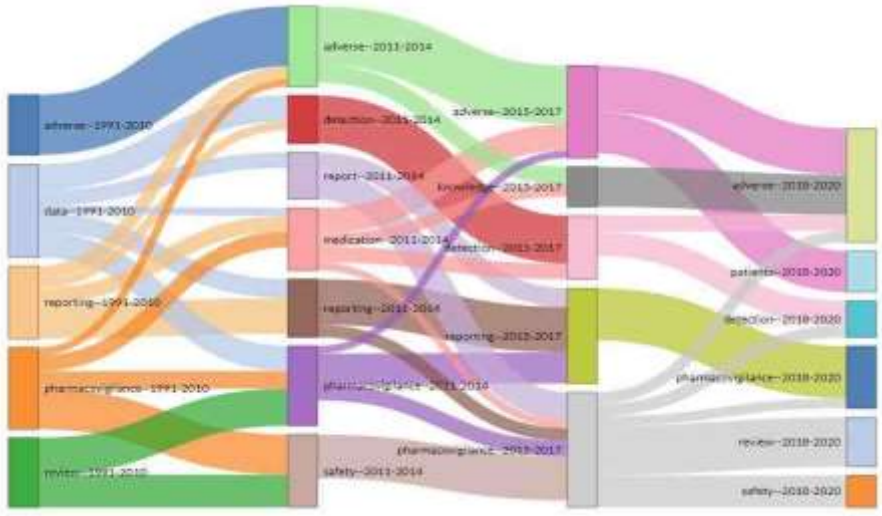


Figure 8. Thematic Evolution

Figure 8 illustrates the thematic development of the research. Thematic evolution is a graphical study of how themes emerge and are used over time. Accordingly, it is possible to understand the development of the themes used in studies on the subject over time. According to the figure, the themes of "adverse, data, reporting, pharmacovigilance and review" were used between 1991-2010. It was determined that the themes of "adverse, patients, detection, data, pharmocivigilance, review and safety" came to the fore between 2018-2020.

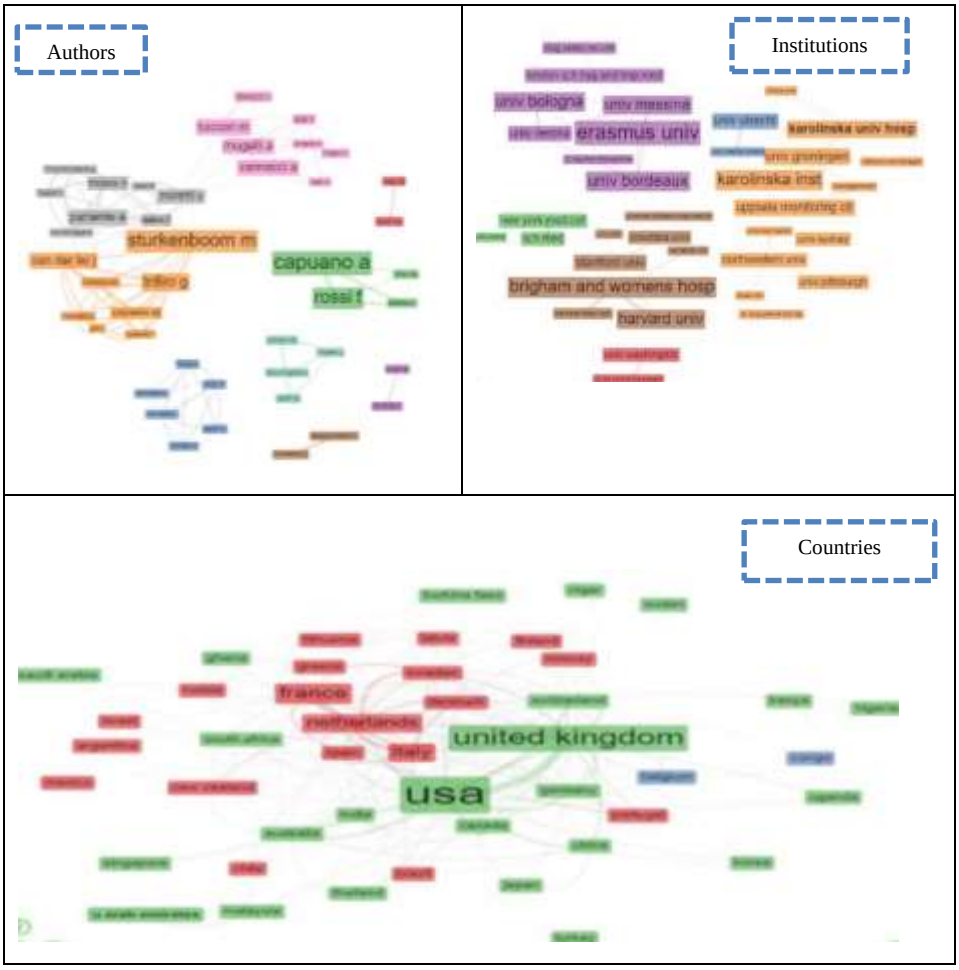


Figure 9. Authors / Universities / Countries Collaboration Network

In Figure 9, the analysis of the authors' collaboration (Authors Collaboration Network), the analysis of the institutional cooperation (Institutions Collaboration Network) and the cooperation between countries (Countries Collaboration Network) are given. In the analysis of collaboration between the authors, 44 spheres were taken as the basis for analysis. Each ellipse sphere represents an author. The connecting lines between the spheres mean that there is a relationship between the spheres to which it is connected. The thickness of the lines is directly proportional to the density of the relationship. In the given Figure, it is seen that there are 9 clusters. It is seen

that two authors are working together in 3 clusters. Orange and green clusters are centralized clusters and "Sturkenboom M, Capuano, A" are at the center of the collaboration between authors. It is seen that the authors working together in the orange cluster focused on adverse reactions experienced in electronic health record systems in their studies. The authors working together in the green cluster are noted for their work on the causality of adverse drug reactions. The authors working together on the lilac cluster, on the other hand, conduct studies on hospitalizations caused by adverse drug events. The authors working together in the gray cluster studied the damage caused by anticoagulant drugs and adverse reactions in cardiovascular diseases. Collaborative authors in the dark blue cluster focus on the adverse reporting system and adverse reactions in pediatric patients. Authors working together in the light blue cluster are conducting studies on adverse reactions at the immune checkpoint. The authors working together in the brown cluster were found to collaborate on adverse reactions experienced in different departments in the hospital (emergency department, pediatrics, etc.), gender differences in adverse reactions, the preventability of adverse drug reactions, and drug-drug interactions. Collaborating authors in the purple cluster studied adverse reactions and adverse drug events leading to death in cancer patients. Collaborating authors in the red cluster focused on studies such as adverse drug events and reporting and monitoring of adverse reactions in treated patients.

In the inter-institutional cooperation analysis, 36 nodes were taken as the basis. Each node represents an institution. In the figure, it is seen that there are 6 clusters. It is seen that two institutions work together in 1 cluster. The purple, brown, and orange clusters are centralized clusters and are centrally located in the inter-institutional collaboration of “Erasmus University, University Bologna, Univ Messina, Univ Bordeaux, Brigham and Womens Hosp, Harvard University, Karolinska University Hosp, Karolinska inst”. In the analysis of cooperation between countries, 45 spheres are taken as the basis. Green clusters are centralized clusters and "USA" and "United Kingdom" are at the center of the cooperation between countries.

Table 4. Source Impact

Source	h_index	g_index	m_index	TC	NP	PY_start
Drug Safety	39	64		5672	196	1993
Pharmacoepidemiology And Drug Safety	32	53	1,33	3344	129	1997
Expert Opinion On Drug Safety	18	25	1,28	788	60	2007
European Journal Of Clınıcal Pharmacology	19	32	0,70	1119	46	1994
Brıtısh Journal Of Clinical Pharmacology	23	41	0,85	1761	45	1994
Plos One	15	28	1,5	838	37	2011
Vaccine	15	21	0,78	489	34	2002
International Journal Of Clinical Pharmacy	8	10	0,8	154	24	2011
Clinical Pharmacology & Therapeutics	14	22	1	810	22	2007
BMJ Open	8	12	0,88	174	20	2012
Drug Information Journal	6	9	0,26	110	20	1998
Annals Of Pharmacotherapy	17	19	0,89	1161	19	2002
Frontıers In Pharmacology	6	9	1,2	110	19	2016
Malaria Journal	10	17	0,71	306	18	2007
Journal Of The American Medical Informatics Associatıon	13	17	0,92	841	17	2007

Journal Of Clinical Pharmacy And Therapeutıcs	9	14	0,42	213	16	2000
Indian Journal Of Pharmacology	6	10	0,46	115	14	2008
Clinical Drug Investigation	7	10	0,28	117	13	1996
International Journal Of Medıcal Sciences	8	13	0,8	358	13	2011
Journal Of Biomedical Informatics	8	13	0,72	234	13	2010

The quality of a journal is measured by how many citations are made to the average article published in that journal over a period of time. Therefore, a researcher is not interested in how many citations are made to each individual article. The important thing for the researcher is that all articles published in a particular journal are, on average, more or less cited than other journals (Tonta, 2014). In this context, various indexes (h, g, m) are used to evaluate the quality of journals. According to Table 5, the journal Drug Safety has the highest h index (39) and g index (64), and the journal Plos ONE has the highest m index (1.5) (Table 4).

Table 5. Author Impact

Author	h_index	g_index	m_index	TC	NP	PY_start
HAUBEN M	15	28	0,83	828	28	2003
MONTASTRUC JL	12	19	0,63	371	21	2002
PARIENTE A	13	21	0,92	675	21	2007
STURKENBOOM M	14	21	0,77	755	21	2003
MOORE N	15	20	0,65	933	20	1998
BEGAUD B	14	19	0,46	609	19	1991
MORETTI U	15	19	0,68	710	19	1999
CAPUANO A	12	17	0,70	305	18	2004
TRIFIRO G	15	18	1,25	836	18	2009

LAPEYRE-MESTRE M	12	17	0,63	330	17	2002
HARAMBURU F	12	16	0,41	552	16	1992
SALVO F	10	16	0,66	371	16	2006
LEUFKENS HGM	11	15	0,5	321	15	1999
MIREMONT-SALAME G	13	15	0,81	511	15	2005
POLUZZI E	12	15	1	622	15	2009
RASCHI E	11	15	0,91	451	15	2009
ROSSI F	11	15	0,64	269	15	2004
SHAH NH	11	15	1,37	1060	15	2013
DE PONTI F	10	14	0,83	421	14	2009
SCHUEMIE MJ	12	14	1,2	518	14	2011

The h, g and m indices are among the index types that aim to measure scientific achievement in terms of productivity and impact (Tonta, 2014). According to Table 6, Hauben has the highest h index (15) and g index (28) and Shah has the highest m index of (1.37) (Table 5).

Factor Analysis

Factor analysis provides advantages such as visualizing and easily interpreting the analysis by collecting the correlated variables into a category, obtaining fewer factors, and reducing the number of variables (one dimension reduction) (Yaşlıoğlu, 2017). Factor analysis of adverse drug reactions was performed in the images below.

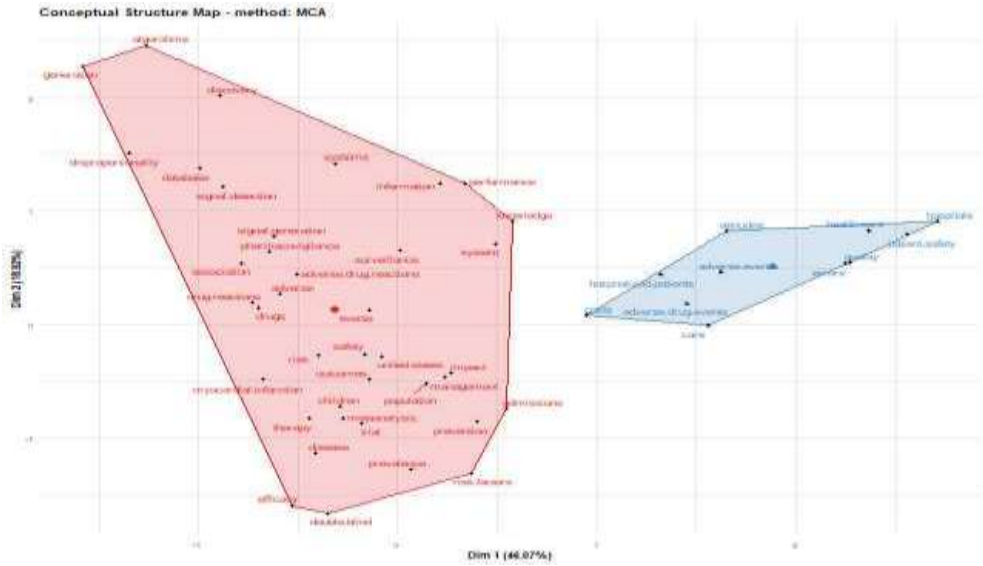


Figure 10. Multiple Correspondence Analyses / KeyWords Plus

There are 2 different clusters in the figure, red and blue. The red cluster is a heterogeneous and large cluster. There are 7 different sub-clusters in the red cluster. From these clusters, it is possible to give the sub-cluster containing the concepts of “generation”, “algorithms” and “discovery” the heading “generation of algorithms”. Secondly, it is possible to give the heading of "information and performance system" to the sub-cluster that includes the concepts of "systems", "system", "information", "performance" and "knowledge". Thirdly, it is possible to give the heading of "disproportionality in signal determination from the data set" to the sub-cluster that includes the concepts of "disproportionality", "database" and "signal detection". Fourthly, it is possible to give the sub-cluster containing the concepts of "signal generation”, “pharmacovigilance”, “association”, “adverse drug reactions”, “surveillance”, “drug reactions”, “adverse”, “drugs” and “events” the heading of "surveillance of adverse drug reactions". Fifthly, it is possible to give the heading of "meta-analysis results of the risk of myocardial infarction in children" to the sub-cluster that includes the concepts of “risk”, “safety”, “myocardial infarction”, “outcomes”, “united states”, “impact”, “therapy”, “children”, “population”, “management”, “disease”, “trial” and “meta-analysis”. Sixthly, it is possible to give the sub-cluster, which includes the concepts of " prevalence", "prevention", "admissions" and "risk factors", with the heading of "preventing the prevalence of risk factors". Seventhly, it is possible to give the heading of "activity due to double

blindness" to the sub-cluster that includes the concepts of "efficacy" and "double-blind".

There are 3 different sub-clusters in the blue cluster. From these clusters, it is possible to give the sub-cluster containing the concepts “costs”, “advertising drug events”, “care” and “hospitalized patients” to the heading "cost of adverse drug events in inpatient patients". Secondly, it is possible to give the sub-cluster containing the concepts “adverse event” and “attitudes” the heading of "attitudes in adverse events". Thirdly, it is possible to give the heading "patient safety and quality in health care" to the sub-cluster that includes the concepts of "errors", "quality", "patient safety", "hospitals" and "healthcare" (Figure 11).

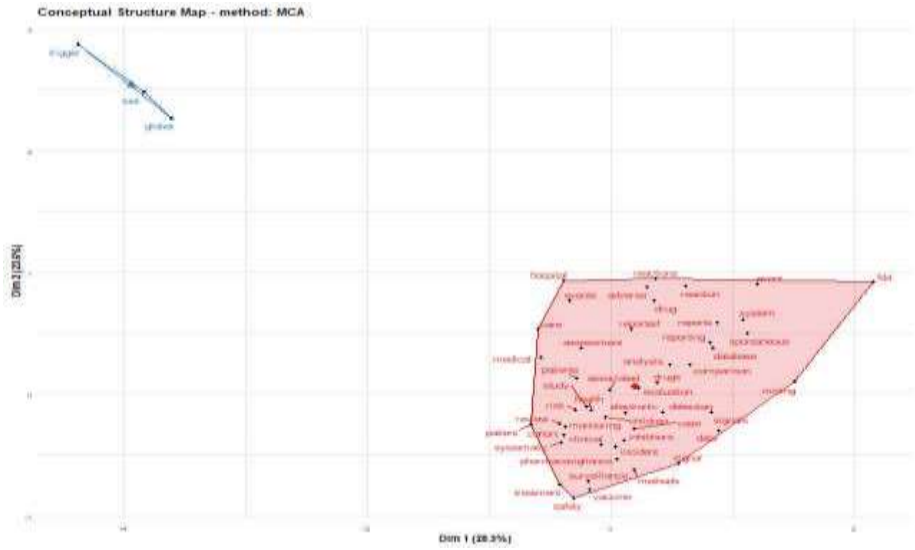


Figure 11. Multiple Correspondence Analyses / Titles

There are 2 different clusters in the figure: red and blue. The red cluster is a heterogeneous and large cluster. There are 8 different sub-clusters within the red cluster. Among these clusters, the sub-cluster that includes the concepts of "hospital", "care", "events", "adverse" and "reactions" can be given the heading "adverse reactions in health care". Secondly, it is possible to give the heading "adverse events according to FDA" to the sub-cluster that includes the concepts of "event" and "FDA". Thirdly, it is possible to give the sub-cluster of "reaction", "drug", "reported", "reports", "reporting" and "system" with the heading "reporting of drug reactions". Fourthly, it is possible to give the heading "comparison in databases" to the sub-cluster that

includes the terms "spontaneous", "database", "comparison" and "mining". Fifthly, it is possible to give the sub-cluster of "medical", " assessment", "patients", "study", "risk", "associated" and "analysis" with the heading "risk analysis in medical evaluations". Sixthly, it is possible to give the sub-cluster of “drugs”, “evaluation”, “detection”, “case”, “signals” and “data” with the heading “evaluation of drug signals”. Seventhly, it is possible to give the heading "signals of inhibitory events in pharmacovigilance" to the sub-cluster that includes the concepts of "inhibitor", "incident", "signal", "methods" and " pharmacovigilance". Eighthly, it is possible to give the sub-cluster of "review", "patient", "cohort", "systematic", "clinical" and "monitoring" concepts with the heading "cohort studies in clinical patients". Ninthly, it is possible to give the sub-cluster of "treatment", "surveillance", "vaccine" and "safety" with the heading "surveillance in vaccine treatment". The concepts included in the blue cluster are "global", "tool" and "trigger" and it is possible to give the heading "global trigger tool".

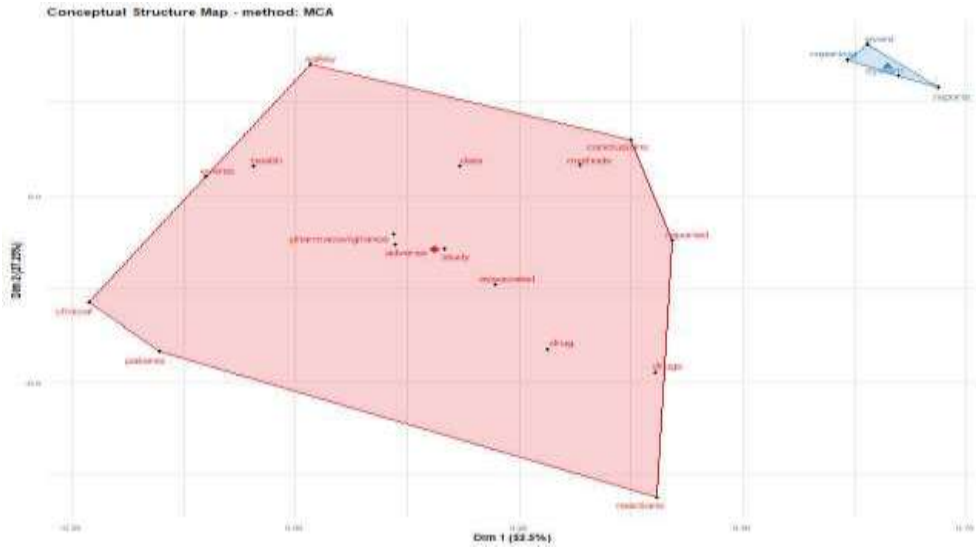


Figure 12. Multiple Correspondence Analyses / Abstracts

There are 2 different clusters in the figure, red and blue. The red cluster is a heterogeneous and large cluster. There are 5 different sub-clusters in the red cluster. Among these clusters, it is possible to give the sub-cluster of "safety", "events" and "health" with the heading "safety in health". Secondly, it is possible to give the heading "results of data reports" to the sub-

cluster that includes the concepts of "data", "conclusions", "methods" and "reported". Thirdly, it is possible to give the heading “pharmacovigilance in adverse studies” to the sub-cluster that includes the terms "pharmacovigilance", "adverse", "study" and "associated". Fourthly; it is possible to give the heading of "clinical patients" to the sub-cluster that includes the concepts of "clinical" and "patients". Fifthly; it is possible to give the "drug reactions" heading to the sub-cluster that includes the concepts of "drug", "drugs" and "reactions". There are 2 different sub-clusters in the blue cluster. Of these clusters, it is possible to give the sub-cluster, which includes the concepts of "events" and "reporting", with the heading "reporting the event". Secondly, it is possible to give the sub-cluster that includes the concepts of "system" and "reports" with the heading "system reports".

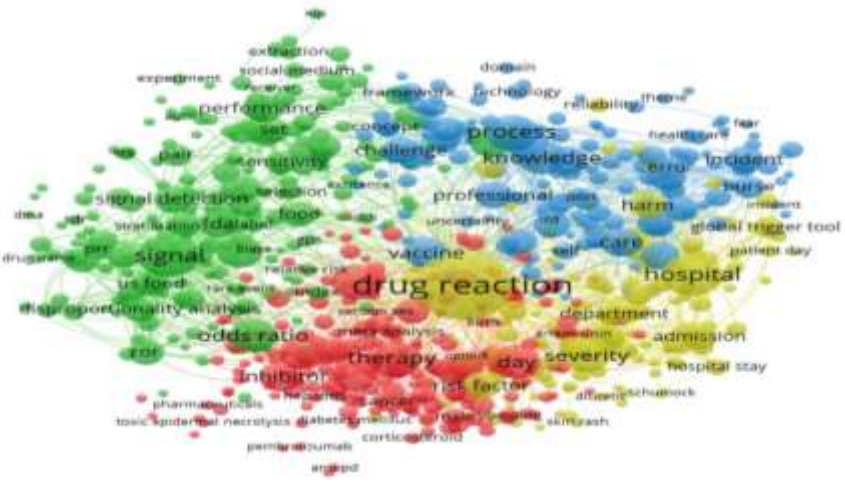


Figure 13. Adverse Drug Reaction Vosviwer Analysis

When the figure is examined, it is seen that keywords such as "drug reaction", "process", "hospital", "therapy" and "signal" appear the most in the formation network related to adverse drug reactions. A total of four clusters are represented in four different colors. The clusters with the most members are red (n = 223), green (n = 209), blue (n = 174) and yellow (n = 142) clusters, respectively. The most repeated clusters in the red cluster with the most members are therapy (n = 203), trial (n = 200) and day (n = 182), respectively (Figure 13).

Figure 14. Most Used Keywords of the Time Series Analysis Studies in ADR

The searched data obtained through the Web of Science database was analyzed using Vosviewer. The Sunburst chart was obtained using the words obtained from here (https://app.fourish.studio/). When words are formed by clustering, they are surrounded by 4 main colors (blue, purple, yellow and green). The words that stand out in the colors are “adverse drug risk, adverse drug reporting, health care and adverse effect measurement”, respectively.

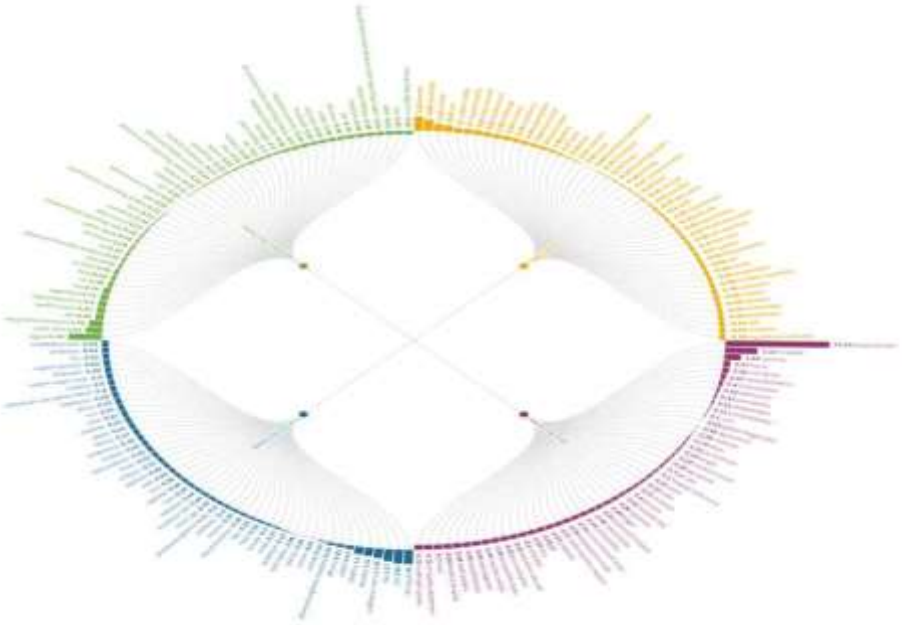


Figure 15. Emerging Subjects of the ADR Field

The figure shows the most frequently used keywords in articles and reviews studied in the field of adverse drug reactions between 1980 and 2020. The figure shows a keyword network that includes 4 clusters. The group with the highest number of words in the literature (n = 223) is the one under the heading "adverse effect measurement" shown in blue. The most frequently repeated words in this group are "therapy, trial and day". The second most repetitive word group (n = 209) is the "adverse drug reporting" group shown in green. The most repeated words in this group are "signal, odds ratio and drug administration". The third most repetitive word group (n = 174) is the "health care" group shown in yellow. The most repeated words in this group are "process, knowledge and vaccine". The fourth most repetitive word group (n = 142) is the “adverse drug risk” group shown in purple. The most frequently repeated words in this group are "drug reaction, hospital and severity".

DISCUSSION

An adverse drug event (ADE) is “an adverse medical event” that occurs in association with the use of a particular drug (Zhan et al., 2020). In

other words, it is a significantly harmful or unpleasant reaction that results from an intervention in the use of a medical drug and has a therapeutic purpose for the prevention of danger (Yuan and Woo, 2015). According to research by Evans et al. (2001), 70% of drugs have a known side effect. According to the study conducted by Van Der Hooft et al. (2006), the most common adverse reactions in inpatients were bleeding (n = 1048), adverse effects in drug use (n = 438), low blood sugar (n = 375) and fever (n = 347). The drugs that cause the most frequent adverse drug events are anticoagulants (n = 2185), cancer drugs (n = 1809) and diuretic drugs (n = 979). According to the study of Schwan et al. (2010), it is possible to experience adverse errors in epilepsy drugs. According to the study of Van Der Hooft et al. (2006), antithrombotics and anti-infectives also cause adverse drug events. According to the study of Nebeker et al. (2006), coronary stents cause adverse events. According to the study of Lucas et al. (1999), antiretroviral drugs cause adverse drug errors. According to the study of Dvorackova et al. (2020), it is seen that the most adverse drug reactions are experienced with oral anticoagulants. According to the study of Moura et al. (2020), anticonvulsant drugs cause adverse drug reactions.

In the study of Van Der Hooft et al. (2006), it was determined that 6% of the patients hospitalized in inpatient units due to adverse drug errors ended their lives. According to the study of Van Der Hooft et al. (2008), deaths due to adverse drug errors are 0.31%. 40% of the cases are preventable.

Studies have determined that adverse drug events are not sufficiently reported (Green et al., 2001; Schroeder, 1998; Belton et al., 1995). In the study conducted by Belton et al. (1995), it was determined that 63% of healthcare workers reported adverse cases they encountered, and 37% did not. Among these, it was concluded that 77% of general practitioners and 55% of other physicians reported adverse cases (Belton et al., 1995). When it is investigated why adverse cases are not reported, it is seen that they are caused by the lack of reporting forms, lack of time, the unwillingness of healthcare professionals to be punished, the belief that the incident will not contribute to medical information, the belief that only serious damage should be reported, the fear of violating patient privacy, or the healthcare professionals' fear of seeming ignorant (Herdeiro et. al., 2005; Belton et al., 1997; Belton et al., 1995).

When the studies carried out so far were examined, it was observed that adverse drug reactions were experienced in inpatients (Hamilton et al.,

2011; Lazarou et al., 1998; Cullen et al., 1997; Bates et al., 1993), who were shown as the reason for hospitalization (Pirmohamed et. al., 2004; Beijer and De Blaey, 2002; McDonnell and Jacobs, 2002) admitted to the emergency department (Budnitz et. al., 2007; Hohl et. al., 2001) discharged (Forster et. al., 2005) and received outpatient services (Budnitz et. al., 2006; Gandhi, 2003; Gurwitz et al., 2003; Hanlon et al., 1997). In addition, in the studies conducted, it was determined that the groups with the most adverse drug reactions were children (Impicciatore et. al., 2001; Kaushal et. al., 2001) and the elderly (Gurwitz et. al., 2000; Lindley, 1992).

When the studies on adverse drug reactions are examined in terms of their subjects, the preventability of adverse drug reactions (Bates et al., 1995), their determination (Edwards and Aronson, 2000), their relationship with compounding systems (Van Puijenbroek et al., 2002; Evans et al., 2001; Bate et.al., 1998; Jha et al., 1998; Raschke et al., 1998; Classen et. al., 1991), their costs (Classen et al., 1997), errors caused by pharmacists (Leape et al., 1999), their reporting (Carson et al., 2009; Moore et al., 2007), their relationship with drug errors (Bates et al., 1995; Col et al., 1990), their relationship with genetics (Ozeki et al., 2011; Hung et al., 2006), their relationship with pharmacogenetics (Meyer et al., 2000), their relationship with eosinophilia and systemic symptoms (Kardaun et al., 2013), their relationship with iron deficiency (Chertow et al, 2006), their relationship with quality (Cullen et al., 1995) comes to the fore in the studies.

When the recent studies on adverse drug reactions are examined in terms of their subjects, it is seen that the relation of adverse drug reactions with social media use (De Rosa et al., 2021), their effect on newspaper news (Postma and Donyai, 2020), their relationship with technology (Kadima et al., 2020), their relationship with psychology (Riera-Arnau et al., 2020; Sönmez-Güngör et al., 2020), their effect on hospital stay (Sandoval et al., 2020), their incidence in emergency services (Kauppila et al., 2020), the risk of cutaneous adverse drug reactions (Panickar et al., 2020), their reporting (Kim et al., 2020), their definition according to ICD-10 (Cheng et al., 2020) and their experience in outpatient treatment (Adedapo et al., 2020) are mostly examined. In addition, in recent studies, it has been observed that the most adverse drug reactions are experienced in patients with Covid-19 (Grandvuillemin et al., 2020; Shiohara et al., 2020; Sönmez-Güngör et al., 2020; Sun et al., 2020), cancer (Park et al., 2020), rheumatoid arthritis (Giraud et al., 2020), tuberculosis (Noor et al., 2020) and epilepsy (Lee et al., 2020).

The aim of this study is to determine the worldwide trend of scientific production regarding adverse drug events. For this purpose, a bibliometrix analysis was performed using the bibliometrix-R tool in the period from 1991 to 2019.

Co-authorship and coexistence analysis in the research is not only examined at the individual level in terms of research collaborators but also at the country level (Jalal, 2019). In the study, it is possible to say that there is scientific cooperation between countries such as China, New Zealand, Canada, France, Denmark, Germany, India, Malaysia and Singapore, and in the quantitative and graphical analyzes from different perspectives based on publication data, the connections with other countries were established to conduct research on the subject.

Word analysis can also be performed with the help of Bibliometrix analysis. In the research conducted by Jalal (2019), it was revealed that the prominent keywords were concepts such as "mortality, diseases, prevalence". In the study, the keywords that stand out in the title of the article are words such as "adverse, drug, reactions, reporting, pharmacovigilance and events". It was found that concepts such as "adverse, events, drugs, patient, reporting, address, safety, data, reports and methods" were used more in the abstracts.

The most cited countries in bibliometric analyzes are the world's most research-intensive countries such as the UK, USA, China, Japan, Germany, Italy, Canada and France (Kisjes, 2013). However, the eight most productive countries in the study are the USA, France, United Kingdom, Italy, Netherlands, Australia, China and Germany. Only five countries USA, France, Italy, China and Germany Canada are on the above list and their rankings differ. The efficiency of these countries may be related to specific funding opportunities, the number of laboratories and the number of teaching programs in these countries.

The thematic evolution map used in the study helps to identify the main research areas related to adverse drug events. It is also used as a graphical study in terms of how the themes emerge, how they are used over time and to guide future research. In the research, it was determined that the themes of "adverse, data, reporting, pharmacovigilance and review" between 1991 and 2010 were used in the foreground and the themes of “adverse, patients, detection, data, pharmacovigilance, review and safety” stood out between 2018-2020. It can be said that global cooperation on these themes

should be encouraged, supported and implemented in order to progress on adverse drug events.

LIMITATIONS OF STUDY

There are some limitations to the bibliometric analysis tools in this study. By its very nature, it is impossible to create a perfect and all-encompassing research query, so there is always the possibility to have false positive and false negative results in any bibliometric search.

Citation analysis represents an objective and quantitative measure of research but it does not provide information about its quality or impact on clinical practice. However, it can be hypothesized that the more citations an article receives, the greater the impact the article can have on scientific research (Fortuna et al., 2020).

It is not possible to say that this study is a comprehensive review of the literature on the adverse drug reaction process, as it is studied only with raw data for articles from the Web of Science. However, databases such as Scopus, PubMed and Google Scholar have strengths and weaknesses (Falagas et al., 2008). For example, although there are many studies in the Pubmed database, not all bibliometric analyses can be performed with downloaded raw data.

There are other limitations in this analysis:

- Although the words of adverse drug reactions and other search strategies are determined quite comprehensively and the search terms appear in the article title/abstract /keywords, they may not be included in the full text of the articles.
- Self-citations of the articles were not excluded.
- In this analysis, WOS does not allow electronic access to articles published before 1975. This means we may have skipped some articles. Additionally, many other articles may have been published in journals that have not yet been indexed.

This study was also limited to the English language, 670 journal categories, and article and review types. Besides, some research articles on adverse drug reactions in other databases and in languages other than English may be overlooked. Given all these limitations, the number of publications analyzed in this study may not fully reflect all global research activity on

adverse drug reactions, but the data presented are likely to provide important insight into trends that have evolved over the past three decades.

There are some drawbacks inherent in citation analysis. Bibliometric analyzes have the potential to feed the presumption of poor quality of non-cited or rarely cited studies (MacRoberts and MacRoberts, 2010). In addition, the results of the bibliometric analysis can vary widely with different search strategies and inclusion and exclusion criteria (Huang et al. 2019). With bibliometric analysis results, researchers can learn more about the history of adverse drug reactions. Analysis results have the potential to predict the course of development of adverse drug reactions.

CONCLUSION

Science mapping is an important activity for those working in all discipline areas. Results from science mapping, data visualization, and bibliometric software are also one of the most rational inputs used for policymaking. Through the various techniques used in the bibliometric method adopted in this study (such as collaboration analysis and science mapping), a comprehensive picture of the co-production network in the field of adverse drug reactions was established. Along with this article, we tried to provide a valuable reference for scientists to understand research trends and understand current issues related to the field within the scope of adverse drug errors. In addition, mapping results provide a valuable tool for researchers to access the literature in this field, and drug errors and adverse drug events can be used to help determine the direction of future research.

REFERENCES

Adedapo, A. D., Adedeji, W. A., Adedapo, I. A., & Adedapo, K. S. (2021). Cohort Study On Adverse Drug Reactions In Adults Admitted To The Medical Wards Of A Tertiary Hospital In Nigeria: Prevalence, İncidence, Risk Factors And Fatality. *British Journal of Clinical Pharmacology*, *87*(4), 1878-1889.

Al Rihani, S. B., Smith, M. K., Bikmetov, R., Deodhar, M., Dow, P., Turgeon, J., & Michaud, V. (2020). Risk Of Adverse Drug Events Following The Virtual Addition Of COVID-19 Repurposed Drugs To Drug Regimens Of Frail Older Adults With Polypharmacy. *Journal Of Clinical Medicine*, *9*(8), 2591.

Al-Hashar, A., Al-Zakwani, I., Eriksson, T., Sarakbi, A., Al-Zadjali, B., Al Mubaihsi, S., & Al Za'abi, M. (2018). Impact Of Medication Reconciliation and Review And Counselling, On Adverse Drug Events And Healthcare Resource Use. *International Journal Of Clinical Pharmacy*, *40*, 1154-1164.

Aria, M., & Cuccurullo, C. (2017). Bibliometrix: An R-Tool For Comprehensive Science Mapping Analysis. *Journal of informetrics*, *11*(4), 959-975.

Baker, J., Brovman, E. Y., Rao, N., Beutler, S. S., & Urman, R. D. (2020). Potential Opioid-Related Adverse Drug Events Are Associated With Decreased Revenue İn Hip Replacement Surgery İn The Older Population. *Geriatric Orthopaedic Surgery & Rehabilitation*, *11*, 2151459320915328.

Bankes, D. L., Jin, H., Finnel, S., Michaud, V., Knowlton, C. H., Turgeon, J., & Stein, A. (2020). Association of a novel medication risk score with adverse drug events and other pertinent outcomes among participants of the programs of all-inclusive care for the elderly. *Pharmacy*, *8*(2), 87.

Bate, A., Lindquist, M., Edwards, I. R., Olsson, S., Orre, R., Lansner, A., & De Freitas, R. M. (1998). A Bayesian Neural Network Method For Adverse Drug Reaction Signal Generation. *European Journal Of Clinical Pharmacology*, *54*, 315-321.

Bates, D. W., Cullen, D. J., Laird, N., Petersen, L. A., Small, S. D., Servi, D., ... & Edmondson, A. (1995). Incidence Of Adverse Drug Events And Potential Adverse Drug Events: İmplications For Prevention. *Jama*, *274*(1), 29-34.

Bates, D. W., Leape, L. L., & Petrycki, S. (1993). Incidence And Preventability Of Adverse Drug Events In Hospitalized Adults. *Journal Of General İnternal Medicine*, *8*, 289-294.

Beijer, H. J. M., & De Blaey, C. J. (2002). Hospitalisations Caused By Adverse Drug Reactions (ADR): A Meta-Analysis Of Observational Studies. *Pharmacy World and Science*, *24*(2), 46-54.

Belton, K. J., & European Pharmacovigilance Research Group. (1997). Attitude Survey Of Adverse Drug-Reaction Reporting By Health Care Professionals Across The European Union. *European Journal Of Clinical Pharmacology*, *52*, 423-427.

Belton, K. J., Lewis, S. C., Payne, S., Rawlins, M. D., & Wood, S. M. (1995). Attitudinal Survey Of Adverse Drug Reaction Reporting By Medical Practitioners in The United Kingdom [See Comments]. *British journal of clinical pharmacology*, *39*(3), 223-226.

Budnitz, D. S., Pollock, D. A., Weidenbach, K. N., Mendelsohn, A. B., Schroeder, T. J., & Annest, J. L. (2006). National Surveillance Of Emergency Department Visits For Outpatient Adverse Drug Events. *Jama*, *296*(15), 1858-1866.

Budnitz, D. S., Shehab, N., Kegler, S. R., & Richards, C. L. (2007). Medication Use Leading To Emergency Department Visits For Adverse Drug Events In Older Adults. *Annals Of Internal Medicine*, *147*(11), 755-765.

Carson, K. R., Evens, A. M., Richey, E. A., Habermann, T. M., Focosi, D., Seymour, J. F., ... & Bennett, C. L. (2009). Progressive Multifocal Leukoencephalopathy After Rituximab Therapy in HIV-Negative Patients: A Report Of 57 Cases From the Research on Adverse Drug Events and Reports project. *Blood, The Journal of the American Society of Hematology*, *113*(20), 4834-4840.

Cheng, Y. F., Cheng, C. Y., Wang, S. H., Lin, Y. T., & Tsai, T. C. (2021). Use Of ICD-10-CM T Codes In Hospital Claims Data To İdentify Adverse Drug Events In Taiwan. *Journal Of Clinical Pharmacy and Therapeutics*, *46*(2), 476-483.

Chertow, G. M., Mason, P. D., Vaage-Nilsen, O., & Ahlmen, J. (2006). Update On Adverse Drug Events Associated With Parenteral Iron. *Nephrology Dialysis Transplantation*, *21*(2), 378-382.

Classen, D. C., Pestotnik, S. L., Evans, R. S., & Burke, J. P. (1991). Computerized Surveillance Of Adverse Drug Events In Hospital Patients. *Jama*, *266*(20), 2847-2851.

Classen, D. C., Pestotnik, S. L., Evans, R. S., Lloyd, J. F., & Burke, J. P. (1997). Adverse Drug Events In Hospitalized Patients: Excess Length Of Stay, Extra Costs, and Attributable Mortality. *Jama*, *277*(4), 301-306.

Cobo, M. J., López-Herrera, A. G., Herrera-Viedma, E., & Herrera, F. (2012). SciMAT: A New Science Mapping Analysis Software Tool. *Journal of the American Society for Information Science and Technology*, *63*(8), 1609-1630.

Col, N., Fanale, J. E., & Kronholm, P. (1990). The Role Of Medication Noncompliance And Adverse Drug Reactions In Hospitalizations Of The Elderly. *Archives of internal medicine*, *150*(4), 841-845.

Conyers, R., Devaraja, S., & Elliott, D. (2018). Systematic Review Of Pharmacogenomics and Adverse Drug Reactions In Paediatric Oncology Patients. *Pediatric Blood & Cancer*, *65*(4), e26937.

Cullen, D. J., Bates, D. W., Small, S. D., Cooper, J. B., Nemeskal, A. R., & Leape, L. L. (1995). The incident reporting system does not detect adverse drug events: a problem for quality improvement. *The Joint Commission journal on quality improvement*, *21*(10), 541-548.

Cullen, D. J., Sweitzer, B. J., Bates, D. W., Burdick, E., Edmondson, A., & Leape, L. L. (1997). Preventable adverse drug events in hospitalized patients: a comparative study of intensive care and general care units. *Critical care medicine*, *25*(8), 1289-1297.

Dabbagh, M., Sookhak, M., & Safa, N. S. (2019). The Evolution Of Blockchain: A Bibliometric Study. *IEEE access*, *7*, 19212-19221.

Dadkhah, M., Lagzan, M., Rahimnia, F., & Kimiafar, K. (2020). What Do Publications Say About The Internet Of Things Challenges/Barriers To Uninformed Authors?: A Bibliometric Analysis. *What do Publications say about the Internet of Things Challenges/Barriers to uninformed Authors?: a bibliometric Analysis*, 77-98.

De Rosa, M., Fenza, G., Gallo, A., Gallo, M., & Loia, V. (2021). Pharmacovigilance in the era of social media: discovering adverse drug events cross-relating Twitter and PubMed. *Future Generation Computer Systems*, *114*, 394-402.

Derviş, H. (2019). Bibliometric Analysis Using Bibliometrix An R Package. *Journal of Scientometric Research*, *8*(3), 156-160.

Dvorackova, S., Mala-Ladova, K., Zimcikova, E., Jirsova, E., Steurbaut, S., Kubena, A. A., ... & Maly, J. (2021). Spontaneous reports of adverse

drug reactions related to oral anticoagulants in the Czech Republic. *International Journal of Clinical Pharmacy*, *43*, 948-957.

Edwards, I. R., & Aronson, J. K. (2000). Adverse Drug Reactions: Definitions, Diagnosis, And Management. *The lancet*, *356*(9237), 1255-1259.

Evans, S. J., Waller, P. C., & Davis, S. (2001). Use Of Proportional Reporting Ratios (PRRS) For Signal Generation From Spontaneous Adverse Drug Reaction Reports. *Pharmacoepidemiology and drug safety*, *10*(6), 483-486.

Fabretti, S. D. C., Brassica, S. C., Cianciarullo, M. A., & Romano Lieber, N. S. (2018). Triggers For Active Surveillance Of Adverse Drug Events In Newborns. *Cadernos de Saúde Pública*, *34*.

Falagas, M. E., Pitsouni, E. I., Malietzis, G. A., & Pappas, G. (2008). Comparison of PubMed, Scopus, web of science, and Google scholar: strengths and weaknesses. *The FASEB journal*, *22*(2), 338-342.

Forster, A. J., Murff, H. J., Peterson, J. F., Gandhi, T. K., & Bates, D. W. (2005). Adverse drug events occurring following hospital discharge. *Journal of general internal medicine*, *20*, 317-323.

Fortuna, G., Aria, M., Iorio, C., Mignogna, M. D., & Klasser, G. D. (2020). Global research trends in complex oral sensitivity disorder: A systematic bibliometric analysis of the framework. *Journal of Oral Pathology & Medicine*, *49*(6), 555-564.

Gandhi, T. K., Weingart, S. N., Borus, J., Seger, A. C., Peterson, J., Burdick, E., ... & Bates, D. W. (2003). Adverse drug events in ambulatory care. *New England journal of medicine*, *348*(16), 1556-1564.

Giraud, E. L., Jessurun, N. T., van Hunsel, F. P., van Puijenbroek, E. P., van Tubergen, A., Ten Klooster, P. M., & Vonkeman, H. E. (2020). Frequency of real-world reported adverse drug reactions in rheumatoid arthritis patients. *Expert opinion on drug safety*, *19*(12), 1617-1624.

Girgin, M.C. (2012). *Dokuz Eylül Üniversitesi Acil Servisine Başvuran Hastalarda Advers İlaç Reaksiyonu Sıklığının Saptanması*. Uzmanlık Tezi, Dokuz Eylül Üniversitesi Tıp Fakültesi, İzmir.

Göksel Ülker, S. (2012). İlaç Etkileşmeleri ve Advers İlaç Reaksiyonlarına Yaklaşım. *Ege Tıp Dergisi*, *51*, 53-64.

Grandvuillemin, A., Fresse, A., Cholle, C., Yamani, S., Dautriche, A., & French Network of Regional Pharmacovigilance Centres. (2020). Adverse drug reactions of hydroxychloroquine: Analysis of French pre-

pandemic SARS-CoV2 pharmacovigilance data. *Therapies*, *75*(4), 385-387.

Green, C. F., Mottram, D. R., Rowe, P. H., & Pirmohamed, M. (2001). Attitudes and knowledge of hospital pharmacists to adverse drug reaction reporting. *British journal of clinical pharmacology*, *51*(1), 81-86.

Gurwitz, J. H., Field, T. S., Avorn, J., McCormick, D., Jain, S., Eckler, M., ... & Bates, D. W. (2000). Incidence and preventability of adverse drug events in nursing homes. *The American journal of medicine*, *109*(2), 87-94.

Gurwitz, J. H., Field, T. S., Harrold, L. R., Rothschild, J., Debellis, K., Seger, A. C., ... & Bates, D. W. (2003). Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *Jama*, *289*(9), 1107-1116.

Hamilton, H., Gallagher, P., Ryan, C., Byrne, S., & O'Mahony, D. (2011). Potentially inappropriate medications defined by STOPP criteria and the risk of adverse drug events in older hospitalized patients. *Archives of internal medicine*, *171*(11), 1013-1019.

Hanlon, J. T., Schmader, K. E., Koronkowski, M. J., Weinberger, M., Landsman, P. B., Samsa, G. P., & Lewis, I. K. (1997). Adverse drug events in high risk older outpatients. *Journal of the American Geriatrics Society*, *45*(8), 945-948.

He, X., Wu, Y., Yu, D., & Merigó, J. M. (2017). Exploring the ordered weighted averaging operator knowledge domain: a bibliometric analysis. *International Journal of Intelligent Systems*, *32*(11), 1151-1166.

Herdeiro, M. T., Figueiras, A., Polónia, J., & Gestal-Otero, J. J. (2005). Physicians' attitudes and adverse drug reaction reporting: a case-control study in Portugal. *Drug safety*, *28*, 825-833.

Hohl, C. M., Dankoff, J., Colacone, A., & Afilalo, M. (2001). Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. *Annals of emergency medicine*, *38*(6), 666-671.

Huang, H. C., Wang, C. H., Chen, P. C., & Lee, Y. D. (2019). Bibliometric analysis of medication errors and adverse drug events studies. *Journal of Patient Safety*, *15*(2), 128-134.

Hung, S. I., Chung, W. H., Jee, S. H., Chen, W. C., Chang, Y. T., Lee, W. R., ... & Chen, Y. T. (2006). Genetic susceptibility to carbamazepine-

induced cutaneous adverse drug reactions. *Pharmacogenetics and genomics*, *16*(4), 297-306.

Impicciatore, P., Choonara, I., Clarkson, A., Provasi, D., Pandolfini, C., & Bonati, M. (2001). Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. *British journal of clinical pharmacology*, *52*(1), 77-83.

Jalal, S. K. (2019). Co-authorship and co-occurrences analysis using Bibliometrix R-package: A casestudy of India and Bangladesh. *Annals of Library and Information Studies (ALIS)*, *66*(2), 57-64.

Jha, A. K., Kuperman, G. J., Teich, J. M., Leape, L., Shea, B., Rittenberg, E., ... & Bates, D. W. (1998). Identifying adverse drug events: development of a computer-based monitor and comparison with chart review and stimulated voluntary report. *Journal of the American Medical Informatics Association*, *5*(3), 305-314.

Kadima, N. J., Nyiranteziryayo, R., Umumararungu, T., & Adedeji, A. A. (2021). Use of mobile phones for patient self-reporting adverse drug reactions: A pilot study at a tertiary hospital in Rwanda. *Health and Technology*, *11*, 185-191.

Kardaun, S. H., Sekula, P., Valeyrie-Allanore, L., Liss, Y., Chu, C. Y., Creamer, D., ... & RegiSCAR Study Group. (2013). Drug reaction with eosinophilia and systemic symptoms (DRESS): an original multisystem adverse drug reaction. Results from the prospective RegiSCAR study. *British Journal of dermatology*, *169*(5), 1071-1080.

Kauppila, M., Backman, J. T., Niemi, M., & Lapatto-Reiniluoto, O. (2021). Incidence, preventability, and causality of adverse drug reactions at a university hospital emergency department. *European Journal of Clinical Pharmacology*, *77*, 643-650.

Kaushal, R., Bates, D. W., Landrigan, C., McKenna, K. J., Clapp, M. D., Federico, F., & Goldmann, D. A. (2001). Medication errors and adverse drug events in pediatric inpatients. *Jama*, *285*(16), 2114-2120.

Kefale, B., Degu, A., & Tegegne, G. T. (2020). Medication-related problems and adverse drug reactions in Ethiopia: A systematic review. *Pharmacology research & perspectives*, *8*(5), e00641.

Khan, Z., Muhammad, K., Karataş, Y., Bilen, Ç., Khan, F. U., & Khan, F. U., (2020). Pharmacovigilance and incidence of adverse drug reactions in hospitalized pediatric patients: a mini systematic review. *Egyptian PediatricAssociation Gazette* , vol.46.

Kim, S., Yu, Y. M., You, M., Jeong, K. H., & Lee, E. (2020). A cross sectional survey of knowledge, attitude, and willingness to engage in spontaneous reporting of adverse drug reactions by Korean consumers. *BMC Public Health*, *20*, 1-11.

Kisjes, I. (2013). Report: How Do The Large Research Nations Compare?.

Lazarou, J., Pomeranz, B. H., & Corey, P. N. (1998). Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *Jama*, *279*(15), 1200-1205.

Leape, L. L., Cullen, D. J., Clapp, M. D., Burdick, E., Demonaco, H. J., Erickson, J. I., & Bates, D. W. (1999). Pharmacist participation on physician rounds and adverse drug events in the intensive care unit. *Jama*, *282*(3), 267-270.

Lee, J. E., Min, K. R., Kim, S. H., Kim, A. H., & Kim, S. T. (2020). Analysis of adverse drug reactions with carbamazepine and oxcarbazepine at a tertiary care hospital. *Yonsei medical journal*, *61*(10), 875.

Lindley, C. M., Tully, M. P., Paramsothy, V., & Tallis, R. C. (1992). Inappropriate medication is a major cause of adverse drug reactions in elderly patients. *Age and ageing*, *21*(4), 294-300.

Lucas, G. M., Chaisson, R. E., & Moore, R. D. (1999). Highly active antiretroviral therapy in a large urban clinic: risk factors for virologic failure and adverse drug reactions. *Annals of internal medicine*, *131*(2), 81-87.

MacRoberts, M. H., & MacRoberts, B. R. (2010). Problems of citation analysis: A study of uncited and seldom-cited influences. *Journal of the American Society for Information Science and Technology*, *61*(1), 1-12.

McDonnell, P. J., & Jacobs, M. R. (2002). Hospital admissions resulting from preventable adverse drug reactions. *Annals of Pharmacotherapy*, *36*(9), 1331-1336.

Meyer, U. A. (2000). Pharmacogenetics and adverse drug reactions. *The Lancet*, *356*(9242), 1667-1671.

Moore, T. J., Cohen, M. R., & Furberg, C. D. (2007). Serious adverse drug events reported to the Food and Drug Administration, 1998-2005. *Archives of internal medicine*, *167*(16), 1752-1759.

Moura, L. M., Smith, J. R., Yan, Z., Blacker, D., Schwamm, L. H.,

Newhouse, J. P., ... & Hsu, J. (2021). Patterns of anticonvulsant use and adverse drug events in older adults. *Pharmacoepidemiology and drug safety*, *30*(1), 28-36.

Nebeker, J. R., Virmani, R., Bennett, C. L., Hoffman, J. M., Samore,

M. H., Alvarez, J., ... & Feldman, M. D. (2006). Hypersensitivity cases associated with drug-eluting coronary stents: a review of available cases from the Research on Adverse Drug Events and Reports (RADAR) project. *Journal of the American College of Cardiology*, *47*(1), 175-181.

Noor, S., Ismail, M., & Khan, F. (2021). Drug safety in hospitalized patients with tuberculosis: Drug interactions and adverse drug effects. *The Clinical Respiratory Journal*, *15*(1), 97-108.

Ozeki, T., Mushiroda, T., Yowang, A., Takahashi, A., Kubo, M., Shirakata, Y., ... & Nakamura, Y. (2011). Genome-wide association study identifies HLA-A* 3101 allele as a genetic risk factor for carbamazepine-induced cutaneous adverse drug reactions in Japanese population. *Human molecular genetics*, *20*(5), 1034-1041.

Panickar, R., Wo, W. K., Ali, N. M., Tang, M. M., Ramanathan, G. L., Kamarulzaman, A., & Aziz, Z. (2020). Allopurinol-induced severe cutaneous adverse drug reactions: Risk minimization measures in Malaysia. *Pharmacoepidemiology and drug safety*, *29*(10), 1254-1262.

Park, H. K., Lee, S. J., Kim, S., Lee, J. M., & Hong, D. G. (2020). Does carboplatin rapid desensitization change its adverse drug reactions other than hypersensitivity and efficacy in patients with ovarian cancer?. *Allergy, Asthma & Immunology Research*, *12*(6), 1046.

Pirmohamed, M., James, S., Meakin, S., Green, C., Scott, A. K., Walley, T. J., ... & Breckenridge, A. M. (2004). Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *Bmj*, *329*(7456), 15-19.

Postma, L. G. M., & Donyai, P. (2021). The cooccurrence of heightened media attention and adverse drug reaction reports for hormonal contraception in the United Kingdom between 2014 and 2017. *British Journal of Clinical Pharmacology*, *87*(4), 1768-1777.

Raschke, R. A., Gollihare, B., Wunderlich, T. A., Guidry, J. R., Leibowitz, A. I., Peirce, J. C., ... & Susong, C. (1998). A computer alert system to prevent injury from adverse drug events: development and evaluation in a community teaching hospital. *Jama*, *280*(15), 1317-1320.

Riera-Arnau, J., Alvarado Aguirre, L. A., Garcia Dolade, N., Vidal Guitart, X., Figueras, A., & Cereza Garcia, G. (2021). Patients' contribution to drug safety in Catalonia: The interest of personal feelings on adverse drug reactions. *European Journal of Clinical Pharmacology*, *77*, 637-642.

Rodríguez-Soler, R., Uribe-Toril, J., & Valenciano, J. D. P. (2020). Worldwide trends in the scientific production on rural depopulation, a bibliometric analysis using bibliometrix R-tool. *Land Use Policy*, *97*, 104787.

Sakiris, M. A., Sawan, M., Hilmer, S. N., Awadalla, R., & Gnjidic, D. (2021). Prevalence of adverse drug events and adverse drug reactions in hospital among older patients with dementia: A systematic review. *British Journal of Clinical Pharmacology*, *87*(2), 375-385.

Sandoval, T., Martínez, M., Miranda, F., & Jirón, M. (2021). Incident adverse drug reactions and their effect on the length of hospital stay in older inpatients. *International Journal of Clinical Pharmacy*, *43*, 839-846.

Schroeder, D. R. (1998). Statistics: detecting a rare adverse drug reaction using spontaneous reports. *Regional anesthesia and pain medicine*, *23*(6), 183.

Schwan, S., Sundström, A., Stjernberg, E., Hallberg, E., & Hallberg, P. (2010). A signal for an abuse liability for pregabalin—results from the Swedish spontaneous adverse drug reaction reporting system. *European journal of clinical pharmacology*, *66*, 947-953.

Sessa, M., Rossi, C., Mascolo, A., Scafuro, A., Ruggiero, R., Mauro, G. D., ... & Rafaniello, C. (2018). Contribution of Italian clinical research for contrast media-induced nonrenal adverse drug reactions over the last three decades: A systematic review. *Journal of Pharmacology and Pharmacotherapeutics*, *9*(3), 131-146.

Shiohara, T., & Mizukawa, Y. (2020). Comment On 'Drug Reaction With Eosinophilia And Systemic Symptoms Syndrome İn A Patient With COVID-19': Involvement Of Herpesvirus Reactivations And Adverse Drug Reactions In Diverse Cutaneous Manifestations And Overall Disease Severity Of COVID-19. *Journal Of The European Academy Of Dermatology And Venereology*.

Sönmez Güngör, E., Yalçın, M., Yerebakan Tüzer, M., Beşikçi Keleş,, D., Öcek Baş, T., Ergelen, M., ... & Güneş, M. (2021). Adverse drug reactions associated with concurrent acute psychiatric treatment and Covid-19 drug therapy. *International Journal of Psychiatry in Clinical Practice*, *25*(2), 142-146.

Sun, J., Deng, X., Chen, X., Huang, J., Huang, S., Li, Y., ... & He, G. (2020). Incidence of adverse drug reactions in COVID-19 patients in China: an active monitoring study by hospital pharmacovigilance system. *Clinical Pharmacology & Therapeutics*, *108*(4), 791-797.

Tonta, Y. (2014). Akademik performans, öğretim üyeliğine yükseltme ve yayın destekleme ölçütleriyle ilgili bir değerlendirme (An Evaluation of criteria on academic performance, tenure and publication support).

Vaismoradi, M., Logan, P. A., Jordan, S., & Sletvold, H. (2019). Adverse drug reactions in norway: a systematic review. *Pharmacy, 7*(3), 102.

Van der Hooft, C. S., Dieleman, J. P., Siemes, C., Aarnoudse, A. J. L., Verhamme, K. M., Stricker, B. H., & Sturkenboom, M. C. (2008). Adverse Drug Reaction-Related Hospitalisations: A Population-Based Cohort Study. *Pharmacoepidemiology And Drug Safety*. 17(4); 365-371.

Van Der Hooft, C. S., Sturkenboom, M. C., van Grootheest, K., Kingma, H. J., & Stricker, B. H. C. (2006). Adverse drug reaction-related hospitalisations: a nationwide study in The Netherlands. *Drug safety, 29*, 161-168.

Van Puijenbroek, E. P., Bate, A., Leufkens, H. G., Lindquist, M., Orre, R., & Egberts, A. C. (2002). A comparison of measures of disproportionality for signal detection in spontaneous reporting systems for adverse drug reactions. *Pharmacoepidemiology and drug safety*, *11*(1), 3-10.

Waltman, L. (2016). A review of the literature on citation impact indicators. *Journal of informetrics*, *10*(2), 365-391.

Yaşlıoğlu, M. M. (2017). Sosyal bilimlerde faktör analizi ve geçerlilik: Keşfedici ve doğrulayıcı faktör analizlerinin kullanılması. *İstanbul Üniversitesi İşletme Fakültesi Dergisi*, *46*, 74-85.

Yu, D., Sheets, J., Suppes, S., & Goldman, J. (2019). Characterization of severe adverse drug reactions at a free-standing children's hospital. *The Journal of Clinical Pharmacology*, *59*(12), 1569-1572.

Yuan, A., & Woo, S. B. (2015). Adverse drug events in the oral cavity. *Oral surgery, oral medicine, oral pathology and oral radiology*, *119*(1), 35-47.

Zhan, C., Roughead, E., Liu, L., Pratt, N., & Li, J. (2020). Detecting potential signals of adverse drug events from prescription data. *Artificial intelligence in medicine*, *104*, 101839.

Zupic, I., & Čater, T. (2015). Bibliometric methods in management and organization. *Organizational research methods*, *18*(3), 429-472.

CHAPTER 8

CHIARI MALFORMATION: A CASE PRESENTATION AND GENERAL OVERVIEW

Assoc. Prof. Dr. Hüseyin Erdem AK[1]

[1] Bilecik Şeyh Edebali University, Department of Neurosurgery, Bilecik
ORCID: 0000-0002-0823-0594. E-Mail: erdem.ak@bilecik.edu.tr

INTRODUCTION

Chiari malformations are a structural brain anomaly where the cerebellar tonsils abnormally protrude below the level of the foramen magnum into the spinal canal. This condition can obstruct the fluid flow between the brain and the spinal cord, leading to various symptoms.

Chiari malformation (CM) was described by Hans Chiari in 1891. This malformation is characterized by the displacement of the cerebellar tonsils into the spinal canal (Koehler, 1991; Ropper and Williams, 2013; Speer, et al., 2020). In most cases, the cause of the disease is unknown. It is thought that Chiari malformation is associated with genetic and environmental factors. This congenital condition can be detected later in life (Koehler, 1991; Saletti et al., 2019). Chiari malformation type 1 is found in less than 1% of magnetic resonance imaging (MRI) scans, and most patients are asymptomatic (Milhorat, et al., 199; Oldfield, et al., 1994).

There are four types of this malformation, and each has different clinical features, diagnostic methods, and treatment approaches (Heiss, 1999; Rosenblum, et al., 2022; Speer, et al., 2020).

1. Type I: mild and common form. The tonsils are seen to be displaced downward by 5 mm or more. The bony posterior fossa volume is small in most cases. Patients may have varying degrees of syringomyelia. Symptoms usually appear in adulthood.

2. Type II: Associated with congenital spina bifida. The cerebellum and brainstem are more prominently displaced. Syringomyelia is present, and hydrocephalus may occur.

3. Type III: Rare and most severe form. The cerebellum and brainstem protrude more from the spinal canal, and symptoms begin at birth.

4. Type IV: The rarest form with incomplete cerebellar development, it usually results in fatal outcomes at birth.

Symptoms of Chiari malformation vary greatly. Headaches increase when neck movements, coughing, sneezing, or applying abdominal pressure. Headaches start from the back of the head and spread upward. Some patients may have no symptoms. The most common symptoms are as follows (Fric, et al., 2019; Milhorat, et al., 1999; Nagib, M. G., 2011; Oldfield, et al., 1994; Ropper and Williams, 2013; Tubbs, et al., 2011).

1. Headache
2. Neck pain
3. Weakness in the extremities
4. Imbalance
5. Vertigo
6. Quick fatigue
7. Difficulty swallowing
8. Sleep apnea

Magnetic resonance imaging (MRI) is the most common and reliable method for diagnosing Chiari malformation. Through this imaging technique, abnormalities in the cerebellum and brainstem, as well as conditions such as syringomyelia and hydrocephalus in the medulla spinalis, can be detected (Heiss, 1999; Speer, et al., 2020; Tubbs, et al., 2011).

Surgical treatment indication criteria may vary among neurosurgeons. Surgical indication exists in patients with MRI findings, medical history, and symptoms specific to Chiari malformation type 1 that affect their quality of life. Surgical treatment is rarely planned for patients thought to be symptomatic. In these patients, medications are used to alleviate symptoms and exercises are recommended (Fric, et al., 2019).

Surgical interventions can include methods such as decompression surgery or shunt application. For patients without syringomyelia, posterior fossa decompression alone is sufficient. In the majority of patients with syringomyelia resulting from the structure of the foramen magnum in Chiari malformation type 1, it spontaneously decreases or stabilizes after decompression alone. Therefore, intervention in syringomyelia is not necessary (Milhrat, et al., 2010; Nagib, 2011). The reduction or non-increase of syringomyelia is dependent on the permanent creation of a subarachnoid space at the foramen magnum (Rosenblum, et al., 2022; Yan, et al., 2016). Surgical intervention involving suboccipital craniectomy, C-1 laminectomy, and duraplasty expands the CSF space in the foramen magnum and resolves the syrinx. After the surgical procedure, the cerebellar tonsils take a proper shape and rise towards the foramen magnum (2). If necessary, syringo-

subarachnoid or -pleural shunt surgeries can be performed. Radiological or clinical worsening of syringomyelia is very rare after adequate decompression of the foramen magnum (Rosenblum, et al., 2022; Yan, et al., 2016).

Case Presentation

The patient, E.C. is 36-year-old, female, presented with complaints of persistent headaches throughout the day, neck pain, balance issues, difficulty swallowing, occasional transient vision loss, and numbness in the extremities for several months. A detailed medical history and neurological examination were conducted. Her headache worsened when she touched her chin to her chest and coughed. The patient reported that her symptoms were progressively worsening and negatively affecting her daily life. She also had complaints of difficulty swallowing and nausea. Slight truncal ataxia was detected while walking. She described atypical sensory deficits in her upper extremities. It was learned that the patient had not experienced any trauma or surgical intervention and that there were no other individuals with similar conditions in her family.

Considering the patient's symptoms and physical examination findings, magnetic resonance imaging (MRI) was performed. The MRI revealed the patient's cerebellar tonsils protruding into the spinal canal, compressing the medulla spinalis. There was syringomyelia in the cervical region of the medulla spinalis. C4, C5, C6, C7 levels show multisegmental syrinx formations, with the most prominent reaching a diameter of 7 mm. There is observed narrowing of the subarachnoid space at the level of the foramen magnum. The distal clivus and occipital condyles appear hypoplastic in structure. At the level of the foramen magnum, there is approximately 9 mm of tonsillar herniation. These images were reported radiologically as Chiari malformation Type I (Figure 1).

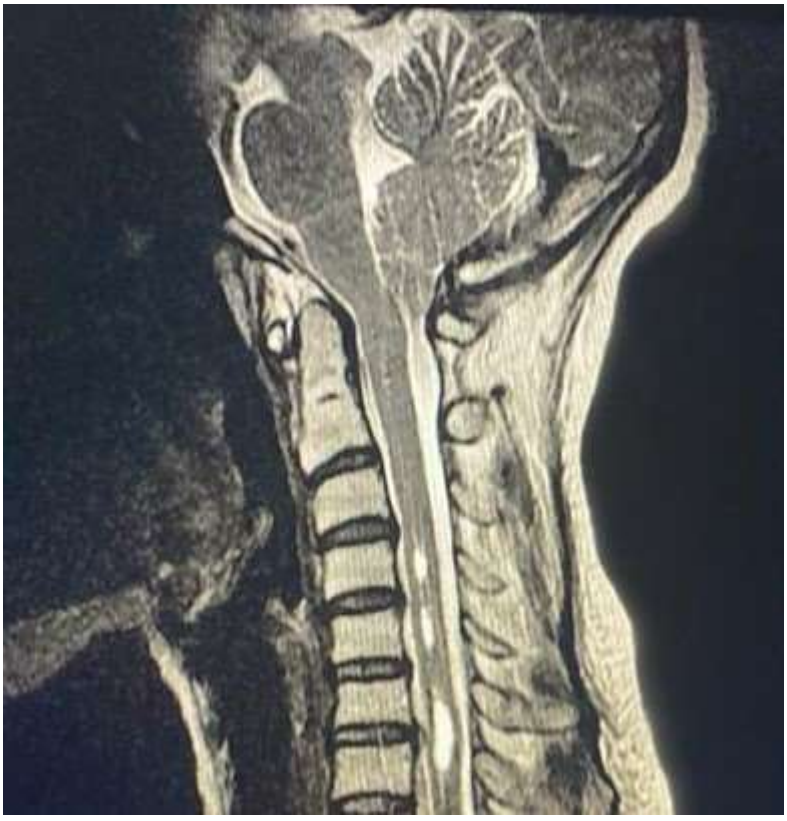


Figure 1. Patient's preoperative MRI image

Treatment options were presented to the patient based on the severity of her symptoms and their impact on her quality of life. The patient's condition was monitored for one month, starting with medication treatment and lifestyle changes. There was no improvement in the patient's complaints and symptoms. Posterior fossa decompression surgery was recommended to the patient. Decompression was achieved by performing a C1 laminectomy and craniectomy in the occipital bone. Additionally, duraplasty was performed to relieve the spinal cord and cerebellar tonsils. Tissel was used to prevent CSF leakage. The patient was discharged without any postoperative complications.

The patient was called for regular check-ups at three-month intervals after the surgery. It was determined that her symptoms had largely disappeared. In particular, her headache was completely gone. The patient's quality of life improved significantly. Regular check-ups are ongoing. Postoperative control MRI appearance (Figure 2).

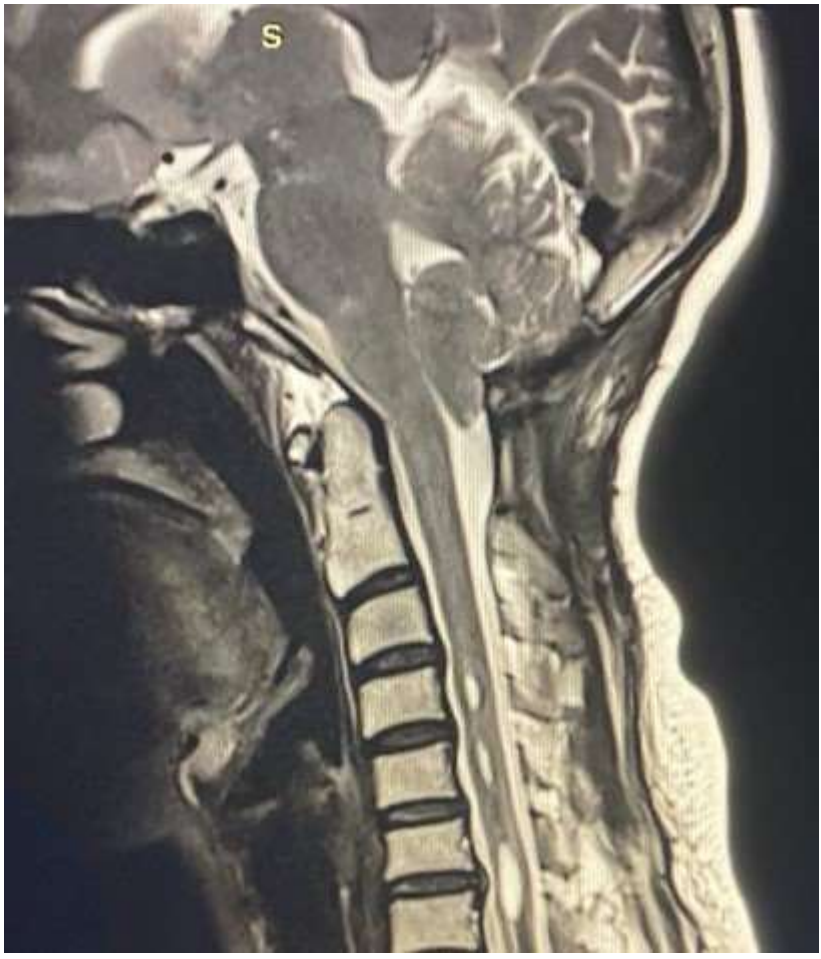


Figure 2. Patient's MRI image three months after surgery

DISCUSSION

Chiari malformation occurs as a result of the downward displacement of the cerebellar tonsils through the foramen magnum and the pushing of the lower part of the brainstem into the skull. This condition affects the normal functioning of the brainstem and causes various symptoms. Chiari malformation is usually congenital and may have a genetic basis in some cases. It can occur when the brainstem does not develop properly. Chiari malformation disrupts the flow of cerebrospinal fluid, leading to hydrocephalus and the formation of syringomyelia in the spinal canal (Milhrat, et al., 2010; Oldfield, 2017).

Chiari malformation can often cause symptoms such as headache, neck pain, imbalance, vertigo, and balance disturbances. These symptoms can vary depending on the patient's age, the degree of pressure, and their social life. This condition significantly affects the patients' quality of life and requires treatment (Milhorat, et al., 1999; Speer, et al., 2020).

Diagnosis of Chiari malformations is made using MRI. The diagnostic process is complex and requires careful evaluation, depending on the severity of the symptoms and the patient's age. Chiari malformations can significantly impact a patient's quality of life. The severity of symptoms and the appropriate treatment options have a significant effect on quality of life (Milhorat, et al., 1999; Oldfield, 2017; Oldfield, et al., 1994).

Treatment of Chiari malformation may vary depending on the symptoms and the patient's condition. Treatment options can include medications, surgical intervention, and physical therapy. For mild symptoms, pain relievers and lifestyle changes may be sufficient. In severe cases, surgical intervention may be required. Surgical treatment aims to correct the brain and spinal cord structures, contributing to symptom relief and improved quality of life (Oldfield, etal, 1994; Rosenblum, et al., 2022; Tubbs, et al., 2011). Surgical treatment outcomes are generally good in patients with typical symptoms and radiological findings. Proper patient selection for surgery is crucial. Patients should be informed that symptom improvement may take a long time after surgery. Persistent nausea and dizziness, as well as muscle pain in the neck, are common in the postoperative period as a result of surgical intervention at the foramen magnum (Milhrat, et al., 2010; Tubbs, et al., 2011).

In selected CM cases without syringomyelia, less invasive interventions such as posterior fossa decompression alone are sufficient. Patient selection and appropriate surgical intervention choice are crucial for the successful resolution of CM and syringomyelia symptoms and signs. After surgical treatment, many patients' symptoms disappear, and their quality of life improves (Oldfield, 2017; Rosenblum, et al., 2022; Yan, et al., 2016).

In conclusion, Chiari malformation is a complex and rare brain anomaly. Early diagnosis and appropriate treatment methods enhance patients' quality of life and prevent potential complications. Diagnosis is made through neurological examination and imaging scans. Surgical intervention is an effective option for symptom reduction.

REFERENCES

Fric R, Ringstad G, Eide PK.Tidsskr Nor Laegeforen. 2019 Jun 11;139(10). doi: 10.4045/tidsskr.18.0455. Print 2019 Jun 25.PMID: 31238671.

Heiss JD, Patronas N, DeVroom HL, Shawker T, Ernis R, Kammerer W, Eidsath A, Talbot T, Morris J, Eskioglu E, Oldfield EH., 1999. Elucidating the pathophysiology of syringomyelia. J Neurosurg. 91(4):553–62.

Koehler PJ.1991. Chiari's description of cerebellar ectopy. With a summary of Cleland's and Arnold's contributions and some early observations on neural-tube defects. J Neurosurg. 75:823–826.

Milhorat, T. H., Chou, M. W., Trinidad, E. M., Kula, R. W., and Mandell, M., 1999. Chiari I malformation redefined: clinical and radiographic findings for 364 symptomatic patients. Neurosurgery, 44(5), 1005-1017.

Milhrat, T. H., Nishikawa, M., Kula, R. W., & Dlugacz, Y. D., 2010. Mechanisms of cerebellar tonsil herniation in patients with Chiari malformations as guide to clinical management. Acta Neurochirurgica, (2010). 152(7), 1117-1127.

Nagib, M. G., 2011. An approach to symptomatic children (ages 4-14 years) with Chiari type I malformation. Child's Nervous System, 27(6), 891-897.

Oldfield EH., 2017. Pathogenesis of Chiari I-Pathophysiology of Syringomyelia: Implications for Therapy: A Summary of 3 Decades of Clinical Research. Neurosurgery, 64(CN_suppl_1):66–77.

Oldfield, E. H., Muraszko, K., Shawker, T. H., & Patronas, N. J. , 1994. Pathophysiology of syringomyelia associated with Chiari I malformation of the cerebellar tonsils. Implications for diagnosis and treatment. Journal of neurosurgery, 80(1), 3-15.

Ropper AH, and Williams RS., 2013. Relationship of the tonsils and foramen magnum in the Chiari I malformation. Journal o Neurology, Neurosurgery & Psychiatry, 84(10), 1166-1167.

Rosenblum JS, Pomeraniec IJ, Heiss JD.,2022. Chiari Malformation (Update on Diagnosis and Treatment). Neurol Clin. 2022 May;40(2):297-307.

Saletti V, Viganò I, Melloni G, Pantaleoni C, Vetrano IG, Valentini LG. 2019. Chiari I, malformation in defined genetic syndromes in children: are there common pathways? Childs Nerv Syst. 2019 Oct;35(10):1727-1739.

Speer MC, Enterline DS, Mehltretter L, Hammock P, Joseph J, Dickerson M, Rosser TL., 2020. Chiari type I malformation with or without syringomyelia: Prevalence and genetics. Journal of Genetic Counseling. 12(4), 297-311.

Tubbs RS, Beckman J, Naftel RP, Chern JJ, Wellons JC, Rozzelle CJ, Oakes WJ., 2011. Institutional experience with 500 cases of surgically treated pediatric Chiari malformation Type I. Journal of neurosurgery: Pediatrics, (2011). 7(3), 248-256.

Yan H, Han X, Jin M, Liu Z, Xie D, Sha S, Qiu Y, Zhu Z.2016. Morphometric features of posterior cranial fossa are different between Chiari I malformation with and without syringomyelia. Eur Spine, 25(7):2202-9.

CHAPTER 10

THE ROLE OF VITAMIN B12 IN ALZHEIMER PATIENTS

Assist. Prof. Dr. Veysel TAHİROĞLU[1]

Dr. Elif UĞUR[2]

Dr. Erkam COŞKUN[3]

Assoc. Prof. Dr. Naci Ömer ALAYUNT[4]

Dr. Gülşah ZÖRGÖR[5]

[1] Şırnak University, Faculty of Health Sciences,Department of Nursing, Şırnak Turkey. Orcid: 0000-0003-3516- 5561 veysel.tahiroglu@sirnak.edu.tr

[2] Şırnak State Hospital, Neurology Outpatient Clinic, Şırnak, Türkiye. Orcid:0000-0003-0006-850X

[3] Şırnak State Hospital, Clinic of Medical Biochemistry, Şırnak, Turkey. Orcid: 0000-0001-5471-8606

[4] Siirt University Faculty of Medicine, Department of Medical Biochemistry, Siirt, Turkey. Orcid: 0000-0003-2215-0934

[5] Şırnak State Hospital, Neurology Outpatient Clinic, Şırnak, Türkiye. Orcid: 0000-0003-2071-5276

INTRODUCTION

Cognitive impairment is a hallmark of Alzheimer's disease (AD), a chronic, progressive neurodegenerative condition. It is the most common form of dementia in the elderly population and its impact is increasing worldwide. It is estimated that 47 million individuals worldwide suffer from this illness. Current treatment approaches and knowledge of the epidemiology, genetics, pathology, and aetiology of AD are presented (Lane et al.,2018; Gulmammadli et al., 2022). Age is the main risk factor for this illness, and studies have shown that those over 60 are more likely to develop AD (Dos Santos et al.2018). AD has a progressively worsening and fatal process. Although the disease is generally seen above 65 years of age, it can also occur at an early age. The disease, which was seen in 26.6 million people (Ane et al.,2014; Wikipedia, 2023) worldwide in 2006, is estimated to affect one out of every 85 people in 2050 (Wikipedia, 2023). Although age is the main risk factor for the disease, the presence of the ApoE4 genotype and family history of the disease are also significant genetic risk factors. Lifestyle choices including gender, education, food, and physical exercise are additional risk factors (Lopes et al., 2014). According to epidemiological research, there may be a link between the condition and a diet high in alcohol intake and saturated fatty acids but low in vitamins and antioxidants. Rich in vegetables, fruits and unsaturated fatty acids; According to certain theories, dementia and cognitive impairment may be decreased by a diet reduced in refined sugar and saturated fat (Gu et al.,2010; Lopes et al.,2014). Studies indicate that dietary habits are strongly associated with disease development. It is stated that the increase in the consumption of cruciferous vegetables, fruit, fish, and salad and the decrease in the consumption of fatty dairy products, red meat, organ meats and fat reduce the risk of disease development (Gu et al.,2010).

B-group vitamins are important for neural functions and perception. These vitamins were identified as essential nutrients at the beginning of the 20th century to prevent diseases such as Beriberi and Pellagra that affect the nervous system. Subsequently, there have been studies showing that many nutrients, including choline, antioxidants and omega-3 fatty acids, affect brain function. Therefore, it is assumed that these nutrients have a role in the pathophysiological process of AD. Therefore, increased levels of some nutrients may regulate synaptic function, prevent neurodegeneration and nerve loss (Lopes et al et al., 2014). Red blood cell production and the stability of the central nervous system are both aided by vitamin B12.

Neurological symptoms including paresthesia in the hands and feet, cramping in the muscles, lightheadedness, cognitive difficulties, ataxia, and mental symptoms like erectile dysfunction, exhaustion, and depression are the most typical signs of vitamin insufficiency (Wolffenbuttel et al., 2019). Folate transfers single carbon groups to biological processes including DNA synthesis, methylation, and homocysteine metabolism in a process known as one carbon metabolism (OCM). In OCM, folate and vitamin B12 function as substrates or cofactors of enzymes. People who are deficient in these vitamins experience anemia, and vitamin B12 deficiency causes severe neurological issues. Adults who lack vitamin B12 and folate are more likely to develop cancer, cardiovascular problems, and neurodegenerative illnesses like AD (Grarup et al., 2013). Blood levels of vitamin B12 and folate have been found to promote the onset of AD and dementia, according to research (Wang et al.,2001; Quadriet al.,2004; Ravagliaet al.,2005) that looked at the impact of dietary habits on AD and cognitive aging. This study aims to investigate the effect of vitamin B12 in relation to AD.

2. MATERIAL and METHOD

2.1.Design

The goals of the Helsinki Declaration were the context within which this research was conducted. The Siirt University Non-Interventional Clinical Research Ethics Committee granted the required approvals prior to the trial (Date: 30.05.2022, No: 2022/04.06). The study's patient group comprised of 40 newly diagnosed volunteers with AD and 40 volunteers without Alzheimer's or any other neurological illness. It was prepared by neurologists working in the Neurology outpatient clinics at Şırnak State Hospital. The study was cross-sectional, and it satisfies the requirements of the "Diagnostic and Statistical Manual of Mental Disorders (DSM-V), National Institute of Neurological and Communication Disorders and Stroke, and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA)" (Black and Grant,2014; Maszota-Zieleniak et al.,2021). The age range was established as 45–90 years with regard to the inclusion criteria for all patients to be included in the research. The study's exclusion criteria for the patient group included those with neurological conditions and/or psychiatric disorders other than Alzheimer's disease, clinical depression, brain tumours, subdural hematomas, chronic alcoholism, cognitive dysfunction brought on by strenuous exercise and fasting for longer than 24 hours, use of antioxidant supplements, and those who voluntarily wanted to leave the study. The existence of dementia or

another neurodegenerative condition, intense activity, fasting for longer than 24 hours, drug usage, alcohol consumption, use of antioxidant supplements, and readiness to leave the research were all reasons for exclusion from the control group.

2.2. Sample Collection

Fasting venous blood samples of the participants in the research were obtained between 8 and 10 am following a night fasting period of 10 to 12 hours (accepting the Informed Consent Form). Blood samples were collected from brachial veins into tubes without anticoagulant (SST Vacusera, 5 mL, 235305; Disera A.S, İzmir, TR). The tubes were slightly inverted several times. Blood samples in tubes without anticoagulant were centrifuged at 4ºC for 10 minutes at 4000 rpm. B12 (Roche Cobas 6000 c601 Roche, Mannheim, Germany) was immediately measured in the Medical Biochemistry Laboratory of Şırnak State Hospital.

2.3.Statistical Analysis

The SPSS 21.0 package application (SPSS, Version 21.0. Armonk, NY: IBM USA) was used to conduct the statistical analysis. Shapiro-Wilk and Kolmogorov-Smirnov tests were used to determine if the data in the groups were normally distributed. Nonparametric data were used to compare mean plasma peptide levels between groups using the Mann-Whitney U test. To look at the correlations between the data, Spearman's correlation analysis was used. For numerical variables, median, minimum, and maximum data are displayed along with descriptive statistics. $P<0.005$ was seen as a notable value.

3. ANALYSIS and FINDINGS

There were 80 participants in this study, 40 of whom were healthy and 40 of whom had AD. Although the patient group's mean age in our study was higher than the control group's mean age (76.43±10.75 years), the difference between the two groups was found to be statistically insignificant ($p>0.005$) (Table 1). Evaluation of vitamin B12 parameter Table 1 has also been given. According to the table, the median value of the vitamin B12 control group was 281 pg/ml, and the median value of the patient group was 302 pg/ml, which was not statistically significant ($p>0.005$) (Table 1).

Table 1. Mean Age and Median Vitamin B12 Levels Vary Between Groups

	Control (n=40)		Alzheimer's patients (n:40)		p
	Median(min-max)	IQR	Median(min-max)	IQR	
Age	79 (49-89)	15	79 (65-90)	15	>0.005
B12(pg/ml)	281 (67-834)	178	302 (69-714)	140	>0.005

4. CONCLUSION

It is a water-soluble vitamin, vitamin B12. Numerous degenerative issues and dementia, including Alzheimer's, can develop when lacking. Like every other nutrient, adequate intake of vitamin B12 is necessary for the continuity of metabolic processes in the body. These processes include cognitive development, memory and concentration. Vitamin deficiency can cause Alzheimer's Disease or worsen the process of the illness by affecting the homocysteine cycle. Raising awareness in society about adequate and balanced nutrition and making necessary interventions are essential to prevent progressive health problems such as Alzheimer's Disease for which there is no cure yet (Smith et al., 2010). Table 2 provides details on research on the association between vitamin B12 and Alzheimer's disease.

Table 2. The Role of Vitamin B12 in Studies on Alzheimer's Disease

Study	**N**	**Protocol**	**Conclusion**	**P**
(Douaud et al.,2003)	156	S: 0.8 mg folic acid + 20 mg vitamin B6 + 0.5 mg vitamin B12	7-fold reduction in the rate of atrophy in the gray layer of the brain	p<0.05*
(Scheltens et al.,2012)	259	3 mcg/g B12	memory improvement	p<0.05*
(Bozoğlu and Işık,2010)	87	First month 1000 mcg/week Next 5 months 1000	Decreased scores on the Clock Scratch Test and	p<0.05*

		mcg/month IM B12	the Yesavage Geriatric Depression Scale	
(Chan et al., 2010)	115	S: 400 mcg folic acid + 6 mcg B12 + 30 IU α-tocopherol K: Placebo	Increase in cognitive performance	p<0.05*
(Smith et al.,2010)	251	S: 0.8 mg folic acid + 0.5 mg B12 + 20 mg B6 K: Placebo	Brain atrophy 29.6% decrease in	p=0.001*
(Aisen et al.,2008)	354	S: 5 mg folate + 25 mg vitamin B6 + 1 mg vitamin B12 K: Placebo	No slowdown in cognitive decline	P>0.05
(Morris et al.,2005)	3718	Individual intake of different amounts of vitamin B12	difference in understanding	P>0.05
(Tucker et al.,2005))	321	Basal Hcy, folate, vitamin B12, B6 levels and dietary intake of B vitamins and cognitive variability examined	difference in understanding	P>0.05

It is interesting to note that in our investigation, the sick group's vitamin B12 level was found to be greater than that of the control group. However, it was not statistically important (p>0.005). The reason for this may be that those who are sick may have taken vitamin B12 supplements. A significant public health issue that affects a sizable portion of the global population is Alzheimer's disease. Its average annual cost is a huge burden for the world economy. We believe that there is no effective approach for curing the condition and that larger-scale clinical and experimental investigations are required to stop or postpone the disease's progression and lessen its symptoms.

ACKNOWLEDGEMENTS

None.

DECLARATIONS

The writers' contributions Equal contributions were made by each author. Before publication, they evaluated and gave their approval to the final manuscript.

Conflict of interest

The authors say they have no competing interests. ethical endorsements The Siirt University Non-Interventional Clinical Research Ethics Committee (2022/04.06) gave its ethical approval to this investigation.

Funding resources

The Scientific Research Projects Coordinatorship at Şırnak University provided funding for this work under project number 2022.FNAP.18.03.01.

REFERENCES

Aisen, P. S., Schneider, L. S., Sano, M., Diaz-Arrastia, R., van Dyck, C. H., Weiner, M. F., Bottiglieri, T., Jin, S., Stokes, K. T., Thomas, R. G., Thal, L. J., & Alzheimer Disease Cooperative Study (2008). High-dose B vitamin supplementation and cognitive decline in Alzheimer disease: a randomized controlled trial. JAMA, 300(15), 1774–1783.

Black, D.W., Grant, J.E. (2014). DSM-5® guidebook: the essential companion to the diagnostic and statistical manual of mental disorders, 5th ed. Arlington, VA: American Psychiatric .

Bozoğlu, E., Işık, A.T. (2010): When do elderly patients with Alzheimer's disease need the vitamin B12 supplementation? Alzheimer's & Dementia; 6(4):571.

Chan, A., Remington, R., Kotyla, E., Lepore, A., Zemianek, J., & Shea, T. B. (2010). A vitamin/nutriceutical formulation improves memory and cognitive performance in community-dwelling adults without dementia. The journal of nutrition, health & aging, 14(3), 224–230.

Dos Santos Picanco, L. C., Ozela, P. F., de Fatima de Brito Brito, M., Pinheiro, A. A., Padilha, E. C., Braga, F. S., de Paula da Silva, C. H. T., Dos Santos, C. B. R., Rosa, J. M. C., & da Silva Hage-Melim, L. I. (2018). Alzheimer's Disease: A Review from the Pathophysiology to Diagnosis, New Perspectives for Pharmacological Treatment. *Current medicinal chemistry*, *25*(26), 3141–3159.

Douaud, G., Refsum, H., de Jager, C. A., Jacoby, R., Nichols, T. E., Smith, S. M., & Smith, A. D. (2013). Preventing Alzheimer's disease-related gray matter atrophy by B-vitamin treatment. Proceedings of the National Academy of Sciences of the United States of America, 110(23), 9523–9528.

Grarup, N., Sulem, P., Sandholt, C. H., Thorleifsson, G., Ahluwalia, T. S., Steinthorsdottir, V., Bjarnason, H., Gudbjartsson, D. F., Magnusson, O. T., Sparsø, T., Albrechtsen, A., Kong, A., Masson, G., Tian, G., Cao, H., Nie, C., Kristiansen, K., Husemoen, L. L., Thuesen, B., Li, Y., Pedersen, O. (2013). Genetic architecture of vitamin B12 and folate levels uncovered by applying deeply sequenced large datasets. PLoS genetics, 9(6), e1003530.

Gu, Y., Nieves, J. W., Stern, Y., Luchsinger, J. A., & Scarmeas, N. (2010). Food combination and Alzheimer disease risk: a protective diet. Archives of neurology, 67(6), 699–706.

Gulmammadli, N., Konukoğlu, D., Merve Kurtuluş, E., Tezen, D., Ibrahim Erbay, M., & Bozluolçay, M. (2022). Serum Sirtuin-1, HMGB1-TLR4, NF-KB and IL-6 levels in Alzheimer's: The Relation Between Neuroinflammatory Pathway and Severity of Dementia. Current Alzheimer research, 10.2174/1567205020666221226140721. Advance online publication.

Lane, C. A., Hardy, J., & Schott, J. M. (2018). Alzheimer's disease. European journal of neurology, 25(1), 59–70.

Lopes da Silva, S., Vellas, B., Elemans, S., Luchsinger, J., Kamphuis, P., Yaffe, K., Sijben, J., Groenendijk, M., & Stijnen, T. (2014). Plasma nutrient status of patients with Alzheimer's disease: Systematic review and meta-analysis. Alzheimer's & dementia : the journal of the Alzheimer's Association, 10(4), 485–502.

Maszota-Zieleniak, M., Danielsson, A., & Samsonov, S. A. (2021). The potential role of glycosaminoglycans in serum amyloid A fibril formation by in silico approaches. Matrix biology plus, 12, 100080.

Morris, M. C., Evans, D. A., Tangney, C. C., Bienias, J. L., Wilson, R. S., Aggarwal, N. T., & Scherr, P. A. (2005). Relation of the tocopherol forms to incident Alzheimer disease and to cognitive change. The American journal of clinical nutrition, 81(2), 508–514.

Otaegui-Arrazola, A., Amiano, P., Elbusto, A., Urdaneta, E., & Martínez-Lage, P. (2014). Diet, cognition, and Alzheimer's disease: food for thought. European journal of nutrition, 53(1), 1–23.

Quadri, P., Fragiacomo, C., Pezzati, R., Zanda, E., Forloni, G., Tettamanti, M., & Lucca, U. (2004). Homocysteine, folate, and vitamin B-12 in mild cognitive impairment, Alzheimer disease, and vascular dementia. The American journal of clinical nutrition, 80(1), 114–122.

Ravaglia, G., Forti, P., Maioli, F., Martelli, M., Servadei, L., Brunetti, N., Porcellini, E., & Licastro, F. (2005). Homocysteine and folate as risk factors for dementia and Alzheimer disease. The American journal of clinical nutrition, 82(3), 636–643.

Scheltens, P., Twisk, J. W., Blesa, R., Scarpini, E., von Arnim, C. A., Bongers, A., Harrison, J., Swinkels, S. H., Stam, C. J., de Waal, H., Wurtman, R. J., Wieggers, R. L., Vellas, B., & Kamphuis, P. J. (2012). Efficacy of Souvenaid in mild Alzheimer's disease: results from a randomized, controlled trial. Journal of Alzheimer's disease: JAD, 31(1), 225–236.

Smith, A. D., Smith, S. M., de Jager, C. A., Whitbread, P., Johnston, C., Agacinski, G., Oulhaj, A., Bradley, K. M., Jacoby, R., & Refsum, H. (2010). Homocysteine-lowering by B vitamins slows the rate of accelerated brain atrophy in mild cognitive impairment: a randomized controlled trial. PloS one, 5(9), e12244.

Tucker, K. L., Qiao, N., Scott, T., Rosenberg, I., & Spiro, A., 3rd (2005). High homocysteine and low B vitamins predict cognitive decline in aging men: the Veterans Affairs Normative Aging Study. The American journal of clinical nutrition, 82(3), 627–635.

Wang, H. X., Wahlin , A., Basun, H., Fastbom, J., Winblad, B., & Fratiglioni, L. (2001). Vitamin B(12) and folate in relation to the development of Alzheimer's disease. Neurology, 56(9), 1188–1194.

Wikipedia.(2023).Alzheimer'sdiseasehttps://www.google.com/search?q=Wikipediaalzheimer%27disease&oq=wikipedia+alzheimer&aqs=chrome.1.69i57j0l5.8871j0j4&sourceid=chrome&ie=UTF-8. Erişim tarihi: 03/05/2023.

Wolffenbuttel, B. H. R., Wouters, H. J. C. M., Heiner-Fokkema, M. R., & van der Klauw, M. M. (2019). The Many Faces of Cobalamin (Vitamin B12) Deficiency. Mayo Clinic proceedings. Innovations, quality & outcomes, 3(2), 200–214.

CHAPTER 10

BENIGN COLORECTAL DISEASES

Hasan OKMEN, MD[1]

Ishak YILDIZ, MD[2]

[1] Saglik Bilimleri Universitesi, Istanbul/Turkey, 0000-0002-2297-3386, hasanokmen@hotmail.com
[2] Istanbul Research and Education Hospital, Istanbul/Turkey, 0000-0003-2597-4736, ishakyildizz@gmail.com

1. INTRODUCTION

Benign colorectal diseases encompass a broad spectrum of disorders affecting the colon and rectum, which play crucial roles in the digestion and elimination of waste. These conditions, although non-malignant in nature, can significantly impact an individual's overall well-being, resulting in discomfort, impaired quality of life, and potential complications. Understanding the pathophysiology, clinical presentation, diagnostic methods, and treatment options for these benign colorectal diseases is of utmost importance for healthcare professionals specializing in colorectal surgery and gastroenterology.

The prevalence of benign colorectal diseases is substantial, with varying incidence rates worldwide. Conditions such as hemorrhoids, anal fissures, inflammatory bowel disease, and benign polyps constitute a significant proportion of cases encountered in clinical practice. Hemorrhoids, for example, affect a large percentage of the adult population, with symptoms ranging from mild discomfort to severe pain and bleeding. Similarly, anal fissures can cause excruciating pain and bleeding during defecation, significantly impacting an individual's daily life.

Risk factors for benign colorectal diseases are multifactorial and include age, genetics, dietary habits, sedentary lifestyle, obesity, chronic constipation, and certain medical conditions. Accurate diagnosis and comprehensive evaluation of benign colorectal diseases rely on a combination of clinical assessment, imaging studies, endoscopic procedures, and histopathological examination. Advancements in diagnostic techniques, such as high-resolution endoscopy and molecular testing, have enhanced our ability to identify and characterize these conditions, aiding in individualized treatment planning.

The management of benign colorectal diseases encompasses both conservative and surgical approaches, tailored to the specific condition and severity. Non-surgical interventions, including lifestyle modifications, dietary changes, topical medications, and minimally invasive procedures, form the cornerstone of initial management. However, surgical intervention may be necessary for certain conditions, such as refractory anal fissures, or anal fistulas.

In this chapter, we aim to provide a comprehensive overview of benign colorectal diseases, their epidemiology, etiology, clinical

manifestations, diagnostic strategies, and contemporary treatment options. Furthermore, we will discuss emerging research and future directions in the field, emphasizing the importance of early detection, accurate diagnosis, and individualized patient management. By expanding our knowledge and understanding of these conditions, healthcare professionals can optimize patient care, improve outcomes, and contribute to ongoing advancements in the field of benign colorectal diseases.

2. ANATOMY

The colon is an organ that descends and ascends inside the abdomen. The posterior part and the distal 2/3 of the rectum are retroperitoneal, while the remaining part of the colon is intraperitoneal. The diameter of the right colon is larger, and the splenic flexure is located higher. (Netter, FH., 2014).

The avascular fascia between the rectum and the anterior neighboring organs in the pelvic region is called the Denon-vilier fascia. The non-vascular region situated posteriorly between the rectum and the sacrum is referred to as Waldeyer's fascia. Within this area, the pelvic floor is composed of the levator ani and puborectalis muscles, forming the region where the rectum reaches the distal anus.These muscles specialize towards the distal end to form the external sphincters. This striated muscle group, which is innervated by the same plexus (sacral 2-4, pudendal nerve), will form the voluntary part of continence. (Standring, S., 2016).

The superior mesenteric artery is responsible for supplying blood to the proximal part of the colon, while the inferior mesenteric artery provides blood to the segment extending from the distal one-third of the transverse colon to the rectum.The distal 2/3 of the rectum is nourished by the middle and inferior hemor,rhoidal arteries that come from the internal iliac artery. (Standring, S., 2016).

Veins and lymphatic channels follow the arteries. There is an anastomosis between the marginal artery and the inferior and superior mesenteric arteries, and in some populations, there is a second anastomosis called the Riolan arch. These anastomoses occur in the distal part of the transverse colon and ensure the circulation of the entire colon. ((Sharma, A., & Patel, K., 2020)

It is important to know that the lymphatic drainage of the distal part of the rectum passes through the iliac channels to the inguinal canal. This is a crucial consideration for malignancies in this area. (Standring, S., 2016).

3. PHYSİOLOGY

The primary function of the colon is water reabsorption. While there is around 8 liters of fluid in the jejunum along with secretion, by the time it reaches the right colon, this amount of fluid has reduced to 1.5 liters (reabsorbed by the jejunum and ileum), and when it is excreted as feces, it has decreased to 0.1 liters. (Guyton and Hall 2015)

The right colon is particularly involved in the reabsorption of fluid, while the sigmoid colon and descending colon are more active in the storage of feces. During water reabsorption, the colon secretes potassium and bicarbonate, while reabsorbing sodium (water) and chloride, and it is essential to keep this in mind. (Johnson, L.R., 1994)

Saprophytic bacteria in the colon are responsible for the production of short-chain fatty acids. These fatty acids play a crucial role as the main source of energy for enterocytes.Additionally, ammonia is produced by the colon flora. As ammonia exacerbates hepatic encephalopathy in patients, reducing the amount of colon bacteria is achieved by using laxatives. (Guyton and Hall 2015)

3.1. Motility

The colon has three types of contractions, retrograde, segmental contractions, and mass movements, which lead to the excretion of feces. CCK, anger, fatty acids, bile, and high-fiber foods increase these movements, while sleep, anxiety, fear, somatostatin, and glucagon decrease them. (Guyton and Hall 2015)

3.2. Neurogenic control

The sympathetic innervation of the colon and rectum is performed from the thoracic 11-12 levels, and the parasympathetic innervation is performed from the vagus and sacral 2-4 levels. The parasympathetic innervation has an activating effect and increases secretion, reabsorption, and motility, as in the entire gastrointestinal system, while sympathetic activation is opposite to parasympathetic activation. (Ganong, W.F., 2015) The nerve ganglia in the enteric area are called Meissner (submucosal), Auerbach (serosal) plexus. Acetylcholine and substance P are excitatory mediators,

while atropine, scopolamine, and vasoactive intestinal peptide (VIP) are inhibitory mediators. (Tortora, G.J., and Derrickson, B.H., 2017)

3.3. Microflora

The intestine, which is sterile during birth, is colonized by bacteria within hours and reaches the same level as adults within three weeks. The most common anaerobic microorganism is Bacteroides fragilis, and the most common gram-negative bacterium is E. coli. The intestinal microflora establishes a symbiotic relationship with the organism by suppressing pathogenic bacteria and participating in the digestion of proteins, carbohydrates, and fats, except for vitamin K synthesis. The intestines and microflora play an active role in the enterohepatic circulation of bilirubin and bile acids, ensuring 95% of bile acid reabsorption, creating an efficient system. (Sekirov, I., Russell, S. L., Antunes, L. C., ve Finlay, B. B., 2010)

4.PHYSİOLOGİCAL DİSEASES OF COLON AND RECTUM

4.1.Irritable Bowel Syndrome

Irritable Bowel Sy,ndrome (IBS) is a disease that causes a patient to present with a range of gastrointestinal symptoms, such as pain, constipation, and diarrhea, despite the absence of an underlying organic pathology.

These patients typically have obsessive, unhappy, and dissatisfied personality traits. They have been examined by many doctors and have a thick medical file. They have used many medications, none of which have provided complete relief.

If the patient is presenting for the first time, or if symptoms suggesting malignancy are present, a thorough examination should be performed. Diagnosis is made by exclusion. Low wave activity and uncoordinated contractions can be detected. (Irritable Bowel Syndrome. National Institute of Diabetes and Digestive and Kidney Diseases, 2017)

4.2.Constipation

Constipation, inertia, and delayed transit are synonymous. A normal person should defecate at least three times a week. Neurological, endocrine (hypothyroidism, diabetes, etc.), Hirschsprung's disease (destru,ction of neural plexuses around the colon), medications used (codeine, anticholinergics, antidepressants), tumors, and outlet obstruction can be effective in etiology. The majority of cases are idiopathic. It is more common in women and older

people. A Western diet low in fiber and inactivity can be an etiolo,gical factor and can exacerbate symptoms. There are two types: total and distal. (Bharucha AE, Enck P., Rao S., Wald A., 2016)

The distal type is also known as outlet obstruction. To make a diagnosis, a barium enema and endoscopy should be performed to exclude malignancy. If malignancy is not present, improvement can be expected after dietary measures (foods containing fiber and bran) and hydration. (Bharucha AE, Enck P., Rao S., Wald A., 2016)

If improvement does not occur, radio-opaque markers are swallowed on an empty stomach before breakfast to distinguish the types. These markers are the size of pills and consist of 18 units. Direct X-rays are taken on the third, fifth, and seventh days. If they are all present on the third day, it indicates that intestinal transit is slow. On the fifth day, 80% should have been expelled, and on the seventh day, all of them should have been expelled. If they are not, it is checked whether the markers are spread throughout the colon or collected in the distal area. If they are spread throughout the colon, total colonic transit delay is considered, and if they are collected in the distal area, outlet obstruction should be considered. (American Gastroenterological Association Medical Position Statement: Diagnosis and Treatment of Colonic Inertia and Slow Transit Constipation. Gastroenterology. 2005)

In cases of total colonic transit delay, dietary measures, hydration, movement, and regular defecation habits (trying to defecate at the same time every day) are recommended. Laxatives can be tried if these fail. (American Gastroenterological Association Medical Position Statement: Diagnosis and Treatment of Colonic Inertia and Slow Transit Constipation. Gastroenterology. 2005)

Impaction of feces, which harden and become calcified, can cause rectal ulcers and obstruction. Surgical treatment is recommended for selected patients, but there is no scientific validity. (American Gastroenterological Association Medical Position Statement: Diagnosis and Treatment of Colonic Inertia and Slow Transit Constipation. Gastroenterology. 2005)

4.3. Anorectal Outlet Obstruction

Anorectal outlet obstruction, puborectal muscle syndrome, and unrelaxed puborectal muscle are synonymous. During defecation, the puborectal muscle, which atta,ches the rectum to the pubis like a rope, relaxes.

With this relaxation, the rectum, which normally maintains a resting position of about 80°, flattens, and defecation occurs. If it does not relax, outlet obstruction is present. (Bharucha AE, 2013)

This disease, which is characterized by a obsessive personality, has a physiological basis. However, the exact cause is unknown. Conservative treatment is initially recommended, and if this fails, surgery may be considered. (Bharucha AE, 2013)

Radio-opaque markers are observed to accumulate in the distal colon. A test called "sinedefekografi" records graphs in the form of a film as the opaque material is expelled during defecation and the inability to pass a 60 ml balloon during defecation confirms the diagnosis. (Bharucha AE, Cosman BC, Wald A, Whitehead WE, 2014)

Attempting to overcome the resistance of the puborectal muscle, the colon may experience intussusception in the rectum or shift anteriorly, leading to the formation of a rectocele. As a result of rectal intussusception, rectal ulcers may be observed due to friction. (Bharucha AE, 2013)

Treatment is difficult. Biofeedback techniques, as in incontinence, are also used here. However, unlike incontinence, the sound or increasing burning lamps that are examined as the puborectal muscle does not relax, increase proportionally with relaxation. With the help of this device, the patient learns to relax the puborectal muscle and perform defecation. (Bharucha AE, Cosman BC, Wald A, Whitehead WE, 2014)

There is no surgical treatment as surgical injury to the puborectal muscle causes permanent incontinence. Cases benefiting from psychiatric treatment have been reported. (Bharucha AE, Cosman BC, Wald A, Whitehead WE, 2014)

4.4. Volvulus

It means twisting or rotation around itself. It is seen in 10% of cases in the United States and 55% in Iran. The reason for this is the higher fiber content in the diet in Iran, which increases the risk of colon length and rotation around itself in this population. (Azarhoush R, Amani H, Amani H, Hamidi M, 2015) There are three types: sigmoid, cecal, and transverse.

Sigmoid colon volvulus is seen with an 80% frequency and if a barium enema is taken, a beak-like appearance occurs with a sausage-shaped

mass on the left side and signs of large bowel obstruction (late-developing vomiting with fecal odor and significant distension).

Cecal volvulus is seen with a 15-20% probability. Signs of small bowel obstruction develop early (early bilious vomiting, low distension). It is 90% completely axial and 10% in a cecal fulcrum shape. During examination, it appears as a kidney-shaped mass in the left upper quadrant. Transverse colon volvulus is very rare. (F. Tolan, S. Gulsen, S. Selcukbiricik, O. Bolukbas, M. E. Cakalagaoglu, and H. Basaklar, 2013)

The twisting can be corrected by colonoscopy, but the recurrence rate is high. Detorsion with barium enema has been suggested but is dangerous due to the high risk of perforation. Surgical treatment provides more permanent solutions.

The choice of surgical procedure relies on the overall health status of the patient and the extent of contamination within the abdominal region. If anastomotic security is inadequate, resection of the necrotic area and colostomy are appropriate options. If there is no necrosis or perforation but the patient's general condition is poor (elderly, with comorbidities), detorsion and fixation methods are applied. The recurrence rate is high after detorsion. (B. T. Henderson ,C. C. Spencer and T. L. Galloway 2021)

If there is necrosis, positive fecal occult blood and lower gastrointestinal bleeding signs may be observed. In cases with perforation, signs of peritonitis and abscess may occur.

4.5. Ogilvie Syndrome

Ogilvie Syndrome is a rare disease in which gas and stool accumulation in the large intestine causes non-mechanical obstruction due to decreased or absent colon movements. This condition is usually seen in elderly patients and has high mortality rates.

Ogilvie Syndrome usually occurs in conjunction with other diseases, so treatment should also include management of the underlying disease. The first step in treatment is to investigate possible causes and eliminate them. For example, electrolyte imbalances should be corrected, fluid intake should be increased, and medications should be discontinued. (Raptopoulos, V., & Kleinman, P. K., 2017)

The next step in treatment is colonoscopic decompression. The end of the colonoscope is placed into the colon to empty the gas and stool. If colonoscopic decompression fails, surgery may be necessary.

If left untreated, Ogilvie Syndrome can cause serious complications such as toxic megacolon, which can be life-threatening. Therefore, early intervention for diagnosis and treatment is very important. (Ali, A. M., Alaqeel, A., & Habib, S., 2021)

5. INFECTİOUS DİSEASES OF THE COLON

5.1. Pseudomembranous colitis

A condition characterized by antibiotic-induced diarrhea, resembling a membrane but not a true membrane, consisting of coagula. It can occur with any antibiotic, but most commonly occurs with clindamycin. Dose and duration are not effective. It is caused by Clostridium difficile.

Clinically, it has two types. The type that resolves spontaneously is most common, while the toxic megacolon type, which rarely requires hospitalization, can also occur.

Toxic megacolon is treated with hospitalization. In addition to fluid resuscitation, the patient is given oral vancomycin 125 mg, cholestyramine to bind toxins, and a resin that binds antibiotics. 20% of patients experience a relapse. In the fulminant type, total colectomy is performed. (Leffler DA, Lamont JT., 2015)

5.2. Amoebic Colitis

A colitis caused by E. histolytica. It can be transmitted fecal-orally or sexually. Some people carry the protozoan form of the microorganism without showing any symptoms, and they cause the disease to spread in the community through their feces.

The trophozoite form causes invasive disease. Invasive disease can manifest itself in the cecum as small ulcers, yellow exudate, and perforation. A mass may be seen in some patients' clinics. This condition is called ameboma.

Crohn's disease is important in the differential diagnosis. If Crohn's disease is misdiagnosed, the steroids used will worsen the disease. Protozoa can be seen on fecal microscopy, but at least three microscopic examinations

should be performed. Yellow exudative ulcers can be seen with full colonoscopy.

Treatment is effective with metronidazole and iodoquinol. In the case of perforation, urgent surgical repair is necessary. (Haque R, Huston CD, Hughes M, Houpt E, Petri WA Jr., 2003)

5.3. Actinomycosis

It is a colitis caused by Actinomyces israelii. It can manifest itself as a mass in the cecum. It is actually a bacterium, but it is called actinomycosis because of its filaments. Yellow granules are seen in its culture. Microbiology laboratory should be notified in case of suspicion because anaerobic culture is required.

If there is an abscess, drainage and treatment with antibiotics containing penicillin or tetracycline are sufficient. (Brook, I., 2016)

5.4. Neutropenic Enterocolitis

Enterocolitis that occurs especially in leukemia patients when receiving chemotherapy containing cytosine arabinoside. It affects the cecum. It is characterized by thrombocytopenia. Antibiotic therapy, rest, and fluid resuscitation are effective treatments. Right hemicolectomy is performed if there is perforation, recurrence persists, or if chemotherapy is still needed. (Bhatt, V. R., Viola, G., Rodriguez, G. H., & Nastoupil, L. J., 2018)

5.5. CMV (Cytomegalovirus)

Cytomegalovirus (CMV) accounts for the majority of intraabdominal emergency surgeries in individuals with AIDS, with AIDS patients constituting approximately 90% of the affected population.Adrenal gland, gastrointestinal system, liver, brain, lung, and anus can be affected. Ulcers are seen in the submucosa and mucosa. When biopsied, cytomegalovirus inclusion bodies are seen. Gastrointestinal bleeding, toxic megacolon, and perforation can occur. Previously, a more passive approach was taken in the treatment of AIDS patients, while now more aggressive treatments are used. Antiviral treatment with ganciclovir or foscarnet is used. In severe cases, surgical intervention may be necessary. (Abutaleb, A., & Badri, M., 2021)

5.6. Chagas

Chagas disease, also known as megacolon, is caused by the parasite Trypanosoma cruzi and is commonly found in Central and South America.

Intramural fibrosis is seen in the Auerbach and myenteric plexus. Clinically, the affected segment of the colon appears as megacolon and sometimes it can involve the entire colon.

In cases where conservative methods and dietary measures fail, removal of the affected segment of the colon is necessary. (Lages-Silva E, Ramirez LE, Pedrosa RC, 2009)

6. VASCULAR COLON DISEASES

6.1. Ischemic Colitis

Ischemic colitis is a type of colitis that develops due to a decrease in the blood supply to the colon. Elderly patients with atherosclerosis or young patients using oral contraceptives are at risk. In addition, it can develop due to thromboangiitis obliterans, periarteritis nodosa, thrombosis, emboli (arrhythmia), or iatrogenic ligation.

It presents itself with nonspecific abdominal pain and examination findings. Risk factors lead to suspicion of the diagnosis. In some patients, there may be positive occult blood in the stool. Hematochezia and paralytic ileus may occur. Edema (fingerprints) in the intestinal wall can be seen on a barium enema, and if colonoscopy is performed, a hemorrhagic black colon mucosa will be seen. Barium enema is contraindicated in patients with atherosclerosis because the contrast agent given can cause critical narrowing to be blocked. Therefore, color Doppler ultrasonography will be a more appropriate option.

Angiography should be performed in acute embolisms, as it also offers the option of thrombolytic treatment. However, diagnosis is usually made by laparotomy with suspicion. If there is necrosis, removal of the necrotic segment is required. Colostomy is a more appropriate option if there is circulatory insufficiency. In some cases, after embolectomy, the abdomen is left open, the patient is heparinized, and re-laparotomy is performed after 24-48 hours. Intestinal circulation is checked. If certain, it is closed. (Scharff, J. R., & Longo, W. E., 2015).

6.2. Radiation Enterocolitis

It is enterocolitis that develops after radiotherapy. It occurs in patients receiving five thousand rads or more of radiotherapy. It creates a serious enterocolitis over six thousand rads. Atherosclerosis, diabetes mellitus,

hypertension, advanced age, and previous abdominal surgery increase the severity of the disease.

The early and self-limiting type is more common. The late type is severe. Progressive periarteritis is present in the late type. Intestinal circulation is impaired.

In the mild type, it is conserved conservatively. If perforation is present, it is repaired surgically. Anastomosis is risky due to circulatory disorders. Healing capacity is limited. Patients should be reevaluated for recurrent carcinoma, and the possibility of developing fistulas, abscesses, and strictures should be considered. (Kim, J., J. Lee, J. H., & Oh, S. T., 2014).

6.3. Angiodysplasia

Angiodysplasia, arteriovenous malformation, and vascular ectasia are synonymous words. It is not congenital. It should be evaluated as vascular degeneration or reaction. It increases with age. It is characterized by recurrent, self-limiting bleeding. In elderly patients, it is the most common cause of lower gastrointestinal bleeding with diverticulitis. In cases of persistent and severe bleeding, a colectomy may be required. In cases requiring colectomy, mortality is around 20-40%. Localization of bleeding is difficult. (Longo, D. L., Fauci, A. S., Kasper, D. L., Hauser, S. L., Jameson, J. L., & Loscalzo, J., 2018)

7. RECTAL PROLAPSE

Rectal prolapse is a medical condition where the rec,tum protrudes through the anus due to weakening of the muscles and ligaments supporting the rectum. It is more commonly seen in elderly women, but can occur in individuals of any age or gender. There are three types of rectal prolapse: internal, external, and complete.

Internal rectal prolapse, also known as mu,cosal prolapse, occurs when the inner lining of the rectum protrudes through the anus. External rectal prolapse, also known as partial prolapse, occurs when the rectum partially protrudes thro,ugh the anus. Complete rectal prolapse, also known as full-thickness prolapse, occurs, when the entire thickness, of the rectum protrudes through the anus. (Rao, S. S. 2014)

The exact cause of rectal prolapse is not fully understood, but risk factors include chronic constipation, diarrhea, childbirth, previous surgery in the anal area, nerve damage, and weakened pelvic muscles. Symptoms of

rectal prolapse include pain during bowel movements, fecal incontinence, bleeding, and a feeling of protrusion or fullness in the rectum or anus.

Diagnosis, of rectal prolapse, is typically made by physical examination, although additional tests such as colonoscopy or MRI may be ordered to rule out other conditions. Treatment options for rectal prolapse depend on the severity of the prolapse and the patient's overall health. In mild cases, lifestyle modifications such as increasing fiber intake and exercising pelvic muscles may be effective. For more severe cases, surgery may be necessary to repair the prolapse. (Wald, A., 2015)

8. HEMORRHOİDAL DİSEASE

Hemorrhoids are submucosal cushions located in the anal canal that contain arterioles, venules, and smooth muscle fibers. They can be identified in the left lateral, right anterior, and right posterior positions. Normally, they assist in maintaining continence by aiding in the complete closure of the anal canal. However, due to factors such as excessive straining, increased intra-abdominal pressure, chronic constipation, hard stools, chronic diarrhea, pregnancy, and heredity, venous congestion and dilation can cause the hemorrhoids to grow and prolapse. This can result in bleeding and thrombosis.

External hemorrhoids are, located distal to the pectinate line and covered with anoderm. They can be very painful if thrombosed and may leave skin tags once healed. Internal hemorrhoids are located proximal to the pectinate line and covered with anorectal mucosa. They can bleed and become thrombosed, and complications such as incarceration, strangulation, and necrosis can occur. However, they are not usually painful unless thrombosis or necrosis develops. Hemorrhoids are classified into four stages based on the degree of prolapse. (Wald, A., 2015)

1st stage: Bleeding occurs, but there is no prolapse. A protrusion forms in the anal canal.

2nd stage: Prolapse occurs with straining, but it reduces spontaneously.

3rd stage: Prolapse occurs with straining and requires manual reduction.

4th stage: Prolapse is constant and cannot be reduced manually.

Mixed hemorrhoids are located both above and below the dentate line and exhibit both external and internal hemorrhoid features. Large mixed hemorrhoids often require hemorrhoidectomy.

Postpartum hemorrhoids result from straining during childbirth and can cause edema, thrombosis, and/or strangulation. In patients with chronic hemorrhoidal complaints, hemorrhoidectomy is recommended. Hemorrhoidectomy should be avoided in patients with portal hypertension.

Surgical or non-surgical treatments are applied depending on the stage of the disease and symptoms. (Lohsiriwat Varut, 2012)

8.1. Non-surgical treatments

Medical treatment: Applied in grade 1-2 hemorrhoids. It is recommended to consume high-fiber food, use stool softeners, drink plenty of fluids and avoid straining.

Rubber band ligation is a treatment method suitable for grade 1-2 hemorrhoids and selected grade 3 hemorrhoids. To minimize pain, the rubber band should be placed approximately 1-2 cm above the dentate line. During a single session, one or two quadrants can be banded. After a period of 7-10 days, the banded pedicle will undergo necrosis and subsequently detach, which may cause bleeding. It is crucial to avoid including the internal sphincter within the band to prevent urinary retention, although this is a rare occurrence. While necrotizing infection is uncommon, it can manifest with severe pain, fever, and urinary retention. In such cases, urgent exploration under anesthesia is necessary in an operating room setting. The management typically involves debridement of necrotic tissue, drainage, and antibiotics.

Infrared photocoagulation: Applied in grade 1-2 hemorrhoids.

Sclerotherapy: Applied in grade 1-2 and some grade 3 hemorrhoids.

Excision of thrombosed external hemorrhoids should be performed within 72 hours.

8.2. Surgical hemorrhoid treatments

Closed submucosal hemorrhoidectomy (Parks, Ferguson).

Open hemorrhoidectomy (Milligan and Morgan).

Whitehead hemorrhoidectomy: Nowadays it is not recommended. It has complications such as ectropion and stenosis.

PPH (Procedure for Prolapse and Hemorrhoids): Cutting the venous branches that feed the hemorrhoidal plexus by performing circular mucosal excision with a stapler after placing a purse-string suture 3-4 cm above the dentate line. The mucosal edges are united with a stapler, and the protruding mucosa is suspended upwards.

Hemorrhoidal artery ligation guided by Doppler (Transanal hemorrhoidal dearterialization).

Hemorrhoidectomies performed with ultrasonic (Harmonic scalpel) and monopolar coagulation energy (Ligasure) are applied to reduce postoperative pain and edema. (Lee M, Jennifer K, 2018)

9. Anal Fissur

Anal fissur refers to a tear in the lining of the anus, specifically in the anoderm at the distal part of the linea dentata. It usually results from trauma, hard stool, and prolonged diarrhea. This tear can cause spasm in the internal anal sphincter, leading to pain and reduced blood supply to the anoderm. If left untreated, the cycle of pain, spasm, and ischemia can lead to the development of chronic fissures.

Most anal fissures occur in the posterior midline, with only 10-15% occurring in the anterior midline and less than 1% occurring laterally. Lateral fissures outside the midline may indicate underlying conditions such as, ulcerative colitis, Crohn's disease, tuberculosis, syphilis, leukemia, cancer, or HIV.

Symptoms of anal fissure include pain during defecation, fresh blood during or after bowel movements, and a painful anal spasm. Physical examination can confirm the presence of the fissure, but it can be difficult for the patient to tolerate procedures such as digital rectal examination, anoscopy, and proctoscopy due to the pain.

Treatment involves stopping the cycle of pain, ischemia and spasm. This includes softening stool, using analgesic creams, and taking warm sitz baths. Nitroglycerin ointment can help by relieving spasm and increasing blood flow, although it can cause side effects such as headache and low blood pressure. Calcium channel blockers, arginine, and bethanechol can also be used. Medical therapy is effective in acute cases but may be ineffective in 50% of chronic cases.

In chronic cases, botulinum toxin injection can temporarily paralyze the muscle and be used as an alternative to sphincterotomy. Sphincterotomy, whether open or closed, is the preferred treatment for fissures that do not respond to medical therapy. The procedure involves cutting up to 30% of the internal sphincter muscle distal to the linea dentata. More than 95% of patients experience healing, although there is a risk of recurrence and incontinence, especially with gas, in 5-15% of patients. (Kumar, V., Abbas, A. K., & Aster, J. C., 2020)

10. ANORECTAL ABSCESSES

Anorectal abscesses are infections that occur in the anal glands and can spread to the perianal, intersphincteric, ischiorectal, deep postanal, and perirectal areas, forming abscesses. The perianal abscess is the prevailing form, presenting as a painful swelling located at the anal verge. Moreover, the infection has the potential to propagate horizontally, resulting in the formation of ischiorectal abscesses. These abscesses can attain a substantial size and might not be visually detectable from the perianal area.Complex horseshoe abscesses occur when the infection spreads circularly to both sides of the intersphincteric, supralevator, or ischiorectal areas. The infected anal gland is located at the back center, around the 6 o'clock position in the lithotomy position. The ischiorectal spaces on both sides merge with the deep postanal space. Intersphincteric abscesses manifest within the intersphincteric region and pose challenges in terms of diagnosis, often necessitating examination under anesthesia. Pelvic and supralevator abscesses, on the other hand, are infrequent occurrences and arise from the upward extension of intersphincteric or ischiorectal abscesses, or the downward progression of intraperitoneal abscesses.Symptoms of anorectal abscesses include severe anal pain, often with a palpable mass in the perianal or rectal area. Patients may also experience fever, urinary retention, or sepsis. Diagnosis is usually made through physical examination, and CT or MRI may be useful in atypical cases. (Felt-Bersma, R. J. F., & Cuesta, M. A., 2013)

Anorectal abscesses must be drained urgently once diagnosed, as antibiotics alone are ineffective. If there is any doubt about the diagnosis, the abscess can be diagnosed and treated simultaneously under anesthesia. Failure to drain or inadequate drainage can result in a widespread, life-threatening necrosis and sepsis. Most perianal abscesses can be drained under local anesthesia, while large and complex abscesses should be drained under

anesthesia in the operating room. Simple ischiorectal abscesses can be drained through incision.

Ischiorectal abscesses can cause single or bilateral abscesses in the ischiorectal fossa (horseshoe abscess). The modified Hanley procedure is used to treat horseshoe abscesses, which involves drainage of the deep postanal space and lateral extensions via an incision that extends from the abscess to the external sphincter, from the midline to the coccyx. Lateral extensions may require a distal incision for drainage or seton placement if a fistula is present. Intersphincteric abscesses may produce minimal swelling and perianal symptoms, making diagnosis difficult. The pain is felt inside and deeply in the anus, and worsens with coughing or straining. Examination under anesthesia may be necessary if there is any doubt about the diagnosis. The drainage of intersphincteric abscesses is typically performed via a posterior partial internal sphincterotomy. Supralevator abscesses are rare and can mimic intra-abdominal events due to their proximity to the peritoneum. A firm, palpable mass above the anorectal ring can be found during rectal examination. The source of the abscess should be determined before treatment. Drainage via the ischiorectal fossa leads to suprasphincteric fistulas. Supralevator abscesses that originate from the pelvis require a more extensive approach, such as transabdominal drainage. (Ramanujam, P. S., & Prasad, M. L. 2018)

11. PERIANAL FISTULAS

Perianal Fistulas commonly arise from an infected glandular crypt in the anal region, where the internal opening is located within the crypt and the external opening usually corresponds to the site of abscess drainage. Approximately 50% of perianal abscesses that are drained successfully heal, while the remaining 50% progress to the formation of a perianal fistula.

Other potential causes of perianal fistulas include Crohn's disease, malignancy, trauma, radiation therapy, actinomycosis, tuberculosis. When dealing with complex, recurrent, or non-healing fistulas, it is essential to consider these underlying causes.

The diagnosis of a perianal fistula is primarily established by observing a continuous discharge from both the internal and external openings, along with the presence of a palpable firm tract. The Goodsall-Salmon rule assists in determining the location of the internal opening. In the case of anterior fistulas, the external opening typically follows a short, direct path to the internal opening. Conversely, for posterior fistulas, the external

openings traverse a curved tract and open onto the midline of the posterior anal canal. If the distance between the external opening and the anus exceeds 3 cm, the internal opening is commonly found on the midline of the posterior anal canal. (Phatak, U. R., & Kao, L. S. 2020)

Perianal fistulas can be categorized into four groups (Park's classification) based on their relationship with the anal sphincter muscles.

Inter-sphincteric fistula: The fistula tract externally opens near the anal verge, traversing through the intersphincteric space and the distal internal sphincter muscle from the internal opening at the dentate line.

Trans-sphincteric fistula: Often occurs following an ischiorectal abscess, and the tract extends through both the internal and external sphincter muscles.

Supra-sphincteric fistula: Develops within the intersphincteric space, with the tract ascending to encompass the entire external sphincter.

Extra-sphincteric fistula: Forms in the rectal wall and travels laterally around both sphincters, typically externalizing through the ischiorectal fossa.

The objective of treatment is to eliminate the fistula while preserving continence mechanisms. Locating the internal opening can be challenging, and the injection of methylene blue or hydrogen peroxide can aid in its identification. Care must be taken during the delineation of the fistula tract to avoid creating false passages or internal openings, which could complicate the fistula.

Simple intersphincteric fistulas are commonly managed with fistulotomy. Treatment for transsphincteric fistulas depends on the location within the sphincter. Sphincterotomy is employed for fistulas involving less than 30% of the sphincter muscle, while high transsphincteric fistulas involving more than 30% of the sphincter muscle may require a seton drain to minimize the risk of incontinence. Suprasphincteric fistulas are typically treated with a seton drain. The management of extrasphincteric fistulas varies depending on the etiology and trajectory. Generally, the extraspincteric portion should be opened and drained, and if a primary tract exists at the level of the linea dentata, it can also be opened.

Multiple tracts and complex fistulas may necessitate multiple procedures to control sepsis and facilitate healing. In cases where healing does not occur, a colostomy may be required for fecal diversion. Complex or non-

healing fistulas can be associated with conditions such as malignancy, Crohn's disease, unusual infections or radiation proctitis. Proctoscopic examination should be performed to assess the rectal mucosa, and a biopsy should be taken to investigate the presence of malignancy.

Horseshoe fistulas typically possess an internal opening in the midline posteriorly, with the fistula branches extending laterally and anteriorly to both ischiorectal fossae. Treatment often involves posterior internal sphincterotomy along with curettage and drainage of the lateral branches.

Seton drains serve not only for fistula drainage but also to induce fibrosis. There are two types of seton drains: cutting and non-cutting. A cutting seton, such as a suture or rubber band, is periodically tightened within the fistula tract to obliterate the fistula while preserving sphincter integrity. On the other hand, a non-cutting seton, typically made of soft plastic, facilitates fistula drainage. After fibrosis formation, the fistula tract can be opened or the seton can be left in place for chronic drainage.The LIFT (ligation of the intersphincteric, fistula tract) technique can also be used in fistulas. This involves identifying the tract with a stylet in the intersphincteric plane and then ligating both ends of the tract. (Chapple, K. S., Spencer, J. A., & Wilson, D., 2019)

12. PILONIDAL DISEASE

Pilonidal disease is a condition that occurs as a result of inflammation of an apocrine gland that becomes blocked by hair follicles in the sacrococcygeal region. This disease is more commonly seen in young adults, with males being more affected than females.

Although the etiology of pilonidal disease is not fully understood, factors such as infection resulting from blocked hair follicles, inflammation of the apocrine gland, immune system dysfunction, and genetic predisposition are thought to play a role.

Pilonidal disease can have an acute or chronic course, and its symptoms include pain, swelling, redness, abscess formation, and development of a fistula. Diagnosis can be made through clinical examination and imaging techniques. (Bruce J., McCallum I, King PM, 2007)

Treatment methods include surgical interventions, pain management, and hygiene measures. Surgical interventions can involve open or closed techniques, and classical or minimally invasive methods.

Minimally invasive techniques such as laser hair removal and endoscopic pilonidal sinus treatment have also been developed to treat pilonidal disease. These techniques have shown promising results in reducing the rate of recurrence and postoperative pain. (Doll D, Matevossian E, Sinicina I, 2011)

REFERENCES

Citation in text: (Netter, FH., 2014).*Netter, FH. (2014). Atlas* of Human Anatomy. Elsevier Health Sciences.

Citation in text: (Standring, S., 2016).Standring, S. (Ed.). (2016). *Gray's anatomy: the anatomical basis of clinical practice. Elsevier Health Sciences.*

Citation in text: (Patel, K. & Sharma, A., 2020) Sharma, A., & Patel, K. (2020). Anatomy, Colon. In StatPearls. StatPearls Publishing.

Citation in text: (Guyton and Hall 2015) Guyton and Hall (2015). *Textbook of Medical Physiology,13th Edition.*

Citation in text: (Johnson, L.R., 1994) Johnson, L.R. (1994). *Gastrointestinal Physiology.* Mosby.

Citation in text: (Ganong, W.F., 2015) Ganong, W.F. (2015). *Review of medical physiology.* New York: McGraw-Hill Education.

Citation in text: (Tortora, G.J., ve Derrickson, B.H., 2017) Tortora, G.J. ve Derrickson, B.H. (2017). *Principles of anatomy and physiology.* Hoboken, NJ: Wiley.

Citation in text: (Sekirov, I., Russell, S. L., Antunes, L. C., ve Finlay, B. B., 2010) Sekirov, I., Russell, S. L., Antunes, L. C., & Finlay, B. B. (2010). Gut microbiota in health and disease. Physiological Reviews, 90(3), 859-904. doi: 10.1152/physrev.00045.2009

Citation in text: (Irritable Bowel Syndrome. National Institute of Diabetes and Digestive and Kidney Diseases, 2017) U.S. Department of Health and Human Services. (2017) *Irritable Bowel Syndrome. National Institute of Diabetes and Digestive and Kidney Diseases.*

Citation in text: (Bharucha AE, Wald A, Enck P, Rao S, 2016) Bharucha AE, Wald A, Enck P, Rao S (2016) Functional anorectal disorders. *Gastroenterology*. 2016;150(6):1430-1442.e4. doi:10.1053/j.gastro.2016.02.033

Citation in text: (American Gastroenterological Association Medical Position Statement: Diagnosis and Treatment of Colonic Inertia and Slow Transit Constipation. Gastroenterology. 2005) American Gastroenterological Association Medical Position Statement: *Diagnosis and Treatment of Colonic Inertia and Slow Transit Constipation.* Gastroenterology, (2005) 2005;129(1): 801-813. doi:10.1053/j.gastro.2005.05.003

Citation in text: (Bharucha AE, 2013) Bharucha AE, (2013) *Update on anorectal disorders for gastroenterologists*. Gastroenterology. 2014;146(1):37-45.e2. doi:10.1053/j.gastro.2013.11.050

Citation in text: (Bharucha AE, Cosman BC, Wald A ,Whitehead WE, 2014) Bharucha AE, Cosman BC, Wald A ,Whitehead WE (2014). ACG clinical guideline: management of benign anorectal disorders. Am J Gastroenterol. 2014;109(8):1141-1157. doi:10.1038/ajg.2014.190

Citation in text: (Amani H, Azarhoush R, Hamidi M, 2015) Amani H, Azarhoush R, Hamidi, (2015). Sigmoid Colon Volvulus: An Iranian Multicenter Study. Ann Colorectal Res. 2015;3(1):e27317. doi:10.5812/acr.27317

Citation in text: (F. Tolan, H. Basaklar, M. E. Cakalagaoglu, O. Bolukbas, S. Gulsen and S. Selcukbiricik 2013) F. Tolan, H. Basaklar, M. E. Cakalagaoglu, O. Bolukbas, S. Gulsen and S. Selcukbiricik (2013) Volvulus: The Whys and Wherefores, The Scientific World Journal, vol. 2013, Article ID 470179, 5 pages, 2013.

Citation in text: (B. T. Henderson, C. C. Spencer and T. L. Galloway, 2021) B. T. Henderson, C. C. Spencer and T. L. Galloway (2021) *Volvulus.* StatPearls

Citation in text: (Raptopoulos, V., & Kleinman, P. K., 2017) Raptopoulos, V., & Kleinman, P. K. (2017). *Diagnostic imaging: abdomen.* Elsevier Health Sciences.

Citation in text: (Ali, A. M., Alaqeel, A., & Habib, S., 2021) Ali, A. M., Alaqeel, A., & Habib, S. (2021). Acute colonic pseudo-obstruction: A review of pathophysiology, diagnosis, and management. *World Journal of Gastroenterology*, 27(31), 5101-5115.

Citation in text: (Leffler DA, Lemont JT., 2015) Leffler DA, Lemont JT. (2015) Clostridium difficile infection. *N Engl J Med.* 2015;372(16):1539-1548. doi: 10.1056/NEJMra1403772.

Citation in text: (Haque R, Huston CD, Hughes M, Houpt E, Petri WA Jr., 2003) Haque R, Huston CD, Hughes M, Houpt E, Petri WA Jr., (2003) Amebiasis. *N Engl J Med.* 2003 Mar 6;348(10):1565-73. doi: 10.1056/NEJMra022710. PMID: 12637607.

Citation in text: (Brook, I., 2016) Brook, I. (2016). Actinomycosis: diagnosis and management. *Southern Medical Journal*, 109(5), 287-293. https://doi.org/10.14423/SMJ.0000000000000476

Citation in text: (Bhatt, V. R., Viola, G., Rodriguez, G. H., & Nastoupil, L. J., 2018) Bhatt, V. R., Viola, G., Rodriguez, G. H., & Nastoupil, L. J.

(2018). Neutropenic enterocolitis in adults: a systematic analysis of the literature. *Annals of Hematology*, 97(2), 201-208.

Citation in text: (Abutaleb, A., & Badri, M., 2021). Abutaleb, A., & Badri, M. (2021). Cytomegalovirus (CMV) Colitis. *In StatPearls. StatPearls Publishing.*

Citation in text: (Lages-Silva E, Ramirez LE, Pedrosa RC, 2009) Lages-Silva E, Ramirez LE, Pedrosa RC (2009). Digestive Chagas disease: morbidity and mortality of chronic Chagas disease patients. *Mem Inst Oswaldo Cruz*. 2009;104 Suppl 1:218-221. doi:10.1590/s0074-02762009000900032

Citation in text: (Scharff, J. R., & Longo, W. E., 2015) Scharff, J. R., & Longo, W. E. (2015). Ischemic colitis: diagnosis and treatment. Current treatment options in gastroenterology, 13(2), 187-198.

Citation in text: (Kim, J., J. Lee, J. H., & Oh, S. T., 2014). Kim, J. J., Lee, J. H., & Oh, S. T. (2014). Radiation-induced intestinal injury. *Clinical endoscopy*, 47(3), 212-218. doi: 10.5946/ce.2014.47.3.212

Citation in text: (Fauci, A. S., Hauser, S., Kasper, D. L., Longo, D. L., L., Jameson, J. L., & Loscalzo, J., 2018) Fauci, A. S., Hauser, S., Kasper, D. L., Longo, D. L., L., Jameson, J. L., & Loscalzo, J., (2018) *Harrison's principles of internal medicine (20th ed.)*

Citation in text: (Rao, S. S. 2014) Rao, S. S. (2014). Diagnosis and management of fecal incontinence and pelvic floor disorders: state of the art. *Reviews in Gastroenterological Disorders*, 14(2), 81-89.

Citation in text: (Wald, A., 2015) Wald, A. (2015). Constipation, diarrhea, and symptomatic hemorrhoids. *In Sleisenger and Fordtran's Gastrointestinal and Liver Disease,*10th ed., pp. 279-298

Citation in text: (Lohsiriwat Varut, 2012) Lohsiriwat Varut (2012) Hemorrhoids: from basic pathophysiology to clinical management. *World Journal of Gastroenterology vol. 18*,17 (2012): 2009-17. doi:10.3748/wjg.v18.i17.2009

Citation in text: (Jennifer K, Lee M 2018) Jennifer K, Lee M (2018) Hemorrhoids: Diagnosis and Treatment Options. American Family Physician vol. 97,3 (2018): 172-179.

Citation in text: (Abbas, A. K., Aster, J. C., Kumar, V (2020). Abbas, A. K., Aster, J. C., Kumar, V (2020). *Robbins and Cotran pathologic basis of disease.*

Citation in text: (Cuesta, M. A, Felt-Bersma, R. J. F., 2013) Cuesta, M. A, Felt-Bersma, R. J. F. (2013) Anorectal sepsis. Digestive diseases, 31(3-4), 335-337.

Citation in text: (Prasad, M. L. & Ramanujam, P. S. 2018). Prasad, M. L. & Ramanujam, P. S. (2018). Clinical practice guidelines for management of anorectal abscess-fistula. *Indian journal of surgery*, 80(5), 499-507.

Citation in text: (Kao, L. S. & Phatak, U. R. 2020) Kao, L. S. & Phatak, U. R. (2020). Perianal abscess and fistula-in-ano. *Clinics in Colon and Rectal Surgery*, 33(5), 337-343.

Citation in text: (Chapple, K. S., Spencer, J. A., & Wilson, D., 2019) Chapple, K. S., Spencer, J. A., & Wilson, D., (2019). A review of the management of anal fistula. Annals of The Royal College of Surgeons of England, 101(8), 539-544

Citation in text: (Bruce J., McCallum I, King PM, 2007) (Bruce J., McCallum I, King PM (2007). Healing by primary versus secondary intention after surgical treatment for pilonidal sinus. *Cochrane Database Syst Rev*. 2007;(4):CD006213. doi:10.1002/14651858.CD006213.pub2

Citation in text: (Doll D, Matevossian E, Sinicina I, 2011) Doll D, Matevossian E, Sinicina I (2011) Minimally invasive pilonidal sinus treatment (MIP) with a laser: a novel technique. Surg Endosc. 2011;25(9):2777-2783. doi:10.1007/s00464-011-1614-4


İKSAD
Publishing House